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Arrhythmia Risk Associated with Sleep Disordered Breathing in Chronic Heart Failure

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Abstract

The intersecting relationships of sleep disordered breathing (SDB), arrhythmogenic risk and chronic heart failure (HF) are complex and most likely multi-directional and synergistic. Autonomic dysfunction is a common pathophysiological feature of each of these entities. Intermittent hypoxia, hypercapnia, mechanical cardiac influences due to upper airway obstruction and rostral fluid shifts are SDB-specific mechanisms which may trigger, perpetuate and exacerbate HF and arrhythmogenesis. Specific pathophysiological mechanisms will vary according to the predominance of central as compared to obstructive sleep apnea. The risk of cardiac arrhythmias and HF attributable to SDB may be considerable given the high prevalence of SDB and its likely physiologic burden. The current review focuses on the data which have accrued elucidating the specific contributory mechanisms of SDB in cardiac arrhythmias and HF, highlighting the clinical relevance and effects of standard SDB treatment on these outcomes and describing the role of novel therapeutics.

Keywords

Acetazolamide; Adaptive servoventilation; Apnea hypopnea index; Arrhythmia; Atrial fibrillation; Autonomic dysfunction; Cardiac resynchonization therapy; Central sleep apnea; Cheyne stokes respirations; Continuous positive airway pressure; Hypoxia; Heart failure; Hypercapnia; Oxygen; Obstructive sleep apnea; Phrenic nerve stimulation; Polysomnography; Renal sympathetic denervation; Sleep disordered breathing; Sudden cardiac death; Theophylline; Ventricular arrhythmia

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Compliance with Ethics Guidelines

Conflict of Interest

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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.

Introduction

Sleep disordered breathing (SDB) is characterized by recurrent apneas and hypopneas, associated with intermittent hypoxemia, hypercapnia, and sympathetic nervous system surges [1]. A large body of research indicates that there is significant overlap in the prevalence and pathophysiologic effects of SDB with cardiac arrhythmias and chronic heart failure (HF) [1]. Autonomic dysfunction is a common pathophysiological feature of each of these entities. Patients with SDB have variable degrees of obstructive and central respiratory events, and SDB subtypes are further associated with specific effects on the cardiovascular system. Although the interrelationships among these disorders are likely multi-directional and synergistic, experimental, clinical and epidemiologic studies support SDB as a causal risk factor in the pathogenesis of arrhythmogenesis and HF. SDB is estimated to afflict between 9% and 24% of adults in the general community when using standard polysomnography-based definitions [2]. Thus, the risk of cardiac arrhythmias and HF attributable to SDB may be considerable given this high prevalence and its likely physiologic burden. Emerging experimental data has improved our understanding of pathogenic underpinnings of SDB in relation to arrhythmogenesis and also evolution of HF and exacerbations of HF [3]. The underlying mechanisms related to SDB that result in a pro-arrhythmogenic state are related to the independent and likely synergistic influences of intermittent bouts of hypoxemia, hypercapnia, sympathetic nervous system discharges and alterations in intrathoracic pressures. The current review focuses on the data which have accrued elucidating the specific contributory mechanisms of SDB in cardiac arrhythmias and HF, highlighting the clinical relevance and effects of standard SDB treatment on these outcomes and describing the role of novel therapeutics such as cardiac resynchronization and phrenic nerve stimulation in central sleep apnea.

Overview of Sleep Disordered Breathing, Arrhythmias and Chronic Heart Failure

SDB, which encompasses both obstructive apnea and central apnea, the latter with or without Cheyne Stokes respirations, has been established to be an independent risk factor for adverse cardiovascular outcomes and mortality [4,5]. Furthermore, SDB is an important, often unrecognized co-morbidity in patients with HF with reduced ejection fraction (EF), affecting 50–75% of cases. [6,7] Chronic HF is estimated to occur in up to 2–3% of the population in industrialized countries and is associated with recurrent hospital admissions and increased mortality despite advances in pharmacologic treatments as well as device-based management [8]. Reversing the adverse physiologic consequences of SDB in HF including addressing SDB-induced cardiac arrhythmias may represent a key opportunity to improve HF-related morbidity and mortality.

