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Sleep Disordered Breathing in Patients with Heart Failure: Pathophysiology and Management

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Opinion statement

Sleep disordered breathing (SDB) is common in heart failure patients across the range of ejection fractions and is associated with adverse prognosis. Although effective pharmacologic and device-based treatment of heart failure may reduce the frequency or severity of SDB, heart failure treatment alone may not be adequate to restore normal breathing during sleep. Continuous positive airway pressure (CPAP) is the major treatment for SDB in heart failure, especially if obstructive rather than central sleep apnea (CSA) predominates. Adequate suppression of CSA by PAP is associated with a heart transplant-free survival benefit, although randomized trials are ongoing. Bilevel PAP (BPAP) may be as effective as CPAP in treating SDB and may be preferable over CPAP in patients who experience expiratory pressure discomfort. Adaptive (or auto) servoventilation (ASV), which adjusts the PAP depending on the patient's airflow or tidal volume, may be useful in congestive heart failure patients if CPAP is ineffective. Other therapies that have been proposed for SDB in congestive heart failure include nocturnal oxygen, CO_2 administration (by adding dead space), theophylline, and acetazolamide; most of which have not been systematically studied in outcome-based prospective randomized trials.

Introduction

Sleep disordered breathing (SDB), including central sleep apnea (CSA) and obstructive sleep apnea (OSA), is common in patients with heart failure (HF), although the diagnosis is frequently missed [1]. The prevalence of SDB is estimated to be as high as 47–76% among those with HF and reduced ejection fraction (EF) [2] and 55% in those with HF and preserved EF [3].SDB in congestive heart failure (CHF)

can be broadly classified into two types: CSA with Cheyne-Stokes breathing (CSA-CSB), and OSA, and the two may exist together. CSB is characterized by crescendo-decrescendo changes in tidal volume that result in central apneas (lack of airflow without respiratory effort (Fig. 1). OSA is characterized by repeated pharyngeal airway collapse during sleep, resulting in repetitive episodes of oxygen desaturation despite ongoing respiratory effort, and arousals (Fig. 2).

Although originally ascribed to reduced stimulation of central chemoreceptors in the setting of diminished cardiac output, CSA in CHF is now thought to be due to instability of the ventilatory system due to increased chemo-responsiveness (which means that the respiratory system is more responsive to even small changes in arterial partial pressure of carbon-dioxide [$PaCO_2$]) [4, 5••, 6, 7]. Hypocapnia due to hyperventilation in response to stimulation of pulmonary vagal irritant receptors (J-receptors) by pulmonary edema [8–11] suppresses ventilation (undershoot), leading to central apneas and associated hypercapnia, which in turn stimulate excessive ventilation (overshoot).

