

Treatment of Cheyne-Stokes Respiration and Central Sleep Apnoea in Chronic Heart Failure

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Summary

Sleep breathing disorders (SBD) are commonly divided in three syndromes: obstructive sleep apnea syndrome (OSA), central sleep apnea-hypopnea syndrome (CSA) and Cheyne-Stokes breathing syndrome (CSR), the latter two both characterized by cyclic non-obstructive breathing patterns.

Because the prevalence of CSA-CSR in chronic heart failure (CHF) population has been reported from 40% to 60%, CSA-CSR is the more frequent respiratory consequence of such cardiovascular illness. CSA-CSR has been associated with increased mortality in heart failure patients, but a causal role for CSA-CSR in the morbidity and mortality of heart failure awaits more definitive evidence.

In fact, it is not yet known whether CSA-CSR is an epiphenomenon in the setting of heart failure or whether it may itself lead to increased risk or progression of heart failure.

CPAP is the most studied form of treatment for CSA-CSR. However, in randomized trials of long term duration, several forms of non-invasive positive airway pressure, including CPAP, bi-level, adaptive pressure support ventilation and nocturnal oxygen therapy, have been shown to alleviate CSA-CSR in heart failure patients.

Nevertheless, at present, none therapeutic approach was ideal with respect to both efficacy and tolerance, nor has any available therapy been demonstrated to improve survival. In CHF patients with CSA-CSR, standard employment of CPAP cannot be recommended at present, though the post hoc analysis of the CANPAP study is intriguing and suggests that CPAP responders may benefit prognostically. Furthermore, the results of the CANPAP study should not be extrapolated to heart failure patients with OSA,

which is much more effectively suppressed by CPAP. Finally, there is a need to examine novel treatment options for CSA-CSR in patients with CHF, as these patients appear to have the worst prognosis and therefore the most to gain if successful treatment of CSA-CSR improves survival.

KEY WORDS: Cheyne-Stokes; Central Sleep Apnea; Heart Failure.

Introduction

One of the most recent and intriguing developments in the field of cardiovascular medicine originated from the observations that some sleep disorders, such as obstructive sleep apnoea-hypopnoea syndrome (OSA), may cause or worsen cardiac disease and, in turn, that certain cardiac diseases, like chronic heart failure (CHF), may bring on sleep disorders such as central sleep apnoea-hypopnoea syndrome (CSA) and Cheyne-Stokes breathing syndrome (CSR). This review will mainly focus on the current treatment options of CSR-CSA in CHF. First we will explore the physiopathology and clinical significance of CSA-CSR in CHF and then we will examine the up-to-date knowledge on the effects of treatment of central sleep disordered breathing in patients with CHF.

Respiratory sleep disorders may cause or worsen cardiac disease. Moreover, cardiac diseases leading to chronic heart failure (CHF) may cause respiratory sleep disorders such as central sleep apnoea-hypopnoea syndrome (CSA) and Cheyne-Stokes breathing syndrome (CSR).

Cheyne-Stokes Respiration/Central Sleep Apnoea in Heart Failure

Sleep breathing disorders (SBD) are commonly divided (1) in three syndromes: obstructive sleep apnoea syndrome, central sleep apnoea-hypopnoea syndrome and Cheyne-Stokes breathing syndrome, the latter two both characterized by cyclic non-obstructive breathing patterns.

