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Targeting Sleep Disordered Breathing to Prevent Heart Failure: What is the Evidence?

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Abstract

The inter-relationships of sleep disordered breathing (SDB) and heart failure (HF) are becoming increasingly well-characterized. The pathways linking the two entities are likely bi-directional and key underlying pathophysiological mechanisms at play include autonomic nervous system fluctuations, intermittent hypoxia, intrathoracic cardiac mechanical influences, rostral fluid shifts and up-regulation of systemic inflammation and oxidative stress. Given the increased morbidity and mortality which accompanies heart failure, the recognition and treatment of factors such as sleep disordered breathing is paramount in order to mitigate these untoward downstream health consequences. Recently, the management of HF requires combining several treatments including pharmacotherapy, electrophysiologic therapy, and cardiac surgery to target the various complex facets of HF. Despite the development of HF treatments, HF remains to pose a great challenge to the general cardiologist. Herein we review several interventional studies highlighting the effects of treating SDB on HF morbidity and mortality with a notable predominance of literature focusing on HF reduced ejection fraction (HF-REF) as well as emerging data describing SDB treatment effects in HF preserved EF (HF-PEF). These data are compelling yet with intrinsic limitations which underscore the need for appropriately powered clinical trials employing rigorous clinical trials methodology to examine the effect of SDB treatment on HF progression and associated adverse outcomes.

Keywords

Sleep disordered breathing; Heart failure; Treatment

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

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Conflict of Interest

Kenya Kusunose has no conflicts of interest.

Introduction

Heart Failure and Emerging Risk of Sleep Disordered Breathing

The burgeoning epidemic of heart failure (HF) is characterized by a prevalence of more than 5.8 million and approximately 670,000 new cases diagnosed per year[1]. Heart failure results in considerable patient morbidity, mortality and increase economic health burden. Specifically, heart failure is associated with both atrial and ventricular cardiac arrhythmias and accompanying challenges related to treatment and management as well as factors that result in perpetuation of heart failure progression. Moreover, patients with HF have a very poor prognosis which is underscored by data which demonstrate that 50% of HF patients die within 4 years of diagnosis and over half with severe HF die within a year. In chronic advanced HF, the mean 5-year survival rate is estimated at 25–50% and is comparable to that observed in cancer[2]. Furthermore, the increased economic burden stems not only from management, which is constituted by pharmacologic and non-pharmacologic strategies, but also from hospital readmissions, which on average occur within 3 months of the prior admission[3]. Of note, severe SDB has been identified to result in a 50% increased risk of readmission in heart failure, thereby representing a viable target to improve HF status and reduce costs[4]. Overall, these adverse consequences and associated increased costs highlight the critical need to identify other therapeutic secondary prevention targets such as sleep disordered breathing (SDB).

SDB is becoming increasingly recognized as an important factor in both the development and progression of heart failure. SDB can be characterized by various phenotypes including an obstructive predominance versus a central predominance of respiratory disturbance both of which have been linked with HF. The distinction of different etiologic bases of heart failure has also been elucidated in recent guidelines[5], i.e. heart failure with reduced ejection fraction (HF-rEF) and heart failure with preserved ejection fraction (HF-pEF). Heart failure and SDB share synergies in terms of respective risk factor profiles and linkages with comorbid factors. For example, it is well established that there is a close relationship with increasing age and increasing prevalence of HF, a phenomenon which is mirrored in individuals with SDB.[6] Although contributions to SDB occur via obesity-dependent and independent pathways, obesity is a firmly established SDB risk factor. Obesity is also recognized as a risk factor for HF associated with various untoward hemodynamic alterations which predispose to cardiac remodeling and ventricular dysfunction[7]. SDB represents an important risk for hypertension with reversal of SDB pathophysiology demonstrating reductions in blood pressure. Along this pathway, hypertension serves as risk for coronary artery disease and ischemic cardiomyopathy as well as diastolic dysfunction contributing to HF-pEF.

Sleep Disordered Breathing Epidemiology and Definition

SDB is characterized by recurrent partial or complete upper airway collapse or airway narrowing with resultant apneas and hypopneas respectively with accompanying intermittent bouts of hypoxemia, hypercapnia, and elevated sympathetic nervous system activation.[8] SDB is a common condition, remains vastly under-recognized and therefore a likely high proportion of avoidable cardiac risk, notably heart failure, is not being effectively addressed

from a therapeutic standpoint. Independent of obesity and other confounding factors, SDB has been associated with increased cardiovascular disease, arrhythmia, stroke and heart failure[9–11]. Epidemiologic data have shown that the prevalence of SDB is approximately 10% in the general population[12]. In the heart failure population with reduced left ventricular ejection fraction (EF≤40%, HF-rEF), SDB has been identified in 50–75% of cases[13, 14], however, SDB prevalence estimates in the HF-pEF population remain somewhat unclear. Although data pertaining to the prevalence of SDB in HF-pEF is relatively scarce, existing data support a prevalence of SDB of approximately 55%[15]

The standard metric to capture the severity of SDB is the apnea hypopnea index (AHI) which is gleaned from overnight polysomnography and defined as the number of apneas and hypopneas which occur per hour of sleep on average. An apnea is defined as cessation of respiratory airflow for ≥10 seconds and scored as an obstructive event in the presence of persistent thoracoabdominal effort or conversely as a central apnea if there is lack of thoracoabdominal effort. Although there have been varying definitions of the hypopnea, most recently this has been defined by the American Academy of Sleep Medicine as a 30% reduction in airflow lasting for ≥10 seconds associated with a ≥3% oxygen desaturation[16]. Although distinguishing obstructive from central hypopnea cannot be reliably performed without more invasive monitoring (i.e. esophageal balloon monitoring), features such as the presence of thoracoabdominal paradox, snoring and flow limitation can be used to assist in the differentiation of the obstructive from the central hypopnea[16]. An apnea hypopnea index of less than 5 events per hour of sleep is considered to be within normal range, while a range of 5–15 is mild, 15–30 is moderate and ≥30 is severe[17]. SDB, in part due to sleep fragmentation, can be associated with decrements in quality of life oftentimes related to excessive daytime somnolence, irritability and negative impact on work performance. Although common signs and symptoms of SDB include snoring, witnessed apneas, daytime sleepiness, gasping/choking episodes, nocturia and morning headaches, symptoms in HF are oftentimes challenging to ascertain given that HF in of itself oftentimes is associated with such symptoms. Under-diagnosis of SDB in this population likely occurs as these symptoms may be attributed to HF rather than raising suspicion for SDB. Furthermore, those with HF may have a less prominent sleepiness phenotype and appear to more commonly present with sleep maintenance insomnia symptoms.

