Prevalence of Sleep-Disordered Breathing in Patients on a Heart Transplant Waiting List*

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We investigated the prevalence of sleep-disordered breathing in 20 outpatients on a heart transplant waiting list. All were younger than 60 years and had severe stable cardiac failure with a cardiac index below 2.5 L/min/m² and a left ventricular ejection fraction below 25%. Nine patients (45%) exhibited ten or more apneas and hypopneas per hour of sleep (apneic group). In all patients but one, apneas and hypopneas were predominantly of the central type and occurred during Cheyne-Stokes respiration. There were no statistically significant differences between the apneic and nonapneic groups of patients in terms of age (51±5 years vs 49±11), body mass index (24±4 kg/m² vs 22±3), cardiac index (1.87±0.35 L/min/m² vs 1.84±0.40), isotopic left ventricular ejection fraction (13±5 vs 12±3%), arterial blood gas, or pulmonary function tests. Hypnogram characteristics showed poorer sleep quality in the apneic group than in the nonapneic group, with a larger number of arousals; this difference was found both for arousals lasting more than 30 s (8±5/h vs 4±2) and for arousals lasting less than 30 s (18±16/h vs 5±6) and was associated with increased wakefulness after sleep onset in the apneic group (138±52 min vs 84±45). Arousals were strongly associated with hyperpneic phases of Cheyne-Stokes respiration. We conclude that sleep-disordered breathing is common in patients with end-stage heart disease and adversely affects the quality of sleep.

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AHI=apnea hypopnea index; BMI=body mass index; LVEF=left ventricular ejection fraction; REM=rapid eye movement; SaO₂=arterial oxygen saturation; TLC=total lung capacity; TST=total sleep time; VC=vital capacity; WASO=wakefulness after sleep onset

Key words: arousals, cardiac failure, Cheyne-Stokes respiration

Only recently has the relationship between sleep and disordered breathing been analyzed in patients with congestive heart failure.1-4 These studies demonstrated that patients with left ventricular heart failure exhibited a high prevalence of abnormal breathing patterns during sleep, nocturnal arousals, and unexpected nocturnal oxygen desaturations, which may increase sympathetic nervous system tone, aggravate myocardial ischemia, and trigger cardiac dysrhythmia. Findley et al1 observed that of 15 patients with left ventricular failure, 6 had breathing disorders (40%). In a larger study of 95 patients hospitalized for acute cardiogenic pulmonary edema, Hoffman et al2 observed a similar prevalence (45%) of sleep-disordered breathing. However, both studies investigated older patients, and similar prevalences of sleep-disordered breathing have been observed in normal subjects in the same age range.5,6 It should also be noted that these studies and others4,7 did not consider the behavior of a population with end-stage heart disease. Therefore, we studied a group of 20 outpatients younger than 60 years of age on a heart transplant waiting list to determine the prevalence of sleep-disordered breathing in such patients with end-stage heart disease despite optimal medical treatment of heart failure. In addition, we attempted to correlate sleep-disordered-breathing with sleep parameters and with left ventricular function.

METHODS

Patient Population and Assessment of Cardiac and Respiratory Functions

The study included 20 consecutive patients who were on the waiting list for heart transplantation because they were limited by chronic stable heart failure due to impaired left ventricular function despite optimal control of fluid retention. Each subject gave informed consent, but was not aware of the objective of the study. Patients were admitted to our hospital for inclusion in the heart transplant list. All subjects had right heart catheterization with a 7F Swan-Ganz catheter inserted percutaneously via the femoral vein and positioned in the pulmonary artery. Cardiac output was measured during quiet wakefulness in a relaxed, supine position. Cardiac index was calculated using data from cardiac output measurements, weight, and height. All patients had a left ventricular ejection fraction (LVEF) determined by 99mTc radi-
onucleide angiography, arterial blood gas analysis, conventional spirometry, including flow-volume expiratory loop and static lung volume measurement by the closed-circuit helium dilution method. Spirometry reference values were those of the European community.8

Sleep Studies

Sleep studies were performed in the hospital room and consisted of full polysomnography, including electroencephalography, electro-oculography, chin electromyography, oronasal airflow, rib cage and abdominal movements (multi-parameter analysis recorder 2/ Medilog 9200; Oxford Medical Instrument, Abington, England), and arterial pulse oximetry (Nellcor BS, Nellcor Inc, Hayward, Calif).