CSA-CSR is a form of periodic breathing characterized by oscillation of ventilation between apnoea and tachypnea,

Patients with heart failure and CSA-CRS have a significantly lower PaCO₂, while awake and asleep, when compared with patients with similar ejection fraction but no CSA-CSR.

with a *crescendo-decrescendo* pattern in the depth of respirations (Figure 1). Central sleep apnoea is a manifestation of respiratory instability and is particularly prone to occur during sleep when the respiratory system becomes critically dependent on the metabolic control system. One of the most well-known mathematical models proposes an explanation to CSA-CSR (2) based on three basic components: a controlling system, a controlled system and a feedback loop. The controlled variables are PaO₂ and PaCO₂. Prolonged circulation time, which is a hallmark of heart failure, promotes a delayed response that may promote respiratory instability. However, it is generally agreed that this mechanism may contribute to the generation of CSA-CSR, but is not alone sufficient (3). The high sensitivity of ventilatory chemoreceptors promotes a strong ventilatory response and blood gas instability. Increased controller gain is well-documented and it is thought to play a central role in the genesis of CSA-CSR in patients with heart failure (4, 5). Plant gain is dependent on lung gas stores, on body stores of oxygen and carbon dioxide, and on the metabolic rate (Figure 2). Reduction in lung volumes increases plant gain because smaller volumes are less effective at damping out changes in PaCO₂ and PaO₂, thus favouring instability (6), and that may explain the increased propensity to CSA-CSR in the supine position (7). Low PaCO₂ levels play a central role in the genesis of apnoeas and hypopnoeas. Patients with heart failure and CSA-CSR have a significantly lower PaCO₂,

while awake and asleep, when compared with patients with similar ejection fraction but no CSA-CSR. It has been shown that the first apnoea is regularly preceded by hyperventilation (4), which caused PaCO₂ to reach the value below the apnoeic threshold; this proved to be the key element in triggering central apnoea (8). Several mechanisms were proposed to explain why patients with heart failure tend to hyperventilate. PaCO₂ levels correlate negatively with pulmonary capillary wedge in patients with HF submitted to cardiac catheterization (9). Therefore, the development of CSA-CSR by state of hyperventilation may be explained as a consequence of pulmonary congestion due to tonic stimulation of pulmonary vagal afferents (10). However, the observation of CSA-CSR in one patient submitted to lung transplantation (11), suggests that other mechanisms, such as cardiac vagal afferents, may also be important. Hyperventilation may be caused by an elevated sympathetic activity upon central and peripheral chemoreceptors (12). While OSA has been identified as a possible independent risk factor for the development of heart and vascular disease, CSA-CSR is a more frequent consequence of such cardiovascular illness. However it is not yet known whether CSA-CSR is an epiphenomenon in the setting of heart failure or whether it may itself lead to increased risk or progression of heart failure (13-16). Lanfranchi et al. (13), while studying a variety of baseline patient characteristics, including New York Heart Association class, left ventricular

