REVIEW ARTICLE

Sleep Disordered Breathing in Heart Failure

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Introduction

Sleep disordered breathing (SDB) represents a spectrum of abnormalities that range in significance from the mild (simple snoring) to the severe (hypoventilation and sleep apnea-hypopnea). In the current literature, SDB is typically defined as an apnea-hypopnea frequency index (AHI) of fifteen or more per hour. SDB is further divided into obstructive sleep apnea (OSA) and central sleep apnea (CSA). In patients with heart failure, Cheyne-Stokes Respiration (CSR), a periodic form of crescendo-decrescendo breathing, is synonymous with CSA.

In OSA, upper airway-occlusion results in cessation of breathing despite continuous respiratory efforts , while in CSA, cessation of breathing primarily occurs due to lack of respiratory efforts for a period, arbitrarily specified as greater then 10 seconds. Breathing abnormalities during sleep are associated with fluctuations in the intra-thoracic pressure, episodic hypoxemia, hypercapnia and arousals. These consequences of SDB adversely affect sleep architect and the cardiovascular system. (1, 2) Considerable data now confirms the important link between SDB and cardiovascular complications, including hypertension, coronary artery disease and heart failure (HF). (3, 4)

That SDB occurs in HF has been known for more than two centuries, (5) but only recently has it become apparent that SDB occurs with higher frequency in patients with HF than in non-HF patients. (6) In recent years, HF has reached epidemic proportions. (7) Because CSR and OSA are both highly prevalent in HF patients, it is less widely appreciated that, along with the HF epidemic, an epidemic of HF-associated SDB has arisen.

Despite the fact that SDB is common in HF and causes serious cardiovascular and neuro-cognitive complications, the majority of SDB sufferers remain undiagnosed. Only by educating physicians who treat HF will this situation change. This chapter addresses the problem of SDB in patients with HF, beginning with some of the historically important developments regarding SDB in HF. The pathogenesis of SDB in HF is then discussed, along with a summary of the clinical presentation, diagnosis and management of SDB in HF patients. The aim of this chapter is to convince readers that SDB in HF is an important problem, that therapies are available for the treatment of SDB in patients with HF, and that appropriate interventions offer the possibility of improved longevity and quality of life for these patients.

Historical perspective

Heart failure has been known for more than two centuries to be associated with sleep-disordered breathing (SDB). In the 18th century, John Hunter, and thereafter John Cheyne and William Stokes in the19th century, described a periodic type of CSA, eventually termed Cheyne-Stokes Respiration (CSR), in patients with HF. (5, 8, 9) In 1934, Harrison et al. detailed the abnormal changes in the breathing pattern and the clinical significance of CSR during sleep in patients with HF. 10 Harrison and his colleagues were the first to recognize the importance of sleep as a precipitating factor in the

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development of CSR, and they recognized the impact of CSR upon sleep quality and daytime fatigue in patients with HF. Hanly et al. in 1989 were the first to describe in detail the polysomnographic features of CSR.(11) Despite considerable work over the decades, the exact mechanism of CSR in patients with HF, and the optimal treatment of CSR in HF, still remains elusive.

Prevalence

Most studies have documented that SDB occurs in about 50% of patients with clinically stable HF due to systolic dysfunction, (12-15) although other studies have found the prevalence to be as high as 80%. (16, 17) For the most part, when HF patients with systolic dysfunction have SDB, it is central sleep apnea (CSA), but many of these patients also have obstructive sleep apnea (OSA). In the only study of HF patients with diastolic dysfunction, 55% had SBD, mainly obstructive apneas. (18)

CSR and Co-morbid medical conditions

CSR is observed in a variety of conditions not related to HF, including high altitude, premature infants, occasionally in normal adults during sleep, and some neurological conditions. Various theories regarding the mechanism responsible for CSR have been proposed, but none of these theories are able to account for all the distinct features of CSR, while simultaneously explaining its occurrence in a multitude of seemingly unrelated conditions. Excellent reviews on this topic are available, and interested physicians are encouraged to read these articles. (19, 20)

Despite the variety of contexts in which CSR occurs, further discussion of CSR in this chapter will focus exclusively on CSR in HF. Another chapter of this book addresses OSA. For the most part, the etiology, pathophysiology and treatment of OSA do not differ between HF and non-HF patients.

