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# Sleep apnea is linked to heart failure, but does treatment improve outcome?

## ■ ABSTRACT

One of the factors that contribute to the progressively declining course of heart failure could be sleep apnea. Whether treating sleep apnea improves the clinical outcomes of patients with heart failure needs to be tested in randomized clinical trials.

## ■ KEY POINTS

Sleep apnea can be due to obstruction of the upper airway or to failure of the central nervous system to generate respiratory drive. In patients with systolic heart failure, central apnea is more common, although obstructive apnea can also occur. Sleep apnea also occurs in diastolic heart failure, though data are very limited.

Both central and obstructive sleep apnea cause arousals and intermittent hypoxemia, hypercapnia, hypocapnia, and changes in intrathoracic pressure. These have deleterious effects on the cardiovascular system, particularly in established heart failure.

The reasons for suspecting obstructive sleep apnea in patients with heart failure are the same as those in the general population, ie, obesity and habitual snoring; the main treatments are weight loss and positive airway pressure devices.

The reasons for suspecting central sleep apnea in patients with heart failure are cardiac findings such as low ejection fraction, higher New York Heart Association class, and arrhythmias; the possible treatments are optimization of cardiac function, nocturnal oxygen therapy, positive airway pressure devices, and theophylline.

\*Dr. Javaheri has indicated that he is on the speaker's bureaus of companies that make devices used to treat sleep apnea.

**H**EART FAILURE is a major risk factor for sleep-related breathing disorders, which, in a vicious circle, may adversely affect cardiovascular function.<sup>1,2</sup>

Although as yet few trials have examined the effect of treating sleep apnea in patients with heart failure, considerable evidence supports the hypothesis that it will improve their outcomes.<sup>1,2</sup>

Unfortunately, in the clinical management of heart failure, sleep-related breathing disorders remain much underdiagnosed owing to unfamiliarity with sleep apnea on the part of primary care physicians, internists, and cardiologists. In this article, we briefly review the epidemiology, diagnosis, and treatment of sleep-related breathing disorders in heart failure.

## ■ THE CARDIOVASCULAR SYSTEM DURING STAGES OF SLEEP

Sleep proceeds through stages, which are monitored during polysomnography (sleep studies) using electroencephalography (usually a central and an occipital channel), chin electromyography, and tracking of eye movements.

Non-rapid eye movement (non-REM) sleep consists of four stages. Falling asleep is stage 1; stages 2, 3, and 4 are increasingly deeper. After stage 4, people cycle backwards through stages 3 and 2 again, and then about 90 minutes after falling asleep go into rapid eye movement (REM) sleep. After REM sleep the cycle begins again, and people go through about five cycles per night. Episodes of REM sleep increase in duration as the night progresses, with most of it occurring in the last cycle before rising in the morning. REM sleep

TABLE 1

**Terms used in the article**

**Apnea:** cessation of breathing for 10 seconds or more

**Obstructive sleep apnea:** apnea due to upper airway occlusion; therefore, naso-oral airflow ceases in spite of activation of inspiratory thoracic pump muscles (diaphragm)

**Central sleep apnea:** apnea due to lack of activation of thoracic pump muscles; therefore, both naso-oral airflow and activity of pump muscles cease

**Hypopnea:** reduction in airflow for 10 seconds or more, resulting in an arousal, an arterial oxyhemoglobin desaturation of 4%, or both

**Apnea-hypopnea index:** the number of episodes of apnea or hypopnea per hour of sleep

**Arousal:** an electroencephalographic definition, characterized by alpha waves (indicating wakefulness) lasting 3 to 14 seconds; activity of 15 seconds or longer is called an awakening

**Arousal index:** the number of arousals per hour of sleep

**'Central sleep apnea' is a more objective term than 'Cheyne-Stokes breathing'**

is characterized by dreaming (and hence, increased cerebral oxygen consumption and blood flow) and skeletal muscle atonia: the "active brain in a paralyzed body."

