Central Sleep Apnea and Cheyne-Stokes Respiration

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Cheyne-Stokes respiration with central sleep apnea (CSR-CSA) is a form of periodic breathing, commonly observed in patients with heart failure (HF), in which central apneas alternate with hyperpneas that have a waxing-waning pattern of tidal volume. Uniform criteria by which to diagnose a clinically significant degree of CSR-CSA have yet to be established. CSR-CSA is caused by respiratory control system instability characterized by a tendency to hyperventilate. Central apnea occurs when Pa_{CO_2} falls below the threshold for apnea during sleep due to ventilatory overshoot. Patients with CSR-CSA are generally hypocapnic, with a Pa_{CO_2} closer than normal to the apneic threshold such that even slight augmentation in ventilation drives Pa_{CO_2} below threshold and triggers apnea. Factors contributing to hyperventilation in HF include stimulation of pulmonary irritant receptors by pulmonary congestion, increased chemoreceptor sensitivity, reduced cerebrovascular blood flow, and recurrent arousals from sleep. Controversy remains as to whether CSR-CSA is simply a reflection of HF severity, or whether it exerts unique adverse effects on prognosis. The main adverse influence of CSR-CSA on cardiovascular function appears to be excessive sympathetic nervous system activity due to apnea-related hypoxia and arousals from sleep. A number of studies have examined the potential relationship between CSR-CSA and mortality in HF. Most reported that CSR-CSA was associated with an increased risk for mortality, but these studies were small. Further research is therefore needed to elucidate mechanisms which contribute to the pathogenesis of CSR-CSA, and to determine whether its treatment can reduce morbidity and mortality in patients with HF.

Keywords: sleep-disordered breathing; heart failure; diagnosis; pathophysiology

Central sleep apnea (CSA) is commonly observed in patients with heart failure (HF), in whom it appears to have adverse prognostic implications (1–5). These observations have stimulated interest among the sleep, respiratory, and cardiovascular research communities in determining its pathophysiology and clinical significance. Our main objective in this article, therefore, is to review the definition, pathophysiology, and clinical significance of CSA in patients with HF. We will confine our discussion to patients with HF secondary to left ventricular (LV) systolic dysfunction. Although a number of clinical trials using various interventions have been performed to determine whether alleviating CSA might improve cardiovascular outcomes in patients with HF, we will not discuss treatment of CSA since we have recently reviewed this topic in depth (6).

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DEFINITION AND DIAGNOSIS OF CENTRAL SLEEP APNEA AND CHEYNE-STOKES RESPIRATION

Central Sleep Apnea

Central sleep apneas and hypopneas arise from complete or partial reductions in central neural outflow to the respiratory muscles during sleep that lead to complete or partial cessation of airflow for at least 10 seconds, respectively (7, 8). In contrast to obstructive apneas, in which inspiratory efforts are made against the occluded upper airway owing to continued presence of respiratory drive, no respiratory effort is generated during central apneas due to cessation of respiratory drive. Thus central apneas are distinguished from obstructive apneas by the absence of respiratory effort, which can be readily detected by routine monitoring techniques such as respiratory inductive plethysmography (RIP) or nasal pressure (8–11). Less sensitive techniques, such as oro-nasal thermistors or piezo-electric crystal bands, have not been proven reliable in this regard.

Distinguishing central from obstructive hypopneas is more difficult, because in both cases, respiratory efforts continue. In the case of obstructive hypopneas, airflow decreases mainly as a consequence of upper airway obstruction, and therefore evidence of upper airway obstruction should be present, such as out-of-phase thoraco-abdominal motion on RIP, or flow limitation on the nasal pressure signal (7, 8, 10, 11). In the case of central hypopneas, airflow decreases mainly as a consequence of reduced respiratory drive, so that there should be no evidence of upper airway obstruction; thoraco-abdominal motion should be in-phase, and there should be no evidence of flow-limitation on the nasal pressure signal. Examples of central and obstructive hypopneas are illustrated in Figure 1. Although the ability of RIP and nasal pressure to distinguish between central and obstructive hypopneas has not been specifically addressed, both techniques have been validated against esophageal pressure as means of detecting airflow limitation (7, 10, 12). Consequently, both techniques can be used under most circumstance to distinguish central from obstructive apneas and hypopneas (8, 13–15). Nevertheless, it is not always possible to distinguish central and obstructive hypopneas with these techniques. In such cases, esophageal pressure and diaphragmatic electromyogram can be used, but are invasive and require specialized equipment not available in most sleep laboratories. These techniques are not suitable for routine monitoring, but are usually reserved for research purposes. During central hypopneas, airflow or tidal volume will decrease in proportion to the fall in inspiratory esophageal pressure swings and diaphragmatic electromyographic activity. In contrast, during obstructive hypopneas, airflow or tidal volume will decrease to a disproportionately greater degree than the reduction in inspiratory esophageal pressure swings and diaphragmatic electromyographic activity, indicating the presence of additional respiratory drive to overcome the increased airflow resistance of the upper airway.

Because most sleep laboratories study patients referred for assessment of snoring and possible obstructive sleep apnea (OSA), and because OSA is far more common in the general population than CSA (16), they frequently do not classify hypopneas as being obstructive or central. In most cases, it is assumed that