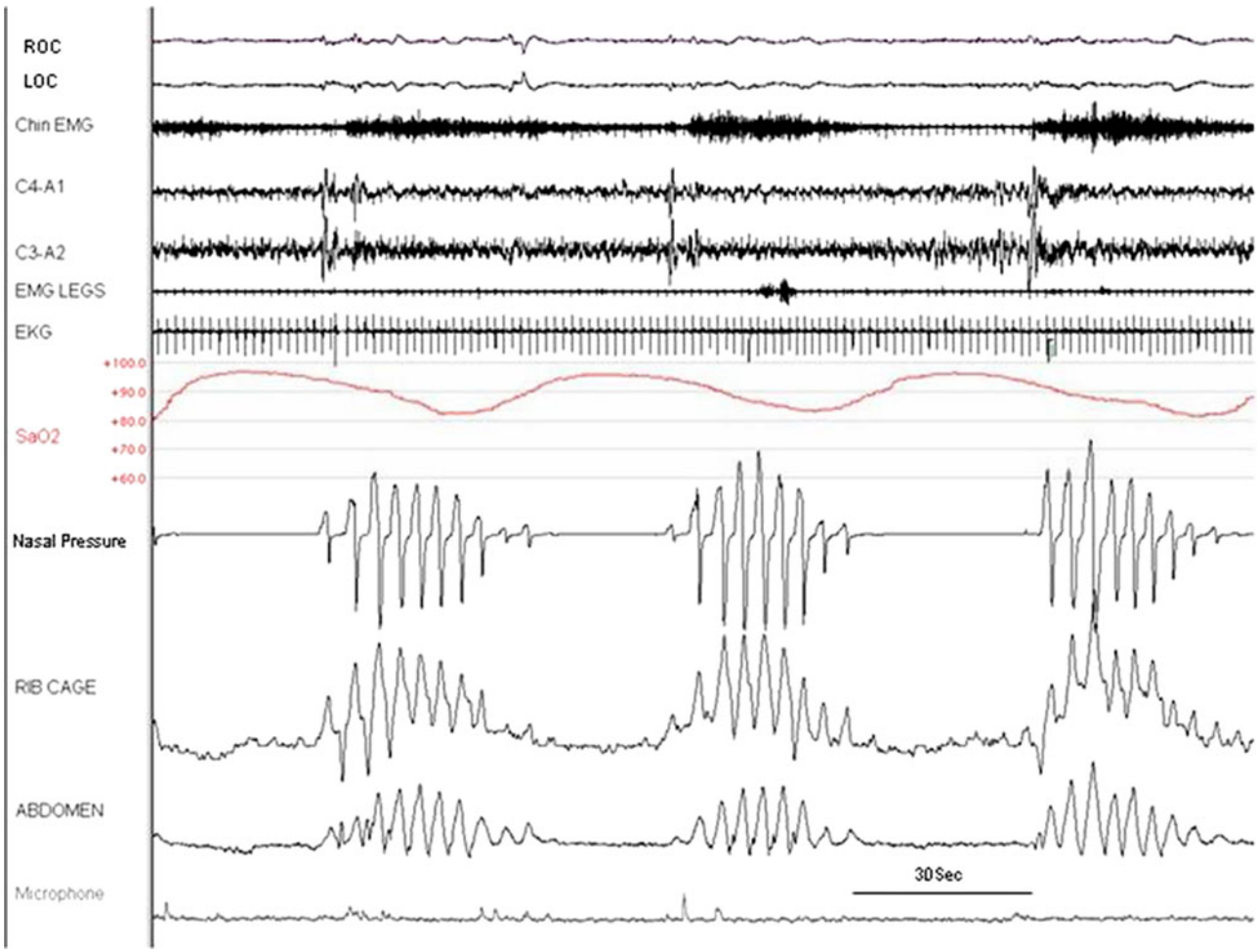

Figure 1. Polysomnogram showing crescendo–decrescendo pattern of breathing (as shown by the rib cage and abdomen movements), known as Cheyne Stokes breathing. Note the central apneas in which cessation of airflow (shown in nasal pressure channel) occurs without respiratory effort (in the rib cage and abdomen belt channels). In addition, desaturations are observed with each apnea, but somewhat delayed in time due to slowed circulation. Arousals from sleep commonly occur during periods of hyperpnea, yielding paroxysmal nocturnal dyspnea.