In the cardiovascular system, the main difference between wakefulness, non-REM sleep, and REM sleep is the level of autonomic nervous system activity, which has a profound effect on cardiovascular function. In non-REM sleep, as we go from stage 1 through stage 4, the activity of the sympathetic nervous system progressively and predictably decreases, while that of the parasympathetic system increases.<sup>1</sup> These changes are reflected in reductions in heart rate, cardiac output, and systemic blood pressure.

In contrast, during REM sleep and arousals from sleep, sympathetic activity increases, and consequently, so does blood pressure and the heart rate.<sup>3</sup> Since non-REM sleep accounts for about 80% of total sleep time and REM sleep for about 20%, most of the time spent in normal sleep is peaceful for the cardiovascular system.

## ■ DISORDERED BREATHING

During polysomnography we also monitor the patient's breathing by recording naso-oral airflow (measured by a variety of instruments placed on the upper lip, such as a temperature probe, a CO<sub>2</sub> analyzer, or a pressure probe); thoracoabdominal excursions, and arterial

oxygen saturation (measured by pulse oximetry). Together, these allow us to detect and characterize episodes of apnea and hypopnea (TABLE 1).

**Apnea** episodes, defined as cessation of naso-oral airflow for at least 10 seconds, may last up to 1½ minutes.

**Obstructive apnea** is due to occlusion of the upper airway because of relaxation of the oropharyngeal muscles. During these episodes, polysomnography shows no naso-oral airflow in spite of continual thoracoabdominal excursions.

**Central apnea** is temporary cessation of breathing due to failure of brain stem centers to generate rhythmic breathing. During these episodes, polysomnography simultaneously shows no naso-oral airflow and no thoracoabdominal excursions.

**Hypopnea** episodes are reductions in airflow and in thoracoabdominal excursions that last at least 10 seconds. Hypopnea can also be classified as either obstructive or central, but making this distinction is often difficult.

**The apnea-hypopnea index** is traditionally used to define the severity of sleep-related breathing disorders. The severity of hypoxemia that results from episodes of apnea and hypopnea is usually reported as the lowest oxyhemoglobin saturation and the time spent below a saturation of 90%. Episodes of apnea and hypopnea cause arousals from sleep, and these are reported as an *arousal index*.



**Periodic breathing** is characterized by cyclic fluctuations in tidal volume. It consists of periodically recurring cycles of apnea or hypopnea or both, followed by hyperpnea. The apnea and hypopnea may be obstructive or central, and both forms occur in patients with heart failure.<sup>1,2</sup>

**Cheyne-Stokes breathing**, which occurs primarily in severe systolic heart failure, is characterized by gradual reduction in tidal volume, with or without intervening episodes of central sleep apnea, followed by a gradual increase in tidal volume. Each cycle is typically prolonged because the arterial circulation time is increased, a pathophysiological feature of severe systolic heart failure. Of note: unlike apnea and hypopnea, Cheyne-Stokes breathing is a subjective description and is not readily quantifiable. For these reasons, the term *central sleep apnea* is preferred.

## ■ HOW SLEEP APNEA MAY WORSEN HEART FAILURE

Systolic heart failure is progressive, and there are several reasons to believe that sleep-related breathing disorders, which are common in patients with heart failure, could contribute to its progression.

Obstructive and central sleep apnea and hypopnea have three main sequelae<sup>1,2</sup>:

- **Intermittent arterial blood gas abnormalities**, ie, hypoxemia (followed by reoxygenation) and hypercapnia (followed by hypocapnia). Hypoxemia and hypercapnia result in increased sympathetic activity and pulmonary arterial vasoconstriction. Hypoxemia may also result in decreased myocardial oxygen delivery, and both hypoxemia and hypoxemia-reoxygenation result in increased expression of redox-sensitive genes that encode inflammatory mediators such as endothelin.<sup>1,2</sup>

These adverse effects of altered blood chemistry may be more deleterious to the cardiovascular system in people with heart failure or coronary artery disease than if the heart is normal.

