Sleep Apnea in 81 Ambulatory Male Patients With Stable Heart Failure

Types and Their Prevalences, Consequences, and Presentations

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Background—Heart failure is a highly prevalent disorder that continues to be associated with repeated hospitalizations, high morbidity, and high mortality. Sleep-related breathing disorders with repetitive episodes of asphyxia may adversely affect heart function. The main aims of this study were to determine the prevalence, consequences, and differences in various sleep-related breathing disorders in ambulatory male patients with stable heart failure.

Methods and Results—This article reports the results of a prospective study of 81 of 92 eligible patients with heart failure and a left ventricular ejection fraction <45%. There were 40 patients without (hourly rate of apnea/hypopnea, 4±4; group 1) and 41 patients with (51% of all patients; hourly rate of apnea/hypopnea, 44±19; group 2) sleep apnea. Sleep disruption and arterial oxyhemoglobin desaturation were significantly more severe and the prevalence of atrial fibrillation (22% versus 5%) and ventricular arrhythmias were greater in group 2 than in group 1. Forty percent of all patients had central sleep apnea, and 11% had obstructive sleep apnea. The latter patients had significantly greater mean body weight (112±30 versus 75±16 kg) and prevalence of habitual snoring (78% versus 28%). However, the hourly rate of episodes of apnea and hypopnea (36±10 versus 47±21), episodes of arousal (20±14 versus 23±11), and desaturation (lowest saturation, 72±11% versus 78±12%) were similar in patients with these different types of apnea.

Conclusions—Fifty-one percent of male patients with stable heart failure suffer from sleep-related breathing disorders: 40% from central and 11% from obstructive sleep apnea. Both obstructive and central types of sleep apnea result in sleep disruption and arterial oxyhemoglobin desaturation. Patients with sleep apnea have a high prevalence of atrial fibrillation and ventricular arrhythmias. **(*Circulation*. 1998;97:2154-2159.)**

Key Words: lung ■ pulmonary heart disease ■ oxygen ■ arrhythmia

In spite of recent advances in the management of heart failure,[1] it remains highly prevalent and is associated with excess morbidity and mortality. Sleep-related periodic breathing with recurrent episodes of apnea (cessation of breathing) and hypopnea (decrease in breathing) is known to occur in patients with heart failure.[2–5] These breathing disorders may be associated with arterial oxyhemoglobin desaturation (impairment of myocardial O_2 demand/supply balance) and excessive arousals, resulting in sympathetic activation.[6,7] These and other pathophysiological consequences of sleep apnea and hypopnea could further contribute to the morbidity and mortality of heart failure patients.

However, few systematic studies of sleep apnea in heart failure have been reported, and large-scale studies with detailed historical and physical findings and laboratory examinations are needed. We studied 81 ambulatory male patients with stable heart failure without major comorbid disorders to determine (1) sleep characteristics and the prevalence of atrial and ventricular arrhythmias in heart failure patients with and without sleep apnea, (2) the prevalence of the two major forms of sleep apnea (obstructive and central) in the ambulatory heart failure population, (3) their clinical features, and (4) polysomnographic consequences.

Methods

Eighty-one ambulatory male patients (including the 41 patients reported earlier in Reference 2) with stable heart failure due to systolic dysfunction (left ventricular ejection fraction <45%) took part in the study. Details have been published previously.[2,8] Most of the patients were recruited within 4 years from primary care and cardiology clinics. Patients who met exclusion criteria (see below) were not studied any further. The primary investigator or the cardiologist coinvestigator evaluated all patients to confirm that they were clinically stable and on standard therapy, with no change in signs or symptoms of heart failure within the previous 4 weeks. Seventy-three patients were on an ACE inhibitor, 5 on hydralazine, 61 on digoxin, 34 on isosorbide dinitrate, and 69 on diuretics. Medication dosages had been adjusted on the basis of the hemodynamic and clinical status of each patient and had not been changed within the previous 4 weeks. The calculated average daily dosage of heart failure medications was 88 mg for captopril, 15 mg for lisinopril, 22 mg for enalapril, 137 mg for hydralazine, 82 mg for isosorbide dinitrate, 0.21 mg for digoxin, and 80 mg for furosemide.

