Sleep-disordered breathing in heart failure: facts and numbers

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Abstract

Sleep-disordered breathing has a high prevalence in the general population, but is especially prominent in patients with heart failure (HF). HF and sleep-disordered breathing share a bidirectional relationship, with sleep-disordered breathing being both cause and effect of poor cardiac functioning. The high inter-individual variability of symptom presentation can impede the clinical diagnostic process. Polysomnography is the gold-standard method of diagnosing sleep-disordered breathing. Therapy of sleep-disordered breathing should always consist of optimizing the treatment of the underlying disorder of HF. Additional therapeutic measures include continuous positive airway pressure ventilation therapy. New therapeutic options using neurostimulation are yielding promising results; however, long-term benefits still need to be confirmed.

Keywords  Sleep apnoea; Heart failure; Therapy

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Introduction

Sleep-disordered breathing is highly prevalent in patients with heart failure (HF) and has a strong impact on clinical outcome. Their relationship is antagonistic: poor cardiac function can induce a breathing disorder, and correspondingly, sleep-disordered breathing can adversely affect the progression of HF. This reinforces a pathophysiological circulus vitiosus. Due to the high prevalence, high morbidity, and high mortality of HF, knowing, diagnosing, and treating the common comorbidity of sleep-disordered breathing become indispensable.

Sleep-disordered breathing includes all disturbances in respiratory behaviour during sleep. The pre- eminent disorders are obstructive sleep apnoea (OSA), central sleep apnoea (CSA), and mixed sleep apnoea, which presents with components of both OSA and CSA. All three forms are characterized by episodes of hypopnoea and/or apnoea, with disease severity increasing with the number of events.1–5 In this context, hypopnoeas are defined as a reduction in nasal flow of ≥50% for ≥10 s combined with arousal or a decline in oxygen saturation ≥4 percentage points. Apnoeas are prolonged pauses in breathing during sleep with a duration of ≥10 s occurring >5 per hour.3 They are likewise associated with a drop in oxygen saturation.

Obstructive sleep apnoea

The most common form of sleep-disordered breathing, OSA, is primarily caused by an obstruction of the upper respiratory tract that results in repeated interruptions of the normal breathing process during sleep. Patients with OSA are often anatomically predisposed to smaller pharyngeal breathing tracts as a result of obesity, enlarged tonsils, adenoids, or tissue irregularities.6,7 During sleep, the pharyngeal dilator muscle activity, which compensatory ensures a regular air passage during wakefulness, is diminished. This leads to a partial or complete airway obstruction, producing hypopnoeas or apnoeas, respectively. The resulting hypoxia and hypercapnia act as strong central stimulants and provoke a reacquisition of normal breathing and/or arousal.3,4,8–10 Patients are not usually aware of such episodes of arousal, but they still cause stress.
Central sleep apnoea

The central form of apnoea is caused by a dysfunction of the ventilatory control system. The patency of the respiratory tract is functional, but the ventilatory effort, the essential central trigger for breathing, is intermittently disrupted. This malfunction can originate from a variety of neurological diseases or HF. In HF, the accepted hypothesis is that pulmonary congestion, which is further aggravated in a horizontal sleeping position due to a higher left ventricular filling pressure, activates lung vagal irritant receptors causing hyperventilation and hypocapnia. The PaCO₂ threshold to stimulate the central respiratory centre is not surpassed. In consequence, the respiratory muscles are insufficiently innervated, and normal breathing surceases. Cheyne–Stokes respiration is a frequent breathing pattern observed in CSA; it is characterized by periodic fluctuations between hypopnoea/apnoea and hyperventilating crescendo and decrescendo respiratory phases. However, Cheyne–Stokes respiration is not a prerequisite for a diagnosis of CSA. This respiration pattern can even be observed during wakefulness and exercise in patients with advanced chronic HF. Central apnoeas may also appear concomitantly to obstructive apnoeas, resulting in mixed sleep apnoea.