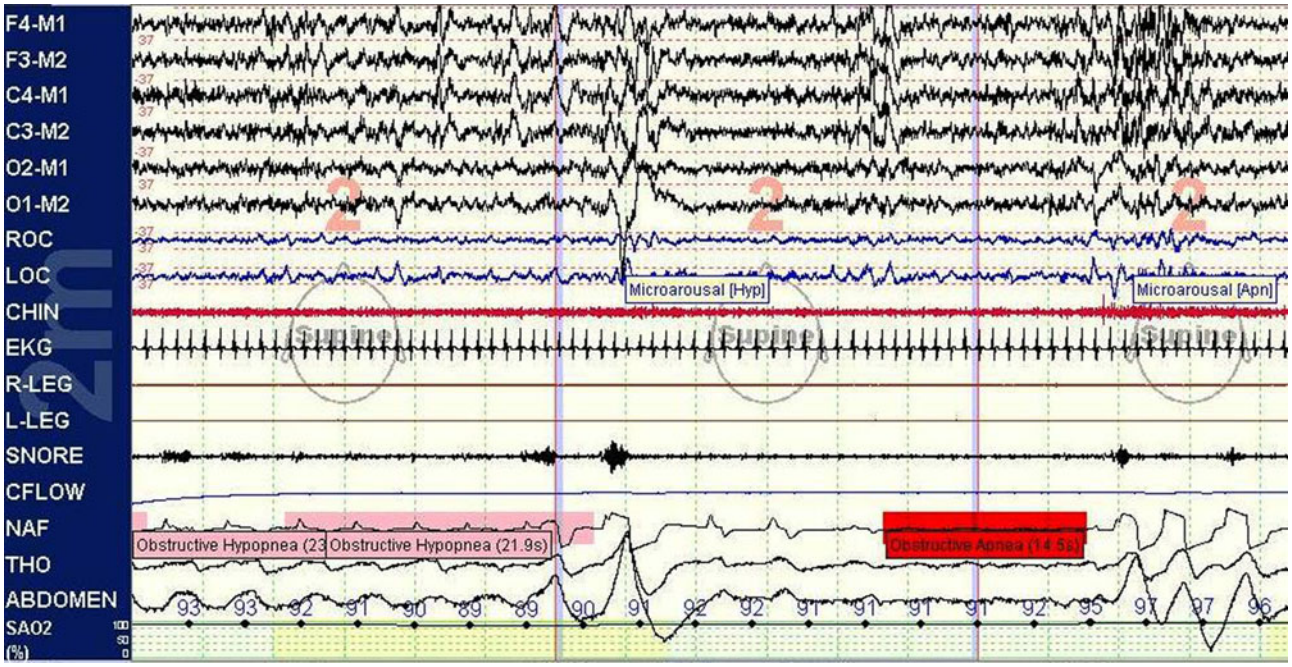

Figure 2. Polysomnogram showing obstructive apnea. Note the cessation of airflow for more than 10 s (detected by nasal thermistor, CFLOW channel) associated with continued respiratory effort as shown by thoracic and abdominal movements (detected in the thoracic and abdominal belt channels). There is also associated snoring. The top 6 channels (F4-M1 to O1-M2) show the electroencephalogram with stage 2 sleep.

This ventilatory undershoot-overshoot cycle leads to CSB. Thus the prerequisites for CSB are pulmonary edema and an unstable ventilatory system. On the other hand, OSA in CHF appears to be due to narrowing of the upper airway due to unfavorable craniofacial structure, perhaps due to pharyngeal wall edema [12] and/or co-existent obesity. Pharyngeal dilator muscle dysfunction and ventilatory control instability also likely play a role, although they have been less carefully studied in CHF patients with OSA.

The presence of SDB in heart failure patients may be associated with adverse prognosis, perhaps due to worsening of ventricular function and heart failure symptoms. OSA may reduce systolic cardiac function by increasing afterload due to negative intrathoracic pressure generated during respiratory efforts against an occluded upper airway and is frequently associated with hypertension and atherosclerotic vascular disease [13, 14]. Both CSA and OSA may also be associated with a higher incidence of atrial and ventricular arrhythmias in HF patients [15, 16]. In some studies, SDB induces cardiac electrical instability (as assessed by indices such as T wave alternans), thus increasing the risk of sudden cardiac death [17]. Interventional studies have shown some improvement in ventricular ectopy with continuous positive airway pressure (CPAP) therapy [18]. Nasal CPAP therapy has yielded improvements in EF in small studies [19–21], although definitive trials are ongoing.

The first goal in the treatment of SDB in CHF is to optimize CHF treatment. Conservative measures for OSA such as weight reduction, avoidance of supine position during sleep, and avoiding alcohol and sedative medications before sleep, are also useful. Nocturnal CPAP therapy may be useful in treating SDB in CHF [1]. Other forms of PAP therapy, such as bilevel PAP (with a backup rate) [20, 21] or the newer adaptive servo-ventilation (ASV) (Table 1) [22–29], [30••], [31, 32], have also been used to treat SDB in CHF, although trials are ongoing regarding effects on outcome. Novel treatment modalities such as carbon dioxide therapy [33], acetazolamide [5••], and theophylline [34] have also been used, although the data are more limited.

Table 1. Published studies showing clinical outcomes with adaptive servo-ventilation in congestive heart failure

Study (year)	HF patients, *n*	Duration of therapy	Outcome
Bitter et al. [32] (2011)	34	14 months	Improved AHI, NYHA class, NT-proBNP, respiratory stability, cardiopulmonary exercise parameters
Oldenburg [22] (2011)	105	Mean 6.7 months	Increased LVEF, respiratory stability, NT-proBNP, NYHA class
Westhoff et al. [25] (2010)	15	6 weeks	Decrease in BNP and AHI
Hastings et al. [26] (2010)	11	6 months	Decrease in AHI, Improved LVEF and QOL
Koyama et al. [23] (2010)	88	12 months	Decrease in CHF exacerbations and BNP, Increase in LVEF
Kasai et al. [24] (2010)	31	3 months	Increase in compliance, QOL and LVEF, decrease in AHI
Oldenburg et al. [27] (2008)	29	Mean 5.7 months	Increase in LVEF and cardiopulmonary exercise parameters, decrease in AHI and pro-BNP
Phillipe et al. [31] (2006)	25	6 months	Increase in LVEF, QOL, better compliance than CPAP
Zhang et al. [28] (2006)	14	14 days	Increase in LVEF and 6-minute walk distance compared with oxygen
Pepperell et al. [29] (2003)	30	1 month	Reduced daytime sleepiness, BNP, urinary catecholamine excretion
Teschler et al. [30] (2001)	14	2 weeks	Better compliance and sleep quality, more suppression of CSA