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The etiologies of heart failure were ischemic cardiomyopathy (30 patients without sleep apnea, group 1, and 31 patients with sleep apnea, group 2), idiopathic cardiomyopathy (7 patients in group 1 and 9 in group 2), and presumed alcoholic cardiomyopathy (3 patients in group 1 and 1 in group 2).

Exclusion criteria included unstable angina; unstable heart failure; acute pulmonary edema; congenital heart disease; intrinsic pulmonary diseases, including interstitial lung disease and obstructive lung defect (ratio of percent predicted forced expiratory volume to forced vital capacity <68%); intrinsic renal and liver disorders; kyphoscoliosis; untreated hypothyroidism; and use of morphine derivatives, benzodiazepines, or theophylline. For uniformity, only male patients were studied, because female patients are seldom referred to this center (therefore, we acknowledge that our results cannot necessarily be extrapolated to women).

Of the 92 eligible patients, 81 (88% recruitment) agreed to participate. The main reasons for refusal were unwillingness to stay in the hospital for sleep studies or unwillingness to travel to the hospital because of distance. The mean left ventricular ejection fraction of 6 of these patients for whom data were available was 18±6%.

At the time of the recruitment, no information was sought about symptoms or risk factors for sleep apnea. The patients were admitted to the hospital for 2 consecutive nights. Caffeinated products were avoided during hospitalization. On the first day, a detailed history was obtained and physical examination was performed. The following tests were also obtained: complete blood count, serum electrolytes, blood urea nitrogen, serum creatinine, thyroxine and digoxin levels, radionuclide ventriculography, arterial blood gases and pH, pulmonary function, and polysomnography with nocturnal Holter monitoring.

Polysomnography

On the first night, the patients slept in the sleep laboratory after the electrodes had been placed, with the intention of familiarizing the patients with the environment of the sleep laboratory. On the second night, polysomnography was performed by use of standard techniques as detailed previously.[2,8–10] For staging sleep, we recorded the electroencephalogram, chin electromyogram, and electro-oculogram. Thoracoabdominal excursions and naso-oral airflow (by use of a thermocouple or a CO_2 analyzer) were measured qualitatively, and arterial blood oxyhemoglobin saturation was recorded with a pulse oximeter. These variables were recorded on a multichannel polygraph (model 78D; Grass Instrument Co).[2,8–10]

Standard definitions were used for sleep-related disordered breathing. Apnea was defined as cessation of inspiratory airflow for ≥10 seconds. Obstructive apnea was defined as the absence of airflow in the presence of rib cage and abdominal excursions. Central apnea was defined as the absence of rib cage and abdominal excursions with an absence of airflow (for further details, see References 2 and 8 through 10). Hypopnea was defined as a reduction of airflow (or thoracoabdominal excursions) lasting 10 seconds or more and associated with at least a 4% drop in arterial oxyhemoglobin saturation or an arousal. An arousal was defined as the appearance of μ waves on the electroencephalogram for at least 3 seconds.[11] The number of episodes of apnea and hypopnea per hour is referred to as the apnea-hypopnea index. Polysomnograms were scored in a blinded manner.

Other Studies

To determine the prevalence of arrhythmias, Holter monitoring was performed during polysomnography as detailed previously.[2] Ventricular tachycardia was defined as the presence of three ventricular premature beats in a row. Right and left ventricular ejection fractions were calculated from gated first-pass and multigated radionuclide ventriculograms, respectively, by standard techniques. Pulmonary function tests and arterial blood samples were obtained according to strict criteria as detailed previously.[12,13]

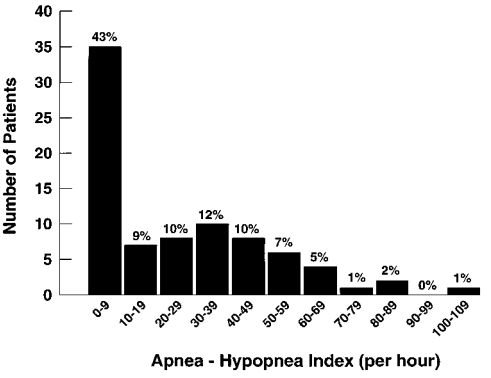

Figure 1. Frequency distribution of apnea-hypopnea index in 10 unit-intervals in 81 male patients with stable, compensated heart failure.

