Current Heart Failure Reports (2018) 15:123–130
https://doi.org/10.1007/s11897-018-0387-7

PHARMACOLOGIC THERAPY (W.H.W. TANG, SECTION EDITOR)

Management of Sleep Disordered Breathing in Patients with Heart Failure

Connor P. Oates[1] · Manjula Ananthram[1] · Stephen S. Gottlieb[1]

Published online: 3 April 2018

Abstract

Purpose of Review This paper reviews treatment options for sleep disordered breathing (SDB) in patients with heart failure. We sought to identify therapies for SDB with the best evidence for long-term use in patients with heart failure and to minimize uncertainties in clinical practice by examining frequently discussed questions: what is the role of continuous positive airway pressure (CPAP) in patients with heart failure? Is adaptive servo-ventilation (ASV) safe in patients with heart failure? To what extent is SDB a modifiable risk factor?

Recent Findings Consistent evidence has demonstrated that the development of SDB in patients with heart failure is a poor prognostic indicator and a risk factor for cardiovascular mortality. However, despite numerous available interventions for obstructive sleep apnea and central sleep apnea, it remains unclear what effect these therapies have on patients with heart failure. To date, all major randomized clinical trials have failed to demonstrate a survival benefit with SDB therapy and one major study investigating the use of adaptive servo-ventilation demonstrated harm.

Summary Significant questions persist regarding the management of SDB in patients with heart failure. Until appropriately powered trials identify a treatment modality that increases cardiovascular survival in patients with SDB and heart failure, a patient's heart failure management should remain the priority of medical care.

Keywords Heart failure · Treatment of sleep disordered breathing · Obstructive sleep apnea · Central sleep apnea · ASV

Introduction

Sleep disordered breathing (SDB) describes a disrupted sleep pattern characterized by pauses in breathing associated with hypoxemia and sympathetic arousals. SDB is defined by the number of total apneas and hypopneas per hour of sleep, known as the apnea hypopnea index (AHI). Many studies define SDB as an AHI ≥ 15 per hour of sleep, although > 5 is considered abnormal. Observational studies estimate the prevalence of SDB among patients with heart failure to be 50–80%, making SDB a primary comorbidity of patients with heart failure. Using a two-channel respiratory monitor, the SchlaHF registry of patients with heart failure with reduced ejection fraction (HFrEF) claimed a 58% prevalence of SDB within their large cohort of 6876 subjects [1•]. Importantly, SDB in patients with HFrEF is a robust predictor of mortality [2, 3].

SDB is traditionally classified as obstructive sleep apnea (OSA), or central sleep apnea (CSA). Recent data demonstrate that a majority of SDB in patients with heart failure is the result of coexisting OSA and CSA, or complex sleep apnea syndrome. In a subgroup of the SchlaHF registry, OSA-CSA was found in 40% of SDB in patients with HFrEF who were given polysomnography [1•]. Mixed OSA-CSA was defined as a proportion of central apneas/hypopneas in relation to total apneas/hypopneas > 20% but less than 80%. It has been suggested that patients with heart failure oscillate between OSA and CSA based on fluid shifts, circulation time, and $PaCO_2$ [4, 5]. The need for additional classification SDB further complicates interpretation of previously published trials and choice of management.

There are a variety of methods to treat SDB, but limited data supporting the long-term benefits of using any one modality in patients with heart failure. This article will review the treatment options for SDB and discuss the impact of intervention on patients with heart failure.

This article is part of the Topical Collection on *Pharmacologic Therapy*

✉ Stephen S. Gottlieb
sgottlie@medicine.umaryland.edu

[1] School of Medicine, University of Maryland, Baltimore, MD, USA

OSA

OSA is caused by repeated episodes of upper airway collapse due to loss of pharyngeal muscle tone. Heart failure may also contribute to OSA by redistribution of fluid to the upper airway [6]. Each airway collapse triggers an episode of hypoxia that results in arousal from sleep. Male sex, aging, and obesity are all strongly associated with OSA. OSA is relatively common, affecting an estimated 15% of the general population and 30–35% of patients with heart failure [7]. After testing 2365 subjects with SDB with polysomnography, OSA comprised 29% of SDB in patients with HFrEF in the SchlaHF registry [1•].

In patients with OSA, physiologic changes in intrathoracic pressure and sympathetic drive could have a direct impact on the progression of cardiovascular disease. After collapse of a patient's airway, continued respiratory efforts generate a large negative intrathoracic pressure. The resulting extracardiac and intracardiac pressure gradient increases transmural wall stress that could contribute to long-term remodeling of the myocardium. Increased transmural wall stress also results in increased afterload. Changes in negative intrathoracic pressure also results in reduced preload. Increased afterload and reduced preload in patients with OSA could decrease stroke volume and cardiac output. Patients with OSA compensate for apneic events with sympathetic surges. Repeated sympathetic surges increase a patient's baseline sympathetic tone and increase systemic vascular resistance over time [8].

