European Heart Journal Supplements (2019) **21** (Supplement M), M36–M39
The Heart of the Matter
doi:10.1093/eurheartj/suz233

ESC
European Society
of Cardiology

Monitoring for sleep-disordered breathing in heart failure

Andrew J. Stewart Coats*

Department of Medical Sciences, Centre for Clinical and Basic Research, IRCCS San Raffaele Pisana, Via di Val Cannuta 247, 00166 Roma, Italy

KEYWORDS
Heart failure;
Sleep apnoea;
Sleep-disordered breathing;
Comorbidities

Sleep-disordered breathing (SDB) is extremely common in heart failure (HF) and it carries with it adverse symptoms and impaired survival. Sleep-disordered breathing has two main types; obstructive sleep apnoea (OSA) and central sleep apnoea (CSA), which can overlap. The differentiation between CSA and OSA is important and is recommended in recent HF guidelines, by recommending a formal sleep study. The reason is that for OSA the main therapy is a positive pressure airway mask, whereas for patients with HFrEF and CSA this mask therapy actually increases cardiovascular mortality, and therefore alternative therapies are required, such as implantable phrenic nerve stimulation to improve sleep and related daytime symptoms attributable to the CSA. This article discusses the detection, screening, and monitoring of SDB in HF patients.

Introduction

Sleep disturbances are common in patients with heart failure (HF). Whilst some may be attributed to the postural change associated with lying down causing elevations in left atrial pressures with consequent early pulmonary alveolar congestion (coined orthopnoea and paroxysmal nocturnal dyspnoea, respectively), others reflect abnormalities in breathing patterns that occur during sleep, or sleep-disordered breathing (SDB). Sleep-disordered breathing is itself a constellation of separate abnormalities and pathophysiological processes that have the fundamental similarity of causing disordered breathing patterns during sleep. They frequently also cause abnormalities in sleep architecture, such as changes in sleep stages, the total duration of sleep, its quality and its effectiveness, such as the likelihood of waking with the residual effects of an inadequate night's sleep, especially daytime drowsiness. Sleep-disordered breathing in HF is classically subdivided into two main types; obstructive sleep apnoea (OSA) and central sleep apnoea (CSA). Both are very common in HF but for different reasons. The risk factors for OSA are similar to the risk factors for HF; male gender, hypertension, coronary artery disease, and obesity, so that the same patients at risk of OSA are also at risk to develop HF. Obstructive sleep apnoea is even a risk factor for the development of HF.[1] Central sleep apnoea, in contrast, is a complication of established HF; in fact, HF is the most common underlying aetiology in cohorts of patients with CSA. So although SDB is common in HF (one study showing 61% of treated HF patients had either central or OSA[2]) it is for two different reasons; because OSA is seen in people who are likely to develop HF and because CSA is consequence of HF. This means that the relative proportions of the two types changes as HF progresses. In early HF and Class I–II New York Heart Association (NYHA), OSA is more common than CSA, whereas in Class III–IV and long-standing HF CSA is the predominant type.[3]

Pathophysiology

Obstructive sleep apnoea is largely an anatomical problem. A thick neck, large tongue, and deep sleep (such as after alcoholic beverages or sleeping tablets at night) predispose to obstruction of the upper airway, with the tongue flopping back to obstruct the tracheal entrance. The patient

*Corresponding author. Tel: +44-7551528636, Email: ajscoats@aol.com

continues to attempt to breathe but there is no effective airflow. Arterial oxygen saturations fall and CO_2 accumulates leading reflexly to an increased drive to breathing, associated with partial or complete awakening and an eventual opening of the airway and resumption of breathing. Early on in this cycle, the airway can be partially blocked leading to snoring due to partial occlusion and vibration of the airway.