SDB is characterized by two primary subtypes, i.e. obstructive sleep apnea (OSA) which involves mechanical upper airway obstruction and central sleep apnea (CSA), the latter which may occur with or without Cheyne Stokes Respirations (CSR). The pathophysiology of OSA is based upon the concept of the airway serving as a Starling resistor during sleep such that under passive conditions the intraluminal pressure falls below the extraluminal pressure[18]. The critical closing pressure is identified as the intraluminal pressure at which there is collapse of the upper airway. The key determinants of the critical closing pressure include intra-luminal and extraluminal pressures, activity of the pharyngeal dilator muscle and compliance of the pharyngeal wall. On the other hand, common predisposing factors for CSA include enhanced central and peripheral chemosensitivity, hypocapnia and left ventricular dysfunction[19]. CSA often involves a high loop gain state with neurologic dysregulation of ventilatory control. CSA in heart failure occurs via mechanisms related to pulmonary congestion resulting in stimulation of the pulmonary vagal irritant receptors

resulting in hyperventilation, hypocapnia and arousals during sleep which then further perpetuate the hypocapnia and central apneas[20]. A narrowing of the “delta gap” occurs, i.e. the difference between the apneic threshold paCO2 and the prevailing arterial paCO2, which then increases vulnerability to central apnea generation. The distribution of obstructive versus central apnea pathophysiology in heart failure appears to vary. CSA has not only been associated with increased hospital readmissions, but also with increased arrhythmogenic risk, accelerated HF progression and increased morbidity and mortality[21]. It is possible that these associations reflect the underlying pathophysiology intrinsic to HF and/or the direct effect of apnea- and hypopnea-induced sympathetic activation which further perpetuates HF progression.

Common Underlying Pathophysiologic Mechanisms Linking Sleep Disordered Breathing and Heart Failure

When placing into context various modalities of treatment amenable to improvement of SDB in HF, it is important to have a firm understanding of the underlying mechanisms at play. Multiple likely bi-directional pathophysiological mechanisms connecting SDB and HF have been elucidated in prior studies. For example, SDB is accompanied by autonomic nervous system dysfunction, augmented systemic inflammation and oxidative stress, elevated blood catecholamine levels and blood pressure, increased peripheral vascular resistance, increased pulmonary artery pressure, right and left ventricular afterload and reduction in the control of baroreceptor reflexes.[22]

Autonomic nervous system influences play a prominent role in SDB and HF development and progression. For example, OSA characterized by repetitive upper airway obstruction, leads to intermittent hypoxia which can stimulate the sympathetic nervous system via reflex mechanisms.[23] This influence becomes even more pronounced in the context of increase CO_2 levels accompanying apnea. Hypoxia also lead to pulmonary vasoconstriction which increases pulmonary artery pressures and myocardial workload, thereby perpetuating HF pathophysiology by increasing myocardial stress and compromising myocardial contractility.[24, 25] Hypoxia, hypercapnia and arousal act in concert to trigger sympathetic nervous system surges and neuronal noradrenaline release resulting in an increase rather than a fall in blood pressure during sleep, i.e. the so-called “non-dipping” blood pressure pattern which is recognized to increase cardiovascular risk.[26] We have published data demonstrating non-dipping blood pressure patterns in those with increasing SDB severity and known or increased cardiovascular disease risk[27]. In addition to systemic influences, it has also been observed that local sympathetic activation responses are at play, particularly at the level of the kidney, with SDB effects resulting in activation of the renal medulla thereby increasing circulating norepinephrine levels in SDB. SDB may also negatively affect the heart in patients with HF in whom muscle sympathetic nerve activity is elevated compared to patients without HF. Sympathetic activation has been observed to be elevated in SDB with HF and increased noradrenalin occurred in the advanced systolic HF.[28] Autonomic nervous system dysfunction has also been identified as a contributing factor in diastolic function including influences on left atrial function highlighting potential implications of SDB effects in HF-pEF as well.[29]

Rostral neck edema characterized by fluid displacement from the lower extremities to the neck may facilitate OSA development during sleep in the recumbent position due to fluid shift-induced parapharyngeal edema and increased tissue pressure resulting in pharyngeal obstruction; i.e. obstructive respiratory events. The resulting higher airway resistance also results in a reduced volume of ventilation and thereby increased $paCO_2$.[30] Central apnea may be stimulated by the rostral fluid shifts in HF due to fluid accumulation in the lungs from pulmonary edema which in turn provokes hyperventilation, hypocapnia and therefore drives down the $paCO_2$ below the apneic threshold thus precipitating a central respiratory event. Overnight rostral fluid shifts appear to augment the severity of SDB; an effect which appears to be most pronounced in males with HF. For example, in non-obese men, OSA severity was strongly related to the degree of overnight leg fluid volume reduction and concordant increase in neck circumference.[31]

Reduction of leg fluid volume was the strongest correlate of the AHI even independent of obesity and accounted for 64% of the variability in AHI[31]. Overnight increase in neck circumference correlates with the overnight reduction in leg fluid volume further supporting the notion of redistribution of fluid from the legs to the neck[32].

