CME Topic

Apneic Disorders Associated with Heart Failure: Pathophysiology and Clinical Management

Faisal Khan, MD, Ribhi Hazin, MD, and Yuchi Han, MD

Abstract: Cardiovascular diseases remain the most common cause of both morbidity and mortality in the industrialized world. The frequency of sleep-related breathing disorders (SRBD) is significantly increased in individuals with cardiovascular diseases such as heart failure. Given the co-morbidities associated with SRBD coexisting with HF, prompt recognition and early management of SRBD is critical to improving the overall prognosis and quality of life in heart failure patients with concomitant SRBD.

Key Words: central sleep apnea, heart failure, obstructive sleep apnea, polysomnogram

Cardiovascular diseases remain the most common cause of morbidity and mortality in the industrialized world.[1,2] Sleep disorders are also highly prevalent, particularly in the United States, where as many as 40 million Americans are believed to be affected.[3] Hence, disorders of sleep and cardiovascular disease frequently coexist.

Sleep-related breathing disorders (SRBD) describe the spectrum of diseases ranging from seemingly innocuous findings such as snoring to more serious conditions such as obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS). SRBD are by far the most common sleep disorders encountered in sleep centers nationwide.[4] The two major types of SRBD in the general population are OSA and central sleep apnea (CSA) with the former being the most common.[5] Despite the fact that patients with SRBD are common in the primary care setting, most physicians lack appropriate training in the diagnosis and treatment of such patients.[4,6] Recent studies have demonstrated a strong link between SRBD and the pathogenesis of metabolic and cardiovascular disorders.[7] This link with systemic diseases along with the relative lack of recognition amongst primary care physicians underscores the need for addressing pertinent clinical aspects of SRBD that would hasten diagnosis, improve treatments, and minimize long-term sequelae in patients with SRBD. The urgency of improving understanding of SRBD amongst first-line clinicians is highlighted by the widespread systemic implications of these disorders, particularly their effects on the cardiovascular system (Table 1).

SRBDs occur with markedly increased frequency in populations afflicted with HF when compared to the general population, where between 2–9% are affected.[5,8] This predilection for SRBD is especially relevant in patients with systolic heart failure.[9–11] Recent epidemiological studies have demonstrated prevalence rates of SRBD in 40–70% of ambulatory male patients with a New York Heart Classification (NYHA) of II and III.[10] In patients with HF, CSA prevalence is between 30 to 40% and OSA prevalence is approximately 30%.[8,11–15] Furthermore, there exists compelling evidence that impaired cardiovascular function contributes significantly to the pathophysiology and progression of SRBD.[16–18] This forms a vicious cycle of functional deterioration through the

Key Points

- There is growing evidence for the need to specifically screen for sleep-related breathing disorders (SRBD) in the following cardiovascular clinical situations: hypertension, congestive heart failure, atrial fibrillation, nocturnal bradyarrhythmias, nocturnal angina.
- A high index of clinical suspicion is necessary for recognizing central sleep apnea (CSA) in patients with congestive heart failure (CHF) since the symptoms of the two conditions often overlap.
- Early recognition of SRBD in heart failure patients is vital to instituting prompt treatment and improving survival and quality of life.
- The Epworth Sleepiness scale may not be the best method for screening SRBD in patients with CHF.
- Effective noninvasive treatment modalities are available for the treatment of sleep-related breathing disorders.

From the Department of Arts and Sciences, Harvard University, Cambridge, MA; Neurodiagnostic and Sleep Center, Gulf Coast Medical Center, Wharton, TX; and Division of Cardiovascular Diseases, Department of Medicine, Beth Israel Deaconness Medical Center and Harvard Medical School, Boston, MA.

Reprint requests to Faisal Khan, MD, Neurodiagnostic and Sleep Center, Gulf Coast Medical Center, Wharton, TX. Email: fskhan786@gmail.com

Accepted May 19, 2009.

None of the authors have any financial disclosures to declare or conflicts of interest to report.

