Cheyne-Stokes Respiration During Sleep in Congestive Heart Failure*

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Cheyne-Stokes respiration (CSR) is a form of sleep-disordered breathing seen in approximately 40% of congestive heart failure patients with a left ventricular ejection fraction of <40%. It is characterized by a crescendo-decrescendo alteration in tidal volume separated by periods of apnea or hypopnea. Sleep is generally disrupted, often with frequent nocturnal arousals. Clinical features include excessive daytime sleepiness, paroxysmal nocturnal dyspnea, insomnia, and snoring. Proposed mechanisms include the following: (1) an increased CNS sensitivity to changes in arterial PCO₂ and PO₂ (increased central controller gain); (2) a decrease in total body stores of CO₂ and O₂ with resulting instability in arterial blood gas tensions in response to changes in ventilation (underdamping); and (3) an increased circulatory time. In addition, hyperventilation-induced hypocapnia seems to be an important determinant for the development of CSR. Mortality appears to be increased in patients with CSR compared to control subjects with a similar degree of left ventricular dysfunction. Therapeutic options include medically maximizing cardiac function, nocturnal oxygen therapy, and nasal continuous positive airway pressure. The role that other therapeutic modalities, such as inhaled CO₂ and acetazolamide, might have in the treatment of CSR associated with congestive heart failure has yet to be determined.

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**Key words:** apnea-hypopnea index; Cheyne-Stokes respiration; circulatory time delay; congestive heart failure; controller gain; hypocapnia; hypoxia; left ventricular ejection fraction; nasal continuous positive airway pressure; sleep-disordered breathing

**Abbreviations:** AHI=apnea-hypopnea index; CHF=congestive heart failure; CPAP=continuous positive airway pressure; CSR=Cheyne-Stokes respiration; LVEF=left ventricular ejection fraction; NREM=nonrapid eye movement; PaCO₂=arterial PCO₂; PaO₂=arterial PO₂; PtcCO₂=transcutaneous CO₂; SaO₂=arterial oxygen saturation; SDB=sleep-disordered breathing

Breathing is normally controlled by a combination of two systems: a metabolic system responsible for the automatic changes directly related to gas exchange and a behavioral system responsible for the voluntary changes originating from cortical and forebrain structures. During normal sleep, the metabolic system, which consists of central controllers, peripheral effectors, and both central and peripheral sensors, plays a more critical role in the regulation of breathing. Pathologic processes that can affect any of these components can lead to changes in the normal respiratory pattern found during sleep.

Sleep disturbances in patients with congestive heart failure (CHF) have long been recognized. Sleep-disordered breathing (SDB) in CHF was first described by Cheyne in 1818 in a 60-year-old obese man with heart failure. In 1854, Stokes described a similar abnormal pattern of respiration leading to apnea. Cheyne-Stokes respiration (CSR) is typically described as a form of periodic breathing with a crescendo-decrescendo alteration in tidal volume separated by periods of apnea or hypopnea (Fig 1). Patients with CSR have fragmented sleep with frequent arousals and nocturnal oxygen desaturations leading to poor sleep efficiency. CSR is by far the most common form of SDB seen in patients with CHF, with an incidence of approximately 40%. It has been suggested to be relatively uncommon in those patients with only moderate left ventricular dysfunction (left ventricular ejection fraction [LVEF] >40%).

CSR is not exclusive to CHF. It is also seen in patients with neurologic disorders (ie, intracerebral hemorrhage, infarction and embolism, tumors, meningitis, encephalitis, and trauma), premature and full-term infants, and healthy subjects at altitude.

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Normal Sleep

Normal sleep onset can be associated with an alteration in the respiratory cycle, with a periodic breathing pattern often noted. During the transition from wakefulness to nonrapid eye movement (NREM) sleep, input from the behavioral control system, a source of nonrespiratory input to the respiratory system during wakefulness, decreases. The metabolic control system, which was active but influenced by the behavioral control system during wakefulness, acts as the primary controller of the respiratory system. The hypoxic drive to breathe is decreased as one enters NREM sleep. The ventilatory response to arterial PCO2 (PaCO2) is dampened and a 1 to 3 mm Hg rise in the PaCO2 threshold is seen. During an arousal, the elevated PaCO2 precipitates hyperventilation in order to drive the PaCO2 down to the awake set point, commonly below the sleeping apneic threshold. Bulow demonstrated that respiratory variation was more common during drowsiness and early NREM sleep (stages 1 and 2), and that respiration appeared to be more regular during delta sleep (stages 3 and 4). Respiratory variation mimicking CSR is seen in normal subjects as they fluctuate between wakefulness and stages 1 and 2 of NREM sleep with a reported incidence of 40 to 80%. This pattern of breathing typically is not seen during rapid eye movement sleep, likely secondary to an increase in the behavioral system's influence on respiration. CSR associated with pathologic conditions such as CHF occur more often after sleep onset has been established, during stages 1 and 2 of sleep.

