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 O2 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.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.
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. For staging sleep, we recorded the electroencephalogram, chin electromyogram, and electro-oculogram. Thoracoabdominal excursions and naso-oral airflow (by use of a electroencephalogram, chin electromyogram, and electro-oculogram. Thoracoabdominal excursions and naso-oral airflow (by use of a thermocouple or a CO₂ analyzer) were measured qualitatively, and thoracoabdominal excursions and naso-oral airflow (by use of a electroencephalogram, chin electromyogram, and electro-oculogram. Thoracoabdominal excursions and naso-oral airflow (by use of a thermocouple or a CO₂ analyzer) were measured qualitatively, and

#### 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. χ² 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.

### Results

The frequency distribution of the 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 have used an apnea-hypopnea index of 10 per hour. In a previous study, we used an apnea-hypopnea index of 20 per hour. However, like others, 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.

#### Other Studies

To determine the prevalence of arrhythmias, Holter monitoring was performed during polysomnography as detailed previously. 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.
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 5.5% 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 \((r=-0.35)\). The arrhythmias occurred randomly throughout the night. There was no significant difference in right ventricular ejection fraction between groups 1 and 2 \(\left(44\pm16\%\, \text{versus}\, 47\pm13\%, \, P=0.51\right)\).

Group 2 patients were further subdivided (Figures 2 and 3) into those with central sleep apnea \(\left(n=32, \, 40\%\, \text{of all}ight)\) and those with 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 \(\text{PaO}_2\) (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 \(\left(22\pm8\%\, \text{versus}\, 27\pm9\%, \, P=0.01\right)\) and the prevalence of atrial fibrillation \(\left(22\%\, \text{versus}\, 5\%, \, P=0.026\right)\) and nocturnal ventricular tachycardia \(\left(51\%\, \text{versus}\, 37\%, \, P=0.23\right)\) were higher in patients with sleep apnea than in those without. Similarly, during sleep the mean values for premature ventricular depolarizations \(\left(178\pm272\, \text{versus}\, 34\pm58\, \text{per hour}, \, P=0.0002\right)\), couplets \(\left(15\pm43\, \text{versus}\, 0.4\pm1.4\, \text{per hour}, \, P=0.0001\right)\), and ventricular tachycardias \(\left(1.3\pm3.8\, \text{versus}\, 0.1\pm0.2\, \text{per hour}, \, P=0.07\right)\) were higher in patients with sleep apnea than in those without. There were significant corre-
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±12 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.
Periodic Breathing and Sleep Characteristics

Owing to the small number of patients in our initial report, 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, 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 PaO₂ (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, as well as daytime dips in saturation, could adversely affect cardiac function by a variety of mechanisms, eventually resulting in an imbalance between myocardial oxygen delivery and consumption. 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. 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, which was approximately 4 times higher in heart failure patients with sleep apnea than in those without, thus confirming our previous findings. 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 (40% of all patients) and those with obstructive sleep apnea (11% of all patients) (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 load 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.

Acknowledgment

This work was supported by Merit Review Grants from the Department of Veterans Affairs to S. Javaheri, MD.

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_Circulation._ 1998;97:2154-2159
doi: 10.1161/01.CIR.97.21.2154

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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