The pathophysiological consequences of regular hypopnoea and apnoea phases are a permanent increase in sympathetic nervous system activity. An increased heart rate, diminished heart rate variability, higher blood pressure, and increased cardiac oxygen demand ensue. Additionally, oxidative stress may be triggered as a result of the repeated hypoxemia and reoxygenation processes in sleep-disordered breathing. The collaborative impact of these factors can contribute to pathological remodelling processes of the myocardium.

Clinical presentation

Common symptoms of sleep-disordered breathing are unrestful sleep, fatigue, hypersomnolence, and cognitive dysfunction. Other clinical signs include headaches, nocturia, erectile dysfunction, reduction of libido and witnessed apnoea, or gasping. Rhonchopathy is especially prevalent in OSA patients, and CSA patients can present with cardiac or neurological manifestations of the underlying condition. There is a high inter-individual variability in the presentation of symptoms in sleep-disordered breathing, with disease severity not necessarily corresponding to symptom severity. Some patients do not present with any symptoms at all. This is particularly true in patients with symptomatic HF, in whom 50–70% of patients are affected by sleep-disordered breathing. Whilst patients with less symptomatic status more often present with OSA, CSA is becoming more prevalent in advanced stages of HF, that is, in patients in New York Heart Association classes III and IV. Even more problematic is the fact that typical signs of sleep-disordered breathing may be absent in patients with HF or they may overlap with symptoms of HF itself, therefore rendering the differential diagnosis difficult. Even screening tools that work well in subjects without HF such as the Epworth Sleepiness Scale have not proven reliable in patients with HF. Other screening questionnaires are the Berlin Questionnaire and the STOP-Bang Sleep Apnea Questionnaire but both have not been validated in patients with HF. The severity of the disease can be screened for using two indices: The Apnoe–Hypopnoe Index (AHI) and Oxygen Desaturation Index (ODI). The AHI represents the number of apnoeas and hypopnoeas per hour of sleep; an AHI <5 per hour is considered physiological. An AHI 5–15 per hour defines a mild, AHI 15–30 per hour a moderate, and AHI >30 per hour a severe form of sleep-disordered breathing. The ODI reflects the number of respiratory events that result in a reduction in oxygen saturation of ≥4%.

Clinical diagnosis

The predominant method of diagnosing sleep-disordered breathing is via polysomnography that is used in the sleep lab or its more elementary counterpart, polygraphy, that can be used on an outpatient basis. A polysomnography is a multi-parametric sleep study that monitors respiratory airflow, oxygen saturation (via pulse oximetry), thoracic and abdominal respiratory effort, rhonchopathy, heart activity (via electrocardiography), skeletal muscle behaviour (via electromyography), electrical brain activity (via electroencephalography), and eye movement (via electro-oculography) during sleep. A polygraphy only includes the recordings of respiratory airflow, oxygen saturation, and thoracic and abdominal movement. The collected parameters are then analysed to obtain AHI, ODI, and cardiac, breathing, or sleep irregularities. The usual approach is to screen patients for the presence of sleep-disordered breathing using polygraphy and to refer those with elevated AHI/ODI values for polysomnography.

Prevalence of sleep-disordered breathing in heart failure

The prevalence of moderate to severe sleep-disordered breathing is currently estimated to be 10–17% in the adult male population and 3–9% in the adult female population in the United States. In patients with HF, the prevalence is significantly higher. In one study, patients with chronic HF (New York Heart Association ≥II or left-ventricular
ejection fraction $\leq$40%) 40% were diagnosed with CSA and 35% with OSA.