AHI apnea-hypopnea index; *CHF* congestive heart failure; *CPAP* continuous positive airway pressure; *CSA* central sleep apnea; *LVEF* left ventricular ejection fraction; *NT-proBNP* N-terminal pro–B-type natriuretic peptide; *NYHA* New York Heart Association; *QOL* quality of life

Treatment

Optimal HF treatment

- The first step in the management of SDB in CHF should be optimization of CHF treatment in accordance with published guidelines [35].
- Administration of diuretics to restore normal fluid balance has been shown to improve OSA in CHF patients with hypervolemia [12].
- Angiotensin-converting enzyme (ACE) inhibitors (eg, captopril) [36] and beta-blockers (eg, carvedilol) [37] reduce CSA in CHF.
- Other treatment modalities for advanced heart failure (HF), such as atrial overdrive pacing (AOP), left ventricular assist device (LVAD), and cardiac resynchronization therapy (CRT), can additionally improve SDB. These assistive devices are used primarily as a treatment for HF and are not generally recommended to treat SDB in HF. However, their use may have a beneficial effect on SDB in HF.

Positive airway pressure therapy

Rationale PAP applies positive pressure to the upper airway and effectively acts like a pneumatic splint to maintain upper airway patency in OSA. It also reduces

pulmonary edema by reducing cardiac preload and afterload, thus reducing CSA.

Evidence

CPAP therapy has been shown to treat OSA, left ventricular EF (LVEF) [38, 39, 41, 44, 45] and reduce sympathetic activity in small studies of CHF [45]. CPAP also improves SDB [38–45] and reduces urinary catecholamine levels [40] in CHF with CSA. The Canadian Positive Airway Pressure Trial for patients with central sleep apnea and heart failure (CANPAP) trial randomized CSA patients with HF due to reduced EF to either CPAP or no CPAP. After 2 years of follow-up, CPAP treatment yielded no improvement in the primary outcome of transplant-free survival although CSA, EF, and exercise capacity were somewhat improved [46]. However, post hoc analysis of the CANPAP study revealed that adequate suppression of CSA by CPAP was associated with improved heart transplant–free survival [47••]. Thus, the data remain unclear whether elimination of apnea yields improved outcome or whether improvement in apnea suggests a good prognosis. Bilevel PAP (BPAP) is as effective as CPAP in improving circulation time, New York Heart Association functional class, and sleep quality in CHF with CSA [20]. Flow or volume-targeted dynamic BPAP may be more effective than CPAP or fixed BPAP in treating CSA in CHF, although outcome data are still evolving [21].

ASV is a new PAP technology that adjusts the delivered pressure support according to the ventilation of the patient. Various companies have slightly different algorithms for these devices, although no comparative effectiveness data are available regarding these devices. ASV reduces SDB [24–27, 30] and systemic inflammation [29] and improves LVEF [22, 28, 31], quality of life [24], exercise capacity [22, 27, 28], and respiratory instability [22] in CHF patients with CSA. ASV was also better than CPAP in improving parameters like SDB, LVEF, and treatment compliance in systolic CHF patients with SDB [31, 32]. Randomized trials are now underway to assess the impact of ASV on outcome of CHF patients with SDB [48, 49].

Standard dosage

The level of CPAP (provides same PAP in both inspiration and expiration) or BPAP (can provide different PAP in inspiration and expiration) used to treat OSA in CHF is usually determined by titrating the PAP level that suppresses SDB. BPAP should generally be provided with a back up rate to avoid any potential worsening of breathing instability. Treatment of CSA with PAP often requires follow-up after weeks to months on therapy to determine the extent of resolution of CSA.

Contraindications

There are no absolute contraindications for CPAP therapy to treat SDB in CHF. However, relative contraindications/caution is advised in active emesis, increased upper airway secretions (for example, due to poor cough or impaired swallowing), potential for upper airway obstruction (upper airway or head and neck tumors), active cardiac arrhythmias, and bullous lung disease. Hypovolemic patients may do poorly with CPAP therapy due to a further drop in preload.

Complications

Dry nose, sore throat, nasal congestion, runny nose, sneezing, irritation of the eyes and the skin on the face, abdominal bloating, and nose bleeds may result due to PAP therapy, although these effects are generally self-limited.