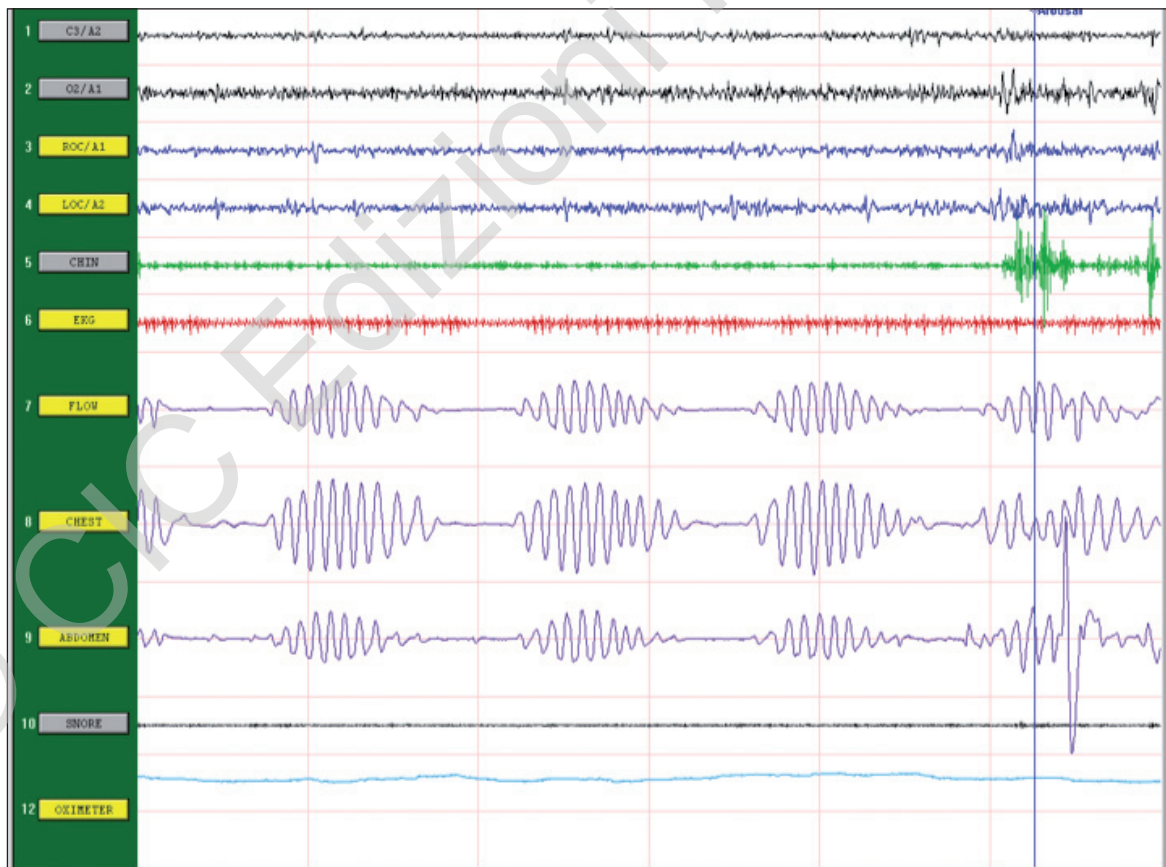


Figure 1 - Polysomnographic example of CSA-CSR (180 sec). On flow trace # 7, Cheyne-Stokes respiration with typical “waxing and waning” pattern and central apnoea with concomitant absent movements of chest (trace # 8) and abdomen (trace # 9). Arousal occurred at the top of “crescendo” flow.