Pathogenesis of CSR in HF

CSR is characterized by a waxing and waning of the tidal volume, in a crescendo-decrescendo pattern, with apnea or hypopnea developing at the nadir of the cycle. Ventilatory instability causes CSR, (21-23) resulting in repeated cycles of ventilatory overshoot (hyperventilation) alternating with ventilatory undershoot (hypoventilation). The degree of hyperventilation during ventilatory overshoot dictates, to a considerable extent, the magnitude of the hypoventilation during ventilatory undershoot. Likewise, the magnitude of ventilatory undershoot, in turn, determines the degree of ventilatory overshoot. Thus, hyperventilation elicits hypoventilation, and vice versa. This self-reinforcing pattern of hyperventilation alternating with hypoventilation results in cyclical, periodic breathing.

A number of hemodynamic and physiological alterations occur in heart failure that influence ventilatory stability. These alterations include an elevated left ventricular end diastolic pressure (LVEDP), pulmonary congestion, increased arteriovenous (AV) gas content difference, and increased circulatory delay. (24, 25) These abnormalities, interacting in a complex fashion, translate into ventilatory instability, resulting in CSR in some patients with heart failure.

One of the key events in the sequence appears to be an elevated left ventricular end-diastolic pressure with simultaneous pulmonary congestion. These physiological abnormalities elicit hyperventilation with resultant hypocapnia. (26) The relevance of hypocapnia to ventilatory stability is well established. Lowering the PCO2 below a critical threshold, termed the CO2-apnea threshold, can trigger apnea during sleep. (27, 28) Several studies have shown that HF subjects with a low arterial PCO2 (i.e. < 35 mm Hg) have a high probability of developing CSR. (2, 29, 30) However, it is probably simplistic to ascribe ventilatory instability to a single abnormality. In fact, many HF patients with CSR appear to have a normal PCO2, (31) thereby suggesting that other factors, including CO2 ventilatory responsiveness, may also play an important mechanistic role. When CO2 ventilatory responsiveness occurs, a large ventilatory response to CO2 may lower the PCO2 below the apneic threshold during sleep, resulting in central apnea. In support of this explanation, termed hypercapneic ventilatory responsiveness, Javaheri has shown that HF patients with CSR have a significantly larger ventilatory response to carbon dioxide than HF patients without CSR. (31)

Another hemodynamic abnormality in HF, prolonged circulatory time, plays a critical role in the development of CSR. (24, 25) The circulatory time in HF is prolonged as a result of reduced cardiac output and increased blood volume. This prolonged circulation time has the potential

to create cascades of changes in ventilatory control mechanisms that result in the development and/or maintenance of CSR. (21, 22, 32) Normally, the arterial blood gas changes that occur in the pulmonary circulation reach the carotid and central chemoreceptors promptly, typically within seven seconds. A prolonged circulation time delays this transfer of information by as much as 20 seconds or more. As a result, what is usually a negative feedback system is transformed into a positive feedback system. In this scenario, the arterial blood gas changes that occur during the apneic phase may reach the chemoreceptors *after* the apnea phase has terminated, thereby triggering ventilatory overshoot during hyperapnea. Guyton et al. confirmed that an increase in lung-chemoreceptor circulation time can result in periodic breathing. (32) However, the delayed circulation time in the Guyton experiment was in the range of up to 5 minutes, a delay that far exceeds the prolongation of the circulatory time that typically occurs in HF. Consequently, while it is apparent that an extremely prolonged circulatory time can produce CSR, it is also clear that the degree of circulatory time prolongation that typically occurs during HF is not the only factor required to produce CSR.