Cost/cost-effectiveness

The fixed cost of a CPAP/BPAP device with the tubing and the mask ranges between $500 and $2,500 depending on the device features and the manufacturer [50]. Some modest variable cost for replacement masks and hoses is also present.

Medications

Nocturnal oxygen therapy

Rationale	Various mechanisms have been proposed to explain therapy of CSA by O_2 administration, which include increase in baseline PCO_2 by O_2 administration, thus reducing the propensity for apnea caused by CO_2 below the apnea threshold [51], and reduction of hypercapnic ventilatory drive [52].
Evidence	Nocturnal oxygen therapy has been shown to reduce CSA and sympathetic activity [53, 54] and improve quality of life [54], LVEF [55], and exercise capacity in CHF patients with CSA [53].
Dosage	The dosage of nocturnal oxygen used in the literature to treat CSA in CHF was 2 to 3 L/min [55].
Contraindications	Active smokers. Caution advised in hypercapnic patients (monitor arterial PCO_2 level).
Complications	Elevation of PCO_2 level in hypercapnic patients (headache, confusion), oxygen toxicity including cardiac suppression in CHF with high oxygen tensions.
Cost/cost-effectiveness	The average monthly cost of nocturnal oxygen therapy is $200.

Carbon dioxide supplementation

Rationale	CO_2 supplementation can cause a small increase in baseline PCO_2, which reduces CSA by the mechanism described earlier [51].
Evidence	CO_2 supplementation is done by adding dead space using a facemask attached to a cylinder of adjustable volume. The procedure reduced CSA and improved sleep quality [33], but is not commonly used due to the side-effects such as panic and insomnia.
Dosage	The amount of CO_2 rebreathed depends on the amount of dead space added (400–600 mL).
Contraindications	Hypercapnic patients.
Complications	Insomnia, anxiety.

Theophylline

Rationale	Theophylline stimulates respiration by antagonizing adenosine. Though the exact mechanisms are unknown, an increase in ventilation by theophylline could decrease the likelihood of developing CSA during sleep by widening the difference between the prevailing PCO_2 and the apneic threshold PCO_2.
Evidence	In a small randomized, placebo-controlled study, theophylline reduced CSA by 50% [34]. Theophylline is not commonly used for treatment of CSA in CHF due to its narrow therapeutic window and potential for arrhythmias.
Dosage	3.3 mg/kg body weight orally twice daily for 5 days [34].
Contraindications	Hypersensitivity to the drug, active peptic ulcer, porphyria.
Adverse effects/complications	Anaphylaxis, seizures, insomnia, cardiac arrhythmias, nausea, vomiting, abdominal pain, diarrhea.
Cost	$ 0.30 per 100-mg tablet.

Acetazolamide

Rationale	Acetazolamide may be beneficial in treating CSA in HF by two mechanisms: 1) it decreases pulmonary venous congestion in HF (which contributes to CSA) through diuresis, and 2) it causes a metabolic acidosis that stimulates respiration. This effect increases the difference between prevailing PCO_2 and apneic threshold PCO_2, thus reducing propensity for central apnea.
Evidence	Acetazolamide treatment for 6 days reduced CSA and daytime sleepiness and improved sleep quality in HF with reduced EF [5••].
Dosage	3.5 mg/kg oral daily for 6 days [5••].
Contraindications	Hypersensitivity to the drug, sulfa drug allergy, pregnancy, sickle cell anemia, liver, or kidney disease.
Adverse effects/complications	Metabolic acidosis, taste alteration, numbness and tingling sensation, blurred vision.
Cost	$0.50 per 125-mg tablet.

Interventional procedures

Atrial overdrive pacing

Rationale	AOP can improve EF in HF, thus reducing pulmonary congestion and improving CSA.
Evidence	AOP reduced CSA in CHF in one study [56], whereas there was no benefit in another study [57]. There was only modest improvement in OSA after AOP, although its effectiveness at reducing OSA is less than that of CPAP [58].
Contraindications	Atrioventricular nodal block, refractory atrial tachyarrhythmias.
Complications	Infection, air embolism, pneumothorax, myocardial perforation, vascular or nerve damage, thrombophlebitis, bleeding, premature atrial contractions, atrial tachycardia, premature ventricular contractions, ventricular tachycardia.

Left ventricular assist device

Evidence	LVAD implantation improves CSA and exercise capacity in HF patients [59].