Classification of Patients

Different thresholds have been used to define the prevalence of sleep apnea. In patients with heart failure, several studies[14,15] have used an apnea-hypopnea index of 10 per hour. In a previous study,[2] we used an apnea-hypopnea index of 20 per hour. However, like others,[14,15] we have encountered patients with an index below this level with significant arterial oxyhemoglobin desaturation. Therefore, for the purpose of this study, an index ≥15 per hour was used. Group 1 consisted of patients without sleep apnea (defined polysomnographically by using an apnea-hypopnea index of <15 per hour). Group 2 patients had sleep apnea, defined by an apnea-hypopnea index ≥15 per hour. Group 2 patients were further subdivided into those with obstructive sleep apnea (obstructive apnea-hypopnea index >15 per hour) and those with central sleep apnea (all of these patients had an obstructive apnea-hypopnea index <10 per hour). In all patients classified as having obstructive or central sleep apnea, that breathing disorder was the predominant pattern.

Statistical Analysis

We used the Wilcoxon rank-sum test to assess significant differences between group 1 and group 2, since the data were not normally distributed. χ^2 was used for comparison of proportions. Similar tests were used to compare significant differences between patients with obstructive and those with central sleep apnea. Spearman correlation coefficients were used to compute correlations between apnea-hypopnea index and certain pathophysiologically related variables. A value of $P<0.05$ was considered significant. Values are reported as mean±SD. Calculations were done with SAS software.[16]

Results

The frequency distribution of the apnea-hypopnea index in 10-unit intervals for the 81 heart failure patients is depicted in Figure 1. According to our defined thresholds, there were 40 patients (group 1, 49% of all patients) who did not have sleep apnea, and the mean (±SD) of the apnea-hypopnea index was 4±4 per hour. In the remaining 41 patients (group 2, 51% of all patients), the mean apnea-hypopnea index was 44±19 per hour.

For group 1 compared with group 2 patients, there were no significant differences in demographics, historical data, and physical examination findings (Table 1). In ≈15% of patients in each group, crackles and third or fourth heart sounds were heard. Mean values of laboratory tests, including serum electrolytes, creatinine (124±53 versus 124±51 μmol/L), hemoglobin (15±2 versus 14±2 g/dL), hematocrit (.43±.05 versus .42±.05), and digoxin (0.9±0.5 versus 1.3±0.6 nmol/L) in group 1 and group 2 patients, respectively, were

TABLE 1. Demographics, Historical Data, and Physical Examination Findings in 81 Male Heart Failure Patients Without (Group 1) or With (Group 2) Sleep-Disordered Breathing

Variable	Group 1	Group 2
Patients, n (%)	40 (49)	41 (51)
Age, y	62±12	66±9
Weight, kg	85±16	83±25
Height, cm	174±6	173±6
Body mass index, kg/m^2	28.0±4.9	27.7±7.3
Patients with habitual snoring, %	50	44
Patients with excess daytime sleepiness, %	15	24
Witnessed sleep apnea, %	15	22
Orthopnea, %	25	24
Paroxysmal nocturnal dyspnea, %	20	15
Systolic blood pressure, mm Hg	124±24	120±18
Diastolic blood pressure, mm Hg	73±9	72±11
New York Heart Association classification		
Classes I and II, %	78	63
Class III, %	23	37

There were no statistical differences between respective variables of the two groups. "Habitual" was defined as almost every night or every night; "excessive daytime sleepiness" was defined as the presence of at least one of the following: falling asleep unintentionally daily at least three times in 1 week, falling asleep while driving a car, or three naps in 1 week despite adequate sleep.

similar. Thyroid function tests were normal in both groups. There were no significant differences when mean values of forced vital capacity, functional residual capacity, total lung capacity, and diffusion for CO were compared (data not shown). However, the mean value of forced expiratory volume in 1 second over forced vital capacity ratio was slightly but significantly lower in group 1 (91±12% predicted) than in group 2 (99±10% predicted), although we had excluded patients with major obstructive airway defects.