Central sleep apnoea is a primary comorbidity in HF, increasing in prevalence with deteriorating cardiac function. Chronic HF is recognized as an independent risk factor for the development of CSA. Concurrently, CSA adversely affects the progression of HF, predominantly through the permanently increased sympathetic nervous system activity and its consequences. Likewise, OSA is also more prevalent in patients with HF as compared with the general population. It is also its own risk factor for cardiovascular disease. The presence of OSA fundamentally contributes to myocardial failure and earlier mortality in patients with HF. Although awareness among physicians of sleep-disordered breathing is growing, clinically significant sleep-disordered breathing is still vastly under-diagnosed and even available tools may be underutilized.

**Therapy of sleep-disordered breathing**

The core therapeutic measure in treating HF patients with the comorbidity of sleep-disordered breathing is always ensuring the patient’s receiving of optimal HF treatment. If the sleep-disordered breathing persists, other additional therapeutic measures may be employed.

In OSA, continuous positive airway pressure (CPAP) ventilation therapy is recommended. The continuous air pressure provided by an overnight mask ensures improved ventilation and ameliorates the patient’s symptoms. Other options are oxygen supplementation, bi-level positive airway pressure, or adaptive servo-ventilation (ASV) therapy, which appropriately adapts the positive airway pressure according to changes in the patient’s breathing pattern, thereby enhancing the ventilatory efficacy. Unfortunately, none of these interventions positively impacts the outcome of HF.

Patients with CSA may also benefit from CPAP, bi-level positive airway pressure, or nocturnal oxygen supplementation therapy. Several studies have demonstrated a therapeutic effectiveness of chronic resynchronization therapy in patients with HF and CSA. A recent study demonstrated that ASV improved CSA, but significantly increased cardiovascular and all-cause mortality. Therefore, ASV is no longer recommended for CSA patients with chronic HF.

Modern, more invasive, yet promising interventions to improve sleep-disordered breathing are nerve stimulations. In patients with OSA, hypoglossal neurostimulation has been shown to reduce AHI and symptom severity by reducing the obstruction of the upper respiratory tract. Further research is necessary, but current results deem it an auspicious therapeutic measure, especially for OSA patients intolerant or non-responsive to CPAP therapy. Unilateral phrenic nerve stimulation is a further treatment option for patients with CSA. Current results indicate a significant reduction in AHI, symptom improvement, and increased quality of life in patients receiving the implantable device; nonetheless, long-term effects still need to be established.

**Conflict of interest**

SvH has been a paid consultant for Respica, Vifor, Roche and B.R.A.H.M.S. CP does not have a conflict of interest.

**References**

1. Linz D, Woehrle H, Bitter T, Fox H, Cowie MR, Böhm M, Oldenburg O. The importance of sleep-disordered breathing in cardiovascular disease. Clin Res Cardiol 2015; 104: 705–718.

2. Gilmartin GS, Daly RW, Thomas RJ. Recognition and management of complex sleep-disordered breathing. Curr Opin Pulm Med 2005; 11: 485–493.

3. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R, Woo M, Young T. 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 Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation 2008; 118: 1080–1111.

4. Bradley TD, Floras JS. Sleep apnea and heart failure part I: obstructive sleep apnea. Circulation 2003; 107: 1671–1678.

5. Bradley TD, Floras JS. Sleep apnea and heart failure: part II: central sleep apnea. Circulation 2003; 107: 1822–1826.

6. Schwab RJ, Paspirstein M, Pierson R, Mackley A, Hachadoorian R, Arens R, Maislin G, Pack AI. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. Am J Respir Crit Care Med 2003; 168: 522–530.

7. Bradley TD, Brown IG, Grossman RF, Zamel N, Martinez D, Phillipson EA, Hofstein V. Pharyngeal size in snorers, nonsnorers, and patients with obstructive sleep apnea. N Engl J Med 1986; 315: 1327–1331.

8. Fogel RB, Malhotra A, Pillar G, Edwards JK, Beauregard J, Shea SA, White DP. Genioglossal activation in patients with obstructive sleep apnea versus control subjects. Mechanisms of muscle control. Am J Respir Crit Care Med 2001; 164: 2025–2030.

