

## Central Sleep Apnea in Heart Failure: Incidence, Prevalence and Treatment

### Introduction

While sleepiness is known to disrupt cognitive, social and/or occupational performance, sleep is becoming increasingly recognized as a contributor to or predictor of a number of chronic conditions including cardiovascular disease, gastroesophageal reflux disease, diabetes, and psychiatric disorders.<sup>1</sup> Approximately 5% of the general population and 30% of those with cardiovascular disease have some type of sleep disorder, and studies have revealed that sleep disordered breathing (SDB) affects 40-60% of those with heart failure (HF).<sup>2-4</sup> Of particular importance is that these individuals are at increased risk for disease progression, declining health status, arrhythmias, and death. As the signs and symptoms seen with sleep disorders are not significantly different from those associated with chronic heart failure, such as fatigue, nocturnal dyspnea and daytime sleepiness, clinicians frequently fail to consider SDB as a possible contributor to or a consequence of HF. Correction of SDB in HF improves sleep quality and myocardial performance, including stroke volume and left ventricular ejection fraction. Since a large portion of patients with systolic left ventricular dysfunction have central sleep apnea (CSA), this article will focus on that condition including the pathophysiology, diagnosis and treatment.

### Sleep and Sleep Disorders

Chronic sleep deprivation and its adverse consequences on health are well documented. Even in short-term experimental conditions, sleep restriction yields a variety of physiologic effects, including hypertension, glucose impairment, elevated inflammatory markers, and increased sympathetic nervous system activation.<sup>5</sup> Chronically, disrupted sleep, as in SDB, negatively impacts the immune and neurohormonal systems and increases risks for the

development of cardiovascular diseases, including HF, hypertension, arrhythmias and stroke.<sup>6</sup> In particular, elevated cytokines and C-reactive protein appear to influence the development and severity of cardiovascular disease through inflammation-driven atherosclerosis.<sup>7</sup> Outcome evaluations of sleep deprivation on mortality have not been as well studied, yet there appear to be increased all-cause mortality rates for both men and women who sleep less than 6 hours per night, as compared to those who report 7-8 hours of sleep.<sup>8,9</sup>

Sleep consists of two distinct stages, nonrapid eye movement (NREM) and rapid eye movement (REM). NREM, making up 80-85% of total sleep time, has 4 stages, beginning with light sleep (stage 1), and progressing to the deeper sleep found in stages 3 and 4. During stages 3 and 4, parasympathetic nervous tone is increased, and the body experiences reductions in cardiac output, systemic vascular resistance, and myocardial oxygen work. Additionally, the wakefulness instinct to breathe is removed during NREM sleep, and respiratory control is driven by metabolism. This metabolic-based respiration is critically dependent on chemical stimuli, particularly  $PCO_2$ .

REM follows NREM sleep and is the period where the deepest level of relaxation occurs. In REM, the body is essentially paralyzed, but the brain remains very active. REM sleep is essential to feeling rested and refreshed upon awakening, yet it is associated with variable and frequently increased blood pressure, heart rate, and respirations due to increased sympathetic and decreased parasympathetic nervous system activities. During the transition from NREM to REM sleep, respiration becomes more dependent on behavioral factors and relies less on metabolism.<sup>10</sup> Relaxation of the nondiaphragmatic respiratory muscles leads to reduced ventilatory effort, hypoxemia, and hypercapnia.

Progression through NREM stages occurs in 4-6 cycles per night, each lasting approximately 90-110 minutes, before entering REM sleep. REM sleep is followed by more stage 2 NREM before resuming the progression toward deeper sleep. Although they are brief (3-14 seconds), arousals or awakenings during sleep alter the cycle with a return to stage 1 NREM. Abrupt increases in sympathetic and decreased parasympathetic activities, exceeding that seen during wakefulness, are observed during arousals. Compared to relaxed awakening, where increased sympathetic activity occurs gradually without an abrupt cessation of parasympathetic activity, this sudden change may account for the dramatic changes in blood pressure and heart rate seen with arousals.<sup>11, 12</sup> Due to the amount of time spent in NREM stages, sleep should be a period of hemodynamic and cardiovascular tranquility; however sleep disorders disrupt this relaxed state and create additional stress for the body.