Systemic inflammation and oxidative stress have been well-studied in OSA, albeit there is a relative dearth of data in up-regulation of these pathways in CSA. Inflammation and oxidative stress have not only been implicated in coronary artery disease thereby contributing to ischemic cardiomyopathy, but also hypertension leading to ventricular hypertrophy/HF-pEF as well as exerting direct effects on cardiac myocytes thereby contributing to the morbidity and mortality of HF. While some studies are conflicting, relative to OSA, meta-analyses of data examining the relationship of C-Reactive Protein, IL-6, IL-8 and TNF-alpha, well-recognized markers implicated in cardiovascular disease, have demonstrated elevated levels in individuals with OSA versus controls[33] as well as benefit of OSA treatment with continuous positive airway pressure (CPAP) resulting in reduction of these markers of inflammation[34]. Therefore, it is plausible that reversing the physiology of OSA may actually have favorable effects on HF outcomes. Myeloid-related protein 8/14 is a heterodimer with intrinsic pro-inflammatory effect and observed to be an independent predictor of cardiovascular events and recent data have demonstrated a potential relationship with measures of hypoxia in OSA[35]. Similar to what has been described in obesity (and potentially with synergistic overlapping influences)[36], SDB via pathways of inflammation and metabolic risk may increase the risk of HF by inducing cardiac structural changes, e.g. cardiac fibrosis by affecting the fibrotic and remodeling response after cardiac injury. OSA is accompanied by impressive levels of intrathoracic pressure alterations approaching negative 65mmHg which has been specifically observed in those with OSA and HF[37]. These OSA-induced increasingly negative intrathoracic pressures have direct mechanical effects on the heart resulting in increased juxtacardiac and transmural pressures and increased ventricular afterload and myocardial oxygen demand[38]. These OSA-related perturbations with cyclic changes in venous return in HF can challenge the already vulnerable heart and contribute to HF progression.

Influence of Sleep Disordered Breathing Treatment on Heart Failure

Recently, the management of HF requires combining several treatments including pharmacotherapy, electrotherapy, and cardiac surgery because of the inherent complexities of HF pathophysiology. Despite the development of novel treatments to mitigate HF progression and morbidity and mortality, HF continues to pose a challenge to effectively treat. In light of plausible underlying biologic mechanisms as outlined above, considering SDB as a secondary preventive target therefore represents a potentially effectual approach to address adverse HF consequences. The majority of data published thus far have focused on HF-rEF with very small scale studies suggesting treatment benefit of SDB for example with adaptive servoventilation (ASV) in HF-pEF[39]. Identification of SDB in HF should always begin with optimization of the medical management of HF according to standard established guidelines. Beyond this, below are other treatment options for SDB in HF which are viable options within our armamentarium.

Supplemental Oxygen

In systolic HF, nocturnal supplemental oxygen has been shown to mitigate central sleep apnea, reduce apnea-related hypoxia, reduce BNP levels and reduce catecholamine levels[40–43]. Mechanistically, it is plausible that supplemental oxygen may improve the ventilatory instability which accompanies central apnea and reduces sympathetic nervous system activation as hypoxia is a recognized stimulus for sympathetic activation. Early work also showed improvement of sleep consolidation with use of nocturnal oxygen therapy by reducing the arousals resulting from the hyperpneic phase of Cheyne Stokes Respirations (CSR)[41]. Follow up work showed that the inhalation of oxygen had immediate effects in improving CSR and this effect may be mediated by the level of the arterial paCO2[44]. This rise in paCO2 leads to widening of the difference between the prevailing paCO2 and the apneic threshold paCO2 which reduces the likelihood of ventilatory instability. Although recently published multicenter interventional trial data highlight the lack of significant benefit of the use of supplemental oxygen alone versus CPAP and versus healthy lifestyle change in terms of reduction of mean arterial blood pressure in moderate to severe OSA, the patients considered for this study overall did not have more advanced stages of HF and therefore findings are not generalizable as such[45]. As there are data demonstrating that even in the setting of OSA, ventilatory instability and high loop gain are important mechanisms, those with HF in particular may derive benefit from supplemental oxygen given that it lowers loop gain and significantly reduces the severity of apnea burden[46]. Supplemental oxygen has been shown to reduce central apnea burden (and as anticipated hypoxia) as well as reduce heart rate in a pre- post-intervention study involving patients with stable HF[47]. Three randomized controlled trials have been performed showing both short-term (12 week) and long-term benefits of supplemental oxygen in those with central predominant apnea in terms of CSA and CSR, NYHA class, activity scale quality of life score and objective measures including left ventricular ejection fraction (LVEF), exercise capacity and cardiac sympathetic nerve activity[48–50].

Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) in general has been considered the mainstay of OSA treatment. In those individuals with compromised left ventricular function and increased left ventricular end diastolic pressure, positive pressure delivered by CPAP exerts benefits in terms of reduction of left ventricular preload by increases in intrathoracic pressure, enhancement of stroke volume, improvement of pulmonary congestion and reduction of cardiac sympathetic activity[20]. In the setting of underlying left ventricular dysfunction, positive pressure also reduces preload by impeding venous return and reducing both right and left ventricular end-diastolic volumes[20]. Based upon results of an initial promising study involving a small sample size (n=29) demonstrating improvement in 5-year mortality and cardiac transplantation in those with HF and CSA who were compliant with therapy, the CANadian Positive Airway Pressure (CANPAP) trial was designed. The CANPAP study was a randomized controlled trial undertaken to examine the effect of CPAP therapy for CSA-CSR in HF-rEF (LVEF<40%) on cardiac transplant-free survival compared to control with a mean follow up period of 2 years[51]. Although treatment with CPAP improved secondary endpoints resulting in increased LVEF, decreased norepinephrine concentration and increased 6-minute walk time, there was no significant improvement on the primary endpoint of transplant-free survival compared to controls[51]. An interesting observation was the early poorer outcomes in the group randomized to receive CPAP treatment which was postulated to be due to CPAP-related reduction in cardiac output in patients with lower filling pressures—this in part resulted in early termination of the trial. The overall better than anticipated survival may have been attributable to timing of the conduct of the trial during a period when beta blocker therapy was just becoming the standard of care and could have mitigated any “above and beyond” benefit of CPAP. Potential explanations for the unanticipated findings include suboptimal reversal of apnea pathophysiology (residual AHI after treatment was greater than 15) due to ineffectiveness of CPAP on improving CSA and/or limited adherence observed during the trial (average CPAP use of 3.6 hours per night at 1 year). To help elucidate whether findings of this study were due to ineffectively reversing CSA pathophysiology, post-hoc analysis revealed that for participants with effective CSA suppression (AHI<15), LVEF and survival was significantly improved compared with untreated controls and compared to those whose CSA was not suppressed (AHI>15)[52]. There are several trials which have demonstrated improvement in LVEF, blood pressure, sympathetic activity and quality of life in patients with OSA and HF treated with CPAP (Table 1).[39, 51–62] Although the long-term survival benefit of CPAP treatment in HF with CSA remains unproven, there are several trials underway designed to investigate the effect of more advanced PAP therapy on HF outcomes.