Another physiological variable that is abnormal in HF is the frequent (though not universal) finding of a reduced functional residual capacity (FRC). (33) The FRC can be reduced as a result of pleural effusions or cardiomegaly. A reduced FRC can result in an increased perturbation in PO2 or PCO2 for a specified change in ventilation. For example, during a given duration of apnea/hypoventilation, a lower FRC will result in a greater reduction in PO2 and a greater increase in PCO2, thereby eliciting a stronger hyperventilatory response with subsequent consequences during the next ventilatory cycle.

In HF patients, CSR does not occur exclusively during sleep, but it is more pronounced and more noticeable during sleep. Sleep amplifies the physiological mechanisms (mentioned above) that promote ventilatory instability, with CSR being the end result. Some of these effects have to do with the changes in posture that characterize sleep, whereas others are related specifically to the effect of the sleep state on ventilatory control.

Supine posture during sleep is associated with a reduction in FRC. As already discussed, a reduced FRC contributes to the development and maintenance of CSR. Supine posture also results in an increased LEVEDP and pulmonary congestion. In addition, during sleep there is a further reduction in cardiac output. These changes accentuate the circulatory delay that is characteristic of HF, thereby promoting ventilatory instability and CSR.

The effect of sleep state on ventilatory control has been a subject of intense research. Only the effects of sleep relevant to ventilatory control and the development of CSR will be mentioned here. First of all, sleep removes nonspecific neural excitation (also termed wakefulness neural drive inputs), one of the key mechanisms that limit ventilatory undershoot. The genesis of CSA during sleep relates specifically to removal of these wakefulness inputs on breathing and to the unmasking of the apneic threshold, the level of PCO2 below which rhythmic breathing ceases. (27, 28) Secondly, alveolar hypoventilation is normally observed during sleep due to reduced ventilation (more than the decline in metabolic rate). This change will result in a greater perturbation of arterial PCO2 and hypoxemia during a given period of apnea, with its own effect on ventilatory stability. (34) Furthermore, upper airway resistance is increased during sleep (35) and, in conjunction with the reduced chemo-responsiveness that occurs during sleep, has the potential to promote ventilatory instability. Lastly, compared to non-HF patients, HF patients spend relatively more sleep time in the light stages of sleep (stages 1 and 2). (11) Sleep stages 1 and 2 are characterized by frequent fluctuations between arousals and sleep, a pattern with a potential to trigger ventilatory oscillations and periodic breathing. In fact, CSR is mostly observed during sleep stages 1 and 2. (11)

Pathogenesis of OSA in HF

Onal and coworkers have advocated that ventilatory instability also underlies or promotes OSA. (36, 37) If this hypothesis is correct, then given similar risk factors regarding obesity and upper airway caliber, HF patients would have a greater likelihood than non-HF patients of developing OSA. Moreover, the jugular venous distension that occurs in HF may also exacerbate upper airway narrowing, thereby increasing the risk of OSA in individuals with HF. Indeed, the prevalence of OSA is significantly higher in patients with HF compared to the non-HF population. (6, 38)

Risk factors

While HF is a risk factor for SDB, several studies have identified factors apart from the HF itself that are associated with SDB. In the largest study to date, a retrospective study of 450 HF patients that included a substantial number of female patients, being a man, being older than age 60, having atrial fibrillation, and having hypocapnia are risk factors for CSA in patients with HF. (29) In addition, among patients with HF, being a man who is obese and being a woman who is older than age 60 are risk factors for OSA. (29) A separate study found that an elevated pulmonary wedge pressure increases the likelihood of having CSA. (26) Finally, two small studies found that HF patients with an elevated pulmonary artery pressure (echocardiographically estimated pulmonary artery pressure $\geq$ 35 mm Hg) have a 90-100% likelihood of having SDB. (39, 40)