SDB is characterized by recurrent apneas or hypopneas during sleep, often with associated symptoms of snoring, awakenings, and daytime sleepiness. SDB is associated with a substantial degree of morbidity and mortality resulting in high population health burden. SDB is highly prevalent, estimated to affect between 9% and 24% of adults in the general community when using standard polysomnography (PSG)-based definitions [2]. Prevalence is estimated to be 2–4% when considering PSG findings in addition to daytime somnolence symptoms,[2] the latter of which are often absent in SDB which occurs in HF. Similar to HF and cardiac arrhythmias such as atrial fibrillation (AF), the prevalence of SDB is much higher in adults older than >65 years as compared to younger individuals. For example, in a community dwelling sample of men age > 67 years, SDB defined as an apnea-hypopnea index (AHI)>15, was found in 21% to 26% of the sample, with some variability depending on SDB definition [9].

The dominant apnea types in SDB are obstructive apnea and central apnea. OSA involves obstruction of the upper airway in the context of continued thoracoabdominal effort and occurs in 20–45% of the HF population [6,7]. CSA occurs when neuromuscular output declines during sleep, resulting in repetitive apneas with resulting intermittent hypoxemia. CSA is often accompanied by Cheyne Stokes respirations, which consists of periods of hyperpnea and crescendo-decrescendo tidal volumes. Both central and obstructive sleep apnea may be associated with a higher incidence of atrial and ventricular arrhythmias in HF patients [10,11]. CSA and Cheyne Stokes Respirations induce and may evolve from alterations in chemosensitivity. Similar to OSA, CSA results in neural and hemodynamic changes and has been identified as an independent risk factor for death [1,12,13]. A potential reason for this increase in CSA-related mortality may be increased risk of malignant ventricular arrhythmias [14].

SDB exposes the individual to chronic intermittent hypoxemia and wide intrathoracic pressure swings altering autonomic balance, preload, and afterload, and also enhances inflammatory and oxidative stresses, which operate to bolster a pro-arrhythmogenic milieu and contribute to HF progression. These exposures may increase arrhythmic risk through a variety of mechanisms including abnormal automaticity, triggered automaticity, or reentry mechanisms. Increased HF morbidity may also occur via pathways of SDB-related effects on vulnerable myocardium. Animal and human experimental studies have identified potential mechanisms by which SDB either through direct or indirect pathways alter the functional and cardiac structural substrate for arrhythmogenesis and worsening cardiac function in HF [3].

Evidence-Based Biologic Mechanisms Characterizing Sleep Disordered Breathing, Arrhythmias and Chronic Heart Failure

Autonomic Nervous System Dysregulation

Autonomic nervous system dysfunction is one of the most studied mechanisms in relationship to SDB, arrhythmia, and HF. In both obstructive and central sleep apnea, hypoxia, hypercapnia and arousal act together to trigger sympathetic nervous system surges and neuronal noradrenaline release resulting in an increase rather than fall in blood pressure during sleep [15]. There is a circadian variability in the immediate influences of SDB such that in HF, the heart is at a disadvantage to cope with the autonomic and chemical demands of SDB during a time when circadian ventricular metabolic gene expression and metabolic capacity are at a nadir [16]. SDB also may particularly negatively affect the heart in patients with HF in whom muscle sympathetic nerve activity is elevated compared to patients without HF. HF patients with SDB compared to those without SDB have further elevatation of sympathetic activation even during wakefulness [17]. In advanced systolic HF, those with increased cardiac noradrenaline spillover and cardiac noradrenaline stores are at greatest risk for sudden cardiac death [18]. There are a myriad of consequences of the increased sympathetic drive noted in SDB on the compromised heart in HF including myocyte necrosis and apoptosis and beta-adrenoreceptor downregulation and desensitization which may therefore predispose to arrhythmic events and increased mortality [19–21].

Exciting experimental models have been developed to elucidate the specific SDB-related pathophysiologic pathways implicated in the generation of arrhythmias. The majority of these studies address AF and focus on the role of autonomic nervous system alterations, a recognized AF risk. [22,23] It has been shown that there is enhanced vagal activity during the apneic or hypopneic events due to hypoxia and upper airway closure leading to carotid body chemoreceptor stimulation and reflex bradycardia via vagal afferents. This is followed by post-event sympathoexcitation resulting in surges in both heart rate and blood pressure in the