OSA is an independent risk factor for a number of cardiovascular diseases including hypertension, cardiac arrhythmias, and heart failure. In patients with HFrEF, untreated OSA is associated with significant mortality compared to patients with mild or no OSA (8.7 vs 4.2 deaths per 100 patient years) [9]. OSA is also associated with increased 90-day readmission in patients with heart failure [10].

Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) is the standard of care for patients with obstructive sleep apnea. The ACC/AHA/HFSA 2017 guidelines recommend the use of CPAP in patients with cardiovascular disease and OSA to improve sleep quality and daytime sleepiness (a IIB recommendation) [11•]. Note that this recommendation is for the direct symptoms caused by sleep apnea and not for the improvement of the heart failure.

Nevertheless, there are small studies suggesting that treatment with CPAP may help cardiac function and symptoms as well. In an observational study, Kasai and colleagues studied a group of 88 patients with moderate to severe obstructive sleep apnea and CHF with ejection fraction less than 50%. Analysis revealed a significantly higher rate of hospitalization and death in the control group compared with the group treated with CPAP. When compliance with CPAP was taken into account, it was noted that prognosis was better in the compliant group (CPAP use average 6 h per night), when compared to the non-compliant group (average CPAP use 3.5 h/night) [12]. CPAP compliance in patients with HFrEF has also been associated with increase in left ventricular ejection fraction (LVEF) and reduction in mortality/cardiac transplantation rate [13]. These studies are limited by then lack of control for other factors which might impact outcomes.

Controlled data are inconclusive regarding cardiovascular outcomes of CPAP for treatment of OSA. For example, CPAP use in patients with HFrEF significantly improves blood pressure [14] and LVEF [15]. There are also effects on myocardial energetics which might be beneficial in the long run [16]. In contrast, the Sleep Apnea Cardiovascular Endpoints (SAVE) trial, the largest prospective randomized trial investigating the role of CPAP as secondary prevention in patients with coronary artery disease and/or cerebrovascular disease, failed to show significant improvement in cardiovascular outcomes. This was true despite significant suppression of AHI [17•]. SAVE excluded patients with heart failure. Cardiovascular outcomes were also not significantly decreased in the RICCADSA trial, although, as with other studies, compliant patients showed improvement [18•].

There are other interventions for obstructive sleep apnea (e.g., surgery, devices) which will not be discussed here as there are no data for their use in patients with heart failure.

CSA

CSA is characterized by a temporary loss of central respiratory drive and thoracoabdominal excursion. A common comorbidity of heart failure, CSA, is estimated to occur in 30–50% of patients with HFrEF and 18–30% of patients with heart failure with preserved ejection fraction (HFpEF) [7]. SchlaHF found that CSA comprised 31% of SDB in patients with HFrEF. In comparison with patients with OSA, patients with CSA are older, more likely to have atrial fibrillation, and have worse LVEF [1].

CSA can be caused by any form of respiratory suppression, but, in patients with decompensated heart failure, CSA tends to occur in a distinctive breathing pattern called Cheyne-Stokes respirations (CSR). In this oscillating pattern of respirations, $PaCO_2$ greater than the central threshold triggers a rapid increase in respirations. Hyperventilation then drives the $PaCO_2$ below the central threshold and leads to a decrease in respiration rate to the point of apnea. Decreased respiration in the setting of underlying heart failure pathophysiology (i.e., low cardiac output, pulmonary vascular congestion, sensitized peripheral chemoreceptors, rostral fluid shifts) perpetuates the pattern by gradually increasing $PaCO_2$ [8, 19].

CSA is intertwined with the pathophysiology of heart failure. Cycles of hypercapnia, tachypnea, arousal, and apnea generate oscillating stimulation of the sympathetic nervous system. The consequences of sympathetic upregulation include tachycardia, increased systemic vascular resistance, and sodium retention. The occurrence and severity of CSA is directly associated with severity of heart failure [20]. In patients with HFrEF, CSA is an independent predictor of cardiac death [21, 22]. CSA in patients with HFrEF is also an independent predictor of cardiac readmission within 6 months [23•]. In a recent study, CSA was prevalent throughout the day and associated with worse prognosis, neurohormonal activation, and arrhythmias [24].

Treat the Heart Failure

The treatment of heart failure itself often improves the prevalence of central sleep apnea. For example, cardiac resynchronization therapy has a beneficial effect on central sleep apnea in patients with chronic heart failure as evidenced by an improvement in the AHI index [25] and attenuation of hypoxia [26]. Similarly, LVAD implantation and cardiac transplantation can decrease the frequency of central sleep apnea [27].

The concept of using cardiac resynchronization therapy (CRT) to treat SDB was first introduced in 2002 by Garrugue et al [28]. Since then, multiple studies have associated CRT with significant decrease in AHI in patients with HFrEF and CSA [26, 29, 30]. The effects of CRT on SBD are likely multifactorial. CRT has been shown to increase LVEF in patients with heart failure. Improved cardiac function decreases pulmonary-vascular congestion while improving systemic oxygenation and increasing the threshold for chemoreceptor-driven apneas. Congruent with this theory, the beneficial effects of CRT are limited to CSA and have not been shown to apply to patients with OSA. A recent meta-analysis found CRT to be associated with a significant reduction in AHI in 133 subjects with CSA, but did not identify a statistically significant reduction in 81 subjects with OSA [31]. Most likely, these findings are related to the improvement in HF with CRT, and any treatment to improve HF should decrease the incidence of CSA.