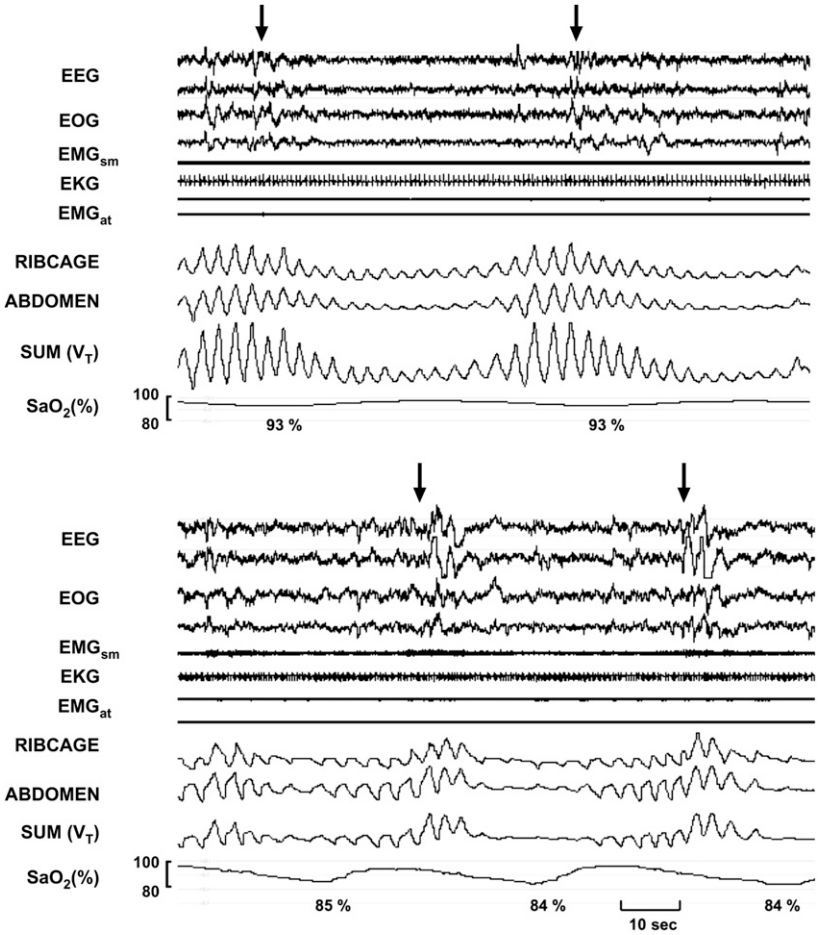

Figure 1. Polysomnographic recordings of central and obstructive hypopneas from patients with heart failure with use of respiratory inductance plethysmography (RIP). The *upper panel* shows a central hypopnea during stage 2 sleep in a patient who has Cheyne-Stokes respiration with central sleep apnea. Note in-phase gradual waxing and waning of tidal volume during hyperpnea, and only minimal O_2 desaturation during hypopnea. Arousal occurs several breaths after termination of the hypopnea. The *lower panel* shows an obstructive hypopnea in a patient with obstructive sleep apnea. Note that in contrast to central hypopnea, rib cage and abdominal motion are out-of-phase and O_2 desaturation is greater during hypopnea, the rise in ventilation following its termination is more abrupt and hyperpneas are shorter. In addition, arousals occur earlier at hypopnea termination. EEG = electroencephalogram; EKG = electrocardiogram; EMG_{sm} = submental electromyogram; EMG_{at} = anterior tibial EMG; EOG = electrooculogram. *Arrows* (↓) indicate arousals.

hypopneas are obstructive. However, when studying patients with cardiovascular diseases, especially those with HF and stroke, where CSA is much commoner than in the general population, distinguishing central from obstructive events assumes greater importance (14, 17, 18). Since, in the majority of patients with sleep apnea, most respiratory events are hypopneas, the determination of hypopnea type is also far more important in patients with cardiovascular diseases than in the general population. This is of practical importance, since in patients with HF, OSA is rapidly and completely reversed by continuous positive airway pressure (CPAP) (19, 20), whereas CSA responds more slowly and less completely to CPAP (15, 21).

The diagnosis of CSA generally requires overnight polysomnography. However, the diagnostic criteria for CSA and CSA syndrome are not well defined. For example, there are no consistent criteria for the total apnea–hypopnea index (AHI), the proportion of central versus obstructive events, nor for the degree of O_2 desaturation in association with a respiratory event required for this diagnosis. There are also no consistent criteria for the diagnosis of CSA syndrome: most HF patients with CSA do not complain of excessive daytime sleepiness or snoring (17), and there are no data on the frequency of potential symptoms, such as nocturnal dyspnea, morning headaches, and restless sleep. Consequently, until more data emerge, the diagnosis of CSA in patients with HF rests on the demonstration of recurrent central apneas and hypopneas during overnight polysomnography. Although there is no consistent AHI criteria to define a clinically significant degree of CSA, the majority of evidence show that in patients with HF, those with CSA defined as an AHI of ≥ 5 to ≥ 30, in which at least 50% of events are central, have worse survival than patients with AHI below these threshold levels after controlling for confounding factors (1–5).

In terms of O_2 desaturation, there is generally less desaturation during central apnea and hypopnea than during obstructive ones in patients with HF (22). Studies on the relationship of Cheyne-Stokes respiration (CSR)-CSA to mortality risk have not identified whether the degree of desaturation related to apneas and hypopneas contributes to mortality (1–5, 23, 24). In addition, Series and colleagues (25) found that a 2% or greater Sa_{O_2} dip rate is more sensitive than a 4% or greater dip rate for identifying apneas and hypopneas defined by reductions in ventilation assessed by RIP. Accordingly, several studies of patients with HF have defined hypopneas by reductions in tidal volume or ventilation alone without any O_2 desaturation criterion (1, 14, 15, 18, 26). Based on these observations, it may not be appropriate to use an O_2 desaturation criterion to define hypopneas during CSR-CSA, because if one did, many episodes in which tidal volumes fell below 50% of baseline would not be considered a hypopnea, and the severity of sleep-disordered breathing would be underestimated. Consequently, the diagnosis of CSA and the rationale for exploring the efficacy of treatments for it rest almost entirely on the evidence that CSA increases the risk of death in patients with HF, but not on evidence that CSA causes distinct clinical symptoms. Based on this evidence, we propose that in patients with HF, a diagnosis of CSA can be established on overnight polysomnography, using either RIP or nasal pressure cannula for respiratory monitoring, when there is an AHI of at least 5 to 15, and when at least 50% of apneas and hypopneas are central. However,

there is a need to establish uniform criteria for the diagnosis of CSA, and to determine whether there are distinct symptoms associated with CSA that would constitute a CSA syndrome.

Cheyne-Stokes Respiration

Cheyne-Stokes respiration (CSR) is a form of periodic breathing in which, according to the original description by Cheyne (27), the ventilatory period is characterized by a prolonged waxing-waning pattern of tidal volume followed by central apnea or hypopnea. It is noteworthy that the patient in whom Cheyne first described this breathing disorder suffered from HF, atrial fibrillation, and a stroke, and undoubtedly had a low cardiac output and prolonged circulation time. It has subsequently been shown that the number of breaths in, and duration of, hyperpnea are directly proportional to the lung to peripheral chemoreceptor circulation time, and inversely proportional to cardiac output (18, 28, 29). In contrast, apnea duration bears no relation to circulation time or cardiac output. Thus variations in the duration of the periodic breathing cycle are more closely linked to variations in the duration of hyperpnea than of apnea.

In patients with HF and CSR, the periodic cycle duration averaged approximately 60 seconds, similar to that described by Cheyne, compared with only 35 seconds in patients with idiopathic CSA or high-altitude periodic breathing without HF (18, 28). Thus it is the presence of a prolonged hyperpnea with a waxing-waning pattern of tidal volume, and prolonged cycle duration, that distinguishes CSR from other forms of periodic breathing. Therefore, if the term "Cheyne-Stokes respiration" is to have any distinctive meaning, its use should be confined to periodic breathing in which the hyperpnea and cycle durations are prolonged. Since this pattern is characteristic of prolonged lung to chemoreceptor circulation time, it appears to be a manifestation of a low cardiac output as one would observe in patients with HF or bradyarrhythmias.