There were remarkable differences in the severity of various disordered breathing events between the two groups (Table 2). Consequently, patients with sleep apnea developed relatively severe oxyhemoglobin desaturation, despite a higher daytime Pao[r]$_2$ (Table 2), and significant sleep disruption (Table 3). In this regard, the mean values of arousal index (number of arousals per hour), stage 1 (light) sleep as a percentage of total sleep time, and wakefulness after sleep onset (Table 3) were significantly greater and total rapid eye movement sleep significantly less in heart failure patients with sleep apnea (group 2) than in those without (group 1).

Left ventricular ejection fraction was significantly lower (22±8% versus 27±9%, $P=0.01$) and the prevalence of atrial fibrillation (22% versus 5%, $P=0.026$) and nocturnal ventricular tachycardia (51% versus 37%, $P=0.23$) were higher in patients with sleep apnea than in those without. Similarly, during sleep the mean values for premature ventricular depolarizations (178±272 versus 34±58 per hour, $P=0.0002$), couplets (15±43 versus 0.4±1.4 per hour, $P=0.0001$), and ventricular tachycardias (1.3±3.8 versus 0.1±0.2 per hour, $P=0.07$) were higher in patients with sleep apnea than in those without. There were significant correlations between apnea-hypopnea index and premature ventricular depolarizations ($r=0.42$), couplets ($r=0.58$), ventricular tachycardias ($r=0.26$), and left ventricular ejection fraction ($r=-.35$). The arrhythmias occurred randomly throughout the night. There was no significant difference in right ventricular ejection fraction between groups 1 and 2 (44±16% versus 47±13%, $P=0.51$).

TABLE 2. Awake Arterial Blood Gases, Sleep-Disordered Breathing Episodes, and Arterial Oxyhemoglobin Saturation in 81 Male Heart Failure Patients Without (Group 1) or With (Group 2) Sleep-Disordered Breathing

Variable	Group 1	Group 2
Breathing events (No. of episodes/h)		
Apnea-hypopnea	4±4	44±19*
Central apnea	2±2	24±21*
Obstructive apnea–hypopnea	0.3±0.8	7±12*
Mixed apnea	0±0	1±2*
Arousals with disordered breathing	3±3	20±13*
Arterial oxyhemoglobin saturation during sleep		
Baseline, %	95±2	95±2
Lowest value, %	89±4	76±12*
<90%, Minutes	4±10	49±53*
<90%, Per total sleep time, %	1±3	19±21*
Awake arterial blood gases		
P_{O_2}, mm Hg	79±11	85±10*
P_{CO_2}, mm Hg	39±4	37±5*
[H^+], nmol/L	37±2	36±3
[HCO_3^-], mmol/L	26±3	25±3

*$P<0.05$ when compared with the respective value in Group 1.

Group 2 patients were further subdivided (Figures 2 and 3) into those with central sleep apnea (n=32, 40% of all

TABLE 3. Sleep Characteristics in 81 Male Heart Failure Patients Without (Group 1) or With (Group 2) Sleep-Disordered Breathing