Metabolic Treatment

Because of the possible metabolic causes of CSA, acetazolamide has been studied as a possible treatment. In small trials, it has been found to be associated with a decrease in AHI, improved O_2 saturation, and patient-perceived improvement in sleep quality [32, 33]. As with any intervention, proof of safety is needed. It is possible that CSR could be beneficial, protecting against metabolic acidosis seen in heart failure. Hence, an attempt to abolish it could theoretically have deleterious consequences in patients with systolic heart failure [34]. If CSR is a protective mechanism, interventions to suppress CSR could potentially be harmful.

Oxygen Therapy

Nocturnal supplemental oxygen is believed to increase the physiologic apneic threshold and has long been known to decrease CSA [35]. Supplemental oxygen has been shown to decrease periodic breathing and sympathetic compensation characteristic of CSA while significantly improving nocturnal oxygenation and normalizing $PaCO_2$ [36]. However, the effects of nocturnal supplemental oxygen in patients with heart failure are less certain. Toyama et al. demonstrated that nocturnal home oxygen therapy in patients with HFrEF and CSA significantly improved LVEF as well as decreased AHI [37]. In a small study, oxygen decreased sympathetic nerve activity and AHI in subjects with CSA, but did not change ejection fraction or quality of life. It had no effect on OSA [38•].

One analysis (CHF-HOT) of 97 randomized (but not blinded) patients found decreased AHI, improved NYHA class, and a trend towards improved ejection fraction. In a post hoc analysis of a subset of CHF-HOT patients, it was noted that nocturnal oxygen therapy was effective in suppressing ventricular ectopy only in a subgroup of patients with severe heart failure and severe SDB [39].

Nocturnal hypoxemia is a predictor of worse outcomes and increased mortality in chronic stable HFpEF patients [40•]. Whether oxygen therapy improves outcomes is unknown. In a review of 17 studies addressing the issue of nocturnal oxygen therapy in patients with heart failure and sleep apnea, there was a consistent decrease in AHI in patients with CSA (but not OSA) and a decrease in time spent with hypoxemia [41]. However, improvement in ejection fraction was rarely seen and even the effect on sympathetic activity and arrhythmias was inconsistent.

However, based on many large studies of oxygen supplementation in patients with acute coronary syndrome, there is real concern of hyperoxemia inducing systemic vasoconstriction and inflammation secondary to reactive oxygen species [42]. The use of O_2 in patients with non-acute heart failure is associated with decreased cardiac output and increased systemic vascular resistance [37, 43]. These data are in contrast to animal evidence suggesting that intermittent hypoxia might be beneficial in heart failure [44].

To date, no trial powered for mortality has investigated the long-term use of supplemental oxygen in patients with heart failure and CSA. Should a definitive association be found between positive pressure ventilation and increased cardiovascular mortality in patients with heart failure, supplemental oxygen is a readily available, non-invasive therapy that merits further investigation.

CPAP

It is unclear what effect CPAP has on patients with CSA and heart failure. The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP) trial randomized subjects with HFrEF and sleep disordered breathing to either CPAP plus standard care or standard of care alone. CANPAP showed no significant difference in the rate of composite death and heart transplantation [45]. These disappointing results were despite improved surrogate heart failure measures, including a reduction in norepinephrine levels, improved LVEF, and increased 6-min walk. A post hoc analysis of the CANPAP trial found that subjects who achieved the set therapeutic goal of < 15 AHI per hour had a significantly greater increase in LVEF and transplant-free survival compared to subjects who did not achieve therapeutic suppression of AHI (9 vs 30% event rate) [46]. This post hoc analysis suggested that compliance was a major confounding factor in the results of CANPAP, but its findings are only hypothesis generating. The limited power of CANPAP makes the results inconclusive.

Adaptive Servo-Ventilation

Adaptive servo-ventilation (ASV) is a non-invasive ventilator that delivers servo-controlled inspiratory pressure on top of continuous expiratory positive airway pressure. ASV adjusts its pressure support breath-to-breath based on changes in the user's ventilation. It was hoped to be superior for treating patients with central sleep apnea [47]. ASV has also demonstrated superior efficacy in treating the apnea of patients with complex sleep apnea syndrome when directly compared with CPAP (89.7 vs 64.5%, AHI < 10 at 90 days) [48].