CSR can be observed both during sleep and wakefulness, although it appears to be far more common during sleep (30, 31). When it occurs during sleep, it is simply a form of CSA with a prolonged hyperpnea. When specifying the occurrence of CSR during sleep, we have used the term "Cheyne-Stokes respiration with central sleep apnea (CSR-CSA)." This term also connotes CSA in the presence of a low cardiac output state. In general, the use of the term "CSA" in patients with HF is synonymous with CSR or CSR-CSA. Because this article focuses on patients with HF, for the sake of clarity, we will use the term "CSR-CSA" when CSR occurs during sleep, and "CSR" when it occurs during wakefulness, or during both wakefulness and sleep. An example of CSR-CSA in a patient with HF, and of CSA in a patient without HF, is shown in Figure 2 to illustrate the difference in the pattern of hyperpnea between the two.

PATHOPHYSIOLOGY

CSR-CSA in patients with HF arises because of respiratory control system instability. Ventilation is dependent mainly on the metabolic rather than the behavioral respiratory control system during sleep, and the primary stimulation for ventilation while asleep is Pa_{CO_2} (30). Central apnea during sleep occurs when Pa_{CO_2} falls below the apnea threshold. CSR-CSA is present when central apnea occurs cyclically. Several factors that destabilize the respiratory control system predispose to the development of CSR-CSA. Figure 3 illustrates the proposed mechanisms leading to periodic oscillations in ventilation in HF. A key factor predisposing to respiratory control system instability and CSR-CSA is chronic hyperventilation with eupneic Pa_{CO_2} close to the apnea threshold. Patients with HF with CSR-CSA have lower Pa_{CO_2} than those without CSR-CSA in both the waking and sleeping states (32, 33). This chronic hyperventilation occurs because of pulmonary vagal irritant receptor

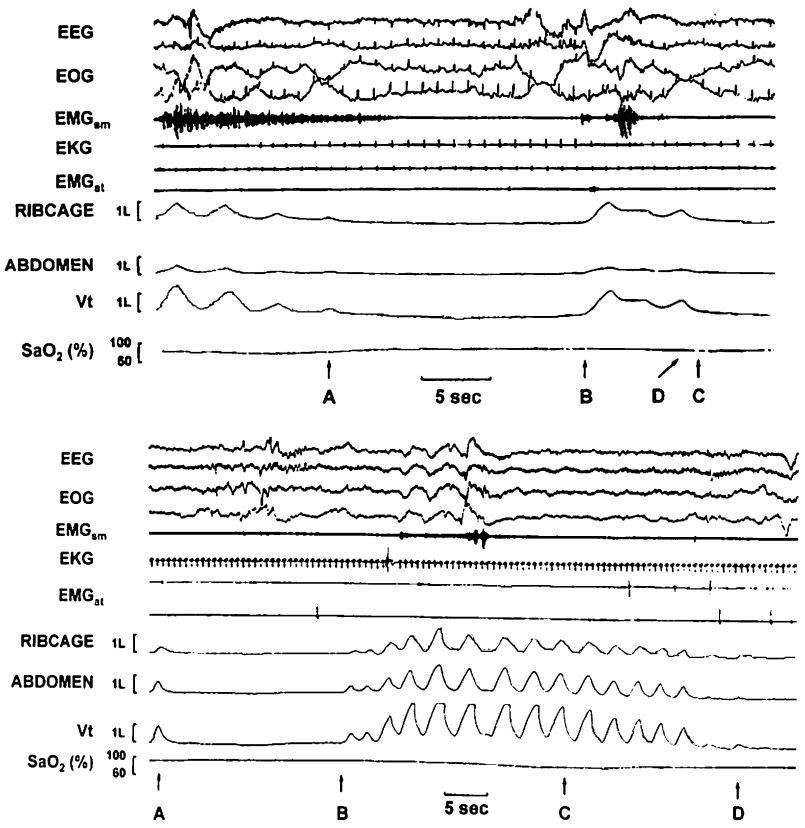

Figure 2. Polysomnographic recordings demonstrating differences in periodic breathing patterns between a patient with and without heart failure (HF). The *upper panel* shows a recording from a patient with idiopathic central sleep apnea (ICSA) during stage 2 sleep. Apnea length (AB) is 18 seconds, hyperpnea length (BD) is 7 seconds, and cycle length (AD) is 25 seconds. C represents the nadir of Sa_{O_2} (arterial oxygen saturation), detected by an oximeter placed on the ear in close proximity to the carotid body chemoreceptors. From the end of apnea (B) to the nadir in Sa_{O_2} (C) is the lung-to-ear circulation time (BC), which is 8 seconds and approximates lung-to-carotid body circulation time. The *lower panel* is a recording from a patient with HF and Cheyne-Stokes respiration with central sleep apnea (CSR-CSA) during stage 2 sleep. Compared with the patient with ICSA, lung-to-ear circulation time (BC = 26 s), hyperpnea (BD = 46 s), and cycle lengths (AD = 65 s) are substantially longer. However, apnea length (AB = 21 s) is similar. Abbreviations are the same as for Figure 1. Adapted by permission from Reference 28.