Variable	Group 1	Group 2
Total time in bed, minutes	392±25	393±19
Total sleep time, minutes	288±64	264±49*
Sleep efficiency (sleep time/time in bed), %	73±15	67±13*
Sleep onset, minutes	18±21	16±16
Wakefulness after sleep onset, minutes	85±46	111±51*
Sleep stage 1, minutes	79±64	111±69*
Sleep stage 1/total sleep time, %	28±21	43±26*
Sleep stage 2, minutes	143±68	108±80*
Sleep stage 2/total sleep time, %	50±20	40±26
Sleep stages 3 and 4, minutes	4±10	0.4±1.4
Sleep stages 3 and 4/total sleep time, %	1±3	0.2±0.5
Rapid eye movement sleep, minutes	62±29	45±35*
Rapid eye movement sleep/total sleep time, %	21±8	17±12*
Non–rapid eye movement sleep, minutes	226±51	219±50
Non–rapid eye movement sleep/total sleep time, %	79±8	83±12*
Arousals/h, n	20±12	33±21*

*$P<0.05$ when compared with the respective mean value in Group 1.

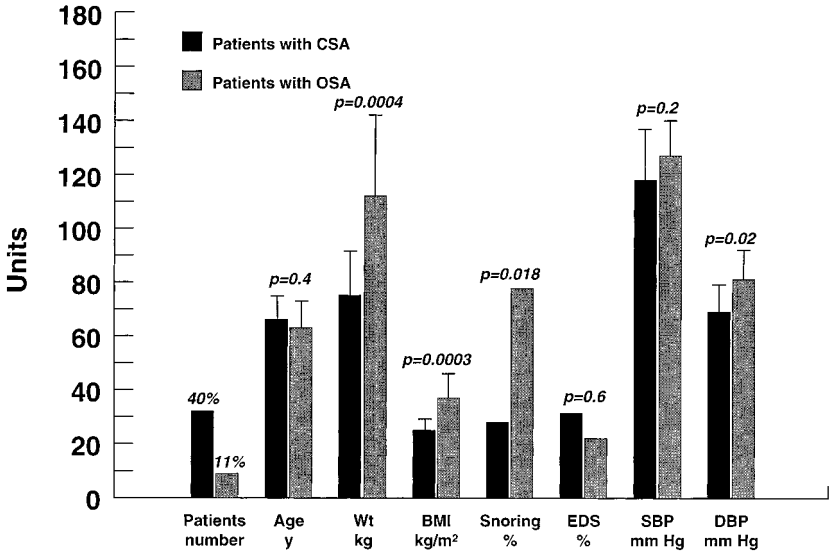

Figure 2. Demographics, historical data, and physical examination findings in male heart failure patients with either central (CSA) or obstructive (OSA) sleep apnea. Wt indicates weight; BMI, body mass index; EDS, excessive daytime sleepiness; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

patients) and those with obstructive sleep apnea (n=9, 11% of all patients) as defined previously. There were no significant differences in height (172±7 versus 174±5 cm); age (66±9 versus 63±10 years); left ventricular ejection fraction (21±8% versus 26±6%); and hourly episodes of premature ventricular contractions (202±298 versus 89±182), couplets (10±18 versus 31±87), or ventricular tachycardias (1.0±2.3 versus 2.3±6.6) during sleep. However, the prevalence of loud snoring and the mean values for body mass index and diastolic blood pressure were significantly lower in patients with central than in those with obstructive sleep apnea (Figure 2). As expected, the mean values of central (45±22 versus 7±7 per hour, $P=0.0001$) and obstructive (1±2 versus 28±8 per hour, $P=0.0001$) sleep-disordered breathing events were significantly different, but the overall mean values for apnea-hypopnea index (47±21 versus 36±10 per hour) and lowest saturation (78±12% versus 72±11%) did not differ significantly. Furthermore, the mean values for total dark time (394±15 versus 388±28 minutes), total sleep time (264±51 versus 265±45 minutes), sleep efficiency (67±13% versus 69±14%), and arousal index (29±18 versus 44±29 per hour) did not differ significantly when patients with central and obstructive sleep apnea were compared.