Bi-level Positive Airway Pressure

In the setting of SDB and HF, there are many that oppose the use of Bilevel PAP given the potential to reduce paCO2 below the apneic threshold and perpetuate central apnea, albeit this route of therapy may be effective in addressing OSA. However, there may be a role for Bilevel PAP with timed back up rate (S/T mode), which provides inspiratory positive airway pressure (IPAP), expiratory positive airway pressure (EPAP) along with a backup respiratory rate, in those unresponsive to CPAP therapy to address prolonged central respiratory events. Bilevel PAP S/T mode triggers IPAP delivery when the flow sensors

detect a spontaneous inspiratory effort. EPAP is then delivered as well as a backup rate to ensure that the patient is receiving a minimum pre-set respiratory rate if spontaneous breathing has not occurred. There are small scale studies that suggest Bilevel PAP with timed back up rate may be beneficial from the standpoint of improved BNP levels and increase in LVEF in patients who are refractory to CPAP therapy (defined as AHI≥15 despite CPAP).[63, 64] These studies are limited by small sample sizes, consideration of only central apnea and there are no longer term studies or consideration of mortality with respect to Bilevel PAP S/T mode.

Adaptive Servo-ventilation

Adaptive servo-ventilation (ASV), a sophisticated mode of positive airway pressure delivery, has changed the landscape of SDB treatment in HF due to its ability to more effectively address the full spectrum of obstructive apnea, central apnea and periodic breathing compared to more traditional PAP therapies. This is of particular importance in light of the data previously mentioned which demonstrated improvement in survival in those with effective suppression of CSA versus less effective suppression with CPAP. As ASV can more effectively treat all apnea subtypes, this may allow for more effective SDB suppression and therefore translate into improvement in HF outcomes. ASV utilizes an anti-cyclic feedback control system delivering variable pressure support according to the sensed minute ventilation or peak respiratory flow based upon breath-to-breath- analysis of a preceding moving window of time. The servo-controlled automatic adjustment of IPAP (and therefore pressure support) is inversely related to the change in either peak flow or volume detected over a preceding window of time, i.e. anticyclic ventilation which serves to reduce the oscillatory breathing pattern characteristic of periodic breathing. Different companies employ differing algorithms in terms of sensing metrics (e.g. flow versus volume) and maximum pressures delivered. For patients who have SDB recalcitrant to standard PAP therapy in terms of effective control, ASV represents a reasonable next step. A meta-analyses was conducted to examine the effect of ASV versus control in adult patients with stable HF and concluded that ASV was more effective than control conditions (and also in subgroup analyses compared to CPAP specifically) in reducing AHI and showed greater improvement in LVEF and exercise capacity compared to control conditions.[65] Although there are some data demonstrating improved 1-year survival and reduction of fatal cardiovascular events in those patients adherent with ASV compared to those who were non-adherent, these prognostic data are limited due to the residual confounding of the potential influence of aggressiveness of medical therapy used and the notion that compliers likely represent a different phenotype compared to non-compliers in terms of compliance with other aspects of their medical care which could impact HF outcomes[61]. In order to more effectively examine the impact of ASV treatment on HF outcomes, large scale multicenter clinical trials are needed. Currently, two large prospective trials (Adaptive Servo Ventilation (ASV) on Survival and Hospital Admissions in Heart Failure (ADVENT-HF) and Treatment of Predominant Central Sleep Apnea by Adaptive Servoventilation in Patients with Heart Failure (SERVE-HF)) are ongoing in addition to a large prospective observational study (SCHLA-H) (Table 2).[66] Patients with HF-rEF and SDB (CSA or OSA in ADVENT-HF and CSA in SERVE-HF) are randomized to receive ASV + standard medical therapy versus standard medical therapy. These trials should provide valuable information to better

elucidate the effect of ASV on clinically relevant outcomes including hospital admission and mortality.

Pharmacologic Approaches

Several pharmacologic approaches have been studied in the setting of SDB and HF including theophylline and acetazolamide.[67, 68] Theophylline is a respiratory stimulant, a result of its competitive adenosine antagonist properties, and is also a phosphodiesterase III inhibitor, the latter resulting in positive inotropic effects. In those with HF-rEF, theophylline has been shown to significantly reduce periodic breathing and central apneas as well as arousals in addition to decreasing the degree of hypoxia exposure[68]. While the respiratory stimulant properties of theophylline may result in improvement in central apnea in HF, positive inotropic effects are recognized to result in unfavorable HF outcomes which in addition to its pro-arrhythmogenic influences preclude the routine use of this medication in the setting of HF. Acetazolamide, a carbonic anhydrase inhibitor resulting in metabolic acidosis and also with diuretic properties, in a small interventional trial served to improve objective measures of central apnea and hypoxia as well as subjective measures of sleep quality and daytime fatigue[67]. Interestingly, although acetazolamide leads to a metabolic acidosis which would via compensatory respiratory mechanisms reduce paCO2, the benefit conferred by reducing central apnea is realized because it widens the gap between the prevailing and the apneic threshold paCO2[69]. It is important to note that these medications are likely best considered as adjunctive measures as although an improvement in SDB indices (typically ~50% reduction in SDB severity) was observed, there was not complete resolution of SDB, thereby rendering potential persistence of exposure to clinically relevant SDB. Larger trials are needed as existing studies while encouraging may have been underpowered.