SDB describes a family of disorders characterized by abnormalities in either the respiratory pattern or the quantity of respirations during sleep. SDB can be classified as either those who “cannot breathe” or those who “will not breathe.” Obstructive sleep apnea (OSA) depicts the “cannot breathe” patient whose oropharyngeal muscles relax during sleep, collapsing the airway and obstructing naso-oral air flow. During these episodes, the patient continues to have thoracoabdominal excursions. The apneic episode ends when the patient is briefly aroused, triggering breathing to resume. This pattern is repeated throughout sleep. Central sleep apnea (CSA), also known as periodic breathing, occurs in those who “will not breathe” resulting from an absence of both airflow and inspiratory effort. CSA is characterized by a temporary cessation of breathing inserted between episodes of increased respiratory rates (hyperpnea) and decreased respiratory rates (hypopnea), or a waxing and waning of tidal volume, and consequently PO<sub>2</sub> and PCO<sub>2</sub> levels.

## Pathophysiology of Central Sleep Apnea

CSA was first described over two centuries ago by John Hunter, a British surgeon.<sup>13</sup> However, John Cheyne and William Stokes are credited with describing periodic breathing in heart failure, in which an apnea or hypopnea episode is sandwiched between the waxing and waning respirations, now known as Cheyne-Stokes breathing.<sup>13</sup>

Alveolar hypoventilation, or reduced gas exchange between the alveoli and pulmonary capillaries, is the hallmark of CSA. The mechanisms for CSA relate to the state of sleep, removal of the wakefulness drive to breathe, and the apneic threshold, defined as the level of  $PCO_2$  below which rhythmic breathing ceases.<sup>13</sup> The inhibitory effects of sleep on ventilatory responsiveness are offset by the neural brainstem mechanisms that stabilize ventilation.

In particular, the difference between the  $PCO_2$  at the apneic threshold minus the prevailing  $PCO_2$  is a critical factor for CSA - the smaller the difference, the greater the chance of CSA. In healthy individuals, sleep is associated with decreased respiratory rates and alveolar ventilation, resulting in increased hypercapnia. However, in HF,  $PCO_2$  does not rise during sleep as it should, and apneas occur because of the narrow margin between the prevailing  $PCO_2$  level and the apneic threshold. While the mechanisms are not totally understood, when patients with systolic HF recline, venous pressures elevate, producing a subsequent rise in left ventricular filling pressure and increased respiratory rates and alveolar ventilation. These mechanisms prevent  $PCO_2$  from rising as it should, and CSA follows. While it is not unusual for healthy individuals to have obstructive or central apneas, they are usually less than 15 seconds in duration and occur at sleep onset or during REM sleep. On the other hand, the majority of CSA events in HF occur after NREM sleep, following arousals and disrupt the sleep cycle with a return to stage 1 NREM.

### Significance

These repetitive episodes of nocturnal apnea make CSA the most common form of SDB seen in HF and neurologic disorders.<sup>14</sup> After controlling for confounding variables, CSA has been identified as an independent risk factor in HF for death or the need for cardiac transplantation.<sup>15-17</sup> This may be due to marked sympathetic nervous system activation, surges in blood pressure and heart rate, or increased incidence of ventricular arrhythmias.<sup>18, 19</sup> Lanfranchi et al have reported a prevalence of CSA in asymptomatic left ventricular dysfunction that is associated with impaired autonomic control, reduced heart rate variability and increased nonsustained ventricular tachycardia.<sup>15</sup> CSA is also the main predictor of ventricular arrhythmias in patients with HF.<sup>20, 21</sup>

A strong relationship between CSA and hypertension is well-established.<sup>4, 22, 23</sup> CSA is an independent risk factor for cerebrovascular accidents (CVA) and transient ischemic attacks (TIA).<sup>24</sup> Following CVA, CSA is associated with increased length of stay.