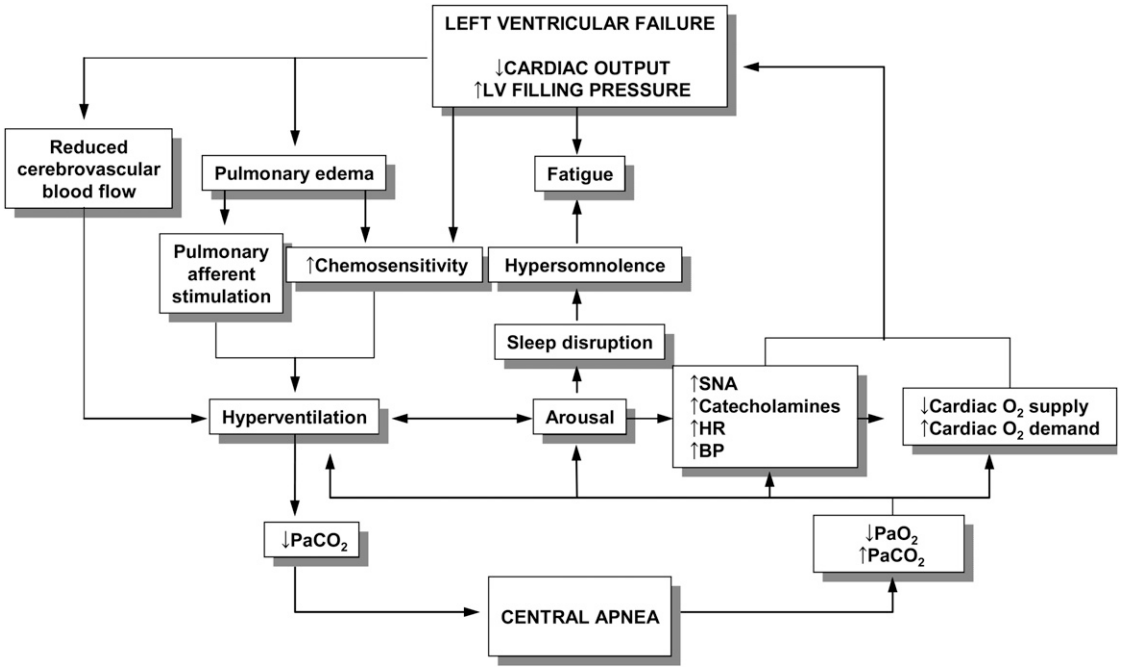

Figure 3. Pathophysiologic scheme of CSR-CSA in heart failure. BP = blood pressure; HR = heart rate; SNA = sympathetic nervous system activity. Modified by permission from Reference 93.

stimulation by pulmonary congestion (34–37) and increases in central and peripheral chemosensitivity (38, 39). Pulmonary congestion activates pulmonary vagal afferent C fibers, which stimulate central respiratory drive (37). Compared with patients with HF without CSR-CSA, those with CSR-CSA have significantly higher pulmonary capillary wedge pressures, and presumably, more pulmonary congestion (35). Indeed, in patients with HF, Pa_{CO_2} is inversely proportional to pulmonary capillary wedge pressure (36). Lowering wedge pressure with drugs or CPAP is associated with a rise in Pa_{CO_2} and alleviation of CSR-CSA (35, 36). Compared with patients with HF without CSR-CSA, those with CSR-CSA have increased peripheral and central chemoresponsiveness that promotes hyperventilation and hypocapnia (38, 39). While the reason for this increased chemoresponsiveness is not well understood, there is evidence that induction of HF in experimental animals augments peripheral chemoresponsiveness, but the mechanism for the effect is poorly understood (40).

CSR occurs more frequently during non–rapid eye movement (NREM) sleep than either wakefulness or REM sleep (30, 31). In NREM sleep, ventilation is predominantly under metabolic control, and therefore is very tightly linked to alterations in Pa_{CO_2}, the apneic threshold for Pa_{CO_2}, and CO_2 sensitivity. Owing to a reduction in central respiratory drive and the loss of the nonchemical wakefulness drive to breath that maintains ventilation even when Pa_{CO_2} falls below the apnea threshold, breathing becomes critically dependent on the metabolic control system during NREM sleep (30, 31). Ventilation therefore decreases, and Pa_{CO_2} and the apneic Pa_{CO_2} threshold increase during the transition from wakefulness to NREM sleep. As long as Pa_{CO_2} remains greater than the apneic threshold, rhythmic breathing continues. However, in patients with HF with CSR-CSA, Pa_{CO_2} tends not to increase from wakefulness to sleep (41, 42), but the apneic threshold does. This predisposes to central apnea in two ways. First, if prevailing Pa_{CO_2} remains below the new, higher apnea threshold at the onset of sleep, central apnea will ensue. Pa_{CO_2} will rise during apnea, and once it reaches the ventilatory threshold for NREM sleep, ventilation will resume. Second, even if Pa_{CO_2} does not remain below the higher apnea threshold of NREM sleep, it will be closer to this apnea threshold than during wakefulness. During NREM sleep, episodes of central apnea are most frequently triggered by abrupt increases in ventilation and reduction in Pa_{CO_2}, usually precipitated by spontaneous arousals from sleep (33). The closer the prevailing Pa_{CO_2} is to the apnea threshold, the more likely it is that central apnea will occur in response to a given increase in ventilation. The critical role of hypocapnia in triggering central apneas is demonstrated by the observation that raising Pa_{CO_2} by inhalation of a CO_2-enriched gas abolishes CSR-CSA instantaneously (43).

While in OSA arousals act as a defense mechanism to terminate apneas, and activate pharyngeal muscles that allow resumption of airflow, in CSA they appear to instigate central apneas by provoking ventilatory overshoot. The important role of arousal in sustaining ventilatory overshoot during periodic breathing is indicated by the strong correlation between the magnitude of arousal, and both ventilation during hyperpnea and subsequent apnea duration (31, 33, 44). Increases in ventilation in response to arousals occur due to both nonchemical and chemical factors. The abrupt change in state elicits reinstitution of the nonchemical, waking neurogenic drive to breathe. In addition, the change in state causes a sudden increase in chemical respiratory drive, and reversion to the lower Pa_{CO_2} set-point of wakefulness. Since Pa_{CO_2} has risen during NREM, following arousal, it is higher than the wakefulness set-point. This, combined with the greater ventilatory responsiveness of wakefulness, causes the respiratory control system to quickly augment ventilation to lower Pa_{CO_2} to the wakefulness set-point (30, 31). If there is an abnormally high sensitivity to Pa_{CO_2}, which is characteristic of patients with HF with CSR-CSA, ventilatory overshoot occurs, which drives Pa_{CO_2} down below the set-point. If the patient then returns to NREM sleep, Pa_{CO_2} is now below the higher apnea threshold, and central apnea occurs. Recurrent arousals during the ventilatory phase of CSR-CSA propagate CSR-CSA (31, 33, 43). However, if recurrent arousals do not occur during the ventilatory phase, ventilatory overshoot is dampened, respiration stabilizes and CSR-CSA resolves. Figure 1 illustrates how arousals occur at the termination of obstructive hypopneas, but that they often occur several breaths after termination of central hypopneas. This latter observation indicates that arousals seem not to play

a critical role in resumption of normal ventilation following central events.