Pathophysiology of Cheyne-Stokes Respiration

The mechanism responsible for the development of CSR still remains unknown. However, several theories have been proposed and it is likely that a combination of these mechanisms is responsible for the CSR seen in patients with CHF.

Controller Gain

The ventilatory response to acute changes in arterial blood gas tensions shows marked variability among individuals. In addition, the body's responses to changes in PaCO2 differ from those to changes in arterial Po2 (PaO2). Normally, respiration increases linearly with increases in PaCO2 and hyperbolically with changes in PaO2. The slope of these ventilatory response curves has been termed the controller gain. Subjects with an increased controller gain appear to be more likely to demonstrate periodic breathing. An increased central sensitivity to CO2 might be one of the mechanisms involved in the development of the baseline hypoxemia noted in patients with CSR. A hyperpnea (such as with an arousal) would lead to a fall in PaCO2 below the sleeping apneic threshold, resulting in an apnea. With an increased controller gain, the elevated PaCO2 that develops at the termination of the apnea would lead to an exaggerated ventilatory response, again placing the PaCO2 below the apneic threshold. This can lead to a periodic breathing pattern, such as that seen with CSR. In addition, the presence of hypoxemia can increase the slope of the ventilatory response.

Figure 1. CSR as recorded on a recording system (Respitrace). Note the crescendo-decrescendo alteration in tidal volume separated by periods of apnea (from reference 29, with permission).
response to hypercapnia, and again lead to an exaggerated decrease in the PaCO\textsubscript{2} to below the apneic threshold.

**Underdamping**

Both oxygen (O\textsubscript{2}) and carbon dioxide (CO\textsubscript{2}) are stored in the body, but because of differences in binding affinity, the tissues store a large amount of CO\textsubscript{2}, but a relatively small amount of O\textsubscript{2}. Thus, for a given increase in PaCO\textsubscript{2}, the amount of stored CO\textsubscript{2} will increase significantly, whereas the O\textsubscript{2} stores of the body will increase only minimally with a similar increase in PaO\textsubscript{2} (Fig 2). This ratio, the volume of stored gas in the body to change in gas tension in the blood, is known as the dampening ratio.\textsuperscript{11-15} Larger stores in CO\textsubscript{2} allow for better buffering and thus stability of arterial blood gas tensions during transient changes in ventilation. In patients with CHF, the functional residual capacity is reduced due to pulmonary vascular congestion and thus pulmonary gas volume is decreased. As a result, total body stores of CO\textsubscript{2} and O\textsubscript{2} are both decreased and the respiratory system becomes much more unstable (under-damped), exaggerating the changes in PaO\textsubscript{2} and PaCO\textsubscript{2} during transient changes in ventilation.

**Circulatory Time Delay**

In patients with CHF, a circulatory time delay\textsuperscript{11-15} can occur between the gas exchange occurring at the alveolar capillary membranes of the lungs and the peripheral chemoreceptors (carotid bodies). This results in delayed information feedback from the peripheral chemoreceptors to the medulla, thus causing an instability of gas homeostasis, which leads to periodic respirations. Guyton et al\textsuperscript{17} were able to reproduce this pattern of breathing by increasing the circulation time to central chemoreceptors in anesthetized dogs. However, their experiments produced circulation times that were much longer than those seen clinically (2 to 5 min), and underlying CNS damage was not excluded. Thus, interpretation of these results is much more difficult. More recently, Naughton et al\textsuperscript{16} found the circulation time to be the same in a group of patients with CSR compared to a control group with a similar degree of left ventricular (LV) dysfunction. In this study, the circulation time was found to be significantly correlated with the CSR cycle length rather than with the presence or absence of periodic breathing.