### Diagnosis of Sleep Apnea

Initial screening for sleep apnea consists of questioning patients about their sleep habits and level of fatigue. The patient's sleep partner may offer additional information about witnessed apneic episodes and restlessness during sleep. Patients with CSA may experience poor sleep quality due to frequent arousals and may report excessive daytime sleepiness and fatigue. The hypoxemia associated with CSA may also trigger nocturnal angina.<sup>25</sup> Traditional tools that are used to screen patients for sleep apnea, such as the Berlin Questionnaire or the Epworth Sleepiness Scale, may be used to elucidate the patient's symptoms. As previously mentioned, many symptoms of CSA, such as nocturia, nocturnal dyspnea, waking up unrefreshed and daytime

sleepiness and fatigue, are very similar to heart failure symptoms. This overlap undoubtedly contributes to the under-diagnosing of CSA in patients with HF.<sup>13</sup> Unlike OSA, snoring and obesity are not risk factors for CSA and, in fact, are often absent.

Markers that may lead to the suspicion of CSA include the presence of hypocapnia, atrial fibrillation, ventricular tachycardia, low left ventricular ejection fraction, New York Heart Class III or IV, and excess premature ventricular beats and couplets.<sup>13</sup> Other hallmarks of CSA in patients with systolic HF include paroxysmal nocturnal dyspnea, restless sleep, insomnia, witnessed apnea, and worsening left ventricular function despite adequate medical therapy.<sup>26</sup>

Objective assessment of CSA is acquired through a polysomnograph recording that is obtained during an overnight sleep study. The patient's stages of sleep are evaluated through continuous overnight recordings of EEG, chest and abdominal muscle excursion, peripheral limb motion, eye movement, respiratory rate and nasal-oral air flow, blood pressure, oxygen saturation and electrocardiogram. Length of time taken to fall asleep and time spent in REM sleep are also recorded. Direct observation of the patient during sleep provides information about the presence or absence of snoring, restless or periodic leg movements, and body activity during sleep. When informing patients about a sleep study, it is important that they are told not to take any sleeping medication or drink alcohol or caffeine-containing drinks prior to arriving for the sleep study, as these things may affect the results of the test.

If the patient is found to have significant CSA, a follow-up sleep study is generally obtained to determine the appropriate level of positive airway pressure (measured in cm H<sub>2</sub>O) that is required to reduce or eradicate the patient's apneic episodes. If the patient is found to have significant sleep apnea early in their sleep study, the sleep technologist may awaken the patient to apply a positive airway pressure mask and titrate treatment as the patient sleeps during

the remainder of the night. In this manner, diagnosis and treatment may be determined within the same night's sleep study, rather than having the patient return for a follow-up sleep study. This is known as a "split" study. Following the sleep study, a full report of the data is sent to the referring health care provider, who prescribes the appropriate positive airway pressure device.

### Treatment

The treatment of CSA begins with optimization of HF therapies. The maximally tolerated doses of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and beta blocker approved for use in HF (bisoprolol, carvedilol, and metoprolol succinate) should be prescribed as appropriate. Diuretics should be used judiciously, but doses that promote removal of excess fluid and decrease filling pressures to within normal limits should be applied. Aldosterone antagonists, digoxin, nitrates and hydralazine should be prescribed to appropriate candidates as outlined in the current evidence-based guidelines for HF therapy.<sup>27</sup> Cardiac resynchronization therapy should be considered in patients who meet the criteria for implant of a biventricular pacemaker. These measures should actually be applied and the patient's condition optimized *before* sending the patient for a sleep study. In many cases, optimization of HF therapy can improve or even eliminate periodic breathing.<sup>26</sup>

Unlike OSA, in which continuous positive airway pressure (CPAP) has been established as the gold standard for treatment, treatment of CSA is not as well defined. Results from a number of interventions are discussed below.