Cardiovascular consequences of SDB in HF

SDB may adversely impact HF by increasing sympathetic nervous system activity (SNSA), by increasing ventricular irritability, and by promoting fluid retention. An elevated SNAS is associated with detrimental outcomes in patients with HF. (41) In a study comprising three groups, subjects with no HF and no SDB, subjects with SDB but without HF, and subjects with HF, there was a stepwise increase in the level of SNAS. (42) Subjects with neither SDB nor HF had the least SNAS, subjects with SDB and no HF had intermediate SNAS, and subjects with HF had the most SNAS. This same study found that the SNAS was not significantly different between HF patients without SDB compared to HF patients with OSA. However, SNAS was higher in subjects with HF and CSA compared to HF patients without SDB and compared to HF patients with OSA. A separate study found similar results, that HF patients with CSR have higher SNAS than HF patients without CSR. (43) Treating the CSR with nasal continuous positive airway pressure (CPAP) reduces the amount of SNAS in HF patients with CSR, thereby indicating a causal relationship between CSR and SNAS in the HF population. (42-44) Similarly, nasal CPAP decreases the SNAS in HF patients with OSA. (45)

Ventricular premature beats occur more often during episodes of CSR than during periods of regular breathing in subjects with HF. (46) Two studies have documented that treating SDB decreases the frequency of ventricular ectopy in HF patients. Among men with HF and SDB who were successfully treated with nasal CPAP, the frequency of nocturnal premature ventricular contractions and couplets decreased compared with men with HF SDB did not respond to nasal CPAP. (47) A separate study demonstrated that nasal CPAP reduces the frequency of ventricular premature beats in HF patients with OSA. (48)

One study has documented higher brain natriuretic peptide levels in HF patients with CSR compared with HF patients without SDB, (49) and another study found that brain natriuretic peptide levels decrease following successful treatment of the CSR in HF patients. (50) These results suggest that CSR is associated with increased intravascular volumes, possibly as a result of increased fluid retention. While there are no other studies evaluating the effect of SDB upon fluid retention in HF patients, several studies involving patients with normal LV function provide evidence that SDB promotes fluid retention. In patients with normal LV function, OSA is associated with fluid retention, at least in women. (51) Furthermore, nasal CPAP reduces the amount of fluid retention in patients with normal LV function and OSA, thereby indicating that OSA can cause fluid retention. (52) While the mechanism by which OSA promotes fluid retention is uncertain, it has been documented that cardiac output declines 30% during apneic episodes in subjects with normal LV function, then returns to baseline once the apnea has resolved. (53) Although the reason for this decrease in cardiac output has not been determined, the most likely explanation is that LV function deteriorates during apneic episodes. While the effects of OSA upon fluid retention and LV function have not been studied in HF patients, the effects are likely to be the same as in patients with normal LV function. Thus, it is probable that OSA promotes fluid retention by episodically worsening the LV ejection fraction in HF patients. Likewise, even though CSA differs from OSA in some important respects, the hemodynamic consequences of the two conditions are likely similar. Consequently, it is probable that CSA promotes fluid retention in patients with HF via a process that is similar to the mechanism by which OSA promotes fluid retention in non-HF patients.

Interrelationship between HF and SDB

HF patients with SDB have a worse prognosis than HF patients without SDB, (54 -56) and the worse the HF, the worse the SDB. (12, 55) Furthermore, treating the HF, or optimizing the treatment of the HF, improves or resolves the SDB. (57, 58) However, the nature of the relationship between SDB and HF may be bidirectional, such that SDB and HF both causally influence one another. Hence, in patients with SDB and HF, treating the SDB improves the HF, (59-64) although one study found that treating the SDB did not improve outcomes in patients with HF. (65)

Clinical Features

The majority of patients with SDB, at least those without HF, present with snoring, nocturnal gasping and daytime somnolence. The symptoms of SDB in HF patients can be different. Difficulty falling asleep and sleep maintenance insomnia are common complaints in patients with HF. (33) Some patients awaken at the onset of sleep complaining of shortness of breath, with a sensation of distress and fear. (10) This coincides with the development of CSR. Patients may develop a fear of falling asleep, resulting in chronic insomnia. Following sleep onset, there are frequent arousals linked to CSR that cause sleep fragmentation. Most of these patients do not enter into restorative delta sleep. The majority of HF patients, with or without SDB, suffer from poor sleep quality and daytime fatigue without daytime sleepiness. (66) Furthermore, the symptoms of heart failure overlap with the symptoms of SDB in HF: insomnia, orthopnea, poor sleep quality, and daytime fatigue. This overlap of symptomatology may contribute to the under-diagnosis of SDB in individuals with HF. In summary, the HF symptoms of poor quality of sleep and daytime fatigue overlap with the symptoms of SDB. (66) Moreover, in contrast to patients with OSA, patients with CSR do not snore and they are often not obese.