Sleep staging was performed according to standard criteria.9 Wakefulness after sleep onset (WASO) included all wakefulness recorded after the onset of sleep, until the final awakening. The EEG arousals were detected by an abrupt shift in EEG frequency, which include theta, alpha, and/or frequencies greater than 16 Hz but not spindles, and were scored according to standard criteria.10 They were classified as longer or shorter than 30 s. An abnormal breathing event during objectively measured sleep was defined according to the commonly used clinical criteria as either complete cessation of airflow lasting 10 s or more (apnea) or a fall in oronasal airflow of 50% for 10 s or more (hypopnea). The average number of episodes of apnea and hypopnea per hour of sleep (apnea-hypopnea index [AHI]) was calculated as the summary measurement of sleep-disordered breathing. For categorical analysis, a cutoff point of AHI=10/h of sleep was used. Cheyne-Stokes respiration was defined as a cyclic pattern of breathing with an increasing then decreasing amplitude of the airflow signal. Apneas were classified as obstructive or central according to whether or not paradoxic chest wall and abdominal motion occurred, respectively.

Statistics

The possible relationship of AHI to other measured parameters was investigated through correlation methods relating AHI and summary measures of daytime cardiac function or sleep characteristics, as well as unpaired t tests contrasting subjects who had AHI>10/h with the remaining subjects on the same measures. Correlations between variables were analyzed using least squares linear regression techniques. Level of significance was set at 5%.

RESULTS

A total of 17 men and 3 women was studied. All were younger than 60 years. Although every patient was taking multiple cardiac medications, none was taking drugs known to alter sleep or neurologic function.

Individual data of sleep-disordered breathing are summarized in Table 1. Sleep-disordered breathing (AHI>10) was noted in nine patients (45%). Among the sleep-disordered breathing patients, all patients but one had central rather than obstructive apneas. Furthermore, for all patients, except the patient with obstructive apneas, the apneas and hypopneas were observed during Cheyne-Stokes respiration and a significant correlation between AHI and Cheyne-Stokes duration (r=0.91, p=0.0001) was observed. Duration of episodes with arterial oxyhemoglobin saturation (SaO2) <90% was greater than 5% of total sleep time (TST) for four patients in the sleep-disordered breathing group and was negligible in every patient of the non-sleep-disordered breathing group.

Age and body mass index (BMI) were similar in both groups (Table 2). There were no female subjects in the group with sleep–disordered breathing (Table 2). There were no loud snorers or patients with a history of nocturnal apneas witnessed by the bed partner in the group without sleep-disordered breathing. In contrast, among patients in the sleep-disordered breathing group, five (56%) were loud snorers and five (56%, four loud snorers and one nonsnorer) had apneas detected by the bed partner. Only one patient in each group complained of excessive daytime somnolence, although no attempt was made to confirm this objectively.

Results of the sleep analysis are shown in Figure 1. In our population TST (540±98 min) was shorter than normal for this age,11 but no between-group difference was observed for this value or for sleep architecture parameters, except for the WASO which was significantly longer (Fig 1A [top]) and arousals

![Figure 1. Nocturnal sleep parameters in the non-sleep-disordered breathing group (AHI<10) and the sleep-disordered breathing group (AHI>10). Data are means±SD. TST=total sleep time; WASO=wakefulness after sleep onset; REM=rapid eye movement sleep.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21704/ on 06/25/2017)
which were more frequent in the sleep-disordered breathing group (Fig 1C [bottom]). Furthermore, a significant correlation was seen between the number of arousals and the AHI (r=0.9, p<0.0001) (Fig 2). We also observed that most arousals shorter than 30 s occurred during the hyperpneic phase of Cheyne-Stokes respiration.

In the non–sleep-disordered breathing group and the sleep-disordered breathing group respectively, the underlying cardiac disease was ischemic disease in seven and three patients, alcoholic cardiomyopathy in zero and two patients, valvular disease in two and zero patients and idiopathic disease in two and four patients. No significant differences were seen between the apneic and non-apneic groups concerning cardiac index (1.87±0.35 L/min/m² vs 1.84±0.40), isotopic left ventricular ejection fraction (13±5% vs 12±3%), and arterial blood gas analysis or conventional spirometry (Table 2). Similarly, there were no correlations between AHI and cardiac index (r=0.03, p=0.90) or LVEF (r=0.13, p=0.57).

**DISCUSSION**

In this study, we explored respiratory events and quality of sleep in patients on a heart transplant waiting list and found that the prevalence of sleep-disordered breathing was 45%. Patients with abnormal breathing during sleep exhibited sleep of a poor quality, and among them 20% of patients had nocturnal hypoxemia.

