Central Sleep Apnea: Clinical Implications, Recognition, and Management

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Central sleep apnea (CSA) is characterized by a lack of respiratory drive during sleep, resulting in repetitive periods of insufficient ventilation and compromised gas exchange. These nighttime breathing disturbances can lead to daytime impairment and poor cardiovascular outcomes. There are several types of CSA, including idiopathic CSA, high altitude-induced periodic breathing, obesity hypoventilation syndrome, drug-induced central apnea, and Cheyne-Stokes breathing pattern. While unstable ventilatory control during sleep is the hallmark of CSA, the pathophysiology and the prevalence of the various forms of CSA varies greatly. Among them, CSA associated with heart failure is well-studied in the respect of clinical impact and management strategy. Through this article, I will summarize the underlying pathophysiology, clinical impacts, and potential treatment of CSA occurring in subjects with heart failure.

Key Words: Sleep disordered breathing, Pathophysiology, Cheyne-Stokes respiration, Continuous positive airway pressure

Sleep is a natural and inevitable part of human being and the average persons spend one third of their lifetime sleeping. If sleep would not do certain vital function, it must be the greatest evolutionary mistake ever made. However in the significant portions of adult, disordered-breathings during sleep disrupts its normal function. 1,2 Sleep-disordered breathing (SDB) imposes adverse impacts through sleep disruption or immediate results associated with SDB itself such as repetitive hypoxia, sympathetic over-activity, hemodynamic stress, or inflammation. 3,4 Accumulating evidences show that SDB has a major role in the development of cardiovascular diseases. 3,4 In this context, the effects of SDB can be more devastating in persons with underlying cardiovascular diseases such as congestive heart failure (CHF). CHF is a common condition with the estimated lifetime risk up to 20%. 5 Moreover, both obstructive and central sleep apneas are prevalent in CHF. 6 Although obstructive (OSA) and central sleep apnea (CSA) may coexist within same patient, CSA is more specifically linked to CHF. CHF is prone to the development of CSA and CSA may promote disease progression and increase mortality independent of underlying cardiac function. Therefore, main objective in this article is review the definition, pathophysiology, clinical implications, and management of CSA in CHF.

Definition and Phenotypes of Central Sleep Apnea

As the name implies, central sleep apnea and hypopnea is defined as a cessation or reduction of breathing that results from lack of or reduction in central respiratory drive. Standard phenotyping is based on polysomnography that measures airflow and respiratory effort. Nasal pressure sensor or respiratory inductance plethysmography (RIP) is a reliable monitoring technique for airflow. 7 Although ther-
mistor or piezo-electric strain gauge is less reliable, ther-
mistor signal is a useful reference for detecting apnea
because it is very sensitive for the presence of airflow.
Operational definition of CSA is that airflow reduction is
more than 90% of baseline amplitude and lasts at least
10 seconds without on-going respiratory effort (Figure 1).7
On the other hand, distinguishing central from obstructive
hypopneas is very difficult or nearly impossible because
of on-going respiratory efforts in both conditions. Theoretically, obstructive hypopnea can be differentiated from
central based on the presence of compensatory increase in
respiratory effort. Esophageal pressure sensor is known to
be reliable, but not universally available.7 Therefore, evidence
of upper airway narrowing might be an alternative criteria
for obstructive hypopnea, reflected in out-of-phase thoraco-
abdominal motion on RIP or flow-limitation on the nasal
pressure signal.8,9 However, upper airway narrowing is
also demonstrated in central hypopnea and even in CSA.10,11
Currently there is no consensus for phenotyping hypopnea
into central or obstructive.7
Although phenotyping of CSA is possible with poly-
somnography, the diagnostic criteria for CSA and CSA
syndrome are not well defined. Even, recently published
criteria of CSA are also confusing and limited in clinical
application, at least in subjects with CHF and CSA. Most
CHF patients with CSA do not complain of excessive day-
time sleepiness or snoring,12 and there are no data on the
frequency of potential symptoms, such as nocturnal dyspnea,
morning headaches, and restless sleep. According to the
diagnosis criteria adopted in the studies showing increased
mortality and poor cardiac outcome in CHF patients with
CSA,13-17 I recommend the following criteria. In patients
with CHF, a diagnosis of CSA should be established on
overnight polysomnography, using either RIP or nasal
pressure sensor, when there is an apnea-hypopnea index
(AHI) of at least 5 to 15, and when at least of 50% of
AHI is central.
Another classic respiratory abnormality described in CHF
is Cheyne-Stokes respiration (CSR).18 CSR is a form of
periodic breathing in which the ventilatory period is charac-
terized by a prolonged waxing-waning pattern of tidal
volume followed by central apnea or hypopnea (Figure 2).