- **Arousals from sleep.** Each arousal is associated with increased sympathetic nervous system activity<sup>3</sup> and decreased parasympathetic activity, which may have deleterious cardiovascular effects, particularly in heart failure.

**TABLE 2**

### Prevalence of sleep-related breathing disorders in heart failure

STUDY	N	LVEF	AHI ≥ 10/HOUR	AHI ≥ 15/HOUR
<b>Systolic heart failure</b>				
Javaheri et al <sup>5*</sup>	81	25	57	51
Tremel et al <sup>10*</sup>	34	30	NA	82
Lanfranchi et al <sup>12*</sup>	66	23	76	NA
Lofaso et al <sup>11*</sup>	20	< 25	45	45
Solin et al <sup>9*</sup>	75	< 40	59	43
Sin et al <sup>8†</sup>	450	27	72	61
<b>Diastolic heart failure</b>				
Chan et al <sup>13*</sup>	20	> 50	55	NA

\*Prospective; †retrospective

LVEF = left ventricular ejection fraction; AHI = apnea-hypopnea index; NA = not available or not reported

- **Large negative swings in intrathoracic pressure**, which occur during obstructive sleep apnea and during the hyperpnea following an episode of central apnea, are reflected in swings in juxtacardiac pressure, increasing the transmural left ventricular pressure and its wall tension.<sup>1,2</sup> This increase in left ventricular afterload is particularly deleterious in people with left ventricular systolic dysfunction. In addition, increased negative pulmonary interstitial pressure promotes pulmonary edema. In patients with heart failure and increased left ventricular end-diastolic pressure, transpulmonary capillary transudation is further augmented by the increased capillary hydrostatic pressure.

## ■ SLEEP APNEA IS COMMON IN HEART FAILURE

The prevalence of sleep-related breathing disorders has been studied in patients with heart failure due to a variety of causes,<sup>4</sup> though most systematically in heart failure due to left ventricular systolic dysfunction (TABLE 2).<sup>5-16</sup>

### Sleep apnea in systolic heart failure

At least 45% of patients with systolic heart failure have an apnea-hypopnea index of at least 10 per hour, and at least 40% have an

**Up to half of patients with heart failure may have sleep apnea**

TABLE 3

### Some hallmarks of sleep apnea in systolic heart failure

#### Obstructive sleep apnea

- Obesity
- Habitual snoring
- Witnessed apnea
- Waking up unrefreshed
- Excessive daytime sleepiness
- Nocturnal angina
- Nocturia
- Nocturnal sweating
- Systemic hypertension
- Pulmonary hypertension

#### Central sleep apnea

- Paroxysmal nocturnal dyspnea
- Restless sleep
- Insomnia
- Witnessed apnea
- Ventricular tachycardia
- Excess premature ventricular beats ( $\geq 30$ /hour) and couplets
- Atrial fibrillation
- Low left ventilation ejection fraction
- Class III and IV New York Heart Association heart failure
- Progressive left ventricular dysfunction in spite of adequate medical therapy

index of at least 15 per hour.

Javaheri et al (our team),<sup>5</sup> in the largest prospective study of this topic, performed polysomnography in 81 ambulatory men with stable, treated heart failure. Forty-one of the patients (51%) had moderate to severe sleep apnea-hypopnea (defined as an apnea-hypopnea index of 15 per hour or greater), and this group had an average index of  $44 \pm 19$  (1 SD) per hour. The occurrence of central sleep apnea was inversely related to ejection fraction but was not predicted by New York Heart Association heart failure class. Approximately 40% of the patients had central sleep apnea and 11% had obstructive sleep apnea.

Sin et al<sup>8</sup> retrospectively studied the polysomnographic findings from 450 men and women with heart failure. Of these, 61% had an apnea-hypopnea index of at least 15 per hour, and the prevalence of obstructive sleep apnea was 32%. These prevalence rates were higher than in our study,<sup>5</sup> most likely because

symptoms and risk factors for sleep apnea (eg, snoring) were among reasons for referral to the sleep laboratory in their study, whereas we sought no such information during recruitment.