0038-4348/0–2000/10300-0044

Table 1. Cardiovascular manifestations of sleep-related breathing disorders (SRBD)[4,5,12]

Systemic hypertension
Pulmonary hypertension
Left ventricular (LV) hypertrophy
LV systolic and diastolic dysfunction
Congestive heart failure
Arrhythmias (atrial fibrillation)
Ischemic cardio/cerebrovascular events
Increased platelet coagulability
Sudden cardiac death
Nocturnal angina

interaction of HF and SRBD. Thus, prompt recognition, appropriate diagnosis, and the early institution of treatment for SRBD remain vital aspects of improving the overall prognosis and quality of life in heart failure patients with concomitant SRBD.[17,18]

The prevalence of heart failure (HF) is on the rise with roughly 5 million Americans affected, or close to 2% of the population.[19] Current estimates have projected the prevalence of heart failure to continue to rise into the 21st century mainly due to improved medical treatment of ischemic coronary artery disease and hypertension. Despite major advances in the medical treatment for heart failure, it continues to represent a major source of morbidity and mortality for patients as well as a monumental burden for healthcare institutions nationwide.[19] The following is a review of SRBD associated with heart failure with a particular emphasis placed upon recognition and clinical management.

Obstructive Sleep Apnea

The most common form of sleep apnea is OSA, which describes the condition in which either partial or complete closure of the upper airway occurs during sleep, leading to intervals of disrupted breathing lasting greater than 10 seconds.[13] Common risk factors that predispose to OSA include obesity, increased neck circumference, narrowed airways, diabetes, and family history.[8,20,21] OSA primarily occurs as a result of blockage or obstruction of the airway but may also arise in the setting of airway collapse.[13] In children and young adults, inflammation or infection can lead to enlargement of airway glands, tonsils, or adenoids and exacerbate airway blockage and OSA symptoms. Many individuals with OSA may also exhibit obstructive hypopneas that are decreases in ventilation associated with decreased oxygen saturation.[22] The diagnosis of OSA hinges on assessing a patient's apnea-hypopnea index (AHI), which records the number of apneas and hypopneas per hour of sleep. An AHI >5 along with daily symptoms of OSA are required for the diagnosis.[13]

Epidemiology of OSA

In the general population, 1 in 5 adults suffers from a mild variant of OSA (ie, AHI ≥5) and approximately 1 in 15 Americans suffers from moderate to severe forms of OSA (ie, AHI ≥15).[22] There appears to be a male predilection for OSA.[23] A recent study found that approximately 64% of individuals from the general population who suffered from sleep apnea were between the ages of 40 and 69 years old with 55.3% being of the male gender.[23]

OSA occurs with increased prevalence in patients with cardiovascular disease.[13,24,25] In fact, OSA affects as many as 30% of patients with hypertension and as many as 50% of patients with other cardiovascular diseases.[13,26,27] A number of population-based studies have illustrated increased prevalence of diabetes, stroke, hypertension, and HF in patients with OSA.[24,28–30] Furthermore, a recent prospect study revealed that the presence of OSA increases the risk of incident hypertension.[22]

Clinical Features of OSA

Individuals with OSA typically complain of restlessness, loud snoring, recurrent awakenings associated with shortness of breath, morning headache, and hypersomnia. Patients diagnosed with OSA are typically overweight with increased neck circumference.[31] In fact, increased neck circumference has been linked to increased severity of apnea.[32,33] Despite conventional beliefs, only a minority of OSA patients complain of excessive daytime somnolence, suggesting that many patients have asymptomatic OSA.[34] Other nonspecific symptoms that may be present on evaluation include morning headaches, memory problems, decreased libido, urinary frequency, nocturia, irritability, anxiety, depression, and mood changes.[35,36]

Pathophysiology of OSA in Heart Failure

Collapse or obstruction of the airway can bring about obstructive sleep apnea.[37,38] OSA sets off dynamic changes in the circulatory, chemical, inflammatory, mechanical and neural mechanisms in the body.[38] These changes initiate hypoxia which ultimately leads to increases in afterload. The hypoxia-induced afterload results in increased occurrence of sleep arousals and commensurate sympathetic nervous activity.[37] Increased sympathetic nervous activity will lead to a higher heart rate and increased myocardial oxygen demand in a setting of hypoxia.[39] In the Sleep Heart Health Study, OSA conferred a 2.38 relative increase in the likelihood of having HF, independent of other known risk factors.[7] The mortality of patients with CHF and untreated OSA is nearly twofold greater than that of patients with CHF alone.[16]