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Figure 1. Polysomnography demonstrating typical central sleep apnea (five-minute epoch). Recurrent absences of airflow (FLWe channel) lasting more than 10 seconds are associated without on-going respiratory effort (THD and ABD channel). FLW channel is non-functional.
Duration of hyperpnea are directly proportional to the lung to peripheral chemoreceptor circulation time, and inversely proportional to cardiac output. Detailed mechanism will be described below. CSR can be diagnosed when there are at least 3 consecutive cycles of cyclical crescendo and decrescendo change in airflow amplitude with central apnea index at least 5 or cyclic change lasting at least 10 consecutive minute.7 CSR can be observed both during sleep and wakefulness, although it appears to be far more common during sleep.19 CSR during wakefulness usually occurs in patients with severe CHF and suggests worse cardiovascular outcome.20

Pathophysiology

CSR-CSA in CHF arises because of respiratory control

Figure 2. Example of typical Cheyne-Stokes respiration. Consecutive cyclic changes in airflow (nasal pressure sensor, upper most in the box) and respiratory effort (thoracic and abdominal respiratory inductance plethysmography, lower two channels in the box) are characteristic. Notes that changes in oxygen saturation during the cycles is quite negligible when compared with typical obstructive hypopneas.
system instability. During sleep, ventilation is mainly dependent on the metabolic control and the primary stimulation for ventilation is PaCO₂.³³ I recommend the excellent review article for the comprehension of respiratory physiology during sleep.³⁴ CSA occurs when PaCO₂ falls below the apnea threshold. Apnea threshold is the PaCO₂ level that central respiratory center / driving respiratory apparatus and CO₂ reservoir is the difference between the eupneic CO₂ level and apnea threshold (Figure 3). In normal subjects, the eupneic CO₂ level during sleep is 3-8 mmHg higher than the waking.³⁴ But in patients with CHF, a key factor predisposing to respiratory control instability is chronic hyperventilation with eupneic CO₂ close to the apnea threshold, i.e. with little increase in eupneic CO₂ during sleep compared with the waking CO₂ level. Patients with CHF and CSR-CSA have lower PaCO₂ than those without CSR-CSA in both the waking and sleeping states.³⁵,³⁶ This chronic hyperventilation occurs because of pulmonary vagal irritant receptor stimulation by pulmonary congestion³⁷-⁴⁰ and increases in central and peripheral chemosensitivity.⁴¹,⁴²

CSR-CSA occurs more frequently during non-rapid eye movement (NREM) sleep than either wakefulness or REM sleep.¹⁹,³³ In NREM sleep, ventilation is predominantly under metabolic control, therefore very tightly linked to alterations in PaCO₂, the apneic threshold, and CO₂ sensitivity. Furthermore, PaCO₂ tends not to increase from wakefulness to sleep in patients with CHF and CSR-CSA. Therefore, relatively hypocapnic subjects with CHF falls asleep and then CSA tends to ensue because their CO₂ level is far below the apnea threshold during sleep.⁴³ PaCO₂ will rise during apnea, once it reaches the ventilatory threshold for NREM sleep, ventilation will resume. Moreover, even though eucapnic CO₂ level is still higher than apnea threshold in CHF, CO₂ reserve tends to be small. That makes subjects vulnerable to CSA. Even when spontaneous arousals precipitate abrupt increases in ventilation and reduction in PaCO₂, episodes of CSA can be easily triggered.

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 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.⁴⁴ 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 CHF patients with and without CSR-CSA.³⁶,³⁸ 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.⁴⁵ 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 PaCO₂ has risen above the apnea threshold, increases in tidal volumes and venti-
Dilation occur, gradually reaching a peak only several breaths after apnea termination. Similarly, as PaCO₂ falls in response to the gradual increase in the preceding ventilation, tidal volumes diminish gradually until apnea ensues once PaCO₂ 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 PaCO₂. Compared with patients with CSA but without CHF, patients with HF and CSR-CSA have much longer hyperpnea with more gradual increases and decreases in tidal volume, but similar apnea duration. Thus, differences in the total cycle duration of periodic breathing between patients with and without CHF are primarily modulated by differences in hyperpnea, but not apnea duration.