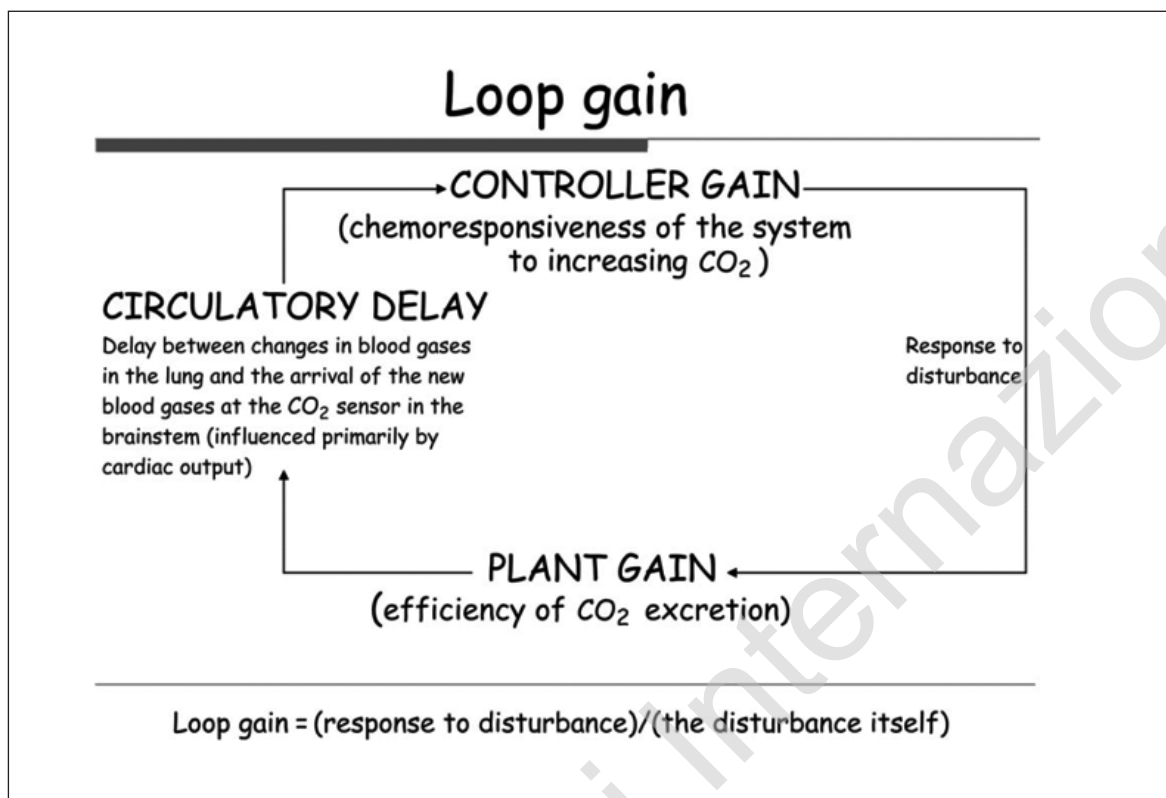


Figure 2 - Schematic representation of loop gain (see text for details).

ejection fraction, and exercise capacity, found that the left atrial area and the apnoea/hypopnoea index (AHI) emerged as the two most potent predictors of mortality. Other studies suggested that the higher rates of death and cardiac transplantation seen in patients with heart failure, along with low diastolic BP and severe right ventricular dysfunction (17), were proportional to the frequency of central apnoeic events (15). Another issue that should be stressed is that central and obstructive events are not independent phenomena, in fact they often coexist in patients with heart failure, who may convert OSA to CSA during the course of a single night (18) and over a longer period of time (19).

Treatment of central sleep disordered breathing in chronic heart failure

CPAP is the most studied form of treatment for CSA-CSR. Nevertheless, in randomized trials of long term duration, several forms of non-invasive positive airway pressure, including CPAP, bi-level, and adaptive pressure support servo-ventilation, have been shown to alleviate CSA-CSR in heart failure patients (20-22). The mechanisms by which CPAP exerts the beneficial effects in HF without obstruction of the upper airways during sleep are not completely understood, but the primary effect may be on the cardiovascular system by reducing the preload and afterload (23). This may be due to the increase of the intrathoracic pressure and the decrease of the transmural pressure of the intrathoracic structures.

CPAP also reduces the work of breathing in patients with HF (24). In randomized trials, nightly application of CPAP for three months increased left ventricular ejection fraction, reduced mitral regurgitation and nocturnal urinary and daytime plasma nor-epinephrine, and improved quality of life (24, 25). Sin et al. (16) studied patients with HF and CSA-CSR and reported a significant improvement in LVEF and transplant-free survival in those randomized to CPAP therapy, if they complied with treatment, compared to control with no CPAP. Bradley et al. (26) carried out the largest randomized prospective study on the use of nasal CPAP therapy in 258 HF patients with CSA-CSR (CANPAP study). They found no difference in 2-year survival or atrial natriuretic peptide plasma level despite significant improvements in LVEF, lower nor-adrenaline levels and increased mean 6-minute walk test distance in patients randomized to CPAP. The authors suggested that current medical therapies for HF (particularly beta-blockers) led to significant improvement in prognosis, with a fall in the mortality of both control and treatment groups which reduced the study's power to detect a treatment difference. In addition, the mean reduction of AHI in the treatment arm was to a level above the inclusion AHI threshold of 15. Moreover, the issues of compliance and efficacy may be relevant. At one year, CPAP was used for 3.6 hours per night and attenuated AHI by 50%, indicating only a partial reduction in "apnoea burden". A recent post hoc analysis of CANPAP study showed that responders to CPAP had a significant improvement in LVEF and transplant-free survival compared to non-responders or controls (27). Although