Diagnosis of OSA

The Epworth Sleepiness Scale (ESS) is a questionnaire often used to evaluate daytime sleepiness in individuals sus-

Table 2. The Epworth sleepiness scale[11a]

Situation	Chance of dozing or sleeping
Sitting and reading	—
Watching TV	—
Being a passenger in a vehicle (>1 h)	—
Lying down during the day	—
Sitting and talking to someone	—
Sitting quietly after a noon meal	—
Stopping in traffic (for 1–4 min)	—
Total Epworth score	—

[a]The following scores are used to determine the risk of sleeping disorders in at-risk patients. A total of 7–8 is within normal range while patients with scores of 9 and above should be thoroughly evaluated by a sleep specialist.[44]

0, never doze or sleep.

1, slight chance of dozing or sleeping.

2, moderate chance of dozing or sleeping.

3. high chance of dozing or sleeping.

pected of sleep apnea. The Epworth scale can be a helpful tool in diagnosing sleep apnea. Individuals scoring 10 or more on the ESS should be encouraged to see a sleep specialist[40] (Table 2). Overnight diagnostic polysomnogram (PSG) is the gold standard procedure for arriving at an accurate diagnosis in patients suspected of OSA.[37,38]

Treatment of OSA

The simplest form of recommended treatment is weight loss, particularly if the patient is obese. Notwithstanding, exercise and diet regimens should be monitored by the treating physician to ensure appropriate compliance and reduce injuries.[38] Other lifestyle modifications recommended for OSA patients include abstinence from alcohol and sedatives as these two groups of agents can predispose to pharyngeal collapse during sleep.[41]

Continuous positive airway pressure, (CPAP) has been traditionally used to treat obstructive sleep apnea.[38] CPAP is a device designed to deliver compressed, pressurized air into the airway in order to maintain its patency during sleep. By maintaining nocturnal airway patency, the immersion of pressurized air from the CPAP enables breathing during sleep and thus, reduces or eliminates nocturnal apneas and hypopneas. CPAP has been shown to reduce the blood pressure, overnight nor epinephrine excretion, left ventricular systolic function and quality of life in patients with CHF and OSA.[42] In fact, recent studies suggest that therapy with CPAP significantly reduces the risk of death and hospitalization among patients with HF and OSA.[43]

Surgical intervention may be warranted in cases of OSA where the airway obstruction is caused by the soft palate, uvula, or the adenoids and tonsils.[44] Uvulopalatopharyngoplasty (UPPP), which involves surgical resection of most soft tissues at the back of the throat, may be indicated for some individuals with OSA. The UPPP procedure improves symptoms of OSA by increasing the width of the airway and improving the movement of the soft palate during breathing.[44]

Central Sleep Apnea (CSA)

CSA describes the condition characterized by repetitive interruptions of breathing that occur from a loss of central ventilator drive.[22,45] Unlike OSA in which the patient attempts to breath but is unable to, in CSA no respiratory effort occurs because the brain fails to transmit appropriate signals to the muscles that control breathing.[45,46]

CSA may arise in the setting of cardiovascular disease or neurological conditions such as Shy-Drager syndrome or stroke.[8,47] Given the fact that breathing is controlled by the brain stem, CSA can also be observed in individuals with brain stem lesions or any disease injury affecting the lower brain stem. Neurodegenerative conditions, poliomyelitis, encephalitis, and other infectious diseases affecting the brain stem may cause CSA during sleep, even in patients who exhibit no abnormalities in breathing during wakefulness.[8,46] Signs and symptoms of central sleep apnea include difficulty staying asleep, abrupt awakenings accompanied by shortness of breath.[46]