However, the frequency of apneas is only a surrogate endpoint, and the consequences on mortality, heart failure, or other symptoms could be different. Despite benefits seen on apnea frequency, there is now convincing evidence that the use of ASV (of at least some types) to treat CSA in patients with HFrEF is harmful. The SERVE-HF (Treatment of Sleep Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure) trial investigated the effects of adaptive servo-ventilation in patients with heart failure with reduced ejection fraction (LVEF < 45%) and a predominance of central sleep apnea. Contrary to expectations, all-cause mortality (HR 1.28, $p = 0.01$) and cardiovascular mortality (HR 1.34, $p = 0.006$) were higher compared to the control group. There was no significant effect of ASV on the composite endpoint of death from any cause [49•]. The results of SERVE_HF were surprising in light of studies demonstrating ASV to be superior to CPAP at treating central apneas like those associated with heart failure [50]. Indeed, ASV effectively treated sleep apnea as evidenced by a decrease in the mean AHI to 6.6 events per hour and decrease in the oxygenation and the oxygen desaturation index to 8.6 events per hour. Similarly, the decrease in the Epworth Sleepiness Scale score was greater in the ASV group than the control group.

The reasons for the adverse effects on mortality are not known, but studies have tried to analyze the findings to detect plausible hypotheses. Analysis of the SERVE-HF treatment population associated ASV use with increased risk of cardiovascular death without previous hospital admission (HR 2.59) and cardiovascular death after a life-saving event (HR 1.57) [51•]. These findings suggest that patients with HFrEF and CSA treated with ASV were at increased risk of sudden death from cardiac events.

There are several theories to explain why SERVE-HF demonstrated increased all-cause mortality and cardiovascular mortality, especially sudden death. Perhaps it was related to the device used. The ASV used in SERVE-HF has a fixed expiratory positive airway pressure (EPAP). Low fixed EPAP with concurrent whole-face mask use can enhance rebreathing of CO_2 [52]. Resulting alkalosis could place patients with HFrEF at risk for increased arrhythmias and sudden death.

It has been suggested that compliance played a major role in patient outcomes in SERVE-HF. Mean nightly ASV use was only 3.7 h per night. This is similar compared to usage of intervention in CANPAP after 1 year (3.6 h per night after 1 year). Nearly 29% of patients randomized to the ASV arm dropped out of the study, while 16% of the control patients complicated intention-to-treat analysis by starting ASV use during the trial. This might explain inadequate power to detect benefit, but should not explain harm.

Another hypothesis is based on recent evidence that patients with heart failure and SDB tend to oscillate between CSA and OSA [1]. If SDB should be subdivided beyond OSA and CSA in patients with HFrEF to incorporate complex sleep apnea syndrome, it is uncertain whether particular phenotypes of SDB, perhaps those with exclusively central apneas, are more likely to benefit from ASV. This is a particularly relevant discussion since the ASV used in SERVE-HF provided fixed EPAP that could be inadequate to treat some OSA [52].

Lastly, some have even suggested that the classical understanding Cheyne-Stokes physiology is incorrect and CSR might be adaptive for patients with heart failure [53]. Though this theory sparks interesting discussion, it runs counter-current to decades of observational findings and is not supported by the surrogate endpoints and post hoc analyses of CANPAP [46].

Perhaps increased intrathoracic pressure caused by ASV decreases venous return while increasing pulmonary vascular resistance and right ventricular afterload. Subgroup analysis of SERVE-HF demonstrated that the incidence of the primary endpoint and cardiovascular mortality occurs significantly more often in subjects with LVEF < 30% compared to subjects with LVEF > 30, suggesting that negative effects occur only in

the most severely ill patients. Similarly, the incidence of the primary endpoint and cardiovascular mortality were positively associated with the frequency of CSR [50]. Both decreased LVEF and presence of CSR are signs of decompensated heart failure and would indicate patients more susceptible to negative hemodynamic effects of ASV. A similar argument can be made for patients with heart failure treated with excessive positive airway pressure from CPAP and might be appreciated in subjects with more decompensated heart failure. Subjects classified NYHA class III/IV comprised 70% of SERVE-HF compared to only 34% of CANPAP. It is therefore important to adequately test the impact of CPAP in patients with severe heart failure.

ADVENT-HF is an ongoing trial designed to assess effects of treating sleep disordered breathing with adaptive servo-ventilation in patients with heart failure with reduced ejection fraction [54•]. In this study, the ASV device employs peak flow to trigger pressure support, whereas minute volume of ventilation was used to trigger pressure support in the SERVE-HF trial. The ASV device default settings used in SERVE-HF were relatively high compared to the settings used in ADVENT-HF. This trial should help clarify whether the results of SERVE-HF are related to the type of device or treatment algorithms used in the ASV device, or if it is an adverse effect of positive airway therapy on cardiac function.

HFpEF

The findings of the SERVE-HF study resulted in the early termination of another trial randomizing subjects with acute decompensated HFrEF or HFpEF and SDB to ASV or standard of care (CAT-HF trial) [55•]. Analysis of the premature data revealed no significant difference in mortality, rate of hospitalization due to cardiovascular disease, and/or change in 6-min walk test. The study did identify a decrease in composite outcomes in subjects randomized to use ASV within a small subset of subjects with HFpEF. Such a result from a subgroup analysis would need to be supported by an adequately powered trial.