this was a post hoc analysis, it is hypothesis generating and provides directions for future research on CPAP in HF patients with CSA-CSR responsive to CPAP because better-tolerated and more effective treatment of CSA-CSR might have resulted in improved survival (27-29). Another point of interest regards the theoretical possibility that other forms of non-invasive ventilation able to abolish CSA-CSR may be effective in the treatment of the cardiovascular consequences associated with CSA-CSR. Because CPAP is not effective in reducing CSA-CSR in a significant number of patients, other forms of non-invasive ventilation, including bi-level positive airway pressure (BiPAP) and adaptive pressure support ventilation (ASV), have been proposed as alternative.

Bi-level positive airway pressure (BiPAP) is a ventilatory mode that delivers two pressure levels, a higher inspiratory pressure and a lower expiratory pressure. BiPAP has been postulated to be superior to CPAP in HF patients because the typically lower expiratory pressure may not impede stroke volume in patients with low cardiac filling pressures, as may occur with CPAP (30). Despite the general concern that these patients already hyperventilate, and further increasing ventilation may not necessarily be a good approach, possibly leading to hypocapnic alkalotic glottic closure, recently Khayat et al. (31), in moderate-severe HF patients randomly assigned to CPAP or BiPAP treatment, found that LVEF improved significantly in the BiPAP group but not the CPAP group. Previously, on the other hand, Konhlein et al. (32) in a random, crossover study design concluded

CPAP, and several mode of nocturnal noninvasive ventilation have been shown to alleviate CSA-CSR, but despite promising results, further studies are needed to establish this treatment for respiratory sleep disorders in patients with CHF.

that both CPAP and BiPAP treatments equally and effectively improve Cheyne-Stokes respiration in HF patients. At any rate, it's important to highlight the setting values of the bi-level devices employed in aforementioned studies (31, 32) because the very low span used (mean 3 cmH₂O) between inspiratory and expiratory pressure really suggest a CPAP-like effect more than a pressure support ventilation. One interesting and relatively new format of treatment is the adaptive pressure support ventilation (ASV). This is a novel form of bi-level PAP in which the flow generator provides a fixed end expiratory pressure that should be titrated to abolish upper airway obstructive events. The inspiratory pressure support level then varies in accordance to an algorithm that aims at stabilizing ventilation at an approximate 80% of the baseline minute ventilation. Adaptive pressure support ventilation results in acute suppression of CSA-CSR (21) that is more effective than CPAP and may result in better compliance and a greater improvement in heart function (22).

A prospective study used a randomized parallel design in treating 26 CSA-CSR in heart failure patients, comparing one month of therapeutic and sub therapeutic ASV (33). Active treatment attenuated daytime sleepiness (primary end point), plasma brain natriuretic peptide and urine nor-adrenaline (secondary end points). Despite these promising results, further studies are needed to clarify the

optimal ventilation strategy for patients with CSA-CSR and HF.

As an alternative approach nocturnal oxygen therapy has been reported to improve CSA in patients with systolic heart failure (34-36). Hanly et al. (35) should be credited for the first randomized, placebo controlled study. In nine

Nocturnal oxygen therapy decreases periodic breathing, but failed to show complete reversal of sleep apnea in patients with CHF.

subjects with systolic heart failure, the authors showed that the administration of nasal oxygen for one night (when compared to nasal air) improved CSA-CSR, sleep architecture (*i.e.* decreased arousals and shifted sleep to deep stages), and arterial oxyhaemoglobin desaturation. Two studies of Andreas et al. (37) and Staniforth (38) et al. indicated that in systolic heart failure, oxygen decreases sympathetic activity due to CSA. Another study of Sasayama (39) showed that supplemental nocturnal oxygen therapy for three months, compared to control, significantly improved CSA-CSR, LVEF and quality of life in patients with HF and central sleep breathing disorders.