### Oxygen

Supplemental nasal oxygen applied at night at 2-3 L/min has been shown to improve CSA by reducing duration of Cheyne-Stokes respiration, improving sleep quality by decreasing arousals, and enhancing daytime cognitive function.<sup>28</sup> Sympathetic activity in HF patients is also

reduced when supplemental oxygen is applied via nasal cannula.<sup>29</sup> Supplemental oxygen may reduce CSA by increasing stores of oxygen in the lung and blood, thereby decreasing periodic breathing, and it may restore the patient's ventilatory response to CO<sub>2</sub>.<sup>30</sup>

### Positive Airway Pressure Devices

CPAP via a facemask or nasal mask has been studied extensively in patients with HF. Through this device, air is forced into the nasal passages at pressures high enough to overcome obstructions in the airway and stimulate normal respirations. In essence, CPAP acts as a pneumatic splint for the oropharyngeal airway. CPAP increases lung volume and improves functional residual capacity, thus reducing the apnea-hypopnea index (AHI).<sup>17</sup> In addition, CPAP reduces arrhythmias, decreases sympathetic activity and improves left ventricular ejection fraction in patients with HF.<sup>18</sup> Systolic blood pressure, heart rate and left ventricular end-systolic dimension have also been shown to be reduced with CPAP therapy.<sup>31</sup> Supplemental oxygen may be added to the CPAP airflow in patients requiring oxygen therapy.

With CPAP, the pressure delivered into the upper airway is continuous throughout the respiratory cycle. Some patients find it uncomfortable to exhale against the pressure administered during CPAP, and compliance may become an issue. Patients with HF and concomitant chronic obstructive pulmonary disease may experience increased work of breathing when attempting to exhale against positive airway pressure, and may get a feeling of "smothering" when placed on CPAP therapy. Bi-level positive airway pressure is similar to CPAP. However, the airway pressure during expiration may be adjusted separately from the pressure during inspiration. The bi-level device tracks the patient's respirations and, at the end of inhalation and beginning of expiration, reduces airflow delivery. This reduces the pressure against which the patient must exhale. Bi-level therapy has also been found to improve sleep

apnea and cardiac function and to reduce sympathetic nervous system activity in patients with HF.<sup>32</sup>

Not all HF patients with CSA respond to CPAP. There have been several negative studies reported with CPAP in HF patients.<sup>33</sup> Venous return may be decreased with CPAP due to increased intrathoracic pressure, resulting in reduced stroke volume and hypotension. HF patients with atrial fibrillation or hypovolemia may also experience hypotension with CPAP, and if cardiac output is diminished, a reduction in coronary blood flow could lead to ischemia.<sup>13</sup> The Canadian Continuous Positive Airway Pressure Trial (CANPAP) recently halted its enrollment of HF patients with CSA due to futility in demonstrating improvement in morbidity or mortality for this population.<sup>34</sup> This study had several important limitations, in that the patients assigned to CPAP continued to have a substantial AHI, despite using CPAP and compliance to CPAP therapy was marginal, at best.

A relatively new positive airway pressure modality for CSA is that of adaptive pressure support servoventilation (ASV). This device provides fluctuating amounts of ventilatory support during the various phases of Cheyne-Stokes respirations. It continuously monitors and records the patient's minute ventilation, creating a template to adjust pressure support from 3cm H<sub>2</sub>O to 15cm H<sub>2</sub>O to maintain the patient's target ventilation. The device automatically adjusts the pressure support on a breath-by-breath basis to provide comfortable, minimal support during the hyperpneas and increase the support during hypopneas or apneas.<sup>35</sup> If the patient does not spontaneously begin an inhalation within a set time, the device will automatically initiate a breath. By correcting episodes of apnea and hypoventilation, the device reduces arousal, sleep fragmentation and sympathetic activation.<sup>36</sup> In a recent study comparing ASV to CPAP in HF patients with CSA, patients receiving ASV therapy were found to have corrected CSA, improved

quality of life, maintained compliance with positive pressure therapy, and had a significant increase in left ventricular ejection fraction.<sup>37</sup> Another study found that, compared to bi-level, ASV further reduced the AHI and sleep arousals, and improved CSA. Furthermore, ASV was subjectively preferred over CPAP and bi-level among study participants.<sup>38</sup>