The sleep apnea syndrome is classically defined as an apnea index greater than 5 apneas per hour of sleep causing adverse mental and physical effects. However, this definition has recently been the focus of considerable debate following the identification of normal subjects with an index greater than 5.13,14

| Table 1—Sleep-Disordered Breathing Characteristics of the Studied Patients |
|-------------------------|----------------|----------------|----------------|----------------|----------------|
| Patients                | AHI | Central Apneas, % AHI | Obstructive Apneas, % AHI | Hypopneas, % AHI | Cheyne-Stokes Duration, % TST |
| Non-sleep-disordered breathing group (AHI <10/h of sleep) | 1 | 0 | ... | ... | 0 | <1 |
| 2 | 0 | ... | ... | ... | 0 | <1 |
| 3 | 6 | 16 | 0 | 84 | 0 | <1 |
| 4 | 4 | 8 | 0 | 92 | 9 | <1 |
| 5 | 5 | 58 | 0 | 42 | 12 | <1 |
| 6 | 0 | ... | ... | ... | 0 | <1 |
| 7 | 0 | ... | ... | ... | 4 | <1 |
| 8 | 5 | 43 | 0 | 57 | 7 | <1 |
| 9 | 3 | 0 | 0 | 100 | 0 | <1 |
| 10 | 4 | 77 | 0 | 23 | 1 | <1 |
| 11 | 0 | ... | ... | ... | 0 | <1 |
| Sleep-disordered breathing group (AHI >10/h of sleep) | 12 | 15 | 12 | 0 | 88 | 25 | <1 |
| 13 | 19 | 42 | 7 | 51 | 40 | <1 |
| 14 | 19 | 0 | 62 | 38 | 0 | <1 |
| 15 | 59 | 100 | 0 | 0 | 78 | 6 |
| 16 | 36 | 61 | 12 | 27 | 82 | 19 |
| 17 | 37 | 87 | 5 | 8 | 70 | 12 |
| 18 | 13 | 17 | 0 | 83 | 20 | <1 |
| 19 | 59 | 70 | 0 | 30 | 64 | 6 |
| 20 | 12 | 53 | 3 | 44 | 18 | 2 |

**Table 2—Clinical Characteristics and Pulmonary Function Studies***

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>BMI, kg/m²</th>
<th>Sex ratio, M/F</th>
<th>TLC, % pred</th>
<th>VC, % pred</th>
<th>FEV₁, % pred</th>
<th>PaO₂, mm Hg</th>
<th>PaCO₂, mm Hg</th>
<th>pH</th>
<th>t Test</th>
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<tbody>
<tr>
<td>Non-sleep-disordered Breathing Group</td>
<td>AHI &lt;10, Mean ± SD</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>AHI &lt;10, Mean ± SD</td>
<td>49±11</td>
<td>22±3</td>
<td>8/3</td>
<td>80±10</td>
<td>78±21</td>
<td>71±22</td>
<td>85±10</td>
<td>33±4</td>
<td>7.46±0.05</td>
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<tr>
<td>Sleep-disordered Breathing Group</td>
<td>AHI &gt;10, Mean ± SD</td>
<td></td>
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<td></td>
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<tr>
<td>AHI &gt;10, Mean ± SD</td>
<td>51±5</td>
<td>24±4</td>
<td>9/0</td>
<td>82±13</td>
<td>85±13</td>
<td>84±12</td>
<td>85±10</td>
<td>33±3</td>
<td>7.43±0.06</td>
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<tr>
<td>t Test</td>
<td>p Value</td>
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*Predicted values were those of the European community (Quanjer P*).
†NS=not significant.
Furthermore, it has now been established that hypopnea is clinically significant. Based on these findings, most sleep centers now use an AH1=10 apneas per hour of sleep to define sleep-disordered breathing.

It is well known that the prevalence of abnormal breathing during sleep is highly dependent on age. All of our patients were younger than 60 years and none had other detectable causes of abnormal breathing during sleep, such as neurologic disease or obesity. The highest prevalence of sleep-disordered breathing observed in a population of middle-aged men was 15% in the study by Young et al. Our results clearly indicate an abnormally high prevalence of sleep-disordered breathing in our subjects with end-stage cardiac failure.

Previous studies of the prevalence and severity of sleep-disordered breathing in patients with congestive heart failure included subjects with an LVEF >25%, a criterion that encompasses mild cardiac failure and terminal cardiac failure. We restricted our study to a fairly homogeneous group of patients. All had severe stable cardiac failure with a cardiac index below 2.5 L/min/m² and an LVEF below 25%.