This sequence of events illustrates how shifts in state of consciousness, either due to transition from wakefulness to NREM sleep, or to spontaneous arousals from sleep, destabilize the respiratory control system and facilitate the development of central apneas and periodic breathing. Because CSR-CSA is a consequence of instability of the respiratory metabolic control system, it occurs mainly during NREM sleep when breathing is predominantly under metabolic control. In contrast, CSR occurs much less frequently in wakefulness where breathing is less dependent on the metabolic control system, and where the nonchemical wakefulness drive to breath stabilizes breathing (30, 31, 45). Similarly, CSR-CSA is much less common in REM sleep than in NREM sleep for several reasons (13, 33). First, ventilation is under predominantly behavioral rather than metabolic control, such that it is insensitive to changes in Pa_{CO_2}. Second, respiratory drive and muscle activity are reduced in REM sleep, such that Pa_{CO_2} rises above NREM levels and the difference between prevailing Pa_{CO_2} and the apnea threshold increases (46). Third, arousability to chemical respiratory stimuli is diminished compared with NREM sleep, and this, combined with weakness of the respiratory muscles, diminishes the likelihood of ventilatory overshoot and hypocapnia (31, 47).

Abnormalities of cerebrovascular reactivity to CO_2 in patients with HF may also contribute to respiratory instability. Normal reflex changes in cerebrovascular blood flow provides an important counterregulatory mechanism that serves to minimize the change in hydrogen ion concentration ($[H^+]$) at the central chemoreceptor, thereby stabilizing the breathing pattern in the face of perturbations in Pa_{CO_2}. For example, arterial hypocapnia normally causes marked cerebral vasoconstriction and reduced cerebral blood flow, which attenuates the decrease in brain Pa_{CO_2} relative to that in the arterial blood. Accordingly, ventilatory inhibition in response to reduced arterial Pa_{CO_2} will be diminished due to the attenuated decrease in central chemoreceptor $[H^+]$. Compared with patients with HF without CSR-CSA, those with CSR-CSA have impaired cerebral blood flow responses to CO_2, such that the fall in flow for a given decrease in arterial Pa_{CO_2} is reduced. This permits a greater reduction in brain Pa_{CO_2} and $[H^+]$. The chemoreceptors will then be exposed to a greater degree of alkalosis than normal, with a consequent greater tendency to develop ventilatory undershoot, and hence, central apnea (48). An impaired vasodilator response to increasing arterial Pa_{CO_2} during apnea will have the opposite effect and hence promote ventilatory overshoot at apnea termination (48). Accordingly, compromised cerebrovascular blood flow responsiveness to CO_2 may contribute to breathing instabilities during NREM sleep, and predispose to CSR-CSA.

Several additional factors, such as metabolic alkalosis, low functional residual capacity, upper airway instability, and hypoxia, may further contribute to respiratory instability and CSR-CSA. Metabolic alkalosis resulting from diuretic use in patients with HF could cause a decrease in the gap between prevailing and apneic threshold Pa_{CO_2} (49). In sleeping dogs, metabolic alkalosis increases the apnea threshold to a greater degree than it increases eupneic Pa_{CO_2}. As a result, dogs are more susceptible to periodic breathing during metabolic alkalosis (50). Indeed, Javaheri (51) showed in humans with HF that CSR-CSA improved in response to induction of metabolic acidosis by administration of acetazolamide even though it reduced Pa_{CO_2}. Induction of metabolic acidosis therefore provides a constant drive to breathe through production of H^+, and emphasizes that the effects of Pa_{CO_2} on ventilatory drive occur secondary to its effects on hydrogen ion concentration and pH. In the case of acetazolamide, the increased hydrogen ion concentration reduces prevailing pH and widens the gap between it and the higher pH threshold for apnea, and thus stabilizes breathing (49). Another way to look at this is that acetazolamide decreases prevailing Pa_{CO_2} to a lesser extent than it decreases the apnea threshold for Pa_{CO_2}, and thus widens the difference between the two. Thus, in the genesis of CSR-CSA, a reduced difference between prevailing Pa_{CO_2} and apnea threshold for Pa_{CO_2} is more important than the prevailing Pa_{CO_2} itself. In any case, diuretic-induced metabolic alkalosis may facilitate CSR-CSA in a substantial number of patients, since a recent study by Milionis and coworkers (52) demonstrated that 25% of patients with HF had metabolic alkalosis, either alone or with coexisting respiratory alkalosis.

Patients with HF may have reduced functional residual capacity for several reasons, including cardiomegaly, pleural effusion, and pulmonary edema. Large functional residual capacity acts as an O_2 and CO_2 reservoir that dampens oscillations in Pa_{O_2} and Pa_{CO_2} that occur during apneas (53, 54), and therefore tends to stabilize respiration. A reduction in functional residual capacity reduces lung O_2 and CO_2 reservoirs such that, for a given apnea duration, the fall in Pa_{O_2} and rise in Pa_{CO_2} will be greater than they would if functional residual capacity was normal. This could contribute to post apneic ventilatory overshoot and instability of the respiratory control system. However, Naughton and colleagues (33) reported that lung volume in stable ambulatory patients with HF with CSR-CSA does not differ from that in patients without it. Thus, the role of reduced lung volume in the pathogenesis of CSR-CSA remains unclear.

Upper airway instability may also play a role in the pathogenesis of CSR-CSA. Alex and coworkers (55) described upper airway occlusion at the onset and end of some central apneas in selected patients with HF. If upper airway resistance increases as ventilation decreases during the decrescendo phase of the hyperpneic segment of CSR-CSA, ventilatory undershoot is more likely to occur. The occasional occluded breath noted at the onset of central apnea during CSR-CSA is compatible with this (55). However, a decrease in resistance as ventilation increases during the crescendo phase of hyperpnea could facilitate ventilatory overshoot, making post-hyperventilation apnea more likely to occur. In addition, upper airway collapse itself may precipitate central apnea reflexively (56). Passive collapse of the upper airway after the onset of central apnea could also play a role in the pathogenesis of mixed apneas (57), such that once chemical drive increases above the apnea threshold, inspiratory efforts are then generated against an occluded pharynx. Therefore, one potential mechanism through which CPAP may attenuate CSR-CSA is by stabilizing the upper airway (15, 58–60). However, CPAP exerts many other effects that could dampen periodic breathing, such as lung inflation, augmentation of cardiac output, and reductions in LV filling pressure and pulmonary edema (61).

Hypoxia precipitates CSA at high altitude by causing hyperventilation and lowering Pa_{CO_2} below the apnea threshold (62). High-altitude periodic breathing can be abolished either by administration of supplemental O_2 or CO_2 (62). However, patients with HF with CSR-CSA are generally not hypoxic, so that hypoxia is unlikely to be a primary cause of CSR-CSA in most (32, 33). Nevertheless, hypoxic dips during apneas could accentuate the tendency to hyperventilate upon central apnea termination by amplifying the ventilatory overshoot in response to CO_2 when Pa_{CO_2} increases above the ventilatory threshold (45). Ventilatory overshoot with propagation of CSR-CSA may therefore be facilitated by even mild apnea-related hypoxia. Several studies investigated the effects of supplemental oxygen in patients with HF and CSR-CSA (63–67). All consistently found small but significant reductions in the AHI. These data support

the hypothesis that hypoxia plays a role in aggravating CSR-CSA, but that it is not the major determinant of its development in patients with HF.