post-apneic ventilatory phase, resulting in increased myocardial strain and oxygen consumption as well as depressed myocardial contractility [24,25]. Although the etiology of sympathetic nervous system discharges are likely attributable to the hypoxic stimulus, upper airway closure elicited reflexes, hypercarbia and arousals may also be etiologic contributors. There appear to be differential effects of vagal versus sympathetic nervous system activation relative to the root cause of the arrhythmia. For example, vagally-mediated influences favor macro-reentry and reduce the effective refractory period which increases AF propensity [26]. Conversely, sympathetic activation favors abnormal automaticity and triggered atrial activity [26]. Supporting this biologic basis, experimental animal data indicate attenuation of apnea-mediated AF after autonomic blockade via ganglionated plexi neural ablation [27]. The role of autonomic imbalance in obstructive apnea-associated AF is further corroborated by shortening of the atrial effective refractory period subsequent to tracheal occlusion resulting in increased AF inducibility mainly via enhanced vagal activation [28]. Furthermore, renal sympathetic denervation modulates vagally-mediated negative tracheal pressure. This in turnnduces shortening of the atrial effective refractory period which highlights the importance of autonomic imbalance in OSA-associated AF [28]. It bears mention that although much of the experimental data has focused on OSA physiology, CSA has been associated with sympatho-excitation which may similarly also lead to increased arrhythmia risk perhaps with differential temporal patterns relative to apnea. Muscle sympathetic nerve activity appears to peak during the apneic phase in obstructive apnea compared to the hyperpneic phase of central apnea [29,30].

Ventricular arrhythmias in SDB may be generated through pathways of enhanced automaticity or triggered activity. In both cases, sympathetic nervous system activation appears to play a key role. Premature ventricular beats are also increased in frequency before and after waking, supporting a role of the sympathetic nervous system in the generation of ventricular ectopy [31]. The sympathetic nervous system activation in OSA may initiate ventricular arrhythmias directly through effects on cardiac electrophysiology or indirectly by affecting heart rate, blood pressure and coronary blood flow. For example, stimulation of sympathetic fibers could shorten the ventricular refractory period, lower the ventricular fibrillation threshold, and thereby increase propensity for a potentially lethal event [32]. Sympathetic stimulation may also induce ventricular fibrillation in the setting of myocardial ischemia and ischemic cardiomyopathy in systolic HF. The nocturnal predilection of sudden cardiac death in SDB suggests that exposure to immediate SDB-related pathophysiology influences such as autonomic fluctuations may lead to a lethal ventricular arrhythmia [33]. Survivors of spontaneous out-of-hospital ventricular fibrillation or tachycardia also exhibit a selective increase in cardiac noradrenaline spillover regardless of EF, further implicating the role of sympathetic activation as a lethal culprit [34].

Hypoxic and Hypercapnic Influences

Arrhythmogenesis in HF also may be attributable to impaired gas exchange and tissue hypoxia, which has a myriad of effects. Hypoxia can stimulate the sympathetic nervous system via reflex mechanisms. This influence becomes even more pronounced in the context of increased CO_2 levels accompanying apnea [35]. Hypoxia also leads to pulmonary vasoconstriction which increases pulmonary arterial pressures and myocardial workload, thereby perpetuating HF pathophysiology by increasing myocardial strain and compromising myocardial contractility [36,37]. Long-term exposure to hypoxia and hypercapnia may lead to arrhythmias via pulmonary vascular remodeling which may lead to right ventricular hypertension, right atrial dilatation, and potentially increased transmural pressures impinging on endocardial vessels, thereby altering the distribution of blood flow and further perpetuating HF progression. The hypoxemia that results from apneas and hypopneas also occurs in association with reoxygenation; these repetitive perturbations

result in increased inflammation as well as production of oxygen-derived free radicals, with resultant tissue damage. Hypoxia and oxygen-derived free radicals also can damage cardiac myocytes and affect myocyte ion exchange, and thereby increase likelihood of deterioration of cardiac function as well as facilitate arrhythmogenesis. Up-regulation of pathways of systemic inflammation may represent a final common pathway of autonomic dysfunction, hypoxia/hypercapnia and mechanical cardiac influences from increasingly negative intrathoracic pressures. Recent data have identified the association of CSA and up-regulation of pathways of inflammation with arrhythmia in patients with HF. Specifically, central apnea was related to night-time prevalent AF, sinus pauses and both daytime and night-time nonsustained ventricular tachycardia and increased C-reactive protein during a mean follow-up period of approximately 2 years [38].