Device Implantation Interventional Procedures

Phrenic nerve stimulation offers a novel alternative means to regulate breathing by utilizing a physiological approach to initiate respiration. This innovative modality may particularly represent an attractive option for patients who are PAP-resistant or non-adherent. A small-scale feasibility study showed improvement in SDB measures including the AHI, central apnea index, 4% oxygen desaturation index and reduced arousal index with the use of unilateral transvenous phrenic nerve stimulation therapy.[70] An ongoing multicenter adequately powered randomized controlled trial has been designed to more definitively address the efficacy of this approach. Cardiac resynchronization therapy, a therapy for patients with HF-rEF, works by simultaneously pacing both the right and left ventricles serving to reduce mechanical dyssynchrony and improve cardiac output, thereby conferring hemodynamic benefit. Limited data support an improvement, albeit without resolution, of both obstructive and central sleep apnea with the use of cardiac resynchronization therapy[71, 72].

Alternative Options

In those with HF, it is possible that maneuvers to reduce rostral neck edema could improve the degree of both obstructive and central sleep apnea. For example, the use of venous compression stockings reduced the fluid accumulation in the legs and translated into

improvement in the extent of rostral fluid collection at night reducing the frequency of apneic events by a third[30]. Intensification of diuretic therapy may represent another method to reduce rostral neck edema as well. Supplemental CO2 may be beneficial by raising the paCO2 above the apneic threshold in those with HF and hypocapnic CSA, however, holds limited practicability given the need for a closed circuit for CO2 delivery and carries side effects of anxiety and insomnia.

Conclusion

SDB and HF share common risks and appear to have bi-directional pathophysiologic underpinnings. SDB-related autonomic nervous system dysfunction, intermittent hypoxia, increased negative intra-thoracic pressure and rostral fluid shifts play a role in pathogenesis of HF. While traditional PAP therapies to treat SDB appear to demonstrate benefit in HF-rEF in terms of improving quality of life and ventricular function, reversal of central apnea pathophysiology with this mode of therapy is inconsistent at best. ASV offers a more sophisticated approach to address not only obstructive sleep apnea, but also more effectively combat central apnea and periodic breathing pathology commonly observed in HF and apparently translates into superior effectiveness compared to traditional PAP in improving the severity of SDB, augmenting LVEF and improving exercise capacity based upon controlled studies and clinical trial data. While pharmacologic treatment with medications such as acetazolamide may be effective in improving in particular the central component of SDB, data indicate lack of effective SDB resolution suggesting its role as a possible adjunctive therapy. Novel therapies such as phrenic nerve stimulation may also offer important therapeutic options particularly for those who are non-adherent with more standard PAP therapies. Studies are underway to more conclusively address benefits of SDB treatment on HF outcomes including readmissions and mortality. Future work is needed to further clarify the biologic relationships at hand relative to SDB and HF with a focus on understudied areas such as the role of systemic inflammation and oxidative stress in CSA as well as potential benefits of SDB treatment in HF-pEF.

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References

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

• Of importance

1. Writing Group M, Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Roger VL, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J. American Heart Association Statistics C, Stroke Statistics S. Heart disease and stroke statistics--2010 update: A report from the american heart association. Circulation. 2010; 121:e46–e215. [PubMed: 20019324]

2. Gandhi PU, Pinney S. Management of chronic heart failure: Biomarkers, monitors, and disease management programs. Annals of global health. 2014; 80:46–54. [PubMed: 24751564]
3. Heidenreich PA, Zhao X, Hernandez AF, Yancy CW, Fonarow GC. Patient and hospital characteristics associated with traditional measures of inpatient quality of care for patients with heart failure. American heart journal. 2012; 163:239–245. e233. [PubMed: 22305842]
4. Khayat R, Abraham W, Patt B, Brinkman V, Wannemacher J, Porter K, Jarjoura D. Central sleep apnea is a predictor of cardiac readmission in hospitalized patients with systolic heart failure. Journal of cardiac failure. 2012; 18:534–540. [PubMed: 22748486]
5. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Task Force for the D, Treatment of A, Chronic Heart Failure of the European Society of C. Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. Guidelines ESCCfP. Esc guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the european society of cardiology. Developed in collaboration with the heart failure association (hfa) of the esc. European journal of heart failure. 2012; 14:803–869. [PubMed: 22828712]
6. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 accf/aha guideline for the management of heart failure: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. J Am Coll Cardiol. 2013; 62:e147–e239. [PubMed: 23747642]
7. Alpert MA, Omran J, Mehra A, Ardhanari S. Impact of obesity and weight loss on cardiac performance and morphology in adults. Progress in cardiovascular diseases. 2014; 56:391–400. [PubMed: 24438730]
8. 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. American Heart Association Council for High Blood Pressure Research Professional Education Committee CoCC, American Heart Association Stroke C, American Heart Association Council on Cardiovascular N, American College of Cardiology F. 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. [PubMed: 18725495]
9. 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. [PubMed: 20625114]
10. Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, Sahadevan J, Redline S. Sleep Heart Health S. Association of nocturnal arrhythmias with sleep-disordered breathing: The sleep heart health study. American journal of respiratory and critical care medicine. 2006; 173:910–916. [PubMed: 16424443]
11. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, Shahar E, Unruh ML, Samet JM. Sleep-disordered breathing and mortality: A prospective cohort study. PLoS Med. 2009; 6:e1000132. [PubMed: 19688045]
12. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. American journal of epidemiology. 2013; 177:1006–1014. [PubMed: 23589584]