Central sleep apnoea in contrast is largely a neurological disorder. Central sleep apnoea is of two types, a periodic form with cycles of about 1–2 min where regular fluctuations in breathing intensity oscillate with a predictable periodicity and frequently leading to alternating phases of apnoea and hyperpnoea that each start and finish slowly. It is thought to be due to a harmonic oscillation of reflex feedback loops,[4] a phenomenon well known in control systems theory. This type is almost indistinguishable from Cheyne–Stokes respiration (CSR) and it seems to be associated with features that make the largely chemoreflex-mediated ventilatory reflexes less stable; these include increased gain of the chemoreflexes, a slowed circulation and lowered arterial CO_2 levels.[5] The other type is of episodes of irregular (non-rhythmic) apnoeas of central origin (loss of central drive to breathing), which are more commonly seen in brain injuries, rather than in HF. The CSR type of CSA is extremely common in HF [and also in atrial fibrillation (AF)] and can present with similar symptoms to OSA, although snoring may be less prominent. Interrogating the sleep partner may pick up a clue that the patient is suffering from CSA rather than OSA because of the classic description of the patient ceasing to breath for 30–60 s, but remaining quiet followed by a progressively increasing pattern of breathing over the subsequent minute. To make matters more difficult the two distinct patterns of SDB can overlap, and a significant proportion of HF patients can demonstrate a mixed pattern of SDB even over a single night. Indeed each type of apnoea can actually lead to the other. For a CSA patient the hypoxia that occurs during an apnoeic phase can lead to loss of upper airway tone and cause an obstruction that can precipitate an obstructive episode, and for a predominately OSA type patient the hyperventilation that follows an obstructive apnoea can reduce arterial CO_2 levels so low that reach a threshold that can trigger the classical oscillations of CSA in the minutes that follow. For these reasons, it is essential to perform formal sleep studies to diagnose which type of SDB the patient has, and in what proportions apnoeic events are of CSA and OSA type. This difference is made all the more urgent given the unexpected adverse results of the SERVE-HF trial that showed, in patients with HFrEF with predominately CSA-type sleep apnoea, positive pressure airway mask treatment significantly increased cardiovascular mortality.[6] The SERVE-HF trial randomized 1325 HFrEF patients with predominantly CSA (central AHI >15) to a form of positive pressure airway mask therapy called adaptive servo ventilation (ASV) or control. The primary endpoint (death, cardiac death equivalent, or HF hospitalization) did not differ, but there was a significant excess in total mortality [hazard ratio (HR) 1.28, 95% confidence interval (CI) 1.06–1.55; $P = 0.01$] and cardiac related mortality (HR 1.34, 95% CI 1.09–1.65; $P = 0.006$). This is despite ASV therapy improving the CSA sleep AHI averages.

Consequences of sleep-disordered breathing in heart failure

Each apnoeic episode is associated almost immediately with features that appear likely to be adverse for a patient with significant HF. These include hypoxaemia, reflex sympatho-excitation and vasoconstriction, sleep fragmentation, and increased intra-thoracic pressure swings that can increase transmural pressure gradients across the right and left ventricular walls. Although it is hard to be certain that the cumulative effects of these frequently repetitive adverse effects lead to poorer outcomes for the patient, it is quite conceivable that the combination of hypoxaemia with a surge in sympathetic drive may be a recipe for opportunistic ventricular arrhythmias or AF. What is known is that in HF both OSA and CSA are associated with worse outcomes, an increase in mortality and repeat hospitalizations.[7–9] These conditions also severely impact on patient quality of life. Both forms of SDB are associated with excessive daytime sleepiness, increased cognitive impairment, chronic fatigue, depression, and memory deficits.[10–12]

Monitoring of sleep-disordered breathing in heart failure

Although simplified wearable monitors have been developed to detect features associated with SDB they do not formally record all the physiological parameters needed to make an accurate diagnosis of the pattern and type of SDB.[13] As a result, these devices can be used to look for at-risk patients, but they cannot accurately differentiate between OSA and CSA. For this purpose, a formal sleep study in an accredited sleep laboratory is required. In their most recent update, the 2017 ACC/AHA/HFSA heart failure focused update on HF[14] makes three SDB-related recommendations:

- In patients with NYHA Class II–IV HF and suspicion of SDB or excessive daytime sleepiness, *a formal sleep assessment is reasonable* (*IIa, C-LD: recommendation reflects clinical necessity to distinguish obstructive versus central*).
- In patients with cardiovascular disease and *obstructive sleep apnoea, CPAP may be reasonable* to improve sleep quality and daytime sleepiness (*IIb, B-R: new data demonstrate the limited scope of benefit expected from CPAP for obstructive sleep apnoea*).
- In patients with NYHA Class II–IV HFrEF and *central sleep apnoea, adaptive servo-ventilation causes harm* (*III: Harm, B-R: new data demonstrate a signal of harm when adaptive servo-ventilation is used for central sleep apnoea)*.