Studies had previously shown that ASV use in patients with HFpEF is associated with a significant decrease in AHI, improved measures of diastolic function, and significant reduction in the subjective NYHA class [56, 57]. More recently, Heider et al. confirmed that ASV therapy significantly reduces AHI and arousal frequency in patients with CSA and HFpEF [58]. The results of previous studies and data from the CAT-HF trial suggest that treatment of SDB with ASV in patients with HFpEF is worthy of further investigation.

Phrenic Nerve Stimulation

Zhang et al. first demonstrated the safety and efficacy of phrenic nerve stimulation to treat SDB in patients with HFrEF [59]. The fully automated Remedē® System directly stimulates the phrenic nerve via a transvenous stimulation. It has complex software to ensure that the stimulation only occurs when the patient is sleeping, as stimulation while awake is not tolerated. Careful and knowledgeable adjustment of the parameters is essential. Initial feasibility studies showed a 55% reduction in AHI in patients with CSA and heart failure after 3 months of therapy with a phrenic nerve stimulator (22.4 ± 13.6 episodes vs 49.5 ± 14.6) [60]. Follow-up data after 12 months demonstrated sustained reductions in mean AHI and improved quality of life measures without serious adverse events [61]. A small case series reports continued efficacy in limiting AHI and oxygen desaturation after 4 years [62]. A prospective randomized controlled trial found that this phrenic stimulation in patients with CSA significantly decreased incidence of AHI, oxygen desaturations, and arousals compared to standard of care [63•]. Based on these data, the FDA approved the use of the Remedē® System for treatment of moderate to severe CSA in October of 2017. These exciting findings are tempered by the fact that 64% of subjects had a history of heart failure and a mere 39% of the subjects would have met criteria for the SERVE-HF trial.

More importantly, no study has been powered to investigate cardiovascular mortality in patients with heart failure and CSA treated with diaphragmatic stimulators. Following the failure of CANPAP and SERVE-HF to produce positive mortality outcomes even with positive effects on surrogate endpoints, additional investigation is needed. Direct phrenic nerve stimulation directly addresses several concerns about CPAP or ASV intervention. Facemask compliance is not an issue, and the effect of excessive positive airway pressure on hemodynamics is not a concern. Nevertheless, the cause of the failure of ASV is not known, making evaluation of mortality endpoints essential in future studies.

Carotid Body Ablation

Direct augmentation of the body's chemoreceptors through carotid body ablation has been proposed as an invasive method of treating SDB in patients with heart failure. The carotid body is the body's primary chemoreceptor that modulates reflex cardiorespiratory responses in response to changes in PaO_2, $PaCO_2$, pH, and arterial blood flow [64•]. In patients with heart failure, the carotid bodies become acutely responsive to a low flow state, driving increased sympathetic response and contributing to the physiological response of SDB.

In rat models of HFrEF, denervation of the carotid bodies normalized measures of sympathetic tone, reduced the

number of apneic events (8.0 ± 1.4 vs 16.8 ± 1.8 events), and increased 16-week survival by nearly 90% [65, 66]. No human trials have investigated carotid body ablation as an intervention for SDB in heart failure and several obstacles exist to the therapy. The upper threshold for inhibition of the sympathetic reflex in patients with heart failure is not well established. There are also anatomical complexities to the procedure that might limit its application to specific subsets of patients, such as individuals without significant atherosclerotic lesions [67].

Conclusions

Despite the high prevalence of SDB among patients with heart failure, testing for SDB is not routine in patients with heart failure, partly because the optimal management in these patients is complex and uncertain. Consistent evidence has demonstrated that the development of SDB in patients with heart failure is poor prognostic indicator and a risk factor for cardiovascular mortality. However, no major randomized trial (CANPAP, SERVE-HF, CAT-HF, SAVE) has demonstrated a survival benefit with SDB therapy. These studies have made clear that we do not know the cardiovascular consequences of treatment.

The existing literature thus leaves physicians with uncertainty in the clinical arena, but certain conclusions are clear. In patients with heart failure and OSA, the use of CPAP is recommended to improve daytime sleepiness and sleep quality. It is also clear that ASV should not be used in patients with CSA and heart failure unless they are participants in a study. The potential long-term benefits of phrenic nerve stimulation are exciting, but benefit needs to be proven. We do know that lifestyle measures such as weight loss should be encouraged. Avoidance of alcohol and respiratory depressants such as sedatives and narcotics can be helpful. In patients with sleep disordered breathing in the supine position, changing to the lateral sleeping position has been shown to decrease the severity of sleep apnea, more so in obstructive sleep apnea than with central sleep apnea [68•].

In all patients with heart failure who exhibit SDB, the patient's heart failure management should be the priority. It is tempting to treat SDB as a readily modifiable risk factor in patients with heart failure, but seeking improvement in surrogate markers of heart failure is not the same as treating heart failure itself.