Oxygen administration decreased periodic breathing with the most significant effect on CSA. While the patients were receiving oxygen, desaturation was virtually eliminated. Unfortunately not all patients with heart failure and CSA-CSR have a complete reversal of sleep apnoea with oxygen. It was noted (40) that in patients fully responsive to oxygen therapy the PaCO₂ values of the subjects were within the normal range while in patients which oxygen therapy resulted in only partial response, the PaCO₂ values of the subject were lower than normal range. The mechanisms of the therapeutic effects of oxygen on CSA are multifactorial. These include a rise in PCO₂ and, presumably, a widening of the difference between the eucapnic PCO₂ and the PCO₂ at the apnoeic threshold, the suppression of ventilatory response to hypercapnia, and an increase in the body stores of oxygen. Taken together, this should dampen the respiratory loop-gain (change of ventilation for a given change of ventilation) (41) and decrease the likelihood of ventilatory instability promoting CSA-CSR. It was speculated (40) that subjects that resulted as only partial responders to oxygen therapy have such an intense non-chemical ventilatory stimuli that oxygen failed to raise their baseline PCO₂ in the transition from wakefulness to sleep. Because oxygen decreases sympathetic activity and eliminates desaturation, long-term therapy may potentially decrease the morbidity and mortality of subjects with HF. Nevertheless, careful, randomized, placebo controlled, multicenter studies with mortality as the end point are required to prove nocturnal oxygen therapy as a long-term helpful treatment modality in HF with CSA-CSR.

In accordance to point of view that CSA-CSR is a consequence of a failing heart, all therapies able to ameliorate heart function may be helpful in reducing CSA-CSR.

In effect CSA-CSR was abolished in patients underwent to heart transplant for CHF (42). Some, but not all, studies indicate that beta-blockers and furosemide ameliorate CSA-CSR (43, 44). Also theophylline (45), acetazolamide (46), administration of carbon dioxide (47) and addition of dead space (48) can reduce CSA-CSR; however there is

a general concern that to use drugs or devices with a strong stimulatory effect on respiratory drive in patients with CHF and CSA/CSR, already hyperventilate, may not be beneficial.

Cardiac resynchronization therapy also appears to improve CSA-CSR in HF, but only in those patients whose cardiac function improved with the resynchronization therapy (24), suggesting that improved cardiac function may have reduced the severity of CSA-CSR. Changes in CSA-CSR seemed to be associated with CRT-induced changes in mitral regurgitation but further studies are required to confirm these early results, to determine the exact mechanisms by which CRT might improve CSA-CSR, and to identify which CSA-CSR patients with heart failure would benefit from such interventions.

Conclusions

Although CSA-CSR has been associated with increased mortality in CHF patients, a causal role for CSA-CSR in the morbidity and mortality of heart failure awaits more definitive evidence. A number of treatment strategies for CSA have been tested, but presently none is ideal with respect to both efficacy and tolerance, nor has any available therapy been demonstrated to improve survival. For CSA-CSR, use of CPAP cannot be recommended at present, though the post hoc analysis of the CANPAP study (27) is intriguing and suggests that CPAP responders may benefit prognostically. Furthermore, the results of the CANPAP study should not be extrapolated to heart failure patients with OSA, which is much more effectively suppressed by CPAP. Finally, there is a need to examine novel treatment options for CSA-CSR in patients with HF, as these patients appear to have the worst prognosis and therefore the most to gain if successful treatment of CSA-CSR improves survival.