Cardiac resynchronization therapy

Evidence	CRT has been shown to reduce CSA [60] as well as OSA [61] in HF patients with reduced EF. There is minor improvement in CSA when CRT is combined with AOP compared with CRT alone [62]. CRT also improves clinical outcome in HF patients in whom CSB persists despite modern optimal HF therapy [63].

Physical/speech therapy and exercise

Rationale	Exercise may be useful by reducing body weight and thus improving OSA. It may also improve CSA by normalizing chemosensitivity [64].
Evidence	A 6-month aerobic exercise program reduced CSA but not OSA in HF [65]. A 4-month exercise program improved OSA in HF patients with reduced EF [66]. Oropharyngeal exercises derived from speech therapy can improve OSA [67].

Surgery

Cardiac transplant surgery

	Cardiac transplantation for end-stage HF may impact SDB, although it is not recommended solely to treat SDB in HF.
Evidence	Cardiac transplantation may be useful in reducing CSA in HF, although CSA may still persist in some patients [68]. On the other hand, some HF patients may develop OSA after the surgery due to increased weight gain due to use of steroids and other immunosuppressants.
Contraindications	Advanced liver or renal failure, insulin-dependent diabetes, peripheral vascular disease, recent thromboembolism, alcohol/drug/tobacco abuse, pulmonary hypertension.
Complications	Infections, graft rejection, renal failure, complications (such as osteoporosis, hyperglycemia, hypertension and so forth) due to steroid therapy, allograft coronary artery disease, increased incidence of malignancies.

Pediatric considerations

- The general algorithm for diagnosis and treatment of SDB in the pediatric population is similar to adults.

Disclosure

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Javaheri S, Caref EB, Chen E, et al. Sleep apnea testing and outcomes in a large cohort of Medicare beneficiaries with newly diagnosed heart failure. Am J Respir Crit Care Med. 2011;183:539–46.
2. Sharma B, Owens R, Malhotra A. Med Clin N Am. 2010;94:447–64.
3. Chan J, Sanderson J, Chan W, et al. Prevalence of sleep-disordered breathing in diastolic heart failure. Chest. 1997;111:1488–93.
4. Bradley TD. Crossing the threshold: implications for central sleep apnea. Am J Respir Crit Care Med. 2002;165:1203–4.
5.•• Javaheri S: Acetazolamide improves central sleep apnea in congestive heart failure: a double-blind, prospective study. Am J Respir Crit Care Med 2006, 173:234–237.

This double-blind, prospective study showed that a single dose of acetazolamide taken before bedtime for 6 days reduced central apnea and sleep quality compared to placebo in systolic CHF.

6. Solin P, Roebuck T, Johns DP, et al. Peripheral and central ventilatory responses in central sleep apnea with and without congestive heart failure. Am J Respir Crit Care Med. 2000;162:2194–200.