Discussion

This report represents the only large-scale, systematic study of heart failure with well-defined criteria in patients who have undergone sleep studies and other detailed laboratory tests to determine the prevalence, consequences, and factors associated with various forms of sleep-related breathing disorders in this population. The results show that (1) 51% of the patients have relatively severe periodic breathing during sleep, with an average apnea-hypopnea index of ≈44 per hour; (2) central sleep apnea occurs in 40% and obstructive sleep apnea in 11% of the patients; (3) both central and obstructive forms of sleep apnea result in sleep disruption and arterial oxyhemoglobin desaturation; and (4) three factors associated with sleep apnea in heart failure are atrial fibrillation, ventricular arrhythmias, and low left ventricular ejection fraction.

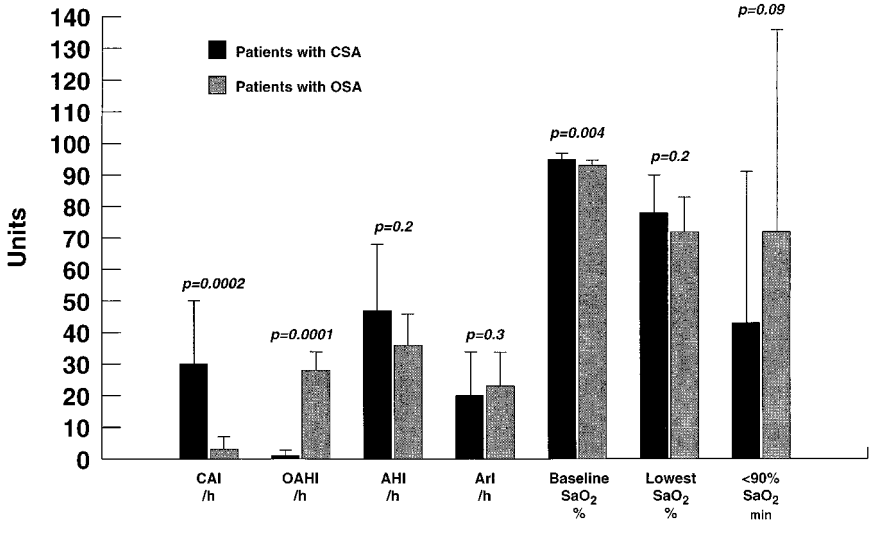

Figure 3. Polysomnographic findings in male heart failure patients with either central (CSA) or obstructive (OSA) sleep apnea. CAI indicates central apnea index; OAHI, obstructive apnea-hypopnea index; AHI, apnea-hypopnea index; ArI, arousal index; and Sa_{O_2}, arterial oxyhemoglobin saturation.

Periodic Breathing and Sleep Characteristics

Owing to the small number of patients in our initial report,[2] there were no significant differences in most sleep parameters of patients with and those without sleep apnea. However, the present data (Table 3) show that heart failure patients with sleep apnea slept significantly less and had a significantly greater proportion of stage 1 (light) sleep and less rapid eye movement sleep than did heart failure patients without sleep apnea. These abnormalities in sleep characteristics may result in daytime fatigue and sleepiness when measured quantitatively,[17] and we found a tendency for a greater prevalence of subjective excessive daytime sleepiness in patients with sleep-disordered breathing (Table 1).

Periodic Breathing, Oxyhemoglobin Desaturation, and Cardiac Dysfunction

Periodic breathing also resulted in severe arterial oxyhemoglobin desaturation, with an average low level of 76±12% and the patients' spending ≈19% of their total sleep time at or below a saturation of 90% (Table 2). Nocturnal arterial oxyhemoglobin desaturation occurred despite a normal baseline Pa_{O_2} (Table 2). Periodic breathing also resulted in an excessive number of arousals in patients with sleep apnea, with an average of 20 per hour compared with 3 per hour in patients without sleep apnea (Table 2). Recurrent episodes of nocturnal oxyhemoglobin desaturation, arousals, and changes in intrathoracic pressure due to periodic breathing while asleep,[18] as well as daytime dips in saturation,[19] could adversely affect cardiac function by a variety of mechanisms,[6,7,20–24] eventually resulting in an imbalance between myocardial oxygen delivery and consumption.[3] In this context, left ventricular ejection fraction was significantly lower in patients with sleep apnea (group 2) than in patients without, thus confirming our previous findings.[2] Furthermore, the new observation is the increased prevalence of atrial fibrillation, which was approximately 4 times higher in heart failure patients with sleep apnea than in those without. Atrial fibrillation might have been caused in part by the increased right heart afterload due to hypoxic vasoconstriction and pulmonary hypertension.[24] These data suggest that atrial fibrillation in particular should serve as a clinical marker for development of periodic breathing during sleep.