### Theophylline

Theophylline has been shown to reduce the AHI by about 50% and increase oxyhemoglobin saturation in patients who have HF and CSA.<sup>39</sup> The mechanism by which this occurs is unclear, but theophylline inhibits intrinsic respiratory depressants, thereby increasing ventilation. Conceivably, this could decrease the likelihood of central apnea during sleep. While theophylline has been found to decrease central apneas events, it has no effect on obstructive sleep apnea.<sup>26</sup> Larger studies are needed to determine long-term safety when using theophylline in HF patients.

### Acetazolamide

Acetazolamide is a mild diuretic and a respiratory stimulant that is thought to improve respiratory drive by producing a metabolic acidosis. It is used to treat periodic breathing at high altitude. One small study of 12 HF patients with CSA showed that acetazolamide reduced the hourly number of CSA episodes, improved oxyhemoglobin saturation, increased subjective perception of overall sleep quality, enhanced the feeling of being rested upon awakening. It also decreased daytime fatigue and reduced daytime sleep episodes.<sup>40</sup>

### Cardiac Interventions

A case report of a patient with HF and CSA describes the improvement of the patient's CSA following percutaneous coronary intervention that resulted in improved cardiac function.<sup>41</sup> Cardiac transplantation has been shown to eliminate CSA in patients with systolic HF; however,

many of those patients went on to gain weight after transplant surgery and later developed OSA.<sup>18</sup> Cardiac resynchronization therapy (CRT) has been found to improve cardiac function and significantly decrease the AHI and sleep quality, while increasing oxygen saturation in patients with HF and CSA.<sup>42</sup> One possible explanation for this is that CRT improves the efficiency of left ventricular contraction and reduces functional mitral regurgitation, which may in turn reduce pulmonary congestion as a triggering factor for Cheyne-Stokes respirations.

### Summary

Sleep disordered breathing, and specifically CSA, is a powerful predictor of poor prognosis in patients with moderate to severe HF. Current therapies for CSA include optimization of HF therapy, nasal oxygen, positive pressure airway devices, and to a smaller degree, some pharmacologic therapies. By far, the treatment that has been shown to significantly reduce or eradicate CSA is positive pressure ventilation. Unfortunately, compliance remains a concern with these devices. Technology in the treatment of CSA continues to evolve. New modalities, such as ASV, may increase the comfort of positive airway pressure devices and ultimately improve patient compliance. Larger outcome trials are needed to determine the best method of treatment of CSA for patients with heart failure.

## Appendix 1. Clinical Definitions Used in Sleep Medicine

**Apnea Hypopnea Index (AHI):** Clinical measurement of severity of sleep disorder; computed as the number of apneas and hypopneas recorded during a sleep study divided by the total sleep time in hours. AHI are classified: less than 5 events per hour of sleep = normal; 5-14 events/hour = mild; 15-30 events/hour = moderate; greater than 30 events/hour = severe. Also known as Respiratory Disturbance Index (RDI)

**Apnea:** Cessation of breathing for 10 seconds or more on PSG.

**Arousal:** A disruption of sleep, frequently following an apneic episode and triggered by the “need” to resume breathing.

**Awakening:** Return to awake state from NREM or REM sleep.

**Hypopnea:** Transient reduction in airflow for 10 seconds associated with a fall in oxygen saturation and an arousal on PSG.

**NREM:** Non rapid eye movement stage of sleep.

**Polysomnogram (PSG):** Sleep study, usually performed in a sleep lab, to evaluate sleep stages and patterns, including oxygen saturation, respiratory effort, heart rate and rhythm, electroencephalography, and muscle movement.

**REM:** Rapid eye movement stage of sleep; associated with highest brain activity and dreaming; usually comprises 20 to 25% of total sleep time.