#### Sleep apnea in diastolic heart failure

Chan et al,<sup>13</sup> in a small study, found that approximately 50% of patients with isolated diastolic heart failure had an apnea-hypopnea index of at least 10 per hour (TABLE 2). However, large-scale epidemiologic studies are needed to define the prevalence of sleep apnea-hypopnea in isolated diastolic heart failure. The topic is important because many elderly patients with symptoms of congestive heart failure have isolated diastolic heart failure, and sleep-related breathing disorders are also common in this cohort.

#### WHICH HEART-FAILURE PATIENTS NEED A SLEEP STUDY?

In the absence of evidence-based guidelines for when to consider sleep studies in patients with heart failure, we suggest the following, based on the results of studies in our laboratory and others.

The reasons for suspecting obstructive sleep apnea in patients with heart failure are the same as those in the general population. The main criteria are obesity and habitual snoring. However, some other symptoms such as excessive daytime sleepiness may be absent.

The indications for a sleep study to rule out central sleep apnea are different (TABLE 3). Many patients with central sleep apnea are thin and may not snore. In this group of patients, the major criteria are cardiac findings such as low ejection fraction, higher New York Heart Association class, and arrhythmias.

#### TREATING SLEEP APNEA IN HEART FAILURE

The approach to treatment of sleep apnea in heart failure depends on whether the apnea is predominantly obstructive or central (TABLE 4).

#### Treatment of obstructive sleep apnea

Treatment of obstructive sleep apnea-hypopnea in heart failure<sup>1,2</sup> is similar to that in people without heart failure. The two main ther-



**TABLE 4**

## Potential treatments for sleep apnea-hypopnea in heart failure

### Obstructive sleep apnea-hypopnea

- Optimization of medical therapy of heart failure
- Weight loss
- Positive airway pressure devices (continuous positive airway pressure [CPAP]; bilevel pressure for CPAP noncompliance)
- Oxygen for patients noncompliant with positive airway pressure devices

### Central sleep apnea

- Optimization of medical therapy of heart failure
- Nocturnal oxygen
- CPAP or bilevel pressure device
- Cardiac transplantation
- Theophylline

apies are weight loss and nasal positive airway pressure devices.

**Weight loss.** Obesity is the major known risk factor for obstructive sleep apnea in the general population<sup>17</sup> and also in patients with heart failure.<sup>5,8</sup> Furthermore, recent data from the Framingham Heart Study<sup>18</sup> show that being overweight or obese is associated with increased risks of heart failure and death, primarily owing to cardiovascular causes.<sup>19</sup> Undiagnosed obstructive sleep apnea could be an important contributing factor linking obesity to the heart failure and cardiovascular mortality reported in these two studies.<sup>18,19</sup>

Overweight and obese patients with heart failure should receive dietary consultation and be encouraged to lose weight, which has been shown to decrease the obstructive sleep apnea-hypopnea index.<sup>17</sup> Bariatric surgery is becoming another option for patients with morbid obesity, though there are no studies in patients with heart failure.

**Noninvasive positive airway pressure devices** (continuous positive airway pressure [CPAP] and bilevel) prevent obstruction of the upper airway and are used to treat obstructive sleep apnea in the general population. There are also limited reports on the use of nasal CPAP for treatment of obstructive sleep apnea in heart failure.<sup>20,21</sup>

Nasal CPAP eliminates obstructive episodes of disordered breathing and arterial oxyhemoglobin desaturation.<sup>20-22</sup> Moreover, the left ventricular ejection fraction has been

reported to increase with long-term use of CPAP.<sup>21,22</sup> This is an important finding, since the left ventricular ejection fraction is a predictor of survival in systolic heart failure.

In the general population, treatment of obstructive sleep apnea with nasal CPAP reverses a number of neurohormonal abnormalities, such as abnormal endothelium-dependent vasodilatation, hypercoagulopathy, and leukocyte activation.<sup>23</sup> Similar effects in the heart failure population would be of obvious benefit.