We emphasize that these data do not permit us to determine whether sleep-disordered breathing exacerbates left ventricular dysfunction or alternatively, that patients with more impaired cardiac function were more likely to have excessive sleep-disordered breathing. However, we speculate that the interaction between sleep-disordered breathing and left ventricular dysfunction[3] could result in a vicious circle, further increasing morbidity and mortality in patients with heart failure.

Periodic Breathing and Central and Obstructive Sleep Apnea

We found that there was a surprisingly high prevalence (51% of patients) of sleep-disordered breathing, which in our population would not have been suspected clinically (Table 1). This observation is in contrast with the obstructive sleep apnea–hypopnea syndrome.[25] The prevalence of habitual snoring and daytime sleepiness, major symptoms of the obstructive sleep apnea–hypopnea syndrome, did not differ significantly between the two groups (Table 1), and there were no distinguishing features during the general physical examination (eg, hypertension, obesity, etc; Table 1). This result confirms our previous observation[2] in a smaller number of patients. In the present study, however, when heart failure patients with sleep apnea were classified in a blinded manner (without the investigator's knowledge of their clinical presentations) according to polysomnographic findings as those with central sleep apnea (40% of all patients) and those with obstructive sleep apnea (11% of all patients) (Figure 2), the prevalence of snoring was significantly greater in the latter group. Only nine of the 32 patients (28%) with central sleep apnea had habitual snoring, which was significantly less than the 78% of patients with heart failure and obstructive sleep apnea. Furthermore, body weight, body mass index, and the diastolic blood pressure of patients classified as having obstructive sleep apnea were significantly greater than those with central sleep apnea (Figure 2). Therefore, the reason why sleep-disordered breathing in heart failure remains relatively occult (Table 1) is in part due to the predominance (40% of the patients) of central sleep apnea. Our data (Figure 2) show that this disorder is less frequently associated with loud snoring and excessive body weight, which are the hallmarks of the obstructive sleep apnea–hypopnea syndrome with or without heart failure. We emphasize, however, that the severity of arterial oxyhemoglobin desaturation and the number of arousals were similar in both central and obstructive sleep apnea patients (Figure 3).

In summary, the present study shows that 51% of patients with stable heart failure due to systolic dysfunction suffer from a moderate to severe degree of sleep-disordered breathing. Patients with heart failure and sleep apnea have a higher prevalence of atrial fibrillation, ventricular arrhythmias, and lower left ventricular ejection fraction than do heart failure patients without sleep apnea. Central sleep apnea accounted for 40% and obstructive sleep apnea for 11%. Heart failure patients with obstructive sleep apnea were typically obese and had a history of habitual snoring, features that were relatively scarce in patients with central sleep apnea. Both central and obstructive sleep apnea may result in recurrent episodes of arousal and arterial oxyhemoglobin desaturation. The pathophysiological consequences of sleep apnea may ultimately affect the morbidity and mortality of patients with heart failure.

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References

1. Cohn JN. The management of chronic heart failure. *N Engl J Med*. 1996; 335:490–498.
2. Javaheri S, Parker TJ, Wexler L, Michaels SE, Stanberry E, Nishyama H, Roselle GA. Occult sleep-disordered breathing in stable congestive heart failure [published erratum appears in *Ann Intern Med*. 1995;123:77]. *Ann Intern Med*. 1995;122:487–492.
3. Javaheri S. Central sleep apnea-hypopnea syndrome in heart failure: prevalence, impact and treatment. *Sleep*. 1996;19:S229–S231.