Epidemiology of CSA

Although not as prevalent as OSA, CSA also affects males more commonly than females.[23] Further, CSA can be equally detrimental to an individual's health and may impair quality of life in affected individuals.[38] Whereas OSA has a higher prevalence in patients with hypertension and other cardiovascular diseases, CSA occurs mainly in patients with HF.[13,24,25,39] The three largest studies involving 450, 81, and 203 HF patients reported prevalences of CSA in 33%, 40%, and 28%, respectively.[8,11,12] In all cases, CSA remained an independent risk factor for death or cardiac transplantation. This pathological relationship may be attributed to marked neurohumoral activation, surges in blood pressure and heart rate and a greater propensity to lethal arrhythmias induced by CSA.[17,18,48]

Clinical Features of CSA

CSA presents differently from OSA. Patients with CSA typically complain of frequent nocturnal arousals characterized by shortness of breath, insomnia, and daytime sleepiness.[45,46] Cheyne-Stokes respiration, or the crescendo-decrescendo pattern of breathing, is a form of periodic breathing in which central apnea or hypopneas alternate with periods of hyperventilation,[49,50] which typically occurs in patients with CSA.[46] Although used interchangeably, the American Academy of Sleep recommends differentiating pure central sleep apnea from the CSA subset that is associated with Cheyne-Stokes respiration (CSR).[21] Typically, breathing in CSR consists of alternating cycles of normal breathing that involve

slowed breathing which gives way to breath-holding which is ultimately followed by a recovery period of accelerated breathing.[50] Patients with CSR typically have longer recovery periods which reflect the long circulation time associated with systolic heart failure.[50] The presence of these characteristics can facilitate differentiation of CSR from other periodic breathing with central sleep apnea conditions. This is particularly relevant with idiopathic forms of CSA in which the recovery period is abrupt and short rather that smooth and prolonged.[48]

Unlike the typical individual profile who is overweight and has increased neck girth (often greater than 16 inches in circumference)[31] in OSA, individuals with CSA tend to be of thin physical stature.[51] Furthermore, despite experiencing fragmented sleep due to recurrent arousals, patients with CSA typically do not snore heavily nor do they complain of excessive daytime somnolence.[48] These clinical manifestations demonstrate why individuals with CSA may elude diagnosis particularly with clinicians who depend upon the Epworth Sleepiness Scale, a diagnostic questionnaire that relies heavily on assessing a patient's likelihood of daytime sleepiness.[52,53] Patients who woke up during the peak of ventilation after apnea may complain of paroxysmal nocturnal dyspnea which again can be easily attributed to HF rather than SRBD. Moreover, the symptoms resulting from CSA usually overlap with the classic heart failure symptoms, such as orthopnea, nocturnal dyspnea, cough, neurocognitive problems, nocturia, waking up unrested, sleep fragmentation and fatigue.[48] Thus in heart failure patients, CSA remains occult.[19]

Pathophysiology of CSA in Relation to Heart Failure

CSA is characterized by a lack of central drive to breathe during sleep.[24] The previously described periods of insufficient ventilation that occur during CSA episodes result in compromised gas exchange and chronic hypoxemia, both conditions which adversely affect cardiovascular function.[24,48] These consequences of CSA are most detrimental in patients with pre-existing left ventricular (LV) systolic and diastolic dysfunction and coronary artery disease (CAD).[48] The left ventricular filling pressures are increased in HF, which potentiates the sympathetic effect on central and peripheral chemoreceptors.[48] This results in pulmonary congestion that activates the J receptors (vagal irritant receptors), ultimately stimulating hyperventilation and hypocapnia.[48] In such a setting, central apnea arises from increases in ventilation and due to the fact that $PaCO_2$ is driven below the threshold for ventilation.[48] Apnea persists until $PaCO_2$ rises above the threshold which requires stimulating ventilation.[54] Incidentally, CSA will elicit chemical, neural, and hemodynamic oscillations similar to those observed in OSA. Other possible causes of CSA that should be ruled out in patients with the disease profile are included in Table 3.

Table 3. Possible causes of CSA[46,48]

Encephalitis
Complications of surgery cervical spine
Complications of radiation therapy on the cervical spine
Poliomyelitis
Stroke

CSA, central sleep apnea.