Polysomnographic Findings

During polysomnography, respiratory efforts are monitored by thoraco-abdominal motion by utilizing inductive plethysmogrpahy or strain gauge. Apneas are considered central when there is no detectable respiratory effort. In contrast, during obstructive apnea or hypopnea, respiratory efforts persist and continue to crescendo until the apnea is terminated.

CSR is characterized by waxing and waning cycles of hyperventilation–hypoventilation, including apneas that recur with amazingly regular periodicity. The crescendo-decrescendo breathing of CSR typically has a cycle length of sixty seconds that continues for 10 minutes at a stretch. CSR predominantly occurs during sleep stages 1 and 2 and lessens during REM sleep, (11) whereas OSA usually worsens during REM sleep.

CSR is frequently accompanied by multiple electroencephalographic arousals, usually coinciding with the peak of the hyperventilation phase. Arousals associated with CSR may play a role in the pathogenesis of CSR, i.e. the arousals may increase the magnitude of the ventilatory overshoot during hyperpnea with a subsequent undershoot during hypoventilation. Arousals during OSA are dissimilar in that they occur at the end of apnea and may play a role in the resumption of breathing.

Overall sleep architecture in patients with CSR and HF is notable for several abnormalities, predominantly delayed sleep onset, frequent wakening and markedly reduced delta sleep stages 3-4. (11) These changes in sleep parameters are also found in HF patients who lack SDB.

Treatment of OSA in HF

For HF patients with OSA, the initial treatment of the OSA is the same as for OSA patients without HF. Weight loss, avoidance of alcohol and avoidance of sedative medications should be advised. (67)

Nasal CPAP is a logical intervention for treating OSA in the setting of HF if lifestyle changes are ineffective. Nasal CPAP reduces left ventricular afterload in patients with HF and OSA. (68) In the most important study to date regarding nasal CPAP, OSA and HF, a randomized, placebo controlled trial involving 24 subjects that lasted for one month, nasal CPAP improved the LV ejection fraction in HF patients with OSA from a pre-treatment LV ejection fraction of 25 to a post-treatment LV ejection fraction of 34. (64) Other studies have also documented that treating the OSA in patients with HF improves LV ejection fractions considerably. (59, 63) While it is logical to expect that a higher LV ejection fraction translates into improved mortality and morbidity, and while nasal CPAP has been demonstrated to reduce cardiovascular

deaths in OSA patients (only a fraction of whom had HF), (70) there has been no longitudinal, placebo controlled study to verify that nasal CPAP improves long-term survival in HF patients who have OSA. Despite inadequate long-term data, the benefits of short-term nasal CPAP in HF patients with OSA warrant prescribing nasal CPAP for these patients.

Mandibular advancement devices are a recognized treatment for OSA in the non-HF population. A Swedish group has shown that mandibular advancement devices may have a place in the treatment of HF patients with OSA since these devices lessen the AHI in HF patients with SDB. (71, 72)

Treatment of CSR in HF

Optimization of heart failure therapy with diuretics, angiotensin-converting enzyme inhibitors, beta blockers, and angiotensin receptor blockers improves, and may even eliminate, CSR. In addition, after cardiac transplantion, CSR is virtually eliminated. The treatment for persistent CSR in HF is problematic because there is little evidence that therapeutic interventions benefit long-term survival. Consequently, there is currently no consensus on whether to treat, or how to treat, CSR in patients with underlying HF. Interventions that have shown promise include theophylline, supplemental oxygen, nasal CPAP and resynchronization therapy.