**Sleep efficiency:** Total amount of time asleep divided ed by total time in bed; normal is at least 85%.

**Sleep latency:** Amount of time it takes to fall asleep; normal is 15-20 minutes.

## References

1. Ancoli-Israel S. The impact and prevalence of chronic insomnia and other sleep disturbances associated with chronic illness. *American Journal of Managed Care*. 2006;12:S221-S229.
2. Lanfranchi P, Somers V. Sleep-disordered breathing in heart failure: characteristics and implications. *Respiratory Physiology Neurobiology*. 2003;136:153-165.
3. Trupp R, Hardesty P, Osbourne J et al. Prevalence of sleep disordered breathing in a heart failure program. *Congestive Heart Failure*. 2004;10(217-220).
4. Peppard P, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *New England Journal of Medicine*. 2000;324:1378-1384.
5. Alvarez G, Ayas N. The impact of daily sleep duration on health: A review of the literature. *Progress in Cardiovascular Nursing*. 2004;19(2):56-59.
6. Shahar E, Whitney C, Redline S et al. Sleep-disordered breathing and cardiovascular disease: Cross-sectional results of the Sleep Heart Health Study. *American Journal of Respiratory Critical Care Medicine*. 2001;163:19-25.
7. Mann D. Activation of inflammatory mediators in heart failure. In: Mann D, ed. *Heart Failure: A Companion to Braunwald's Heart Disease*. Philadelphia: Saunders; 2004.
8. Wingard D, Berkman L. Mortality risk associated with sleeping patterns among adults. *Sleep*. 1983;6:102-107.
9. Kripke D, Garfinkel L, DL Wingard et al. Mortality associated with sleep deprivation and insomnia. *Archives of General Psychiatry*. 2004;59:131-136.

10. Trinder J, Merson R, Rosenberg J et al. Pathophysiological interactions of ventilation, arousals, and blood pressure oscillations during Cheyne-Stokes respiration in patients with heart failure. *American Journal of Respiratory Critical Care Medicine*. 2000;162:808-813.
11. Baldwin C, Griffith K, Nieto J et al. The association of sleep disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. *Sleep*. 2001.
12. Hanley P, Zuberi-Khokhar N. Increased mortality associated with Cheyne-Stokes respiration in patients with congestive cardiac failure. *American Journal of Respiratory Critical Care Medicine*. 1996;153:272-276.
13. Javaheri S. Central sleep apnea in congestive heart failure: prevalence, mechanisms, impact and therapeutic options. *Seminars in Respiratory Critical Care Medicine*. 2005;26(1):44-55.
14. Dowdell W, Javaheri S, McGinnis W. Cheyne-Stokes respiration presenting as sleep apnea syndrome: clinical and polysomnographic features. *American Reviews in Respiratory Disease*. 1990;141:871-879.
15. Lanfranchi P, Somers V, Braghiroli A, Corra U, Eleuteri E, Giannuzzi P. Central sleep apnea in left ventricular dysfunction: Prevalence and implications for arrhythmic risk. *Circulation*. 2003;107:727-732.
16. Lanfranchi P, Braghiroli A, Bosimini E et al. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. *Circulation*. 1999;99:1435-1440.
17. Sin D, Logan A, Fitzgerald F et al. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. *Circulation*. 2000;102:61-66.

18. Naughton M, Benard D, Liu P et al. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. *American Journal of Respiratory Critical Care Medicine*. 1995;152:473-479.
19. Javaheri S, Corbett W. Association of low PaCO<sub>2</sub> with central sleep apnea and ventricular arrhythmias in patients with heart failure and central sleep apnea. *American Journal of Respiratory Critical Care Medicine*. 1995;128:204.
20. Naughton M. Heart failure and central apnoea. *Sleep Medicine Review*. 1998;2:105-116.
21. Sin D, Fitzgerald F, Parker J et al. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *American Journal of Respiratory Critical Care Medicine*. 1999;160:1101-1106.
22. Wolk R, Shamasuzzaman A, Somers V. Obesity, sleep apnea, and hypertension. *Hypertension*. 2003;42:1378-1384.
23. Nieto F, Young T, Lind B et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA*. 2000;283:1880-1881.
24. Palomaki H, Partinen M, Erkinjuntti T et al. Snoring, sleep apnea syndrome and stroke. *Neurology*. 1992;42:75-81.
25. Franklin K, Nilsson J, Sahlin C, Naslund U. Sleep apnoea and nocturnal angina. *Lancet*. 1995;345:1085-1087.
26. Wexler L, Javaheri S. Sleep apnea is linked to heart failure, but does treatment improve outcome? *Cleveland Clinic Journal of Medicine*. 2005;72:929-936.