Diagnosis of CSA

A high index of suspicion is required to adequately recognize CSA in heart failure patients as the clinical picture may not be entirely clear. Standard overnight polysomnography (PSG) remains the diagnostic modality of choice. PSG can differentiate different forms of SRBD and is also helpful in gauging the severity by measuring apnea-hypopnea index. PSG should be considered if a number of factors are present in the heart failure patients (Table 4).

Treatment of CSA

Given the intimate association between CSA and HF, the presence of HF should alert the astute physician to optimize the pharmacological treatment in a manner that appropriately addresses the underlying clinical findings.[55] The currently recommended treatment paradigm should include some combination of inhibition of renin-angiotensin system, beta blockade, digoxin, and fluid management with diuretics.[55] Recent studies have demonstrated that HF patients who are on beta-blocking agents have a lower prevalence and severity of CSR than those who do not.[56]

If CSA still persists following pharmaceutical intervention, a variety of therapeutic options are available. CPAP has shown promising results in treating central apnea from systolic heart failure.[57] Recent findings demonstrate that in heart failure patients with CSA, CPAP improves both left ventricular ejection fraction and heart transplant-free survival, par-

Table 4. Risk factors for Cheyne-Stokes respirations in heart failure patients[48,54a]

Male sex
Age greater than 60 yr
Presence of atrial fibrillation
Ventricular tachycardia
Low left ventricular ejection fraction (<40%)
Hypocapnia (awake PaCo2 of 38 mm Hg or less)
Excess premature ventricular beats and couplets
Refractory CHF with standard medical management

CHF, congestive heart failure; HF, heart failure; CSR, Cheyne-Stokes respirations.

[a]Obesity is not a risk factor. Female patients with HF rarely develop CSR which may explain better prognosis as compared with their male counterparts.

ticularly if CPAP is applied early in the disease course.[58] There are several positive studies showing its benefit on left ventricular ejection fraction as well as in decreasing urinary epinephrine secretions, increasing 6-minute walk distance, and reducing cardiac sympathetic activity.[59] The largest randomized controlled trial studying the use of CPAP in patients with CSA (CANPAP) failed to demonstrate the benefit of CPAP on the transplantation-free survival.[60] A major limitation of the CANPAP study was the failure to reduce AHI levels below 15, which was the inclusion criteria.[61] Later studies revealed that early suppression of CSA by reducing AHI below 15 can significantly improve both LVEF and transplant-free survival.[58,61] Despite its benefits, many patients find it difficult to get used to the CPAP and its cumbersome attachments and straps needed to fit it over the face securely.[62]

Pressure support ventilation like bilevel positive airway pressure (BiPAP) or adaptive servoventilation (ASV) treatment should be offered to the patients who are refractory, noncompliant, or unable to tolerate CPAP.[61] While CPAP operates at the same pressure level during expiration and inspiration, pressure support ventilation acts at lower pressure during expiration and higher pressure to actively support inspiration.[61,63] Adaptive servoventilation represents a newer form of noninvasive pressure support treatment that has shown excellent results in open label studies.[64] Although ASV offers great promise for the future treatment of CSA patients, the absence of long-term placebo controlled trials has limited its use amongst clinicians.[65,66]

A number of pharmaceutical treatment options for CSA with questionable efficacy are also available, such as:

Acetazolamide

Acetazolamide is a carbonic anhydrase inhibitor which causes a mild metabolic acidosis. This, in turn, stimulates the chemoreceptors in the carotid bodies and central chemoreceptors, thus acting as a respiratory stimulant.[67] It has been successfully used in the treatment of idiopathic central sleep apnea and periodic breathing at higher altitude.[68] However, acetazolamide cannot be recommended for therapy of CSA in HF patients because its long-term safety and effectiveness in such patients remains to be demonstrated.[55,68]

Theophylline

Theophylline is a phosphodiesterase inhibitor, but its competitive nature with adenosine is what drives increased ventilation. Studies have shown the efficacy,[9] but potential arrhythmogenic effects and phosphodiesterase inhibition are major concerns for their long-term use.[68]

Oxygen

Nocturnal oxygen supplementation (NOS) with a flow of 2–3 liters per minute have been shown in multiple studies to improve the quality of sleep, sleep-related breathing events and desaturation.[57,63] NOS also decreases the sympathetic activity and urinary norepinephrine excretion.[69] Prospective, randomized, placebo-controlled, long-term studies are required to determine whether this form of treatment has the potential to impact on the morbidity and mortality of patients with HF.[63]