For heart failure patients who have difficulty with expiratory pressure using standard CPAP, a bilevel device should be used. These devices vary the pressure during the breathing cycle, with a lower pressure during exhalation, making it easier to breathe out.

### Treatment of central sleep apnea

The treatment of central sleep apnea in systolic heart failure is somewhat different from that of obstructive sleep apnea.<sup>1,2,24-26</sup> Of utmost importance is to improve cardiorespiratory function before performing polysomnography, given the limited manpower available and the cost of polysomnography.

**Optimization of cardiopulmonary function.** Early studies (reviewed elsewhere<sup>1,2</sup>) and more recent ones<sup>9</sup> show that aggressive treatment of heart failure according to evidence-based guidelines may improve or even eliminate periodic breathing. Several mechanisms may be involved, including decreasing pul-

**Each arousal from sleep activates the sympathetic nervous system**

monary capillary wedge pressure, normalizing the partial pressure of arterial CO<sub>2</sub> (PaCO<sub>2</sub>), increasing stroke volume, improving arterial circulation time, and normalizing functional residual capacity.<sup>1,2</sup>

**Oxygen.** Systematic studies of patients with systolic heart failure<sup>27,28</sup> have shown that giving supplemental oxygen by nasal cannula at night improves central sleep apnea, eliminates desaturations, and may decrease arousals and light sleep (reviewed elsewhere<sup>1,2,29</sup>). In the largest study,<sup>28</sup> in 36 patients with systolic heart failure whose mean left ventricular ejection fraction was about 22%, we observed that the central apnea index decreased significantly from about 28 to 10 per hour. Supplemental nasal oxygen has been shown to decrease sympathetic activity in patients with systolic heart failure, as measured by increased sympathetic activity in muscle<sup>30</sup> and decreased urinary norepinephrine excretion overnight.<sup>31</sup>

These findings are important in relating sleep apnea to progressive heart failure, since increased sympathetic activity has deleterious effects on left ventricular structure and function in patients with systolic heart failure.<sup>1,2</sup> Furthermore, in a randomized, placebo-controlled, double-blind, crossover study, Andreas et al<sup>32</sup> showed that giving supplemental nocturnal oxygen for 1 week improved maximum exercise capacity. This is also an important finding because the maximum oxygen consumption (V<sub>O<sub>2</sub>max</sub>) is an independent predictor of survival in heart failure<sup>33</sup> and coronary artery disease.<sup>34</sup>

Giving oxygen may reduce central sleep apnea by several mechanisms.<sup>29</sup> It may increase the PaCO<sub>2</sub> slightly by decreasing hyperventilation. By increasing stores of oxygen in the lung and blood, oxygen therapy may decrease periodic breathing. Further, administration of oxygen should restore the patient's ventilatory response to CO<sub>2</sub>. Consequently, breathing during sleep should stabilize.<sup>1,2,29</sup>

However, prospective, placebo-controlled, long-term studies are necessary to determine if nocturnal oxygen therapy can decrease the morbidity and mortality of patients with systolic heart failure.<sup>29</sup>

**Nasal positive airway pressure devices.** Various positive airway pressure devices have

been used to treat central sleep apnea in congestive heart failure (reviewed elsewhere<sup>1,2,26</sup>). Nasal CPAP has been studied most extensively, and different laboratories have reported different results.

We studied 21 heart failure patients with central sleep apnea, and 9 (43%) of them responded to CPAP the first night.<sup>20</sup> In these patients, CPAP decreased the apnea-hypopnea index from 36 per hour to 4 per hour and eliminated arterial oxyhemoglobin desaturation. Of importance: in patients whose sleep apnea-hypopnea responded to CPAP, the number of premature ventricular contractions, couplets, and runs of nonsustained ventricular tachycardia decreased. In contrast, CPAP had no significant effect on ventricular irritability in patients whose disordered breathing did not improve. We emphasize, however, that although our study enrolled the largest number of patients in an acute CPAP trial, the number of patients was small and the electrocardiographic findings need to be confirmed in a large study.