Compliance with Ethical Standards

Conflict of Interest Manjula Ananthram and Connor P. Oates declare no conflicts of interest. Stephen S. Gottlieb reports grants from Respicardia and grants from Resmed, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance

1.• Arzt M, Oldernburg O, Graml A, Erdmann E, Teschler H, Wegscheider K, et al. Phenotyping of sleep-disordered breathing in patients with chronic heart failure with reduced ejection fraction—the SchlaHF registry. J Am Heart Assoc. 2017;6:e005899. **Important description of the epidemiology of sleep apnea in heart failure patients.**
2. Oldernburg O, Wellmann B, Buchholz A, Bitter T, Fox H, Thiem U, et al. Nocturnal hypoxaemia is associated with increased mortality in stable heart failure patients. Eur Heart J. 2016;37:1695–703.
3. Damy T, Margarit L, Noroc A, Bodez D, Guendouz S, Boyer L, et al. Prognostic impact of sleep-disordered breathing and its treatment with nocturnal ventilation for chronic heart failure. Eur J Heart Fail. 2012;14:1009–19.
4. Tkacova R, Niroumand M, Lorenzi-Filho G, Bradley TD. Overnight shift from obstructive to central apneas in patients with heart failure: role of PCO_2 and circulatory delay. Circulation. 2001;103:238–43.
5. Ryan CM, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, et al. Shift in sleep apnoea type in heart failure patients in the CANPAP trial. Eur Respir J. 2010;35:592–7.
6. White LH, Bradley TD. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnoea. J Physiol. 2013;591:1179–93.
7. Khayat R, Small R, Rathman L, Krueger S, Gocke B, Clark L, et al. Sleep disordered breathing in heart failure: identifying and treating an important but often unrecognized comorbidity in heart failure patients. J Card Fail. 2013;19:431–44.
8. Bradley TD, Floras JS. Sleep apnea and heart failure: obstructive sleep apnea. Circulation. 2003;107:1671–8.
9. Wang H, Parker JD, Newton GE, Floras JS, Mak S, Chiu KL, et al. Influence of obstructive sleep apnea in patients with heart failure. J Am Coll Cardiol. 2007;49(15):1625–31.
10. Sommerfeld A, Althouse AD, Prince J, Prince J, Atwood CW, Mulukutla SR, et al. Obstructive sleep apnea is associated with increased readmission in heart failure patients. Clin Cardiol. 2017;40:873–8.
11.• Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the Management of Heart Failure. J Card Fail 2017; 23 (8): 628–651. **Important consensus document recommending therapy for heart failure.**
12. Kasai T, Narui K, Dohi T, Yanagisawa N, Ishiwata S, Ohno M, et al. Prognosis of patients with heart failure and obstructive sleep apnea treated with continuous positive airway pressure. Chest. 2008;133(3):690–6.
13. 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.
14. Gottlieb DJ, Punjabi NM, Mehra R, Patel SR, Quan SF, Babineau DC, et al. CPAP versus oxygen in obstructive sleep apnea. N Engl J Med. 2014;370:2276–85.
15. Kaneko Y, Floras JS, Usui K, Plante J, Tkacova R, Kubo T, 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.
16. Yoshinaga K, Burwash IG, Leech JA, Haddad H, Johnson CB, deKemp RA, et al. The effects of continuous positive airway pressure on myocardial energetics in patients with heart failure and obstructive sleep apnea. J Am Coll Cardiol. 2007;49:450–8.
17.• McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med. 2016;375:919–31. **In a large well controlled study, therapy with CPAP did not prevent cardiovascular events.**
18.• Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea; the RICCADSA randomized controlled trial. Am J Respir Crit Care Med. 2016;194:613–20. **Further evidence that treatment of sleep apnea may not improve cardiovascular events in patients without heart failure.**
19. Jaffe LM, Kjekshus J, Gottlieb SS. Importance and management of chronic sleep apnea in cardiology. Eur Heart J. 2013;34:809–15.
20. Oldenburg O, Bitter T, Wiemer M, Langer C, Horstkotte D, Piper C. Pulmonary capillary wedge pressure and pulmonary arterial pressure in heart failure patients with sleep-disordered breathing. Sleep Med. 2009;10(7):726–30.
21. Lanfranchi PA, Braghiroli A, Bosimini E, Mazzuero G, Colombo R, Donner CF, et al. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. Circulation. 1999;99:1435–40.
22. 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.
23.• Khayat R, Abraham W, Patt B, Brinkman V, Wannemacher J, Porter K, et al. Central sleep apnea is a predictor of cardiac readmission in hospitalized patients with systolic heart failure. J Card Fail. 2012;18:534–40. **Supports the concept that CSA reflects severe heart failure.**