Conclusion

Cardiovascular diseases remain the most common cause of both morbidity and mortality in the industrialized world. Sleep-related breathing disorders are also common and occur with markedly increased frequency in populations afflicted with cardiovascular disease, particularly HF. Given the comorbidities associated with SRBD coexisting with HF, prompt recognition, appropriate diagnosis, and the early institution of treatment for SRBD remain vital aspects of improving the overall prognosis and quality of life in heart failure patients with concomitant SRBD.

References

1. American Heart Association. Heart disease and stroke statistics. Available at: www.americanheart.org/statistics/10econom.html. Accessed December 23, 2008.
2. American Heart Association. International cardiovascular disease statistics. Available at: www.americanheart.org/presenter.jhtml?identifier= 3001008. Accessed December 23, 2008.
3. Report of the National commission on Sleep Disorders Research. *Wake Up America: A National Sleep Alert.* Washington D.C, U.S. Government Printing Office, 1995.
4. Ball EM, Simon RD Jr, Tall AA, et al. Diagnosis and treatment of sleep apnea within the community. The Walla Walla project. *Arch Intern Med* 1997;157:419–424.
5. Young T, Palta M, Dempsey J, et al. The occurrence of sleep disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230–1235.
6. Penzel T, Peter JH. Ambulatory diagnosis of sleep-related breathing disorders. *Sleep* 1992;15:S9–S12.
7. Shahar E, Whitney CW, Readline S, et al. Sleep disordered breathing and cardiovascular disease: cross sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med* 2001;163:19–25.
8. Sin D, Fitzgerald F, Parker JD, et al. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med* 1999;160:1101–1106.
9. Javaheri S, Parker TJ, Wexler L, et al. Effect of theophylline on sleep-disordered breathing in heart failure. *N Engl J Med* 1996;335:562–567.
10. Javaheri S, Parker TJ, Wexler L, et al. Occult sleep–disordered breathing in stable congestive heart failure patients. *Ann Intern Med* 1995;122: 487–492.
11. Shulz R, Blau A, Börgel J, et al. Sleep apnoea in heart failure. *Eur Respir J* 2007;29:1201–1205.
12. Javeheri S, Parker TJ, Liming JD, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalence's, consequences, and presentations. *Circulation* 1998;97:2154–2159.
13. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education

59. Sin DD, Logan AG, Fitzgerald FS, 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.

60. Bradley TD, Logan AG, Kimoff RJ, et al; CANPAP Investigators. Continous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med* 2005;353:2025–2033.

61. International Classification of Sleep Disorder (ICSD), Revised Diagnostic and Coding Manual. Available at: http://www.absm.org/PDF/ICSD.pdf. Accessed January 14, 2009.

62. Ballard RD, Gay PC, Strollo PJ. Interventions to improve compliance in sleep apnea patients previously non-compliant with continuous positive airway pressure. *J Clin Sleep Med* 2007;3:706–712.

63. Shigemitsu M, Nishio K, Kusuyama T, et al. Nocturnal oxygen therapy prevents progress of congestive heart failure with central sleep apnea. *Int J Cardiol* 2007;115:354–360.

64. Banno K, Okamura K, Kryger MH. Adaptive servo-ventilation in patients with idiopathic Cheyne-Stokes breathing. *J Clin Sleep Med* 2006;2–186.

65. Pepperell JC, Maskell NA, Jones DR, et al. A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. *Am J Respir Crit Care Med* 2003;168:1109–1114.

66. Philippe C, Stoïca-Herman M, Drouot X, 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.

67 Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. *Am J Respir Crit Care Med* 2006;173: 234–237.

68. Peña F, Garcia O. Breathing generation and potential pharmacotherapeutic approaches to central respiratory disorders. *Curr Med Chem* 2006; 13:2681–2693.

69. Javaheri S, Ahmed M, Parker TJ, et al. Effect of nasal O2 on sleep-related breathing in ambulatory patients with heart failure. *Sleep* 1999; 22:1101–1106.