27. Hunt S, Abraham W, Chin M, Feldman A, Francis G, Ganiats T, Jessup M, Konstam M, Mancini D, Michl K, Oates J. ACC/AHA 2005 Guideline update for the diagnosis and management of chronic heart failure in the adult. *Circulation*. 2005;112:e154-e235.
28. Andreas S, Clemens C, Sandholzer H, Figulla H, Kreuzer H. Improvement of exercise capacity with treatment of Cheyne-Stokes respiration in patients with congestive heart failure. *Journal of American College of Cardiology*. 1996;27(6):1486-1490.
29. Staniforth A, Kinneart W, DJ, Hetmanski, et a. Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyne-Stokes respiration. *European Heart Journal*. 1998;19:922-928.
30. Javaheri S. Pembrey's dream: the time has come for a long-term trial of nocturnal supplemental nasal oxygen to treat central sleep apnea in congestive heart failure. *Chest*. 2003;123:322-325.
31. Kaneko Y, Floras J, Usui K, Plante J, Tkacova R, Kubo T, Ando S, Bradley T. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. *New England Journal of Medicine*. 2003;348(13):1233-1241.
32. Koito H, Kohno K, Maruyama K, Satoshi M, Yutaka H. Long-term effects of domiciliary bilevel noninvasive positive pressure ventilation (NPPV) on sleep apnea, cardiac function and sympathetic nervous activity in stable congestive heart failure. *Chest*. 2004;126(4):826S.
33. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. *Circulation*. 2000;101:392-397.

34. Bradley T, Logan A, Kimoff R, Series F, Morrison D, Ferguson K, et al. Continuous positive airway pressure for central sleep apnea and heart failure. *New England Journal of Medicine*. 2005;353:2025-2033.
35. Ostransky D. Adaptive pressure support servoventilation: a new spin on the treatment of heart failure patients with central sleep apnea. *Sleep Diagnosis and Therapy*. 2006;1(6):1-2.
36. Pepperell J, Maskell N, Jones D, Langford-Wiley B, Crosthwaite N, Stradling F, Davies R. A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. *American Journal of Respiratory Critical Care Medicine*. 2003;168(9):1109-1114.
37. Phillippe C, Stoica-Herman M, Drouot X, Raffestin B, Escourrou P, Hinnering L, et al. Compliance with and effectiveness of adaptive servoventilation versus continuous positive airway pressure in the treatment of Cheyne-Stokes respiration in heart failure over a six month period. *Heart*. 2006;92:337-342.
38. Teschler H, Dohring J, Wang Y, Berthon-Jones M. Adaptive pressure support servoventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. *American Journal of Respiratory Critical Care Medicine*. 2001;164(4):614-619.
39. Javaheri S, Parker T, Wexler L, et al. Effect of theophylline on sleep disordered breathing in heart failure. *New England Journal of Medicine*. 1996;335:562-567.
40. Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind prospective study. *American Journal of Respiratory Critical Care Medicine*. 2006;173:234-237.

41. Betsuyaku T, Yonezawa K, Kitabatake A. Percutaneous coronary intervention for central sleep apnoea with ischaemic cardiomyopathy. *Acta Cardiol.* 2004;59(1):63-65.
42. Sinha A, Skobel E, Breithardt O, Norra C, Markus K, Breuer C, Hanrath P, Stellbrink C. Cardiac resynchronization therapy improves central sleep apnea and Cheyne-Stokes respiration in patients with chronic heart failure. *Journal of American College of Cardiology.* 2004;44:68-71.