Prolongation of circulation time secondary to reduced cardiac output with delayed transmission of alteration in arterial blood gas tensions from the lung to the peripheral and central chemoreceptors could theoretically contribute to the pathogenesis of CSR-CSA by facilitating ventilatory overshoot and undershoot. For example, Crowell and colleagues (68) induced CSR-CSA in sedated dogs by inserting a length of tubing between the heart and brain to prolong the transit time from the lungs to the chemoreceptors. However, CSR-CSA was induced only when the lung to carotid body circulation time exceeded 1 minute, which was far greater than described in patients with HF. In addition, several studies have shown that cardiac output, LV ejection fraction (LVEF) and lung to chemoreceptor circulation time do not differ between patients with HF with and without CSR-CSA (33, 35). Consequently, prolonged circulation time appears not to play a key role in initiating CSR-CSA in most patients with HF. Rather, its major influence appears to be on the durations of the hyperpneic phase and of the total periodic breathing cycle.

Following central apnea, the length of the subsequent ventilatory phase is directly proportional to the lung to peripheral chemoreceptor circulation time and inversely proportional to cardiac output (28). Since the alteration in arterial blood gas tensions that occur in the pulmonary circulation in response to changes in ventilation arrive via the systemic arterial circulation in a graded fashion, once Pa_{CO_2} has risen above the apnea threshold, increases in tidal volumes and ventilation occur, gradually reaching a peak only several breaths after apnea termination. Similarly, as Pa_{CO_2} falls in response to the gradual increase in the preceding ventilation, tidal volumes diminish gradually until apnea ensues once Pa_{CO_2} has fallen below threshold. Thus, the prolonged transit time from the lungs to the chemoreceptors sculpts the classic crescendo-decrescendo pattern of tidal volumes during hyperpnea. However, apnea length appears not to be affected by prolonged circulation time, but rather is proportional to the preceding decrease in Pa_{CO_2} (28, 69). As shown in Figure 2, compared with patients with CSA but without HF, patients with HF and CSR-CSA have much longer hyperpnea with more gradual increases and decreases in tidal volume, but similar apnea duration (18, 28). Thus, differences in the total cycle duration of periodic breathing between patients with and without HF are primarily modulated by differences in hyperpnea, but not apnea duration.

CLINICAL SIGNIFICANCE OF CSR-CSA IN HEART FAILURE

Prevalence

There are few data from well-designed epidemiologic studies on the prevalence of CSR-CSA in patients with HF. In one study involving 100 men with HF (LVEF $\leq$ 45%) who underwent polysomnography within the last several years without regard to suspicion of sleep apnea, Javaheri found that the prevalence of CSR-CSA, defined as an AHI greater than or equal to 15 of which more than 50% were central, was 37% (17). Factors associated with the presence of CSR-CSA were worse New York Heart class (more class III than in patients without CSR-CSA), lower LVEF, a higher prevalence of atrial fibrillation, increased nocturnal cardiac arrhythmias, and a lower awake Pa_{CO_2} compared with those without sleep apnea on univariate analyses. However, because this study included only men, it provided no data on the prevalence of CSR-CSA in women and therefore does not present an overall picture of the prevalence of CSR-CSA in the general population with HF. In addition, because it was performed mainly before the widespread use of β-blockers for HF therapy, only a small minority of patients were on a β-blocker. Since CSR-CSA appears to arise from HF itself, and since there is some evidence that optimizing medical therapy for HF or heart transplantation attenuates CSR-CSA (70–72), the very high prevalence of CSR-CSA reported in that study (17) may not be representative of its prevalence in patients with HF on optimal contemporary medical therapy. Indeed, data from HF cohorts recruited more recently, in whom the great majority of patients were receiving β-blockers, indicate lower prevalences of CSR-CSA. For example, in 87 patients with HF (53 men, 34 women; LVEF $\leq$ 45%), Ferrier and coworkers (42) reported that CSR-CSA was present in only 15%. In the largest cohort studied to date, Wang and colleagues (73) performed sleep studies on 218 consecutive patients with HF (168 men and 50 women with LVEF $\leq$ 45%) enrolled from a single HF clinic between 1997 and 2004 without regard to suspicion of sleep apnea. The prevalence of CSR-CSA, defined as an AHI greater than or equal to 15 of which more than 50% were central, was 21%. Because of the large number of subjects, and the inclusion of both men and women, the prevalence of CSR-CSA reported in this study may be more representative of its prevalence in the general HF population on optimal contemporary HF therapy.

Risk Factors for CSR-CSA in Patients with HF

With regard to risk factors for CSR-CSA, this was assessed in 450 patients with HF (382 men, 68 women) referred to a sleep laboratory because of a suspicion of sleep apnea, or because of HF refractory to therapy (14). Because this was a sleep clinic population, the prevalence of CSR-CSA may not have been representative of its prevalence in the general population with HF. Nevertheless, the prevalences of CSR-CSA at an AHI cutoff of greater than or equal to 10 (33%) and greater than or equal to 15 (29%) were similar to those reported in the epidemiologic cohort of Wang and coworkers (73) from the same laboratory 10 years later. Factors associated independently with the presence of CSR-CSA (with an AHI $\geq$ 10) were older age ($>$ 60 years), male sex, awake hypocapnia ($Pa_{CO_2} \leq$ 38 mm Hg), and atrial fibrillation, but not LVEF. In the smaller studies in which cardiac and respiratory function were assessed in greater detail, the presence of CSR-CSA was associated with higher pulmonary capillary wedge pressure (35), and LV end-diastolic volume (29), and with greater peripheral and central chemosensitivity to CO_2 (39) than in patients with HF without CSR-CSA. CSR-CSA was also associated with induction of periodic breathing during exercise testing (2). However, neither cardiac output nor LVEF differed between those with and without CSR-CSA. Taken together, these data indicate that the key clinically identifiable risk factors for CSR-CSA in patients with HF are older age, male sex, hypocapnia and factors that could contribute to hypocapnia such as elevated LV filling pressure and LV end-diastolic volume, atrial fibrillation, and increased chemosensitivity. However, lower LVEF and cardiac output have not been identified as independent risk factor for CSR-CSA in patients with systolic HF. The reason why men are at higher risk for CSR-CSA remains to be elucidated.