Hypoxic influences also appear to play a role in AF. Desaturation nadirs associated with SDB are often extreme, and are often accompanied by blood pressure and heart rate surges. SDB may be the culprit of the bi-directional relationships observed between AF and HF. Specifically, the cardiac instability caused by AF may contribute to worsening HF via hemodynamic compromise and conversely hypoxia-related worsening of cardiac function may contribute to AF generation and instability. Common mechanisms for AF and SDB are supported by the finding of elevations of the transcription factor, hypoxia inducible factor-1α[39,40], in both disorders [41]. In an animal model, hypoxia has been observed to shorten the action potential in the left atrium, whereas reoxygenation induced pulmonary vein burst firing [42]. Hypercapnia, particularly responses to hypercapnia resolution with ventilation, also have been demonstrated to alter the atrial refractory period; this pattern has been implicated in the increase in AF vulnerability observed in patients as they return to eucapnia [43]. Epidemiological data linking hypoxemia and ventricular arrhythmias were demonstrated in a large cohort of older men (as described below?) [44].

Negative Intrathoracic Pressures and Rostral Fluid Shifts

Repetitive, exaggerated generation of negative intrathoracic pressure against an occluded upper airway which results in substantial negative pressures in the chest cavity (approaching -65mmHg) is observed in patients with OSA and HF [45]. This results in increased juxtacardiac and transmural pressures, thereby increasing left ventricular afterload and myocardial oxygen demand. In HF, this results in a more pronounced and prolonged duration of stroke volume reduction compared to those with normal left ventricular EF [46]. SDB leads to cardiac structural alterations including increased wall stress, increased afterload, increased atrial size [47,48] and impaired diastolic function [47,49] Myocardial ischemia can be precipitated and worsen HF in the setting of increase in the metabolic demands of the myocardium in the face of reduced oxygen supply. Sudden imposition of severe negative intrathoracic pressure also has been shown to cause an abrupt decrease in left atrial volume and reduction in left ventricular systolic performance [50]. The cyclical alteration of intrathoracic pressures in SDB results in acute stretch of the thin-walled atria and pulmonary vein stretch [45,47,48,51], which can lead to stretch-mediated ion channel activation, triggering AF and resulting in further decompensation of HF. Our published data demonstrate increased left ventricular mass index in SDB compared to those without SDB, which is likely attributable to the OSA-related intrathoracic pressures changes and mechanistically explained by the degree of nocturnal hypoxia [52]. Generation of increasingly negative intrathoracic pressures may also contribute to myocyte slippage, contractile dysfunction, and adverse ventricular remodeling in such patients [46]. Thus, the SDB-related fluctuations in end-expiratory volumes along with concordant increases and reductions in venous return may further challenge a compromised heart, and contribute to arrhythmia and HF exacerbation [46].

OSA has been noted to be highly prevalent in patients with hypertrophic cardiomyopathy (40%) [53]. This relationship may reflect the adverse effects of OSA on left atrial and aortic enlargement likely via effects of increasingly negative intrathoracic pressure. Hypertrophic cardiomyopathy is associated with both HF and AF, and AF is a recognized risk factor for cardiovascular death in hypertrophic cardiomyopathy [53]. It is possible that SDB contributes to cardiomyopathy-related death by increasing AF.

Recent research has highlighted the role of nocturnal rostral fluid collection as an important mechanism of upper airway compromise in HF. Specifically, fluid which accumulates in the lower extremities can redistribute to the neck during sleep in the recumbent position and result in parapharyngeal edema and increased tissue pressure, and thereby result in increase in upper airway collapsibility which predisposes to obstructive apnea [54]. The volume of fluid displaced from the legs appears to be strongly related to the degree of overnight increase in neck circumference [54]. Central apnea may also be provoked by the rostral fluid shifts in HF due to fluid accumulation in the lungs, i.e. pulmonary edema, and result in provocation of hyperventilation[54] and hypocapnia, driving CO2 levels below the apnea threshold and precipitating central apnea. Use of venous compression stockings in those with chronic venous insufficiency 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 approximately one third [54].