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References

1. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999; 22:667-89.
2. Khoo MC, Kronauer RE, Strohl KP, Slutsky AS. Factors inducing periodic breathing in humans: a general model. *J Appl Physiol* 1982;53:644-59.
3. Lorenzi-Filho G, Genta PR, Figueiredo AC, Inoue D. Cheyne-Stokes respiration in patients with congestive heart failure: causes and consequences. *Clinics (Sao Paulo)* 2005;60:333-44.
4. Naughton M, Benard D, Tam A, Rutherford R, Bradley TD. Role of hyperventilation in the pathogenesis of central sleep apneas in patients with congestive heart failure. *Am Rev Respir Dis* 1993;148:330-8.
5. Solin P, Roebuck T, Johns DP, Walters EH, Naughton MT. 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.
6. Carley DW, Shannon DC. Relative stability of human respiration during progressive hypoxia. *J Appl Physiol* 1988;65:1389-99.
7. Szollosi I, Roebuck T, Thompson B, Naughton MT. Lateral sleeping position reduces severity of central sleep apnea / Cheyne-Stokes respiration. *Sleep* 2006;29:1045-51.
8. Lorenzi-Filho G, Rankin F, Bies I, Douglas Bradley T. Effects of inhaled carbon dioxide and oxygen on cheyne-stokes respiration in patients with heart failure. *Am J Respir Crit Care Med* 1999;159:1490-8.
9. Lorenzi-Filho G, Azevedo ER, Parker JD, Bradley TD. Relationship of carbon dioxide tension in arterial blood to pulmonary wedge pressure in heart failure. *Eur Respir J* 2002;19:37-40.
10. Roberts AM, Bhattacharya J, Schultz HD, Coleridge HM, Coleridge JC. Stimulation of pulmonary vagal afferent C-fibers by lung edema in dogs. *Circ Res* 1986;58:512-22.
11. Solin P, Snell GI, Williams TJ, Naughton MT. Central sleep apnoea in congestive heart failure despite vagal denervation after bilateral lung transplantation. *Eur Respir J* 1998;12:495-8.
12. Heistad DD, Wheeler RC, Mark AL, Schmid PG, Abboud FM. Effects of adrenergic stimulation on ventilation in man. *J Clin Invest* 1972;51:1469-75.
13. Lanfranchi PA, Somers VK, Braghiroli A, Corra U, Eleuteri E, Giannuzzi P. Central sleep apnea in left ventricular dysfunction: prevalence and implications for arrhythmic risk. *Circulation* 2003;107:727-32.
14. Lanfranchi PA, Braghiroli A, Bosimini E, et al. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. *Circulation* 1999;99:1435-40.
15. Hanly PJ, Zuberi-Khokhar NS. Increased mortality associated with Cheyne-Stokes respiration in patients with congestive heart failure. *Am J Respir Crit Care Med* 1996;153:272-6.
16. Sin DD, Logan AG, Fitzgerald FS, Liu PP, Bradley TD. Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. *Circulation* 2000;102:61-6.
17. Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. *J Am Coll Cardiol* 2007; 49:2028-34.
18. Tkacova R, Niroumand M, Lorenzi-Filho G, Bradley TD. Overnight shift from obstructive to central apneas in patients with heart failure: role of PCO₂ and circulatory delay. *Circulation* 2001;103:238-43.
19. Tkacova R, Wang H, Bradley TD. Night-to-night alterations in sleep apnea type in patients with heart failure. *J Sleep Res* 2006;15:321-8.
20. Naughton MT, Liu PP, Bernard DC, Goldstein RS, Bradley TD. Treatment of congestive heart failure and Cheyne-Stokes respiration during sleep by continuous positive airway pressure. *Am J Respir Crit Care Med* 1995;151:92-7.
21. Teschler H, Dohring J, Wang YM, Berthon-Jones M.