The first is extremely important and it was echoed in the recent guidance paper published by the Heart Failure Association (HFA) of the ESC,[15] which recommended:

- Patients with HF and suspected sleep apnoea who are being considered for positive pressure airway mask therapy *are recommended* to undergo a *specialized sleep study* in order to diagnose the characteristics of the sleep apnoea present, in particular, whether the sleep apnoea is *predominantly obstructive or central in nature*.
- In patients with predominantly CSA and concomitant HFrEF, evidence is insufficient to recommend CSA therapy for any putative benefit in the HF itself, and treatments directed at the CSA should be reviewed and avoided, unless compelling symptomatic indications for treatment of the CSA exist, in which case *positive pressure airway mask therapy should be avoided* and *phrenic nerve stimulation may be considered* as an alternative.

With the high importance of distinguishing between OSA and CSA, given the different responses to treatment and the fact that the ASV form of positive pressure airway mask therapy is harmful for HFrEF patients with predominantly CSA, then a recommendation for monitoring the type of SDB any HFrEF patient has is considered important before anyone considers any therapy for their SDB. Continuous positive airway pressure (CPAP) remains an appropriate therapy for OSA in HF patients, as it has been shown to improve sleep quality, reduces the apnoea–hypopnea index (AHI), improve nocturnal oxygenation, and improve day-time sleepiness[16,17] even though it has a neutral effect on major clinical outcomes.[18] In patients with AF which frequently in seen HF, CPAP for OSA was associated with reduced progression of the AF.[19]

The diagnosis and treatment of obstructive sleep apnoea in heart failure

Sleep-disordered breathing should be considered and investigated in all HF patients given its high prevalence and significant clinical impact. Although considerable overlap can occur, physicians are advised to treat HF patients with SDB as OSA if the hypoxias are predominantly obstructive in nature and as CSA if the hypoxias are predominantly central in nature. Symptoms including nocturnal breathlessness, poor sleep, day-time sleepiness, excessive, nocturia, morning headaches, and diminished concentration and memory should be triggers for further investigation.[20] Questioning the sleep partner may also be of value. An initial accurate diagnosis is required, usually requiring polysomnography (PSG) in a sleep laboratory. Portable or home monitors are insufficiently detailed for an accurate diagnosis. A diagnosis of OSA can be made if PSG shows at least five obstructive-type hypoxaemic episodes per hour of sleep, i.e. an AHI of five or more (or more than 15 in the absence of sleep-related symptoms), and only if the obstructive type predominates.[21]

The main therapeutic option for OSA is a positive airway pressure mask which requires considerable patient engagement if it is to be used successfully.[22] For this reason, the purpose and likely gains from therapy should be discussed with the patient and the sleep partner. Normally a treatment recommendation is to reduce the AHI load to less than 15/h in order to relieve SDB-related symptoms. Compliance with mask therapies may be poor if they are not well explained and if the purpose of therapy is not clearly understood. The main types of positive pressure therapies for OSA are continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP), and BiPAP-ASV in which the two pressures change according to an algorithm with the aim of evening-out the ventilatory patterns. Positive pressure airway therapy should be combined with lifestyle changes, such as weight loss in the obese, regular exercise, and the avoidance of excess alcohol or sleeping medication. Oral devices that push the mandible forward or specially designed mouth guards can sometimes assist to a limited extent. Upper airway reconstructive surgery may be tried in severe cases unresponsive to, or intolerant of, mask therapy, and recently an implantable device to stimulate the glosso-pharyngeal nerve has been approved in the USA to treat OSA, but experience in HF patients remains very limited.[23]