Epidemiologic and Clinical Studies Highlighting the Intersection of Arrhythmias, Heart Failure and Sleep Disordered Breathing

The investigation of arrhythmias in the setting of HF and SDB is of prime importance given that SDB can serve as a trigger and perpetuator of cardiac arrhythmia and consequently arrhythmia can contribute to atrial/ventricular remodeling resulting in HF exacerbations and progression. Identification of novel arrhythmogenic risk factors such as SDB is critical given the burgeoning AF epidemic that is not fully explained by known risk factors such as aging and obesity. Postulated links underlying the association of SDB and AF include hypertension and diastolic dysfunction resulting in long- term atrial remodeling. Clinical and epidemiological research strongly supports a causal link between SDB and AF. Perhaps the first study demonstrating this link was an uncontrolled study noting improvement in nocturnal AF with SDB treatment with positive airway pressure [55]. Among participants in the Sleep Heart Health Study, moderate to severe SDB, as compared to minimal, was associated with a four-fold increase in the adjusted odds of AF on overnight sleep studies even after consideration of confounders such as obesity and reported underlying cardiovascular disease [56]. Among elderly individuals, a large scale study of approximately 3000 older men, however, demonstrated stronger associations between AF and central apnea/Cheyne Stokes Respirations compared to obstructive apnea [44]. A case control study in which both groups were balanced in terms of HF, demonstrated that obstructive apnea ascertained by questionnaire was 2-fold higher in those with AF compared to controls from a general cardiology clinic [57]. Another case control study involving participants with a structurally normal heart demonstrated not only that those with AF had a higher proportion of at least moderate obstructive apnea, but also that those with higher burden of AF defined by frequency of episodes were more likely to have moderate or more severe sleep apnea [58]. In a clinical cohort of over 3500 patients without prevalent AF, SDB was associated with incident AF in those who were less than 65 years of age [59]. Apnea and hypopneas were shown to be discrete triggers of paroxysms of AF or non-sustained ventricular tachycardia identified on overnight polysomnography; in this case crossover analysis, individual apneas/ hypopneas were shown to increase the relative risk of paroxysms of arrhythmia by 18-fold compared to periods of normal nocturnal breathing [60]. There are scant data regarding SDB and post-operative AF. However, one study reported an increase in AF following coronary

artery bypass graft surgery in patients with SDB compared to those without SDB, even after taking into consideration cross-clamp time and left ventricular EF [61]. A topic that has received much attention is the role of SDB in the recurrence of AF subsequent to intervention. OSA has been shown to be associated with non-pulmonary vein antrum triggers and posterior wall firing in both paroxysmal and non-paroxysmal AF, which may render this population less responsive to AF interventions such as pulmonary vein antral isolation [62].

Although arguably the majority of the literature on the relationship of SDB and arrhythmia is focused on AF, there are also data indicating the importance of SDB as a trigger for ventricular arrhythmia leading to sudden cardiac death. In an analysis of data from a middle-aged, predominantly male clinical cohort of over 10,000 individuals undergoing sleep studies, moderate to severe sleep apnea and hypoxemia were identified as predictors of sudden cardiac death (fatal or resuscitated) risk [63]. Once confounders were considered, only nadir oxygen saturation was predictive of sudden cardiac death. Of interest, at least 31% of those with sudden cardiac death had clear ventricular arrhythmias (up to 46% may have had ventricular arrhythmias when including patients who underwent implantable cardiac device therapy and advanced cardiac life support) [63]. Data from the same group of investigators has also characterized the nocturnal predilection of sudden cardiac death in those with OSA compared to those without [33]. In HF, it appears that the highest risk for ventricular arrhythmia occurs during the hyperpneic phase of Cheyne Stokes Respirations supporting the notion that reversal of this periodic breathing may potentially improve ventricular arrhythmogenesis and sudden cardiac death in the HF population [64]. The frequency of implantable cardiac defibrillator (ICD) discharges in those with SDB and cardiac dysfunction has been examined. In patients with HF with an ICD, the presence of SDB has been found to be a common and independent predictor of life-threatening ventricular arrhythmias, which are more likely to occur during sleep [65]. SDB ascertained during ICD pre-implantation predicts not only appropriate, but also inappropriate ICD firing in advanced HF and may increase risk of ventricular arrhythmia in this population [66]. Increased number of EEG arousals, plasma alkalinity, increasing age and smoking were identified as risk factors for ventricular tachycardia in HF, and smoking demonstrated the strongest magnitude of association [67]. Electrophysiologic markers of ventricular arrhythmia and sudden cardiac death have been investigated in SDB and HF. T wave alternans is one such marker. In HF patients, SDB has been observed to induce cardiac electrical instability manifested as T wave alternans and appears to have a nocturnal predominance in some HF patients, findings which are consistent with the increased risk of nocturnal sudden cardiac death in SDB [68].