13. Schulz R, Blau A, Borgel J, Duchna HW, Fietze I, Koper I, Prenzel R, Schadlich S, Schmitt J, Tasci S, Andreas S. working group Kreislauf und Schlaf of the German Sleep S. Sleep apnoea in heart failure. Eur Respir J. 2007; 29:1201–1205. [PubMed: 17360729]
14. 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. European journal of heart failure. 2007; 9:251–257. [PubMed: 17027333]
15. Chan J, Sanderson J, Chan W, Lai C, Choy D, Ho A, Leung R. Prevalence of sleep-disordered breathing in diastolic heart failure. Chest. 1997; 111:1488–1493. [PubMed: 9187161]
16. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, Redline S, Strohl KP, Davidson Ward SL, Tangredi MM. American Academy of Sleep M. Rules for scoring respiratory events in sleep: Update of the 2007 aasm manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the american academy of sleep medicine. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine. 2012; 8:597–619. [PubMed: 23066376]
17. 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. 2009; 22:667–689.
18. Smith PL, Wise RA, Gold AR, Schwartz AR, Permutt S. Upper airway pressure-flow relationships in obstructive sleep apnea. Journal of applied physiology. 1988; 64:789–795. [PubMed: 3372436]
19. Nopmaneejumruslers C, Kaneko Y, Hajek V, Zivanovic V, Bradley TD. Cheyne-stokes respiration in stroke: Relationship to hypocapnia and occult cardiac dysfunction. American journal of respiratory and critical care medicine. 2005; 171:1048–1052. [PubMed: 15665317]
20. Bradley TD, Floras JS. Sleep apnea and heart failure: Part ii: Central sleep apnea. Circulation. 2003; 107:1822–1826. [PubMed: 12682029]
21. 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; 107:727–732. [PubMed: 12578876]
22. Javaheri S. A mechanism of central sleep apnea in patients with heart failure. The New England journal of medicine. 1999; 341:949–954. [PubMed: 10498490]
23. Somers VK, Mark AL, Zavala DC, Abboud FM. Contrasting effects of hypoxia and hypercapnia on ventilation and sympathetic activity in humans. J Appl Physiol. 1989; 67:2101–2106. [PubMed: 2513316]
24. Kusuoka H, Weisfeldt ML, Zweier JL, Jacobus WE, Marban E. Mechanism of early contractile failure during hypoxia in intact ferret heart: Evidence for modulation of maximal ca2+-activated force by inorganic phosphate. Circ Res. 1986; 59:270–282. [PubMed: 2429780]
25. Stoohs R, Guilleminault C. Cardiovascular changes associated with obstructive sleep apnea syndrome. J Appl Physiol. 1992; 72:583–589. [PubMed: 1559936]
26. Parati G, Esler M. The human sympathetic nervous system: Its relevance in hypertension and heart failure. European heart journal. 2012; 33:1058–1066. [PubMed: 22507981]
27. Seif F, Patel SR, Walia HK, Rueschman M, Bhatt DL, Blumenthal RS, Quan SF, Gottlieb DJ, Lewis EF, Patil SP, Punjabi NM, Babineau DC, Redline S, Mehra R. Obstructive sleep apnea and diurnal nondipping hemodynamic indices in patients at increased cardiovascular risk. Journal of hypertension. 2014; 32:267–275. [PubMed: 24351803]
28. Floras JS. Sympathetic nervous system activation in human heart failure: Clinical implications of an updated model. J Am Coll Cardiol. 2009; 54:375–385. [PubMed: 19628111]
29. Kusunose K, Zhang Y, Mazgalev TN, Van Wagoner DR, Thomas JD, Popovic ZB. Impact of vagal nerve stimulation on left atrial structure and function in a canine high-rate pacing model. Circ Heart Fail. 2014; 7:320–326. [PubMed: 24397925]
30. White LH, Bradley TD. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnoea. J Physiol. 2013; 591:1179–1193. [PubMed: 23230237]
31. Redolfi S, Yumino D, Ruttanaumpawan P, Yau B, Su MC, Lam J, Bradley TD. Relationship between overnight rostral fluid shift and obstructive sleep apnea in nonobese men. American journal of respiratory and critical care medicine. 2009; 179:241–246. [PubMed: 19011149]

32. Yumino D, Wang H, Floras JS, Newton GE, Mak S, Ruttanaumpawan P, Parker JD, Bradley TD. Prevalence and physiological predictors of sleep apnea in patients with heart failure and systolic dysfunction. Journal of cardiac failure. 2009; 15:279–285. [PubMed: 19398074]
33. Nadeem R, Molnar J, Madbouly EM, Nida M, Aggarwal S, Sajid H, Naseem J, Loomba R. Serum inflammatory markers in obstructive sleep apnea: A meta-analysis. Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine. 2013; 9:1003–1012. [PubMed: 24127144]
34. Xie X, Pan L, Ren D, Du C, Guo Y. Effects of continuous positive airway pressure therapy on systemic inflammation in obstructive sleep apnea: A meta-analysis. Sleep medicine. 2013; 14:1139–1150. [PubMed: 24054505]
35. Hall TS, Herrscher TE, Jarolim P, Fagerland MW, Jensen T, Agewall S, Atar D, Hallen J. Myeloid-related protein-8/14 and c-reactive protein in individuals evaluated for obstructive sleep apnea. Sleep medicine. 2014; 15:762–768. [PubMed: 24841106]
36. Cavalera M, Wang J, Frangogiannis NG. Obesity, metabolic dysfunction, and cardiac fibrosis: Pathophysiological pathways, molecular mechanisms, and therapeutic opportunities. Translational research: the journal of laboratory and clinical medicine. 2014
37. Somers VK, Dyken ME, Skinner JL. Autonomic and hemodynamic responses and interactions during the mueller maneuver in humans. J Auton Nerv Syst. 1993; 44:253–259. [PubMed: 8227959]
38. Mehra R, Redline S. Arrhythmia risk associated with sleep disordered breathing in chronic heart failure. Current heart failure reports. 2014; 11:88–97. [PubMed: 24234397]
39. Yoshihisa A, Suzuki S, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S, Takeishi Y. Impact of adaptive servo-ventilation on cardiovascular function and prognosis in heart failure patients with preserved left ventricular ejection fraction and sleep-disordered breathing. European journal of heart failure. 2013; 15:543–550. [PubMed: 23250911]
40. Franklin KA, Eriksson P, Sahlin C, Lundgren R. Reversal of central sleep apnea with oxygen. Chest. 1997; 111:163–169. [PubMed: 8996011]
41. 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. Annals of internal medicine. 1989; 111:777–782. [PubMed: 2817624]
42. Shigemitsu M, Nishio K, Kusuyama T, Itoh S, Konno N, Katagiri T. Nocturnal oxygen therapy prevents progress of congestive heart failure with central sleep apnea. International journal of cardiology. 2007; 115:354–360. [PubMed: 16806535]
43. 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. European heart journal. 1998; 19:922–928. [PubMed: 9651717]
44. Javaheri S, Ahmed M, Parker TJ, Brown CR. Effects of nasal o2 on sleep-related disordered breathing in ambulatory patients with stable heart failure. Sleep. 1999; 22:1101–1106. [PubMed: 10617171]
45. Gottlieb DJ, Punjabi NM, Mehra R, Patel SR, Quan SF, Babineau DC, Tracy RP, Rueschman M, Blumenthal RS, Lewis EF, Bhatt DL, Redline S. Cpap versus oxygen in obstructive sleep apnea. The New England journal of medicine. 2014; 370:2276–2285. [PubMed: 24918372] A multicenter randomized controlled clinical trial which demonstrated that unlike continuous positive airway pressure, supplemental oxygen was not effective in significantly improving the primary outcome i.e. reducing mean arterial blood pressure compared to control.
46. Wellman A, Malhotra A, Jordan AS, Stevenson KE, Gautam S, White DP. Effect of oxygen in obstructive sleep apnea: Role of loop gain. Respiratory physiology & neurobiology. 2008; 162:144–151. [PubMed: 18577470]
47. Sakakibara M, Sakata Y, Usui K, Hayama Y, Kanda S, Wada N, Matsui Y, Suto Y, Shimura S, Tanabe T. Effectiveness of short-term treatment with nocturnal oxygen therapy for central sleep apnea in patients with congestive heart failure. Journal of cardiology. 2005; 46:53–61. [PubMed: 16127894]
48. Sasayama S, Izumi T, Matsuzaki M, Matsumori A, Asanoi H, Momomura S, Seino Y, Ueshima K. Group C-HS. Improvement of quality of life with nocturnal oxygen therapy in heart failure