The diagnosis and treatment of central sleep apnoea in heart failure

A formal sleep study is required to accurately diagnose CSA in a HF patient. A clue to nocturnal CSA especially of the CSR type is when similar episodes occur when quietly resting during the day. This is called periodic breathing.[24] Before the SERVE-HF reported ASV type masks were recommended to treat CSA, after an early trial (CANPAP) reported sleep benefits with a neutral effect on major outcomes.[17] In this trial, CPAP improved both the number of apnoeic events per hour (40–19) and left ventricular ejection fraction. Following the SERVE-HF trial, ASV became contraindicated in HFrEF patients with predominant CSA. The reasons for the adverse effects are not known[25] but may involve adverse consequences on right ventricular function of positive intrathoracic pressures.[26–28] Other treatments that have been tried include oxygen therapy, acetazolamide, and theophylline, but these have not been shown to be safe or particularly effective. Given that positive pressure airway masks are contraindicated in HFrEF with CSA,[29] an alternative is needed in patients suffering impaired quality of life and sleep symptoms from CSA as confirmed in a formal sleep study.[30] The development of a novel implantable phrenic nerve stimulator device that improves sleep apnoea metrics and improves quality of life and SDB-related symptoms[31,32] gives an alternative that the HFA guidance statement says may be considered for HFrEF patients to treat CSA-related symptoms and improve quality of life. This device, the remede® System, stimulates the phrenic nerve at night during sleeping hours during periods of apnoea. The primary endpoint of its pivotal trial the proportion of patients having a $\geq$50% reduction in AHI events was easily and significantly met, along with all the major sleep respiratory metrics (AHI, central apnoeas, oxygenation, arousals and % of time in REM sleep) as well as patient-reported outcomes (Patient Global Assessment and Epworth Sleepiness Scale). A subsequent report on the patients with a diagnosis of HF at baseline ($n = 96$) showed that both sleep metrics and quality of life measures

improved over 6 and 12 months (Minnesota Living with Heart Failure Questionnaire, MLHFQ scores changing by -6.8 ± 20.0, $p = 0.005$).[33] The 6-month rate of HF hospitalization was 4.7% in treated HF patients compared to 17.0% in the control group. Larger scale trials will be needed to determine the effects of this device on major clinical outcomes, but at present, it is the preferred treatment option to relieve CSA-related symptoms in HFrEF patients.

Conflict of interest: Professor Coats declares having received honoraria and/or lecture fees from Astra Zeneca, Bayer, Menarini, Novartis, Nutricia, Servier, Vifor, Actimed, Cardiac Dimensions, CVRx, Enopace, Faraday, Gore, Respicardia, Stealth Peptides, V-Wave.