Impact of Sleep Disordered Breathing Treatment on Arrhythmias and Heart Failure

Positive Airway Pressure

In an era in which medical reimbursements are becoming closely tied with readmission rates, the importance of identification and treatment of SDB is underscored by findings that CSA is a predictor of cardiac readmission in hospitalized patients with systolic HF [69]. There are several trials which have demonstrated improvement in left ventricular EF, left ventricular dilatation, systolic blood pressure, sympathetic activity and quality of life in patients with OSA and HF who were treated with continuous positive airway pressure (CPAP) [70]. In a recent meta-analysis, CPAP treatment in OSA and HF was estimated to be associated with a 5.2% improvement in the left ventricular EF [71]. The exact mechanisms by which CPAP treatment affects left ventricular EF in HF are not yet completely understood. CPAP treatment may have a positive impact on left ventricular systolic remodeling

parameters by reducing blood pressure, hypoxemia, rapid intrathoracic pressure changes and secondary hemodynamic disturbances [72]. CPAP treatment could also play an important role in improving LV systolic function, hemodynamics, and subendocardial ischemia [72]. The survival benefit of treating CSA in HF remains unproven. In the Canadian Continuous Positive Airway Pressure for Central Sleep Apnea and HF (CANPAP) trial, the largest randomized controlled trial to date testing the efficacy of nocturnal CPAP in reducing mortality and transplant-free survival in patients with advanced HF, no difference in mortality was noted, although improvements in EF, norepinephrine levels and distance walked in six minutes were observed [73]. Several reasons have been postulated for the unexpected findings including increasing use of beta blockers during the course of the study which may have precluded ascertaining PAP benefit, suboptimal PAP adherence, persistent apnea due to Cheyne Stoke Respirations, and reduced venous return and therefore hemodynamic disadvantage of PAP in those with low volume state. A post-hoc analysis of this trial was performed to evaluate potential differences on outcome between those who were effectively treated for SDB versus those who were not, and findings demonstrated that a substantial improvement in sleep apnea translated into an improved survival until transplantation [74]. Improvement in ventricular arrhythmia in OSA and HF was shown in a randomized controlled trial; specifically, a 58% reduction in the frequency of ventricular premature beats during sleep was noted in the treatment arm while no significant improvement was observed in the control group [75]. Large randomized clinical trials are underway to ascertain the effect of adaptive servo-ventilation on survival in HF including the Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure (ADVENT-HF) trial and the SERVE-HF study which is a multicenter, randomized trial comparing effects of optimal medical management versus adaptive servoventilation [76]. Of note, the use of adaptive servo-ventilation, a device which can eliminate obstructive apnea via a set expiratory pressure, provides variable inspiratory support to address periodic breathing and has a back up rate to treat central apnea; it has shown promising results to treat OSA and CSA in systolic HF[6] and to reduce appropriate defibrillator therapies in those with ICD placement [77].

The treatment of OSA with CPAP has been shown to decrease the recurrence of AF after cardioversion during a one year follow up period compared to untreated sleep apnea and also compared to controls. The level of nocturnal desaturation appeared to best explain increased recurrence rates[78]. A limitation of this study is potential selection bias, as those who do not choose treatment for sleep apnea may also engage inother suboptimal health behaviors. In the absence of HF, treatment of SDB has been observed to result in a dose-response reduction of atrial ectopic beats in relation to increases in PAP pressure and decrease in respiratory disturbance frequency [79]. A prospective study of patients with AF undergoing pulmonary vein antrum isolation demonstrated that a statistically higher proportion of CPAP users (79%) compared to non-CPAP (68%) users were free of AF after a 2.5 year follow-up period[62]. Importantly, treatment with CPAP improved pulmonary vein antrum isolation success rates in all patients with SDB. Furthermore, patients with SDB who were not treated with CPAP and who had non-pulmonary vein triggers, were 8 times more likely to fail the procedure [62]. In a retrospective study evaluating AF intervention in patients with a mean EF of ~60%, SDB treatment with CPAP was found to reduce the recurrence of AF after pulmonary vein isolation catheter ablation. The authors also concluded that treatment of SDB with CPAP improves arrhythmia free survival after pulmonary vein isolation and that the isolation procedure offers limited value to SDB patients not treated with CPAP [80]. Based upon the findings of these studies, it has been proposed that systematic monitoring for SDB should be performed in patients with AF who are refractory to ablation and if SDB is identified, then treatment should be focused in reversing SDB physiology before considering repeated ablation [81].