9. Fogel RB, Trinder J, Malhotra A, Stanchina M, Edwards JK, Schory KE, White DP. Within-breath control of genioglossal muscle activation in humans: effect of sleep-wake state. J Physiol 2003; 550: 899–910.

10. White DP. Pathogenesis of obstructive and central sleep apnea. Am J Respir Crit Care Med 2005; 172: 1363–1370.

11. Bassetti C, Aldrich MS, Chervin RD, Quint D. Sleep apnea in patients with transient ischemic attack and stroke: a prospective study of 59 patients. Neurology 1996; 47: 1167–1173.
12. Iranzo A. Sleep in neurodegenerative diseases. Sleep Med Clin 2016; 11: 1–18.
13. Sankari A, Bascom AT, Choudhuri S, Badr MS. Tetraplegia is a risk factor for central sleep apnea. J Appl Physiol 2014; 116: 345–353.
14. Saletti A. Sleep-disordered breathing in neurodegenerative diseases. Curr Neurol Neurosci Rep 2012; 12: 205–217.
15. Caples SM, Wolk R, Somers VK. Influence of cardiac function and failure on sleep-disordered breathing: evidence for a causative role. J Appl Physiol 2005; 99: 2433–2439.
16. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: pathophysiology and treatment. Chest 2007; 131: 595–607.
17. Olson LJ, Somers VK. Sleep apnea: implications for heart failure. Circ Heart Fail Rep 2007; 4: 63–69.
18. Javaheri S. Heart failure and sleep apnea: emphasis on practical therapeutic options. Clin Chest Med 2003; 24: 207–222.
19. Javaheri S. A mechanism of central sleep apnea in patients with heart failure. N Engl J Med 1999; 341: 949–954.
20. Krawczyk M, Flinta I, Gancarek M, Jankowska EA, Banasiak W, Germany R, Javaheri S, Ponikowski P. Sleep disordered breathing in patients with heart failure. Cardiol J 2013; 20: 345–355.
21. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Oldenburg O. Cheyne-Stokes respiration in chronic heart failure. Treatment with adaptive servo-ventilation therapy. Circ J 2012; 76: 2305–2317.
22. Naughton MT. Epidemiology of central sleep apnea in heart failure. Cardiol J 2013; 20: 345–355.
23. Cowie MR, Woehrel H, Wegscheider K, Angermann C, d’Ortho MP, Erdmann E, Levy P, Simonds AK, Somers VK, Zannad F, Teschler H. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med 2015; 373: 1093–1105.
24. Leite JI, Mansur AJ, de Freitas HF, Chizola PR, Bocchi EA, Terra-Filho M, Neder JA, Lorenzi-Filho G. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. J Am Coll Cardiol 2003; 41: 2175–2181.
25. Arzt M, Barth M, Luchner A, Maders F, Holmer SR, Blumberg FC, Rieger GA, Pfeifer M. Enhanced ventilator response to exercise in patients with chronic heart failure and central sleep apnea. Circulation 2003; 107: 1998–2003.
26. Gottlieb DJ, Yenokyan G, Newman AB, O’Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, Shahar E. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation 2010; 122: 352–360.
27. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995; 96: 1897–1904.
28. Lavi J. Obstructive sleep apnoea syndrome—an oxidative stress disorder. Sleep Med Rev 2003; 7: 35–51.
29. Schulz R, Mahmoudi S, Hattar K, Sibelius U, Olschewski H, Mayer K, Seeger W, Grimminger F. Enhanced release of superoxide from polymorphonuclear neutrophils in obstructive sleep apnea: impact of continuous positive airway pressure therapy. Am J Respir Crit Care Med 2000; 162: 564–570.
30. Hofmann MS, Singh P, Wolk R, Romer-Corral A, Raghavakaimal S, Somers VK. Microarray studies of genomic oxidative stress and cell cycle responses in obstructive sleep apnea. Antioxid Redox Signal 2007; 9: 661–669.
31. Svatikova A, Wolk R, Lerman LO, Juncos LA, Chadha R, Rooney MM, McDonald JP, Somers VK. Oxidative stress in obstructive sleep apnea. Eur Heart J 2005; 26: 2435–2439.
32. Lévy P, Ryan S, Oldenburg O, Parati G. Sleep apnoea and the heart. Eur Respir Rev 2014; 22: 333–353.
33. Kasai T, Floras JS, Bradley TD. Sleep apnoea and cardiovascular disease: a bidirectional relationship. Circulation 2012; 126: 1495–1510.
34. Arzt M, Young T, Palti M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328: 1230–1235.
35. Peppard PE, Young T, Barnet JH, Palti M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 2013; 177: 1006–1014.
36. Javaheri S, Parker TJ, Limos JD, Corbett WS, Nishiyama H, Wexler L, Roselle GA. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. Circulation 1998; 97: 2154–2159.
37. Bitter T, Faber L, Hering D, Langer C, Horstkotte D, Oldenburg O. Sleep-disordered breathing in heart failure with normal left ventricular ejection fraction. Eur J Heart Fail 2009; 11: 602–608.
38. Maeder MT, Schoch OD, Rickli H. A clinical approach to obstructive sleep apnea as a risk factor for cardiovascular disease. Vasc Health Risk Manag 2016; 12: 85–103.
39. Yaggi HK, Mittleman MA, Bravata DM, Concato J, Ware J, Stoney CM, Redline S. Reducing cardiovascular risk through treatment of obstructive sleep apnea: 2 methodological approaches. Am Heart J 2016; 212: 135–143.
40. Shah NA, Yaggi HK, Concato J, Mohsenin V. Obstructive sleep apnea as a risk factor for coronary events or cardiovascular death. Sleep Breath 2010; 14: 131–136.
52. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep 1997; 20: 705–706.