**Hypocapnia**

Hyperventilation-induced hypocapnia appears to be an important determinant for the development of periodic breathing during sleep in patients with CHF.\textsuperscript{16,18} Naughton et al\textsuperscript{16} noted that in patients with similar LVEFs, those patients with CSR had a significantly lower awake PaCO\textsubscript{2} and mean transcutaneous CO\textsubscript{2} (PtcCO\textsubscript{2}) during sleep compared to a control group without CSR. Similar findings have been noted by others.\textsuperscript{18} CSR was typically triggered by an arousal accompanied by a large breath. This increased tidal volume induced an abrupt fall in PaCO\textsubscript{2} probably far below the sleep-related increase in the apneic threshold. Arousal-induced hyperventilation also appears to be the triggering mechanism seen in idiopathic central sleep apnea.\textsuperscript{19} A proposed mechanism for the observed hyperventilation-induced resting hypocapnia includes an increased central controller gain, possibly secondary to pulmonary congestion, with stimulation of pulmonary irritant and juxta-capillary stretch receptors.\textsuperscript{16}

**Hypoxia**

Hypoxia seen at high altitude\textsuperscript{20} is due primarily to hypoxia-induced hyperventilation. Although hypoxia has been shown to have an important role in the pathogenesis of periodic breathing at high altitude, its role in triggering CSR in patients with CHF is less certain. The hypoxia-induced respiratory alkalosis may be a more important determinant for the development of periodic breathing at high altitude than the presence of hypoxemia. Berssenbrugge et al\textsuperscript{21} demonstrated that in normal subjects during sleep at simulated high altitude, the administration of O\textsubscript{2}

**Figure 2.** Volume (in liters) of oxygen (O\textsubscript{2}) and carbon dioxide (CO\textsubscript{2}) stored in the body at different gas tensions. Because of a higher tissue-binding affinity, more CO\textsubscript{2} is stored in the body as compared to O\textsubscript{2}, for a similar increase in gas tension. This larger body store of CO\textsubscript{2} allows for better buffering of arterial blood gas tensions in response to changes in ventilation (dampening) (from reference 11, with permission).
abolished periodic breathing; this was associated with a rise in both arterial oxygen saturation (SaO₂) and PaCO₂. In the same study, periodic breathing was abolished when CO₂ was administered to selectively increase PaCO₂, with nitrogen added to prevent an increase in PaO₂ that would have occurred with associated hyperventilation. Hanly et al. noted no difference in awake or sleep arterial oxyhemoglobin saturation (SaO₂) or percent of total sleep time where the SaO₂ was found to be <90% in patients with CSR compared with a control group. Naughton et al. noted no significant difference in mean SaO₂ during sleep in the group with CSR compared with the control group. Although the lowest SaO₂ was significantly less in the CSR group, the investigators suggest that these “dips” in SaO₂ were more likely the result of the apneas rather than their cause.

CLINICAL FEATURES AND SLEEP ARCHITECTURE

Many patients with CSR present with symptoms of disturbed sleep. This is probably secondary to the multiple arousals that occur during the night; the resultant fragmented sleep often leads to complaints of excessive daytime sleepiness. Others may complain of paroxysmal nocturnal dyspnea with frequent awakenings. Snoring has been noted in approximately 45% of patients. Additionally, many patients will complain of insomnia, with difficulty initiating sleep. This appears to be secondary to fear and anxiety that develops after episodes of awakening dyspnea during CSR at sleep onset.

CSR associated with CHF tends to occur predominantly during stages 1 and 2 of NREM sleep. Patients with CSR have an increase in stages 1 and 2 of sleep and a decrease in delta sleep. Arousals during CSR occur during the hyperpneic phase of the ventilatory cycle.

CARDIOVASCULAR ASSOCIATIONS

In CSR, the increase in circulation time may be a reflection of a decrease in LVEF. Nocturnal hypoxemia can lead to worsening myocardial injury, further inhibiting ventricular performance and thus decreasing the overall ejection fraction. This, however, does not explain why some patients with poor LV function do not have CSR, while others with less severe LV dysfunction exhibit CSR. However, Javaheri et al. did find that LVEF was significantly and negatively correlated with the apnea-hypopnea index (AHI). In addition, it has recently been noted that patients with CHF and CSR had significantly elevated urinary and plasma norepinephrine levels compared to those with CHF alone. This seems to be due to elevated sympathoadrenal activity, possibly secondary to apnea-related hypoxemia and/or arousals from sleep. Thus, besides direct effects on LV dysfunction, hypoxemia can lead to both systemic and pulmonary vasoconstriction and thus an increase in LV and right ventricular afterload. A component of diastolic dysfunction has also been noted during the apneic phase of CSR.