CSR-CSA can also occur in patients with asymptomatic LV systolic dysfunction. Lanfranchi and colleagues (74) reported that 26 of 47 patients with asymptomatic LV systolic dysfunction (LVEF $\leq$ 40%) had CSR-CSA. Nopmaneejumruslers and associates (18) also observed that among 93 patients with stroke, 19% had CSA. The key factors associated with CSA were hypocapnia and asymptomatic LV systolic dysfunction (LVEF $\leq$ 40%), but not the location or type of stroke. Among those with

LVEF less than or equal to 40%, hyperpnea had a waxing and waning pattern of tidal volume and a longer duration, characteristic of CSR, than in those with LVEF over 40%. These data suggest that the presence of CSR-CSA in a patient following a stroke is more likely due to underlying LV systolic dysfunction than the neurological damage caused by the stroke. They concluded that in patients with stroke, CSR-CSA is a sign of occult LV systolic dysfunction.

In a small minority of patients with HF, OSA and CSR-CSA coexist. In one study, Tkacova and colleagues (75) demonstrated that in such patients, there was a shift from predominantly OSA at the beginning of the night to predominantly CSA at the end of the night. This shift in apnea type occurred in association with a prolongation of lung to peripheral chemoreceptor circulation time, a lengthening of hyperpnea and a fall in Pa_{CO_2} from the beginning to the end of the night. They concluded that the shift from predominantly OSA to CSR-CSA occurred in conjunction with an overnight deterioration of cardiac function. Since it has been shown that Pa_{CO_2} varies inversely with LV filling pressure (36), the implication was that OSA itself contributed to the deterioration of cardiac function, and that a rise in LV filling pressure contributed to the overnight decrease in Pa_{CO_2} that probably triggered CSR-CSA once Pa_{CO_2} fell below the apnea threshold. It has also been shown in patients with HF that the predominant type of sleep apnea can shift from obstructive to central in conjunction with an increase in circulation time and fall in nocturnal Pa_{CO_2}, and vice versa over several months (76). These observations raise the possibility that in patients with HF, OSA and CSA can be part of a spectrum of periodic breathing whose predominant type can transform over time in response to alterations in cardiac function. Mechanisms involved in this transformation have not been identified, but may involve fluid displacement into and out of the upper airway and lungs, and alteration in chemosensitivity in relation to alteration in the severity of cardiac failure (40).

Cardiovascular Effects of CSR-CSA

Although CSR-CSA appears to arise secondary to HF, once initiated it may participate in a pathophysiologic vicious cycle that contributes to deterioration in cardiovascular function. However, currently debated is whether CSR-CSA is simply a reflection of severely compromised cardiac function with elevated LV filling pressure (35), or whether CSR-CSA exerts unique and independent pathologic effects on the failing myocardium. Regardless of its etiology, there is evidence that CSR-CSA may have detrimental physiologic effects on the failing heart.

During central apnea, the absence of lung inflation deactivates pulmonary stretch receptors, and disinhibits central sympathetic nervous system outflow. This effect summates with apnea-related hypoxia and rises in Pa_{CO_2}, and with post-apneic arousals to cause cyclical surges in sympathetic nervous system activity (SNA) in synchrony with the ventilatory oscillations of CSR-CSA (77). As a consequence, blood pressure and heart rate oscillate in concert with Cheyne-Stokes cycles, very much as they do during OSA; peaks occur during hyperpneas and dips during apneas (66, 78). These effects cause a generalized increase in sympathetic activity manifest by higher overnight urinary norepinephrine concentration in patients with HF with than in those without CSR-CSA (77). However, Franklin and coworkers (66) and Leung and colleagues (79) found that administration of low flow oxygen at a rate sufficient to just abolish dips in Sa_{O_2}, but not to eliminate CSR-CSA or fluctuations in Pa_{CO_2}, did not influence blood pressure or heart rate oscillations during CSR-CSA. These data indicate that mechanisms other than hypoxic dips are involved in precipitating these surges in blood pressure and heart rate during CSR-CSA. Since there are direct connections between respiratory and cardiovascular sympathetic neurons in the brainstem, it is possible that these cardiovascular oscillations are driven by oscillations in outflow from central respiratory to cardiovascular sympathetic neurons (80).

The sympathetic stimulatory effects of CSR-CSA are not isolated to sleep, but also carry over into wakefulness. Daytime plasma norepinephrine concentration and muscle sympathetic nerve burst frequency are significantly higher in patients with HF with CSR-CSA than in those without it, and they are directly related to the frequency of arousals from sleep and to the degree of apnea-related hypoxia, but not to LVEF (77). Treatment of CSR-CSA with either nocturnal oxygen or CPAP lowers SNA both during sleep and wakefulness (15, 65, 77). These data indicate that CSR-CSA contributes to sympathetic activation.

Increased SNA has a number of adverse effects in patients with HF, including peripheral vasoconstriction, increased tubular reabsorption of sodium, and activation of the renin–angiotensin system (81). The increases in vascular resistance and in blood volume increase preload and afterload and, thus, work for the damaged myocardium. However, it is the increase in SNA itself that is probably the most damaging to the heart over time. Although the increase in SNA provides inotropic support that acts initially to increase cardiac output, in the longer term it promotes disease progression. This is demonstrated by the strong correlation between mortality risk and both plasma norepinephrine levels and cardiac norepinephrine production (81, 82). Chronically elevated SNA is linked to abnormal calcium cycling and calcium leakage in the failing myocardium, contributing to a decrease in myocardial contractility over time (83, 84). In addition, increases in SNA can enhance spontaneous inward currents through calcium channels, enhancing the likelihood of spontaneous repolarization, arrhythmia development, and sudden death (81). Indeed, ventricular arrhythmias are more common in patients with HF with CSR-CSA than in those without it (74). Furthermore, chronic exposure of the myocardium to excess SNA and circulating catecholamines increases cardiac myocyte injury, apoptosis, and necrosis, and contributes to hypertrophy and adverse remodeling (85). Suppression of SNA by long-term attenuation of CSR-CSA by CPAP in patients with HF may be one of the mechanisms that contributed to the associated improvement in LVEF and exercise performance (15). However, these effects were not accompanied by any improvement in survival.