In a small placebo controlled study of men with HF and CSR, orally administered theophylline for 5 days reduced the frequency of apneas and hypopneas. (73) A separate, uncontrolled study found similar results, that theophylline significantly reduced the AHI in 13 subjects with SDB, most of whom had CSA. (74) Neither of these two studies evaluated the effect of theophylline upon the LV ejection fraction. Even more important, there is no data regarding the long-term effect of theophylline upon mortality and morbidity in patients with HF and CSR.

Oxygen therapy improves the AHI in HF patients with CSA in short-term studies lasting for one night. (58, 67, 75-77) As with theophylline, no study of oxygen treatment for CSA in HF patients has documented the effect upon the LV ejection fraction, and there is no long-term data regarding the effect of intranasal oxygen upon survival in HF patients with CSA.

Several placebo controlled, short-term studies, most of which lasted from one to three months, have documented dramatically lower AHIs, and improved LV ejection fractions, in HF patients with CSR treated with nasal CPAP. (60-62) A separate placebo controlled, short-term study demonstrated that bi-level positive airway pressure (bi-level PAP) also improves the LV ejection fraction in HF patients with CSR. (50)

Since nasal CPAP improves LV ejection fractions and lessens sympathetic nervous system activity in HF patients with CSR, one might expect that nasal CPAP would improve the survival of these individuals. However, the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure (CANPAP), a prospective, two year long, randomized, open label trial of CPAP involving 258 HF subjects with CSR, found that the addition of nasal CPAP to conventional HF therapy did not improve mortality, frequency of heart transplantation, or rate of hospitalization for HF, even though nasal CPAP reduced the frequency of apneas and hypopneas per hour (from 40 to 19 in the intervention group versus 40 to 38 in the control group), improved LV ejection fractions (by 2.2% in the intervention group versus 0.4% in the control group), and reduced norepinephrine levels. (78) That nasal CPAP did not improve survival, cardiac transplantation or hospitalization may be attributable to inadequate compliance with CPAP (the average nightly use of CPAP was 4.3 hours during the initial 3 months and 3.6 hours at one year and beyond), lack of efficacy of CPAP (an explanation that is consistent with the modestly improved LV ejection fractions that, while statistically significant, may be clinically trivial), the possibility that CSA does not directly contribute to the progression of HF, but rather represents an epiphenomenon, (79) or the possibility that the AHI must be reduced to some level less than 19 in order to benefit HF patients with CSR. The CANPAP investigators had a difficult time enrolling eligible subjects, suggesting that current pharmacological therapies for HF may be changing the prevalence of CSA in HF patients, (79) and the CANPAP study was terminated early, in part due to a falling rate of death and transplantation in both groups that might be attributable to improved pharmacological therapy for HF in recent years. Until a more definitive study is performed, the CANPAP results argue against the routine use of CPAP in HF patients with CSA.

The most recent intervention for treating HF patients

with CSA is resynchronization therapy. Two studies have documented that this form of treatment decreases the AHI in HF patients with CSR, (80, 81) but there is no available data regarding the effect of resynchronization therapy upon LV ejection fractions and upon survival.

Conclusion

Sleep occupies one third of our lives and has important implications for our daytime functionality and quality of life. OSA and CSR, the most common forms of SDB, affect a disproportionately high number of patients with HF. Breathing abnormalities during sleep result in non-restorative sleep and may contribute to a progressively declining course of heart failure, including daytime functionality and overall survival. Despite the fact that SDB is common in HF and despite the fact that SDB can be easily detected, the majority of HF patients with SDB remain undiagnosed. It is important that sleep specialists educate those physicians who have the most contact with HF patients—cardiologists, internists and family physicians—about the magnitude and importance of SDB in these patients.

While treating HF patients with OSA is warranted, the data regarding the treatment of HF patients with CSR is less clear cut. Nonetheless, if CSR does accelerate the HF disease process, then effective correction of this form of SDB may improve the HF and reduce the associated morbidity and mortality.

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