4. Bradley TD, Floras JS. Pathophysiologic and therapeutic implications of sleep apnea in congestive heart failure. *J Card Fail*. 1996;2: 223–240.
5. Yamashiro Y, Kryger MH. Sleep in heart failure. *Sleep*. 1993;16: 513–523.
6. Somers VK, Dyken M, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest*. 1995;96: 1897–1904.
7. Dempsey JA. Sleep apnea causes daytime hypertension. *J Clin Invest*. 1997;99:1–2.
8. Javaheri S, Parker TJ, Wexler L, Liming JD, Lindower P, Roselle GA. Effect of theophylline on sleep-disordered breathing in heart failure. *N Engl J Med*. 1996;335:562–567.
9. Javaheri S, Colangelo G, Lacey W, Gartside PS. Chronic hypercapnia in obstructive sleep apnea-hypopnea syndrome. *Sleep*. 1994;17:416–423.
10. Dowdell WT, Javaheri S. Lack of effect of external warming on sleep architecture in sleep apnea/hypopnea syndrome. *Am Rev Respir Dis*. 1992;145:137–140.
11. ASDA Report. EEG arousals: scoring rules and examples. *Sleep*. 1992; 15:174–184.
12. Javaheri S, Bosken CH, Lim SP, Dohn MN, Greene NB, Baughman RP. Effects of hypohydration on lung functions in humans. *Am Rev Respir Dis*. 1987;135:597–599.
13. Javaheri S, Guerra LF. Effects of domperidone and medroxyprogesterone acetate on ventilation in man. *Respir Physiol*. 1990;81:359–370.
14. Naughton M, Benard D, Tam A, Rutherford R, Bradley TD. Role of hyperventilation in the pathogenesis of central sleep apneas in patients with congestive heart failure. *Am Rev Respir Dis*. 1993;148:330–338.
15. Naughton MT, Benard DC, Liu PP, Rutherford R, Rankin F, Bradley TD. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. *Am J Respir Crit Care Med*. 1995;152: 473–479.
16. SAS Institute Inc. *SAS/STAT Users Guide. Release 6.03*. Cary, NC: SAS Institute Inc; 1988:1028DD.
17. Hanly P, Zuberi-Khokhar N. Daytime sleepiness in patients with congestive heart failure and Cheyne-Stokes respiration. *Chest*. 1995;107: 952–958.
18. Bradley TD. Right and left ventricular functional impairment and sleep apnea. In: Phillison EA, Bradley T, eds. *Clinics in Chest Medicine*. Philadelphia, Pa: WB Saunders; 1992:13;459–479.
19. Munger MA, Stanek EJ, Nara AR, Strohl KP, Decker MJ, Nair RN. Arterial oxygen saturation in chronic congestive heart failure. *Am J Cardiol*. 1994;73:180–185.
20. Fletcher EC, Lesske J, Qian W, Miller CC, Unger T. Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats. *Hypertension*. 1992;19:555–561.
21. Fletcher EC, Lesske J, Behm R, Miller CC III, Stauss H, Unger T. Carotid chemoreceptors, systemic blood pressure, and chronic episodic hypoxia mimicking sleep apnea. *J Appl Physiol*. 1992;72:1978–1984.
22. Blumberg H, Janig W, Riechmann C, Szulczyk P. Baroreceptor and chemoreceptor reflexes in postganglionic neurones supplying skeletal muscle and hairy skin. *J Auton Nerv Syst*. 1980;2:223–240.
23. Rose CE Jr, Althaus JA, Kaiser DL, Miller ED, Carey RM. Acute hypoxemia and hypercapnia: increase in plasma catecholamines in conscious dogs. *Am J Physiol*. 1983;245:H924–H929.
24. Harvey RM, Enson Y, Ferrer MI. A reconsideration of the origins of pulmonary hypertension. *Chest*. 1971;59:82–94.
25. Young T, Palta M, Dempsey J, Skatrud J, Wever S, Safwan B. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328:1230–1235.