Cardiac dysrhythmia and conduction abnormalities are frequently associated with CSR in the setting of CHF. This can range from simple premature ventricular contractions and couplets to varying degrees of heart block, including first-degree block and complete atrial-ventricular dissociation. Javaheri et al. found that the number of premature ventricular contractions and couplets during the night correlated with the severity of CSR. From early studies, it appeared that most patients with dysrhythmias were those taking digitals, but this has not been substantiated by better controlled studies.

MORTALITY

There has been a suggested increased mortality in CHF patients with CSR. Findley et al. found that all six patients with CSR died within 6 months vs only three of nine patients without CSR but with a similar degree of LV dysfunction (p<0.05). Ancoli-Israel et al. also showed an increase in mortality in patients with severe CSR. More recently, Hanly and Zuberi-Khokhar studied a group of 16 patients with severe, stable CHF (mean LVEF=22.9±5.5%). Those found to have CSR had a significantly lower cumulative survival when followed up to 4.5 years. Thus, appropriate treatment might not only affect daytime symptoms but may improve overall survival.

TREATMENT

Medical Management of CHF

Improvement of cardiac function can improve CSR associated with CHF; thus, optimizing the patient’s therapeutic regimen is of primary importance (Table 1). Harrison et al. have shown that once CHF clinically improved, the CSR resolved. The goal of medical therapy is to reduce the incidence of further myocardial injury and restore adequate ventricular function, thereby increasing cardiac output and mixed venous oxygen concentration.

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Oxygen Therapy

Hanly et al\textsuperscript{32} studied the effects of oxygen administration on nine patients with CSR. They demonstrated a significant decrease in AHI, arousal index, and degree of oxyhemoglobin desaturation with the addition of oxygen. They also noted an increase in total sleep time and decrease in stage 1 sleep. The investigators theorized that supplemental oxygen increased oxygen stores, thereby dampening the respiratory control system and making it more stable. In addition, this would remove the hypoxic stimulus to hyperpnea and allow the PaCO\textsubscript{2} to rise. Thus, while hypoxemia by itself may not play a major role in the development of hypcapnia and CSR, the fact that supplemental O\textsubscript{2} attenuates periodic breathing in this setting suggests that hypoxemia may perpetuate CSR once it is present.

Nasal Continuous Positive Airway Pressure

Nasal CPAP has been investigated for the treatment of CSR associated with CHF. Bradley et al\textsuperscript{33} demonstrated a significant increase in both cardiac index and stroke volume, after 10 min of nasal CPAP at 5 cm H\textsubscript{2}O in those patients with a pulmonary capillary wedge pressure \textgreater;12 mm Hg. Takasaki et al\textsuperscript{34} studied the effects of nasal CPAP in five patients with CHF and CSR. LVEF\textsubscript{s} improved after treatment with nasal CPAP when restudied from 10 days to 4 weeks later. CSR was also noted to improve with a significant decrease in the frequency of central apneas and hypopneas. More recently, Naughton et al\textsuperscript{35} studied the effects of 3 months of nasal CPAP on LVEF in a randomized controlled trial. LVEF, AHI, and symptom score all significantly improved in the nasal CPAP group, whereas no significant change was seen in the control group. One proposed mechanism to explain the beneficial effects of nasal CPAP on LV function is a decrease in LV afterload, by increasing intrathoracic pressure and decreasing the transmural pressure across the LV.\textsuperscript{33} Attenuation of CSR with the use of nasal CPAP appears to be related to its ability to increase PaCO\textsubscript{2}. As noted previously, hyperventilation-induced hypcapnia appears to be an important determinant for the development of CSR associated with CHF.\textsuperscript{16} Naughton et al\textsuperscript{36} studied the effects of 1 month of nasal CPAP on PtcCO\textsubscript{2} and tidal volume during sleep in a group of patients with CHF and CSR. Compared with a control group, in addition to a significant decrease in the AHI, nasal CPAP caused a significant increase in nocturnal PtcCO\textsubscript{2} and decrease in tidal volume. They proposed that the increase in LVEF with nasal CPAP reduced interstitial lung edema and decreased stimulation of pulmonary vagal afferents, which are thought to cause the observed hyperventilation and hypcapnia in these patients.