24. Emdin M, Mirizzi G, Giannoni A, Poletti R, Iudice G, Bramanti F, et al. Prognostic significance of central apneas throughout a 24-hour period in patients with heart failure. J Am Coll Cardiol. 2017;70:1351–64.
25. Lamba J, Simpson CS, Redfearn DP, Lamba J, Simpson CS, Redfearn DP. Cardiac resynchronization therapy for the treatment of sleep apnoea: a meta-analysis. Europace. 2011;13:1174–9.
26. Sinha AM, Skobel EC, Breithardt OA, Norra C, Markus KU, Breuer C, 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.
27. Mansfield DR, Solin P, Roebuck T, Bergin P, Kaye DM, Naughton MT. The effect of successful heart transplant treatment of heart failure on central sleep apnea. Chest. 2003;124:1675–81.
28. Garrigue S, Bordier P, Jaïs P, Shah DC, Hocini M, Raherison C, et al. Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med. 2002;346:404–12.
29. Oldenburg O, Faber L, Vogt J, Dorszewski A, Szabados F, Horstkotte D, et al. Influence of cardiac resynchronisation therapy on different types of sleep disordered breathing. Eur J Heart Fail. 2007;9:820–6.
30. Luthje L, Renner B, Kessels R, Vollmann D, Raupach T, Gerritse B, et al. Cardiac resynchronization therapy and atrial overdrive pacing for the treatment of central sleep apnoea. Eur J Heart Fail. 2009;11:273–80.
31. Lamba J, Simpson CS, Redfearn DP, Michael KA, Fitzpatrick M, Baranchuk A. Cardiac resynchronization therapy for the treatment of sleep apnoea: a meta-analysis. Europace. 2011;13:1174–9.
32. Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. Am J Respir Crit Care Med. 2006;173:234–7.
33. Javaheri S, Sands S, Edwards B. Acetazolamide attenuates Hunter-Cheyne-Stokes breathing but augments the hypercapnic ventilatory response in patients with heart failure. Ann Am Thorac Soc. 2014;11:80–6.
34. Naughton MT. Cheyne–Stokes respiration: friend or foe? Thorax. 2012;67:357–60.
35. Sharokh J. 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.
36. Javaheri S, Ahmed M, Parker TJ, Brown CR. Effects of nasal O_2 on sleep-related disordered breathing in ambulatory patients with stable heart failure. Sleep. 1999;22:1101–6.
37. Toyama T, Seki R, Kasama S, Isobe N, Sakurai S, Adachi H, 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.
38.• Sepehrvand N, Ezekowitz JA. Oxygen therapy in patients with acute heart failure. J Am Coll Cardiol Heart Fail. 2016;4:783–90. **Raises important questions about oxygen therapy in patients with SDB.**
39. Nakao YM, Ueshima K, Yasuno S, Sasayama S. Effects of nocturnal oxygen therapy in patients with chronic heart failure and central sleep apnea: CHF-HOT study. Heart Vessel. 2016;31:165–72.
40.• Oldenburg O, Wellmann B, Buchholz A, Bitter T, Fox H, Thiem U, et al. Nocturnal hypoxaemia is associated with increased mortality in stable heart failure patients. Eur Heart J. 2016;37:1695–703. **Raises concern that hypoxemia may be detrimental in HF patients.**
41. Bordier P, Lataste A, Hofmann P, Robert F, Bourenane G. Nocturnal oxygen therapy in patients with chronic heart failure and sleep apnea: a systematic review. Sleep Med. 2016 Jan;17:149–57.
42. Mak S, Azevedo ER, Liu PP, Newton GE. Effect of hyperoxia on left ventricular function and filling pressures in patients with and without congestive heart failure. Chest. 2001;120(2):467–73.
43. Park JH, Balmain S, Berry C, Morton JJ, McMurray JJ. Potentially detrimental cardiovascular effects of oxygen in patients with chronic left ventricular systolic dysfunction. Heart. 2010;96:533–8.
44. Naghshin J, Rodriguez RH, Davis EM, Romano LC, McGaffin KR, O'Donnell CP. Chronic intermittent hypoxia exposure improves left ventricular contractility in transgenic mice with heart failure. J Appl Physiol (1985). 2012;113(5):791–8.
45. Bradley TD, Logan AG, Kimoff RJ, Sériès F, Morrison D, Ferguson K, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med. 2005;353:2025–33.
46. Arzt M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, 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.
47. Javaheri S, Winslow D, McCullough P, Wylie P, Kryger MH. The use of a fully automated automatic adaptive servoventilation algorithm in the acute and long-term treatment of central sleep apnea. Chest. 2015;148(6):1454–61.
48. Morgenthaler TI, Kuzniar TJ, Wolfe LF, Willes L, McLain WC 3rd, Goldberg R. The complex sleep apnea resolution study: a