53. Kaput V, Strohl KP, Redline S, Iber C, O’Connor G, Nieto J. Underdiagnosis of sleep apnea syndrome in U.S. communities. Sleep Breath 2002; 6: 49–54.

54. Bordier P. Sleep apnoea in patients with heart failure: part II: therapy. Arch Cardiovasc Dis 2009; 102: 711–720.

55. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Rutten FH, van der Meer P, authors/task force members. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129–2200.

56. Oldenburg O, Faber I, Vogt J, Dorszewska A, Szabados F, Horstkotte D, Lamp B. Influence of cardiac resynchronisation therapy on different types of sleep disordered breathing. Eur J Heart Fail 2007; 9: 820–826.

57. Gabor JY, Newman DA, Barnard-Roberts V, Korley V, Mangat I, Dorian P, Hanly PJ. Improvement in Cheyne–Stokes respiration following cardiac resynchronization therapy. Eur Respir J 2005; 26: 95–100.

58. Sinha AM, Skobel EC, Breithardt OA, Norra C, Markus RL, Breuer C, Hanrath P, Stellbrink C. Cardiac resynchronisation therapy improves central sleep apnea and Cheyne–Stokes respiration in patients with chronic heart failure. J Am Coll Cardiol 2004; 44: 68–71.

59. Oliven A. Treating obstructive sleep apnea with hypoglossal nerve stimulation. Curr Opin Pulm Med 2011; 17: 419–424.

60. Heiser C, Hofauer B. Hypoglossal nerve stimulation in patients with CPAP failure: evolution of an alternative treatment for patients with obstructive sleep apnea. HNO 2017; 65: 99–106.

61. Costanzo MR, Ponikowski P, Javaheri S, Augustini R, Goldberg L, Holcomb B, Kao A, Khayat R, Oldenburg O, Stellbrink C, Abraham WT, remedē system pivotal trial study group. Transvenous neurostimulation for central sleep apnoea: a randomized controlled trial. Lancet 2016; 388: 974–982.