7. Javaheri S. A mechanism of central sleep apnea in patients with heart failure. N Engl J Med. 1999;341:949–54.
8. Solin P, Bergin P, Richardson M, et al. Influence of pulmonary capillary wedge pressure on central sleep apnea in heart failure. Circulation. 1999;99:1574–9.
9. Lorenzi-Filho G, Azevedo ER, Parker JD, et al. Relationship of carbon dioxide tension in arterial blood to pulmonary wedge pressure in heart failure. Eur Respir J. 2002;19:37–40.
10. Paintal AS. Vagal sensory receptors and their reflex effects. Physiol Rev. 1973;53:159–227.
11. Oldenburg O, Bitter T, Wiemer M, et al. Pulmonary capillary wedge pressure and pulmonary arterial pressure in heart failure patients with sleep-disordered breathing. Sleep Med. 2009;10:726–30.
12. Bucca CB, Brussino L, Battisti A, et al. Diuretics in obstructive sleep apnea with diastolic heart failure. Chest. 2007;132:440–6.
13. Luo Q, Zhang HL, Tao XC, et al: Impact of untreated sleep apnea on prognosis of patients with congestive heart failure. Int J Cardiol 2009. [Epub ahead of print].
14. Butt M, Dwivedi G, Khair O, et al. Obstructive sleep apnea and cardiovascular disease. Int J Cardiol. 2010;139:7–16.
15. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. Circulation. 2000;101:392–7.
16. Leung RS, Diep TM, Bowman ME, et al. Provocation of ventricular ectopy by Cheyne-Stokes respiration in patients with heart failure. Sleep. 2004;27:1337–43.
17. Takasugi N, Nishigaki K, Kubota T, et al. Sleep apnoea induces cardiac electrical instability assessed by T-wave alternans in patients with congestive heart failure. Eur J Heart Fail. 2009;11:1063–70.
18. Ryan CM, Usui K, Floras JS, et al. Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnoea. Thorax. 2005;60:781–5.
19. Arias MA, Garcıa-Rio F, Alonso-Fernandez A, et al. Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. Circulation. 2005;112:375–83.
20. Kohnlein T, Welte T, Tan LB, et al. Assisted ventilation for heart failure patients with Cheyne-Stokes respiration. Eur Respir J. 2002;20:934–41.
21. Arzt M, Wensel R, Montalvan S, et al. Effects of dynamic bilevel positive airway pressure support on central sleep apnea in men with heart failure. Chest. 2008;134:61–6.
22. Oldenburg O, Bitter T, Lehmann R, et al. Adaptive servoventilation improves cardiac function and respiratory stability. Clin Res Cardiol. 2011;100:107–15.
23. Koyama T, Watanabe H, Kobukai Y, et al. Beneficial effects of adaptive servo ventilation in patients with chronic heart failure. Circ J. 2010;74:2118–24.
24. Kasai T, Usui Y, Yoshioka T, Yanagisawa N, et al: JASV Investigators: Effect of flow-triggered adaptive servo-ventilation compared with continuous positive airway pressure in patients with chronic heart failure with coexisting obstructive sleep apnea and Cheyne-Stokes respiration. Circ Heart Fail 2010, 3:140–148.
25. Westhoff M, Arzt M, Litterst P. Influence of adaptive servoventilation on B-type natriuretic petide in patients with Cheyne-Stokes respiration and mild to moderate systolic and diastolic heart failure. Pneumologie. 2010;64:467–73.
26. Hastings PC, Vazir A, Meadows GE, et al. Adaptive servo-ventilation in heart failure patients with sleep apnea: a real world study. Int J Cardiol. 2010;139:17–24.
27. Oldenburg O, Schmidt A, Lamp B, et al. Adaptive servoventilation improves cardiac function in patients with chronic heart failure and Cheyne-Stokes respiration. Eur J Heart Fail. 2008;10:581–6.
28. Zhang XL, Yin KS, Li XL, et al. Efficacy of adaptive servoventilation in patients with congestive heart failure and Cheyne-Stokes respiration. Chin Med J (Engl). 2006;119:622–7.
29. 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;168:1109–14.
30. Teschler H, Dohring J, Wang YM, et al. Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. Am J Respir Crit Care Med. 2001;164:614–9.
31. 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;92:337–42.
32. Bitter T, Westerheide N, Hossain MS, et al: Complex sleep apnoea in congestive heart failure. Thorax 2011 Mar 10. [Epub ahead of print].
33. Khayat RN, Xie A, Patel AK, et al. Cardiorespiratory effects of added dead space in patients with heart failure and central sleep apnea. Chest. 2003;123:1551–60.
34. Javaheri S, Parker TJ, Wexler L, et al. Effect of theophylline on sleep-disordered breathing in heart failure. N Engl J Med. 1996;335:562–7.
35. Jessup M, Abraham WT, Casey DE, et al. 2009 update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for

Heart and Lung Transplantation. Circulation. 2009;14:1977–2016.

36. Walsh JT, Andrews R, Starling R, et al. Effects of captopril and oxygen on sleep apnoea in patients with mild to moderate congestive cardiac failure. Br Heart J. 1995;73:237–41.
37. Tamura A, Kawano Y, Kadota J, et al. Carvedilol reduces the severity of central sleep apnea in chronic heart failure. Circ J. 2009;73:295–8.
38. Johnson CB, Beanlands RS, Yoshinaga K, et al. Acute and chronic effects of continuous positive airway pressure therapy on left ventricular systolic and diastolic function in patients with obstructive sleep apnea and congestive heart failure. Can J Cardiol. 2008;24:697–704.
39. Egea CJ, Aizpuru F, Pinto JA, et al. Cardiac function after CPAP therapy in patients with chronic heart failure and sleep apnea: a multicenter study. Sleep Med. 2008;9:660–6.
40. Mansfield DR, Gollogly NC, Kaye DM, et al. Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. Am J Respir Crit Care Med. 2004;169:361–6.
41. Kaneko Y, Floras JS, Usui K, et al. Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med. 2003;348:1233–41.
42. Tkacova R, Rankin F, Fitzgerald FS, et al. Effects of continuous positive airway pressure on obstructive sleep apnea and left ventricular afterload in patients with heart failure. Circulation. 1998;98:2269–75.
43. 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;102:61–6.
44. Granton JT, Naughton MT, Benard DC, et al. CPAP improves inspiratory muscle strength in patients with heart failure and central sleep apnea. Am J Respir Crit Care Med. 1996;153:277–82.
45. Naughton MT, Benard DC, Liu PP, et al. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. Am J Respir Crit Care Med. 1995;152:473–9.
46. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med. 2005;353:2025–33.
47.•• Arzt M, Floras JS, Logan AG, et al: Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). Circulation 2007;115(25):3173–80.