- 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.
22. Philippe C, Stoica-Herman M, Drouot X, et al. Compliance with and effectiveness of adaptive servoveililation 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.
 23. Naughton MT, Rahman MA, Hara K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on intrathoracic and left ventricular transmural pressures in patients with congestive heart failure. *Circulation* 1995;91:1725-31.
 24. Oldenburg O, Faber L, Vogt J, et al. Influence of cardiac resynchronisation therapy on different types of sleep disordered breathing. *Eur J Heart Fail* 2007; 9:820-6.
 25. Tkacova R, Liu PP, Naughton MT, Bradley TD. Effect of continuous positive airway pressure on mitral regurgitant fraction and atrial natriuretic peptide in patients with heart failure. *J Am Coll Cardiol* 1997; 30:739-45.
 26. 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.
 27. 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;115:3173-80.
 28. Olson LJ, Somers VK. Treating central sleep apnea in heart failure: outcomes revisited. *Circulation* 2007;115:3140-2.
 29. Somers VK. Sleep-a new cardiovascular frontier. *N Engl J Med* 2005;353:2070-3.
 30. Bradley TD, Hall MJ, Ando S, Floras JS. Hemodynamic effects of simulated obstructive apneas in humans with and without heart failure. *Chest* 2001;119:1827-35.
 31. Khayat RN, Abraham WT, Patt B, Roy M, Hua K, Jarjoura D. Cardiac effects of continuous and bilevel positive airway pressure for patients with heart failure and obstructive sleep apnea: a pilot study. *Chest* 2008;134:1162-8.
 32. Kohnlein T, Welte T, Tan LB, Elliott MW. Assisted ventilation for heart failure patients with Cheyne-Stokes respiration. *Eur Respir J* 2002;20:934-41.
 33. 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.
 34. Walsh JT, Andrews R, Starling R, Cowley AJ, Johnston ID, Kinnear WJ. Effects of captopril and oxygen on sleep apnoea in patients with mild to moderate congestive cardiac failure. *Br Heart J* 1995;73:237-41.
 35. Hanly PJ, Millar TW, Steljes DG, Baert R, Frais MA, Kryger MH. The effect of oxygen on respiration and sleep in patients with congestive heart failure. *Ann Intern Med* 1989;111:777-82.
 36. Andreas S, Clemens C, Sandholzer H, Figulla HR, Kreuzer H. Improvement of exercise capacity with treatment of Cheyne-Stokes respiration in patients with congestive heart failure. *J Am Coll Cardiol* 1996;27:1486-90.
 37. Andreas S, Bingeli C, Mohacsi P, Luscher TF, Noll G. Nasal oxygen and muscle sympathetic nerve activity in heart failure. *Chest* 2003;123:366-71.
 38. Staniforth AD, Kinnear WJ, Starling R, Hetmanski DJ, Cowley AJ. 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.
 39. Sasayama S, Izumi T, Seino Y, Ueshima K, Asanoi H. Effects of nocturnal oxygen therapy on outcome measures in patients with chronic heart failure and cheyne-stokes respiration. *Circ J* 2006;70:1-7.
 40. 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;123:322-5.
 41. Khoo MC. Determinants of ventilatory instability and variability. *Respir Physiol* 2000;122:167-182.
 42. Mansfield DR, Solin P, Roebuck T. The effect of successful heart transplant treatment of heart failure on central sleep apnoea. *Chest* 2003;124:1675-1681.
 43. Tamura A, Kawano Y, Naono S. Relationship between beta-blocker treatment and the severity of central sleep apnea in chronic heart failure. *Chest* 2007;131:130-135.
 44. Solin P, Bergin P, Richardson M. Influence of capillary wedge pressure on central apnea in heart failure. *Circulation* 1998;97:2154-2159.
 45. Javaheri S, Parker TJ, Wexler L. Effect of theophylline on sleep disordered breathing in heart failure. *N Engl J Med* 1996;335:562-567.
 46. Javaheri S. Acetazolamide improves central sleep apnea in heart failure. A double blind prospective trial. *Am J Respir Crit Care Med* 2006;173:234-237.
 47. Lorenzi-Filho G, Rankin F, Bies I. Effects of inhaled carbon dioxide and oxygen on Cheyne-Stokes respiration in patients with heart failure. *Am J Respir Crit Care Med* 1999;159:1490-1498.
 48. Khayat RN, Xie A, Patel AK. Cardiorespiratory effects of added dead space in patients with heart failure and central sleep apnea. *Chest* 2001;123:1551-1560.