The main clinical significance of CSR-CSA in HF is its potential to adversely influence survival. However, there is controversy on this point. As shown in Table 1, a number of studies reported that CSR-CSA is a significant independent predictor of mortality in patients with HF (1–5, 23, 24). Lanfranchi and colleagues (4) examined 62 patients with HF and found that those with CSR-CSA had higher mortality that was proportional to the AHI than patients without CSR-CSA after controlling for confounding factors. In 66 patients with HF, Sin and associates (1) observed a 2.5-fold increased risk of death or cardiac transplantation among the 37 patients with HF with CSR-CSA than in the 29 without it after controlling for confounders. Corra and coworkers (2) found that in 133 patients with HF, an AHI greater than 30 was an independent predictor of mortality. Similarly, Javaheri and colleagues (3) found in 88 patients with HF that CSR-CSA was an independent correlate of worse survival. Conversely, Andreas and coworkers (23) did not observe increased mortality in patients with CSR-CSA during the night, but did observe an increased risk of mortality in patients presenting with CSR while awake. Roebuck and colleagues (24) followed 78 patients with severe HF being assessed for heart transplantation,

TABLE 1. COMPARISON OF STUDIES EXAMINING POTENTIAL RELATIONSHIP BETWEEN CSR-CSA AND MORTALITY

	Author (year)						
Study Characteristics	Hanly (5) (1996)	Andreas (23) (1996)	Lanfranchi (4) (1999)	Sin (1) (2000)	Roebuck (24) (2004)	Corra (2) (2006)	Javaheri (3) (2007)
Number of subjects	16	36	62	66	78	133	88
Primary endpoints	Death + Tx	Death + Tx	Cardiovascular Death	Death + Tx	Death	Death + Tx	Death
Male, %	100	86	88	88	78	94	100
Ischemic etiology, %	100	11	53	64	53	64	75
LVEF, %	23	20	23	22	20	23	24
β-Blocker, %	Not reported	Not reported	Not reported	21	14	53	10
Sleep study	PSG	PSG	No sleep staging	PSG	PSG	No sleep staging	PSG
Criteria for CSR-CSA	Not defined	CSR > 20% of sleep time	AHI ⩾ 10	AHI ⩾ 15	AHI > 5	AHI > 30	AHI ⩾ 5
CSR-CSA risk for death and/or Tx	Yes	No	Yes	Yes	No	Yes	Yes
Others	Enrolled patients with severe HF (NYHA 3 or 4)		Excluded patients with Afib and obesity	Included patients treated for CSR-CSA by CPAP, but this factor was controlled for	Enrolled patients from Tx unit. Included patients treated for CSR-CSA. Excluded patients with obesity		Included patients treated for CSR-CSA with O_2

Definition of abbreviations: Afib = atrial fibrillation; AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; CSR-CSA = Cheyne-Stokes respiration with central sleep apnea; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OSA = obstructive sleep apnea; PSG = polysomnography; Tx = heart transplantation.

of whom 42% had CSR-CSA over a median period of 52 months. The presence of CSR-CSA in patients with severe HF was not significantly associated with increased mortality.

However, these studies have important limitations. First, compared with recent multicenter studies that have examined other risk factors for mortality in hundreds to thousands of patients with HF (86–88), all the studies that have examined CSR-CSA as a possible risk factor for death or heart transplantation have been single-centered and have included far fewer patients (1–5, 23, 24). Second, patients enrolled in these studies were heterogeneous: some studies included patients receiving CSA treatment (oxygen supplementation or CPAP) (1, 3, 24) while others did not (2, 4, 5, 23); some included men and women (1, 2, 4, 23, 24), while others included only men (3, 5); some studies excluded patients with atrial fibrillation or obesity (4, 24), while others did not (1–3, 5, 23). Thus, it is difficult to compare the results of these studies and to generalize from them. Third, the methods of performing sleep studies differed: some used portable tests without sleep stage monitoring (2, 4), while others employed full polysomnography with sleep staging (1, 3, 5, 23, 24). Fourth, the criteria for diagnosing CSR-CSA were inconsistent (*see* Table 1) (1–5, 23, 24). Finally, β-blocker use varied widely among studies (*see* Table 1). Since β-blockers have improved prognosis in HF (89, 90), it is difficult to compare CRS-CSA as a risk factor for morbidity and mortality among studies with low and high β-blocker usage. This is important, because in the Canadian Positive Airway Pressure for Central Sleep Apnea in Heart Failure Trial (CANPAP) (15), there was a dramatic fall in mortality in patients with HF with CSR-CSA between 1998 and 2004 in association with increasing penetration of β-blocker and spironolactone therapy in response to publication of clinical trials demonstrating their efficacy (8, 90, 91).

Notwithstanding the above limitations, the majority of the studies reviewed found an independently increased risk of mortality and/or cardiac transplantation in association with the presence of CSR-CSA in patients with HF. So it is quite possible that CSR-CSA does worsen prognosis in HF. Nevertheless, given these limitations, it remains to be determined whether there is a direct cause–effect relationship between CSR-CSA and risk for morbidity and mortality in patients with HF. Further work will be required to test this possibility.

CONCLUSIONS

In patients with HF, CSR-CSA is common and is due to respiratory control system instability secondary to the effects of elevated LV filling pressures, pulmonary congestion, increased central and peripheral chemoreceptor sensitivity, reduced cerebrovascular blood flow, and possibly other factors. Central apnea occurs when $Pa_{CO_2}/[H^+]$ falls below the threshold for apnea during sleep. Although low cardiac output and increased lung to chemoreceptor circulation time have not been shown to play a direct role in precipitating central apneas, they do sculpt the hyperpneic period into the characteristic prolonged waxing-waning pattern of ventilation.

Although clinical symptoms attributable to CSR-CSA have not been clearly identified, the majority of the evidence indicates that CSR-CSA increases the risk of premature death in HF. This adverse effect has been most closely linked with CSR-CSA–induced sympathetic activation, although other as yet unidentified mechanisms may be involved. Nevertheless, controversy remains as to whether CSR-CSA is simply a reflection of HF severity, or whether it exerts independent adverse effects. While we have not reviewed treatment of CSR-CSA in this article, evidence from one multicenter randomized trial demonstrated that CPAP attenuated CSR-CSA in association with improved LV function, decreased SNA, and increased exercise performance, but not in association with improved survival or reduced hospitalizations (15). Guidelines for HF management (92) lists treatment of sleep apnea under "Drugs and interventions under active investigation" and reports that "It is hoped that such studies will provide information about the efficacy and safety of this approach (to treatment of sleep-disordered breathing) and help identify patients most likely to benefit from treatment." We concur with this view and conclude that more research is required to fully elucidate

mechanisms that contribute to the pathogenesis of CSR-CSA in HF. Hopefully, once such mechanisms have been identified, better approaches to therapy of CSR-CSA will be tested in large randomized trials to determine whether treatment of CSR-CSA can improve clinically important outcomes in patients with HF.

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