This post hoc analysis of the CANPAP trial showed that adequate suppression of CSA (apnea-hypopnea index < 15/hour) by CPAP in systolic CHF resulted in improved survival.

48. http://clinicaltrials.gov/ct2/show/NCT01128816 (Accessed July 18, 2011).
49. http://clinicaltrials.gov/ct2/show/NCT00733343 (Accessed July 18, 2011).
50. http://www.cpapsupplyusa.com/CPAP-Departments/CPAP-and-BiPAP-Machines.aspx (Accessed July 10, 2011).
51. Franklin KA, Eriksson P, Sahlin C, et al. Reversal of central sleep apnea with oxygen. Chest. 1997;111:163–6.
52. Andreas S, Muühlen VZ, Stevens J, et al. Nocturnal oxygen and hypercapnic ventilatory response in patients with congestive heart failure. Respir Med. 1998;92:426–31.
53. Staniforth AD, Kinnear WJ, Starling R, et al. Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyne-Stokes respiration. Eur Heart J. 1998;19:922–8.
54. Sasayama S, Izumi T, Matsuzaki M, et al. Improvement of quality of life with nocturnal oxygen therapy in heart failure patients with central sleep apnea. Circ J. 2009;73:1255–62.
55. Toyama T, Seki R, Kasama S, et al. Effectiveness of nocturnal home oxygen therapy to improve exercise capacity, cardiac function and cardiac sympathetic nerve activity in patients with chronic heart failure and central sleep apnea. Circ J. 2009;73:299–304.
56. Garrigue S, Bordier P, Jaıs P, et al. Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med. 2002;346:404–12.
57. Luthje L, Unterberg-Buchwald C, Dajani D, et al. Atrial overdrive pacing in patients with sleep apnea with implanted pacemaker. Am J Respir Crit Care Med. 2005;172:118–22.
58. Sharafkhaneh A, Sharafkhaneh H, Bredikus A, et al. Effect of atrial overdrive pacing on obstructive sleep apnea in patients with systolic heart failure. Sleep Med. 2007;8:31–6.
59. Vazir A, Hastings PC, Morrell MJ, et al. Resolution of central sleep apnoea following implantation of a left ventricular assist device. Int J Cardiol. 2010;138:317–9.
60. Sinha AM, Skobel EC, Breithardt OA, et al. Cardiac resynchronization therapy improves central sleep apnea and Cheyne-Stokes respiration in patients with chronic heart failure. J Am Coll Cardiol. 2004;44:68–71.
61. Stanchina ML, Ellison K, Malhotra A, et al. The impact of cardiac resynchronization therapy on obstructive sleep apnea in heart failure patients: a pilot study. Chest. 2007;132:433–9.
62. Lüthje L, Renner B, Kessels R, et al. Cardiac resynchronization therapy and atrial overdrive pacing for the treatment of central sleep apnoea. Eur J Heart Fail. 2009;11:273–80.

63. Hagenah G, Zapf A, Schüttert JB. Cheyne-stokes respiration and prognosis in modern-treated congestive heart failure. Lung. 2010;188:309–13.
64. Li YL, Ding Y, Agnew C, Schultz HD. Exercise training improves peripheral chemoreflex function in heart failure rabbits. J Appl Physiol. 2008;105:782–90.
65. Yamamoto U, Mohri M, Shimada K, et al. Six-month aerobic exercise training ameliorates central sleep apnea in patients with chronic heart failure. J Card Fail. 2007;13:825–9.
66. Ueno LM, Drager LF, Rodrigues ACT, et al. Effect of exercise training in chronic heart failure patients with sleep apnea. Sleep. 2009;32:637–47.
67. Guimarães KC, Luciano F, et al. Effects of oropharyngeal exercises on patients with moderate obstructive sleep apnea syndrome. Am J Resp Crit Care Med. 2009;179:962–6.
68. Mansfield DR, Solin P, Roebuck T, et al. The effect of successful heart transplant treatment of heart failure on central sleep apnea. Chest. 2003;124:1675–81.