More recently, nasal CPAP has been shown to significantly improve maximal inspiratory muscle strength after a period of 3 months, compared to a

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control group with a similar degree of CHF and CSR.\textsuperscript{37} The observed improvement in LVEF is postulated to have improved respiratory muscle blood flow, and thus increase respiratory muscle strength, and contribute to the decrease in dyspnea noted in these patients. In addition, nasal CPAP has also been shown to decrease sympatoadrenal activity in patients with CSR as measured by a decrease in urine and plasma norepinephrine levels.\textsuperscript{26} Others have not shown such beneficial results with the use of nasal CPAP. Davies et al\textsuperscript{38} studied eight patients with a mean LVEF of 19\% who were each randomly assigned to 2 weeks of both nasal CPAP at 7.5 cm H\textsubscript{2}O and a placebo. No improvement in exercise tolerance or LVEF was noted with nasal CPAP. It should be noted that nasal CPAP was used for only 2 weeks, and changes in the severity of CSR were not assessed. In addition, a lower level of nasal CPAP was used compared with other studies\textsuperscript{36,34-37} and ventricular function was assessed after therapy in only three of the eight patients.

Other Therapies

Theophylline has been used for the treatment of CSR. Proposed mechanisms include improvement in cardiac function and thus circulation time as well as possible central effects on hypoxic drive.\textsuperscript{39} Dowdell et al\textsuperscript{20} treated four of five patients with CSR with theophylline and noted improvements in sleep, oxygen saturation, and CSR. More recently, Javaheri et al\textsuperscript{40} examined the effects of short-term theophylline therapy on CSR during sleep in 15 patients with stable CHF. Compared with placebo, theophylline significantly decreased the AHI and severity of oxygen desaturation during sleep without a significant change noted in LVEF. They proposed a more central mechanism noting that theophylline competes for adenosine which centrally is a known respiratory depressant. Others have not noted such improvements.\textsuperscript{41}

CO\textsubscript{2} has also been proposed in the treatment of CSR, presumably by increasing the PaCO\textsubscript{2} above the apneic threshold. Steens et al\textsuperscript{42} measured the effects of inhaled 3\% CO\textsubscript{2} on CSR in six patients with LVEFs of <35\%. Compared with a control night, CO\textsubscript{2} virtually eliminated CSR and improved nocturnal oxygen saturation. Objective measurements of sleep, though, showed a decrease in sleep efficiency and no change in multiple sleep latency test scores. This may have been secondary to patient discomfort with the mask device that was used. Badr et al\textsuperscript{43} recently reported the effects of inhaled 2\% CO\textsubscript{2} in a patient with persistent central sleep apnea after being treated with tracheostomy for obstructive sleep apnea. Periodic breathing and sleep archite-
ture were both significantly improved. Its present role in the treatment of CSR is yet to be determined.

Hypnotics such as benzodiazepines have been studied in patients with CSR.\textsuperscript{44,45} Sleep was improved with a decrease in the number of arousals during the night with no change in the severity of CSR as reflected by the AHI and degree of nocturnal oxygen desaturation.

Acetazolamide will produce a metabolic acidosis and thus increase ventilation. Recently, DeBacker et al\textsuperscript{46} examined the effects of acetazolamide on 14 patients with central sleep apnea. They noted a significant decrease in AHI and associated arousals when used initially, with further improvement at 1 month. Its role in the treatment of CSR secondary to CHF still needs to be determined.

Recently, there have been a number of case reports\textsuperscript{47-49} of patients undergoing cardiac transplantation who preoperatively demonstrated CSR, either with exercise or during sleep. Following transplant, patients either displayed resolution of their CSR\textsuperscript{47,49} or in one case a change from predominantly central to obstructive events.\textsuperscript{48}

In conclusion, CSR is a form of SDB that is seen in approximately 40\% of CHF patients who have LVEF of <40\%. Patients can present with symptoms of excessive daytime sleepiness, paroxysmal nocturnal dyspnea, snoring, and not infrequently insomnia. Although the exact mechanism causing CSR is unknown, hyperventilation-induced hypocapnia seems to be important in its development. Therapies include supplemental oxygen and nasal CPAP when CSR persists despite maximizing medical therapy. Whether such therapeutic interventions will have an affect on overall survival awaits further study.

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