patients with central sleep apnea. Circulation journal: official journal of the Japanese Circulation Society. 2009; 73:1255–1262. [PubMed: 19448327]

49. Sasayama S, Izumi T, Seino Y, Ueshima K, Asanoi H. Group C-HS. Effects of nocturnal oxygen therapy on outcome measures in patients with chronic heart failure and cheyne-stokes respiration. Circulation journal: official journal of the Japanese Circulation Society. 2006; 70:1–7. [PubMed: 16377916]
50. Toyama T, Seki R, Kasama S, Isobe N, Sakurai S, Adachi H, Hoshizaki H, Oshima S, Taniguchi K. 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. Circulation journal: official journal of the Japanese Circulation Society. 2009; 73:299–304. [PubMed: 19122308]
51. Bradley TD, Logan AG, Kimoff RJ, Series F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Tomlinson G, Floras JS. Investigators C. Continuous positive airway pressure for central sleep apnea and heart failure. The New England journal of medicine. 2005; 353:2025–2033. [PubMed: 16282177]
52. Arzt M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, Ferguson K, Belenkie I, Pfeifer M, Fleetham J, Hanly P, Smilovitch M, Ryan C, Tomlinson G, Bradley TD. Investigators C. 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. [PubMed: 17562959]
53. Kohnlein T, Welte T, Tan LB, Elliott MW. Assisted ventilation for heart failure patients with cheyne-stokes respiration. Eur Respir J. 2002; 20:934–941. [PubMed: 12412686]
54. Arias MA, Garcia-Rio F, Alonso-Fernandez A, Mediano O, Martinez I, Villamor J. Obstructive sleep apnea syndrome affects left ventricular diastolic function: Effects of nasal continuous positive airway pressure in men. Circulation. 2005; 112:375–383. [PubMed: 16009798]
55. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: An observational study. Lancet. 2005; 365:1046–1053. [PubMed: 15781100]
56. Arzt M, Wensel R, Montalvan S, Schichtl T, Schroll S, Budweiser S, Blumberg FC, Riegger GA, Pfeifer M. Effects of dynamic bilevel positive airway pressure support on central sleep apnea in men with heart failure. Chest. 2008; 134:61–66. [PubMed: 17951617]
57. Oliveira W, Campos O, Cintra F, Matos L, Vieira ML, Rollim B, Fujita L, Tufik S, Poyares D. Impact of continuous positive airway pressure treatment on left atrial volume and function in patients with obstructive sleep apnoea assessed by real-time three-dimensional echocardiography. Heart. 2009; 95:1872–1878. [PubMed: 19643769]
58. Kasai T, Usui Y, Yoshioka T, Yanagisawa N, Takata Y, Narui K, Yamaguchi T, Yamashina A, Momomura SI. Effect of flow-triggered adaptive servo-ventilation compared with continuous positive airway pressure in patients with chronic heart failure with coexisting obstructive sleep apnea and cheyne-stokes respiration. Circ Heart Fail. 2010; 3:140–148. [PubMed: 19933407]
59. Jilek C, Krenn M, Sebah D, Obermeier R, Braune A, Kehl V, Schroll S, Montalvan S, Riegger GA, Pfeifer M, Arzt M. Prognostic impact of sleep disordered breathing and its treatment in heart failure: An observational study. European journal of heart failure. 2011; 13:68–75. [PubMed: 20961913]
60. Oldenburg O, Bitter T, Lehmann R, Korte S, Dimitriadis Z, Faber L, Schmidt A, Westerheide N, Horstkotte D. Adaptive servoventilation improves cardiac function and respiratory stability. Clin Res Cardiol. 2011; 100:107–115. [PubMed: 20835903]
61. Takama N, Kurabayashi M. Effect of adaptive servo-ventilation on 1-year prognosis in heart failure patients. Circulation journal: official journal of the Japanese Circulation Society. 2012; 76:661–667. [PubMed: 22199136]
62. Kahwash R, Kikta D, Khayat R. Recognition and management of sleep-disordered breathing in chronic heart failure. Current heart failure reports. 2011; 8:72–79. [PubMed: 21086079]
63. Dohi T, Kasai T, Narui K, Ishiwata S, Ohno M, Yamaguchi T, Momomura S. Bi-level positive airway pressure ventilation for treating heart failure with central sleep apnea that is unresponsive

to continuous positive airway pressure. Circulation journal: official journal of the Japanese Circulation Society. 2008; 72:1100–1105. [PubMed: 18577818]