In patients with cardiac failure, prolonged circulation time is considered to be the main factor responsible for breathing pattern abnormalities. We were therefore surprised not to find a higher prevalence of sleep-disordered breathing. However, conflicting results have been obtained during studies of breathing pattern abnormality rates in relation to cardiac function. In a small group of six patients with decompensated congestive heart failure, Dark et al found an inverse relationship between the number of breathing pattern abnormalities and the LVEF; furthermore, they noted an improvement in abnormal breathing patterns after therapy for heart failure. In contrast, Findley et al found no correlation between sleep-disordered breathing and left ventricular dysfunction, but observed that Cheyne-Stokes breathing predicted a higher short-term mortality rate. Similarly, in a total of 58 patients recovering from acute cardiogenic pulmonary edema, Hoffman et al found no difference in echographic estimates of LVEF between the groups with and without sleep-disordered breathing. Our data extend these observations to a population with terminal cardiac failure.

Episodes of apnea were of the central type and occurred during Cheyne-Stokes respiration in all our patients but one who had obstructive apneas. It has been demonstrated that respiratory system instability can produce obstructive as well as central apneas.

The comparison of our data to age-specific normal values showed that patients in both groups had sleep of poor quality, as shown by the short TST, reduction in slow-wave sleep, and increase in WASO with frequent arousals. We believe that the short TST is not an artifact due to the recording conditions because all our patients had at least four nights to adapt to the hospital room and many other patients studied in our laboratory using similar techniques had longer sleep times. Furthermore, it has been suggested that there is no significant first night effect with sleep recording apparatus similar to ours. We believe this short TST can be largely explained by the inactivity and anxiety that are usual in patients recently included in a heart transplant list.

Although the distribution of sleep stages was similar in the two groups, we observed a clear difference in quality of sleep, with significantly higher values for the WASO index and number of arousals in the group with sleep-disordered breathing. Paradoxically, daytime sleepiness, which is one of the most common features of the sleep apnea syndrome, was observed only in one patient in each group. Previous studies have reported that patients with cardiac failure and Cheyne-Stokes respiration rarely complained of daytime somnolence. Use of a more accurate tool for assessing sleepiness may be necessary to demonstrate the effects of abnormal respiration: in a simi-
lar cardiac failure population with no subjective daytime somnolence, Hanly and Zuberi\(^1\) found that the multiple sleep latency test\(^23\) was significantly shortened and within the diagnostic range of excessive daytime sleepiness.

Arousals were linked with sleep-disordered breathing. They occurred mainly during Cheyne-Stokes respiration at the peak of the hyperpneic phase. Hanly et al\(^1\) reported the same phenomenon and suggested that these arousals resulted from increased ventilation. Recent studies also suggest that sensations associated with the degree of inspiratory effort may be important in producing arousal.\(^24\-26\) On the other hand, because the nadir of oxygen saturation occurs at the beginning of the hyperpneic phase, it is conceivable that arousals result from blood oxygen desaturation. However, in a similar population, Biberdorf et al\(^27\) observed that arousals sometimes occurred during Cheyne-Stokes respiration without apparent hypoxia. This suggests that hyperventilation is an important stimulus for arousal in such patients.

Arousals are usually considered beneficial when they occur during obstructive apnea since they have the physiologic advantage of restoring breathing; this was obviously not the case in our patients in whom arousals disrupted sleep without providing any benefits. Furthermore, in patients with heart failure, these arousals may cause instability of respiratory control center function, thereby perpetuating Cheyne-Stokes respiration.\(^28\,29\) Studies of the effects of hypnotics in such patients\(^27\,30\) failed to substantiate this hypothesis, since they found no significant effects of benzodiazepines on central apnea and hypopnea. On the other hand, they found that hypnotics improved sleep fragmentation and multiple sleep latency test scores.

Because hypoxia promotes hyperpnea and, therefore, Cheyne-Stokes respiration, oxygen therapy has also been tested in patients similar to ours.\(^31\) A reduction in hypoxia, arousals, and Cheyne-Stokes duration was observed. Studies of long-term oxygen therapy demonstrated similar beneficial effect.\(^32\) In contrast, the effects of nasal continuous positive airway pressure on cardiac output and Cheyne-Stokes respiration remain controversial. Takasaki et al\(^33\) observed a marked improvement in sleep respiration and left ventricular function, whereas others failed to observe beneficial effects on cardiac function, sleep respiration, and sleep quality.\(^30\,34\,35\)

In summary, our findings confirm that apneas and hypopneas associated with Cheyne-Stokes respiration are common during end-stage heart disease. This sleep-disordered breathing is responsible for sleep disruption by arousals and hypoxemia that may play a role in the cardiac dysfunction. If there is a link between cardiac failure and the occurrence of sleep-disordered breathing, evaluation of the effect of allogenic cardiac transplantation on sleep in these patients will improve our understanding of the relationship between cardiac failure and breathing abnormalities.

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