References

1. 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.
2. MacDonald M, Fang J, Pittman SD, White DP, Malhotra A. The current prevalence of sleep disordered breathing in congestive heart failure patients treated with beta- blockers. *J Clin Sleep Med* 2008;**4**:38–42.
3. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. *Eur J Heart Fail* 2007;**9**:251–257.
4. Javaheri S, Dempsey JA. Central sleep apnea. *Compr Physiol* 2013;**3**: 141–163.
5. Dempsey JA. Crossing the apnoeic threshold: causes and consequences. *Exp Physiol* 2005;**90**:13–24.
6. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho M-P, 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**:1095–1105.
7. Khayat R, Jarjoura D, Porter K, Sow A, Wannemacher J, Dohar R, Pleister A, Abraham WT. Sleep disordered breathing and post-discharge mortality in patients with acute heart failure. *Eur Heart J* 2015;**36**:1463–1469.
8. Brenner S, Angermann C, Jany B, Ertl G, Störk S. Sleep-disordered breathing and heart failure;a dangerous liaison. *Trends Cardiovasc Med* 2008;**18**:240–247.
9. 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**: 2028–2034.
10. Bekfani T, Abraham WT. Current and future developments in the field of central sleep apnoea. *Europace* 2016;**18**:1123–1124.
11. Coman AC, Borzan C, Vesa CS, Todea DA. Obstructive sleep apnea syndrome and the quality of life. *Clujul Med* 2016;**89**:390–395.
12. Flemons WW, Tsai W. Quality of life consequences of sleep-disordered breathing. *J Allergy Clin Immunol* 1997;**99**:S750–S756.
13. McDonald K, O'Hanlon R, Savage HO, Khushaba RN, Colefax M, Farrugia S, Javed F, Schindhelm K, Wilcox I, Cowie MR. Sleep-disordered breathing in chronic heart failure is highly variable when measured remotely using a novel non-contact biomotion sensor. *Eur J Heart Fail* 2017;**19**:688–690.
14. Yancy CW, Jessup M, Bozkurt B. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017;**136**:e137–e161.
15. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, Boer RA, Drexel H, Ben Gal T, Hill L, Jaarsma T, Jankowska EA, Anker MS, Lainscak M, Lewis BS, McDonagh T, Metra M, Milicic D, Mullens W, Piepoli MF, Rosano G, Ruschitzka F, Volterrani M, Voors AA, Filippatos G, Coats AJS. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:1169.
16. Arzt M, Floras JS, Logan AG. 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**:3173–3180.
17. Bradley TD, Logan AG, Kimoff RJ, Sériès F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Tomlinson G, Floras JS. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med* 2005;**353**:2025–2033.
18. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, Chen G, Du B, McArdle N, Mukherjee S, Tripathi M, Billot L, Li Q, Lorenzi-Filho G, Barbe F, Redline S, Wang J, Arima H, Neal B, White DP, Grunstein RR, Zhong N, Anderson CS. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016;**375**:919–931.
19. Holmqvist F, Guan N, Zhu Z, Kowey PR, Allen LA, Fonarow GC, Hylek EM, Mahaffey KW, Freeman JV, Chang P, Holmes DN, Peterson ED, Piccini JP, Gersh BJ. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation-Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J* 2015;**169**:647–654.
20. American Academy of Sleep Medicine. *International Classification of Sleep Disorders: Diagnostic and Coding Manual*. 2nd ed. Westchester, IL: American Academy of Sleep Medicine, 2005.
21. Epstein LJ, Kristo D, Strollo PJ Jr, et al.; Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009;**5**:263–276.
22. Stewart Coats AJ, Rosano GM, Lopatin YM. The management of comorbidities in patients with heart failure—obstructive sleep apnoea. *Int Cardiovasc Forum J* 2017;**10**:75–76.
23. Withrow K, Evans S, Harwick J, Kezirian E, Strollo P. Upper airway stimulation response in older adults with moderate to severe obstructive sleep apnea. *Otolaryngol Head Neck Surg* 2019;**161**:714–719.
24. La Rovere MT, Maestri R, Robbi E, Caporotondi A, Guazzotti G, Traversi E, Pinna GD. Daytime periodic breathing during short-term laboratory recordings in heart failure patients: the iceberg tip of central sleep apnoea? *Eur J Heart Fail* 2018;**20**:934–936.
25. Cowie MR, Woehrle H, Wegscheider K, Vettorazzi E, Lezius S, Koenig W, Weidemann F, Smith G, Angermann C, d'Ortho MP, Erdmann E, Levy P, Simonds AK, Somers VK, Zannad F, Teschler H. Adaptive servo-ventilation for central sleep apnoea in systolic heart failure: results of the major substudy of SERVE-HF. *Eur J Heart Fail* 2018;**20**:536–544.
26. Abraham WT, Pleister A, Germany R. Identification and treatment of central sleep apnoea: beyond SERVE-HF. *Card Fail Rev* 2018;**4**:1–53.
27. Cowie MR, Gallagher AM, Simonds AK. Treating central sleep apnoea in heart failure: is pull better than push? *Eur J Heart Fail* 2018;**20**:1755–1759.
28. Ramalho SHR, Shah AM. Central sleep apnoea in heart failure with reduced ejection fraction, adaptive servo-ventilation, and left ventricular ejection fraction: the (still) missing link. *Eur J Heart Fail* 2018;**20**:545–547.
29. Stewart Coats AJ, Shewan LG, Abraham WT. The management of comorbidities in patients with heart failure—central sleep apnoea. *Int Cardiovasc Forum J* 2015;**2**:2.
30. Valika A, Costanzo MR. Sleep-disordered breathing during congestive heart failure: to intervene or not to intervene? *Card Fail Rev* 2017;**3**: 134–139.
31. Costanzo MR, Ponikowski P, Javaheri S, Augostini R, Goldberg L, Holcomb R, Kao A, Khayat RN, Oldenburg O, Stellbrink C, Abraham WT; remedé System Pivotal Trial Study Group. Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial. *Lancet* 2016;**388**:974–982.
32. Fox H, Oldenburg O, Javaheri S, Ponikowski P, Augostini R, Goldberg LR, Stellbrink C, Mckane S, Meyer TE, Abraham WT, Costanzo MR. Long-term efficacy and safety of phrenic nerve stimulation for the treatment of central sleep apnea. *Sleep* 2019;**42**:zsz158.
33. Costanzo MR, Ponikowski P, Coats A, Javaheri S, Augostini R, Goldberg LR, Holcomb R, Kao A, Khayat RN, Oldenburg O, Stellbrink C, McKane S, Abraham WT. Phrenic nerve stimulation to treat patients with central sleep apnoea and heart failure. *Eur J Heart Fail* 2018;**20**:1746–1754.