64. Kasai T, Narui K, Dohi T, Ishiwata S, Yoshimura K, Nishiyama S, Yamaguchi T, Momomura S. Efficacy of nasal bi-level positive airway pressure in congestive heart failure patients with cheyne-stokes respiration and central sleep apnea. Circulation journal: official journal of the Japanese Circulation Society. 2005; 69:913–921. [PubMed: 16041159]
65. Sharma BK, Bakker JP, McSharry DG, Desai AS, Javaheri S, Malhotra A. Adaptive servoventilation for treatment of sleep-disordered breathing in heart failure: A systematic review and meta-analysis. Chest. 2012; 142:1211–1221. [PubMed: 22722232]
66. Woehrle H, Oldenburg O, Arzt M, Graml A, Erdmann E, Teschler H, Wegscheider K. Determining the prevalence and predictors of sleep disordered breathing in patients with chronic heart failure: Rationale and design of the schla-hf registry. BMC Cardiovasc Disord. 2014; 14:46. [PubMed: 24716484]
67. Javaheri S. Acetazolamide improves central sleep apnea in heart failure: A double-blind, prospective study. American journal of respiratory and critical care medicine. 2006; 173:234–237. [PubMed: 16239622]
68. Javaheri S, Parker TJ, Wexler L, Liming JD, Lindower P, Roselle GA. Effect of theophylline on sleep-disordered breathing in heart failure. The New England journal of medicine. 1996; 335:562–567. [PubMed: 8678934]
69. Nakayama H, Smith CA, Rodman JR, Skatrud JB, Dempsey JA. Effect of ventilatory drive on carbon dioxide sensitivity below eupnea during sleep. American journal of respiratory and critical care medicine. 2002; 165:1251–1260. [PubMed: 11991874]
70. Ponikowski P, Javaheri S, Michalkiewicz D, Bart BA, Czarnecka D, Jastrzebski M, Kusiak A, Augostini R, Jagielski D, Witkowski T, Khayat RN, Oldenburg O, Gutleben KJ, Bitter T, Karim R, Iber C, Hasan A, Hibler K, Germany R, Abraham WT. Transvenous phrenic nerve stimulation for the treatment of central sleep apnoea in heart failure. European heart journal. 2012; 33:889–894. [PubMed: 21856678] This article describes phrenic nerve stimulation as a potential novel therapeutic approach.
71. Luthje L, Renner B, Kessels R, Vollmann D, Raupach T, Gerritse B, Tasci S, Schwab JO, Zabel M, Zenker D, Schott P, Hasenfuss G, Unterberg-Buchwald C, Andreas S. Cardiac resynchronization therapy and atrial overdrive pacing for the treatment of central sleep apnoea. European journal of heart failure. 2009; 11:273–280. [PubMed: 19147446]
72. Stanchina ML, Ellison K, Malhotra A, Anderson M, Kirk M, Benser ME, Tosi C, Carlisle C, Millman RP, Buxton A. The impact of cardiac resynchronization therapy on obstructive sleep apnea in heart failure patients: A pilot study. Chest. 2007; 132:433–439. [PubMed: 17573498]

Table 1

Positive Airway Pressure Clinical Studies for the Treatment of Sleep Disordered Breathing in Heart Failure.

PAP treatment	Year	Design	N	Type	EF	Endpoint	Conclusion
Kohnlein et al.	2002	CPAP vs BilevelPAP	16	CSA	24±7	Sleep apnea	CPAP and BiPAP equally improve sleep apnea.
Arias et al.	2005	Sham vs nasal CPAP	27	OSA	67±4	Diastolic function	Nasal CPAP improves LV diastolic function
Bradley et al.	2005	Control vs CPAP	258	CSA	25±8	Survival	No survival benefit between control and CPAP.
Marin et al.	2005	Control vs CPAP	607	OSA	NA	CV event	In severe OSA, CPAP reduces CV events.
Arzt et al.	2007	Control vs CPAP	210	CSA	24±8	EF and survival rate	In suppressed CSA group, CPAP improve LVEF and survival
Arzt et al.	2008	CPAP ve ASV	14	CSA	27±2	Sleep apnea	BilevelPAP support suppresses sleep apnea
Oliveira et al.	2009	Control vs CPAP	56	OSA	NA	Diastolic function	CPAP improved LV diastolic function.
Kasai et al.	2010	CPAP vs ASV	31	OSA and CSA	36±10	EF and sleep apnea	ASV has a greater benefit in EF and sleep apnea than CPAP.
Oldenburg et al.	2011	Control vs ASV	115	CSA	28±8	Cardiac function and sleep apnea	ASV improves parameters of SDB and cardiac function.
Jilek et al.	2011	Control vs PAP treatment	176	OSA and CSA	34 (25; 44)	Survival	PAP treated severe CSA had a better outcome.
Takama et al.	2012	Good vs poor ASV adherence	85	OSA and CSA	41±17	CV event	ASV prevented CV event.
Yoshihisa et al.	2013	Control vs ASV	30	OSA and CSA	56±11	CV event	ASV improved cardiac function and prevented CV event

Abbreviations: Adaptive Servoventilation (ASV), Bilevel Positive Airway Pressure (Bilevel PAP), Cardiovascular (CV), Central Sleep Apnea (CSA), Continuous Positive Airway Pressure (CPAP), Left Ventricular Ejection Fraction (LVEF), Obstructive Sleep Apnea (OSA)

Table 2

Ongoing Large Scale Clinical Trials and Observational Study of Sleep Disordered Breathing and Heart Failure-Reduced Ejection Fraction.

Trial name	Expected end	Design	Estimated patients (n)	Sleep apnea type	Criteria of EF	Endpoint
ADVENT-HF	Mid 2015	Control vs ASV	860	CSA or OSA	EF<45	Death and hospitalization
SERVE-HF	Mid 2015	Control vs ASV	1200	CSA	EF<45	Death and hospitalization
SCHLA-HF	2015	Observation study	1808	CSA or OSA	EF<45	Prevalence of disease and natural outcome