Controlled studies of the long-term effects of CPAP by Naughton et al<sup>35</sup> and Sin et al<sup>36</sup> showed a reduction in the apnea-hypopnea index and arousal index and an increase in left ventricular ejection fraction. Naughton et al<sup>35</sup> also reported that CPAP decreases sympathetic activity as measured by the plasma norepinephrine level and urinary norepinephrine excretion.

No clinical trials to date have had enough statistical power to show the effect of treatment of sleep apnea on survival in patients with heart failure. However, it is reasonable to speculate that nasal CPAP, by decreasing ventricular arrhythmias<sup>20</sup> and improving ejection fraction,<sup>35</sup> may improve survival in patients with systolic heart failure. In this regard, in a small randomized, controlled trial,<sup>36</sup> 14 patients with central sleep apnea received CPAP and another 15 served as controls. Two patients were not compliant with CPAP and were excluded from the analysis. The 3-year incidence of death or cardiac transplantation was significantly lower in the CPAP group ( $P = .017$ ). On intention-to-treat analysis (which includes all patients enrolled), a similar trend was observed but was not statistically significant ( $P = .06$ ).

Many patients with central sleep apnea are thin and do not snore



There are several unresolved issues about the use of CPAP for central sleep apnea in heart failure. We found<sup>20</sup> that 57% of patients with central sleep apnea did not respond to one night of CPAP. These patients had the most severe central sleep apnea and had a tendency to have a low PaCO<sub>2</sub>. Negative studies from other laboratories have been also reported (reviewed elsewhere<sup>1,2,26</sup>).

Because of an increase in intrathoracic pressure, venous return may decrease with CPAP, resulting in decreased stroke volume and hypotension. Heart failure patients with atrial fibrillation, intravascular hypovolemia, and normal left ventricular end-diastolic blood pressure may be more vulnerable to these effects. If CPAP decreases blood pressure, cardiac output, and coronary blood flow, then myocardial ischemia may occur, which could be particularly detrimental in patients with coronary artery disease. In this regard, the results of a Canadian multicenter study using CPAP have been disappointing and the trial was terminated early.

In summary, CPAP is uniformly effective in treating obstructive sleep apnea-hypopnea in heart failure. It may be effective in treating central sleep apnea in some patients, but at this time, we do not recommend its use.

**Theophylline.** Both open and double-blind<sup>37,38</sup> studies have shown theophylline to be effective in treating central sleep apnea in heart failure. In a double-blind, randomized, placebo-controlled, crossover study,<sup>38</sup> in 15 patients with treated, stable systolic heart failure, theophylline twice daily by mouth at

therapeutic plasma concentrations (average 11 µg/mL, range 7–15/ µg/mL) decreased the apnea-hypopnea index by about 50% and improved arterial oxyhemoglobin saturation. Theophylline significantly decreased central apnea but had no effect on obstructive sleep apnea.

Mechanisms of action of theophylline in improving central apnea remain unclear.<sup>38</sup> At therapeutic serum concentrations, theophylline increases ventilation. This probably is due to competitive inhibition of adenosine, which is a respiratory depressant. Conceivably, therefore, an increase in ventilation by theophylline could decrease the likelihood of occurrence of central apnea during sleep.

Potential arrhythmogenic effects and phosphodiesterase inhibition are common concerns with the use of theophylline in patients with heart failure, and further controlled studies are needed to assure its long-term safety.

**Cardiac transplantation.** Limited studies show that in patients with systolic heart failure, cardiac transplantation generally eliminates central sleep apnea (reviewed elsewhere<sup>1,2</sup>). Unfortunately, many of these patients later develop obstructive sleep apnea.<sup>35</sup> Cardiac transplant recipients who gained the most weight after surgery were most likely to develop obstructive sleep apnea, and in these patients, obstructive sleep apnea was associated with hypertension and poor quality of life.<sup>39</sup> Therefore, cardiac transplant recipients need to be monitored for development of obstructive sleep apnea. ■

**We cannot yet recommend CPAP for heart failure patients with central sleep apnea**

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