prospective randomized controlled trial of continuous positive airway pressure versus adaptive servoventilation therapy. Sleep. 2014;37(5):927–34.

49.• Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med. 2015;373:1095–105. **Important demonstration that although ASV improves sleep apnea, it can increase mortality under certain circumstances.**

50. Kasai T, Usui Y, Yoshioka T, Yanagisawa N, Takata Y, Narui K, et al. 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;3:140–8.

51.• Eulenburg C, Wegscheider K, Woehrle H, Angermann C, d'Ortho MP, Erdmann E, et al. Mechanisms underlying increased mortality risk in patients with heart failure and reduced ejection fraction randomly assigned to adaptive servoventilation in the SERVE-HF study: results of a secondary multistate modelling analysis. Lancet Respir Med. 2016;4(11):873–81. **Helping to shed light on possible mechanisms of the results of SERVE-HF.**

52. Javaheri S, Brown LK, Randerath W, Khayat R. SERVE-HF: more questions than answers. Chest. 2016;149(4):900–4.

53. Naughton MT. Cheyne-Stokes respiration: friend or foe? Thorax. 2012;67:357–60.

54.• Lyons OD, Floras JS, Logan AG, Beanlands R, Cantolla JD, Fitzpatrick M, et al. Design of the effect of adaptive servo-ventilation on survival and cardiovascular hospital admissions in patients with heart failure and sleep apnoea: the ADVENT-HF trial. Eur J Heart Fail. 2017;19(4):579–87. **A study which should help us to determine the true effects of ASV in heart failure patients.**

55.• O'Connor CM, Whellan DJ, Fiuzat M, Punjabi NM, Tasissa G, Anstrom KJ, et al. Cardiovascular outcomes with minute ventilation—targeted adaptive servo-ventilation therapy in heart failure. J Am Coll Cardiol. 2017;69(12):1577–158. **Raises questions about the impact of ASV in HFpEf.**

56. Bitter T, Westerheide N, Faber L, Hering D, Prinz C, Langer C, et al. Adaptive servoventilation in diastolic heart failure and Cheyne-Stokes respiration. Eur Respir J. 2010;36(2):385–92.

57. Yoshihisa A, Suzuki S, Yamaki T, Sugimoto K, Kunii H, Nakazato K, et al. Impact of adaptive servo-ventilation on cardiovascular function and prognosis in heart failure patients with preserved left ventricular ejection fraction and sleep-disordered breathing. Eur J Heart Fail. 2013;15(5):543–50.

58. Heider K, Arzt M, Lerzer C, Kolb L, Pfeifer M, Maier LS, Gfüllner F, Malfertheiner MV. Adaptive servo-ventilation and sleep quality in treatment emergent central sleep apnea and central sleep apnea in patients with heart disease and preserved ejection fraction. Clin Res Cardiol. 2018. https://doi.org/10.1007/s00392-018-1203-9.

59. Zhang XL, Ding N, Wang H, Augostini R, Yang B, Xu D, et al. Transvenous phrenic nerve stimulation in patients with Cheyne-Stokes respiration and congestive heart failure. Chest. 2012;142(4):927–34.

60. Oldenburg O, Augostini R, Krueger S, Kolodziej A, Gutleben KJ, Khayat R, et al. Phrenic nerve stimulation for the treatment of central sleep apnea. JACC Heart Fail. 2015;3(5):360–9.

61. Jagielski D, Ponikowski P, Augostini R, Kolodziej A, Khayat R, Abraham WT. Transvenous stimulation of the phrenic nerve for the treatment of central sleep apnea: 12 months experience with Remedē System. Eur J Heart Fail. 2016;18:1386–93.

62. Fox H, Bitter T, Horstkotte D, Oldenburg O, Gutleben KJ. Long-term experience with first-generation implantable neurostimulation device in central sleep apnea. Pacing Clin Electrophysiol. 2017;40(5):498–503.

63.• Costanzo MR, Ponikowski P, Javaheri S, Augostini R, Goldberg L, Holcomb R, et al. Transvenous neurostimulation for central sleep apnoea: a randomized controlled trial. Lancet. 2016;388:974–82. **Demonstration that central sleep apnea can be successfully treated with phrenic pacing.**

64.• Iturriaga R, Del Rio R, Idiaquez J, Somers VK. Carotid body chemoreceptor, sympathetic neural activation and cardiometabolic disease. Biol Res. 2016;49:13. **Interesting concept that CSA can be treated by addressing carotid body chemoreceptors.**

65. Del Rio R, Andrade DC, Marcus NJ, Schultz HD. Selective carotid body ablation in experimental heart failure: a new therapeutic tool to improve cardiorespiratory control. Exp Physiol. 2015;100(2):136–42. **Excellent review of mechanisms by which the carotid body might impact respiration.**

66. Marcus NJ, Del Rio R, Schultz EP, Xia XH, Schultz HD. Carotid body denervation improves autonomic and cardiac function and attenuates disordered breathing in congestive heart failure. J Physiol. 2014;592(2):391–408.

67. Niewinski P. Carotid body modulation in systolic heart failure from the clinical perspective. J Physiol. 2017;595(1):53–61.

68.• Pinna GD, Robbi E, La Rovere MT, Taurino AE, Bruschi C, Guazzotti G, et al. Differential impact of body position on the severity of disordered breathing in heart failure patients with obstructive vs. central sleep apnoea. Eur J Heart Fail. 2015;17:1302–9. **In both CSA and OSA, AHI markedly decreased from the supine to the lateral position.**