Alternative and Novel Therapies

CPAP alternative treatments for SDB in HF include supplemental oxygen and the use of acetazolamide, CO_2 rebreathing and theophylline. Supplemental oxygen reduces the severity of central apneas and suppresses sympathetic activation in patients with HF and Cheyne Stokes Respirations [82]. However, in a patient population with cardiovascular risk factors, a randomized controlled study comparing nocturnal supplemental oxygen to CPAP showed no blood pressure or biochemical benefit of oxygen use. Short-term clinical trial data supports the benefit of the respiratory stimulant carbonic anhydrase inhibitor, acetazolamide as a means to reduce central apnea frequency in HF [83]. However, long term utility of this is unclear. Treatment of CSA with CO_2 rebreathing can change the apneic threshold and alter respiratory drive, and may have a role in reducing Cheyne Stoke Respirations [84]. Short-term treatment with theophylline, a respiratory stimulant, for periodic breathing in patients with HF appears to reduce the number of episodes of apnea and the duration of arterial hypoxemia during sleep; however, there is concern for the potential increase in arrhythmogenic potential, particularly in patients with HF [85]. The role of renal sympathetic denervation in chronic HF has received increasing attention as a means for reducing arrhythmogenesis. This also may represent a potential therapeutic strategy to reduced SDB-related increased sympathetic nerve activation. Although initial proof of concept work appeared to demonstrate improvement in central and obstructive apnea with an overdrive pacing intervention [86], subsequent studies have failed to show consistent findings [46]. Recent data, however, suggest that in those with moderate to severe SDB, overdrive pacing at a rate 20 bpm above the mean nocturnal heart rate resulted in a statistically significant reduction in central apnea burden, however, it is unclear whether this burden reduction translates into clinical significance (central apnea hypopnea index of 23.9 ± 11.8 versus 19.1 ± 12.7) [87]. Unlike the disappointing results of overdrive pacing, cardiac resynchronization therapy (biventricular pacing) appears to be an effective strategy in improving SDB in HF likely because it improves left ventricular EF, increases cardiac output, reduces pulmonary venous pressure and therefore reduces the tendency towards hyperventilation and hypocapnia. Moreover, this intervention may reduce the fluctuation in breathing patterns, preventing the hyperventilation that precedes an apnea event [88]. Although not directly addressed in current studies, resynchronization could play a role in improving arrhythmic events in SDB and HF. Transvenous phrenic nerve stimulation is another exciting modality currently being studied in a multicenter randomized controlled trial as a treatment for central apnea in HF. Preliminary data have shown an improvement in the frequency of apneas and reduction in arousals [89]. The advantage of resynchronization and phrenic nerve stimulation is that the direct implantation overcomes the issue of PAP adherence that plagues treatment of SDB.

Conclusions

Increasing data are emerging to help in our understanding of the overlapping relationships of SDB, HF and cardiac arrhythmias. It is clear that SDB-related autonomic imbalance, hypoxia/reoxygenation, hypercapnia, increased negative intrathoracic pressure resulting in cardiac structural alterations and rostral fluid shifts play a role in the pathogenesis of HF and cardiac arrhythmia. It is also evident that the relationships of HF and cardiac arrhythmia involve a bi-directional dependence. SDB treatment appears to improve EF and other intermediate measures; however, the effect on mortality is unclear. Large-scale clinical trials are underway to more effectively address this question. There are varying susceptibilities in those with differing underlying etiologies of systolic dysfunction which warrants further investigation. For example, mechanisms of SDB-induced arrhymogenesis in ischemic cardiomyopathy may be related to vulnerable hibernating or damaged myocardium compared to myocardial hypertrophy and extracellular fibrosis in hypertrophic cardiomyopathy. The majority of data has focused on investigating relationships of SDB and

systolic HF. However, HF with preserved ejection fraction- also deserves further study as it is prevalent and often occurs in the setting of high blood pressure, the latter shown to improve with SDB treatment. There is also a need to better differentiate the effects of obstructive versus central apnea on HF outcomes and cardiac arrhythmias particularly from the standpoint of treatment responsiveness.

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