**Clinical Implications**

Reported prevalence of CSA-CSR has a wide range from 15 to 37%. Earlier study before the widespread use of beta blocker for CHF therapy showed relative high prevalence because optimizing medical therapy for CHF or heart transplantation attenuates CSR-CSA. Around 20% would be the representative prevalence of CSR-CSA in the general CHF population on optimal contemporary CHF therapy. Taken together, epidemiologic data indicate that the key clinically identifiable risk factors for CSR-CSA in patients with CHF 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. CSR-CSA can also occur in patients with asymptomatic LV systolic dysfunction. Lanfranchi and colleagues reported that 26 of 47 patients with asymptomatic LV systolic dysfunction (LVEF < 40%) had CSR-CSA. Nopmaneemruslers and associates 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<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.

The main clinical significance of CSR-CSA in HF is its potential to adversely influence survival. However, there is controversy on this point. Lanfranchi and colleagues 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 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 found that in 133 patients with HF, an AHI greater than 30 was an independent predictor of mortality. Similarly, Javaheri and colleagues found in 88 patients with HF that CSR-CSA was an independent correlate of worse survival. Conversely, Andreas and coworkers 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 followed 78 patients with severe HF being assessed for 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. CSR-CSA has been to have detrimental physiologic effects on the failing
heart via sympathetic surges, hypoxia, hemodynamic stress, and so on.

Management

Given the paucity of controlled clinical trials, it remains unclear as to whether the targeted treatment of CSR-CSA in the setting of CHF is warranted for improvement in outcomes related to sleep quality, daytime function, or cardiovascular functions. I outline herein the suggested approach to the management of CSR-CSA. Before treating CSR-CSA itself, medical therapy for CHF should be the initial step that should optimized with beta-blocker, angiotensin-converting enzyme inhibitor, diuretics, and its combinations. Despite receiving optimized medical therapy, alternative treatment of the breathing disorder may be considered in patients with persistent CSR-CSA, especially in those patients who have subjective or objective evidence of sleep fragmentation or poor sleep quality. Therapeutic strategies include oxygen, carbon dioxide, theophylline and positive airway pressure therapy.

Positive Airway Pressure

In addition to the expected improvement in sleep quality from the treatment of possible coexisting OSA, short-term studies of CPAP treatment in CSA patients have demonstrated reductions in central respiratory events, O\textsubscript{2} desaturation, and the frequency of arousals.\textsuperscript{55,56} The mechanisms by which CPAP may improve CSA are unclear and may relate to the optimization of intrathoracic hemodynamics. CPAP decreases preload and afterload (probably by increasing intrathoracic pressure), and reduces right ventricular and LV end volumes.\textsuperscript{57,58} CPAP treatment of HF-CSA patients has also been associated with an improvement of LVEF,\textsuperscript{56} reduced mitral regurgitation,\textsuperscript{52} and lower plasma and urinary levels of norepinephrine.\textsuperscript{55} CPAP therapy may also reduce the number of ventricular arrhythmias, paralleling the reduction in respiratory events.\textsuperscript{59} A small, randomized, controlled trial of 66 HF patients (with CSA, 29 patients; without CSA, 37 patients) seemed to provide further strong evidence for the efficacy of CPAP.\textsuperscript{13} Compared with no treatment, CPAP reduced the combined mortality-cardiac transplantation rate in HF patients with CSA, but not in HF patients without CSA, over a median follow-up period of 2.2 years.\textsuperscript{13} The CANPAP, which is the largest randomized, controlled trial published to date evaluating the efficacy of CPAP treatment for patients with CSA, was terminated early when an interim analysis suggested that a difference in transplant-free survival time between groups was unlikely to be detected.\textsuperscript{30} At that point, in fact, there was a trend toward greater mortality in the CPAP-treated group. As suggested by the CANPAP investigators, it is possible that improvements in survival conferred by the increased use of beta-blockers and spironolactone over the past several years may have rendered the trial underpowered. Importantly, CPAP treatment reduced the central AHI by only about 50% (from about 40 to 20 events per hour) and, while only 15% of subjects dropped out of the study, the mean duration of the nightly use of CPAP was about 4 h. Post hoc analysis supports that the sufficient control of CSA by CPAP improves the mortality.\textsuperscript{60} The significance of modest improvements in secondary outcomes such as LVEF and exercise capacity in the CPAP treated group, within the context of the primary findings, is unclear. Adaptive servoventilation (ASV, ResMed Inc., Australia) has become available in the United States after an initial experience in Europe. In a small, crossover trial conducted in 14 patients who were in NYHA class II-III, the use of ASV for 1 night provided an additional 83% reduction in central apneas when compared with treatment using nasal CPAP, and appeared to be better tolerated.\textsuperscript{61} Pepperell et al demonstrated reductions in sleepiness and neurohormonal activation with a month of ASV use in HF-CSA patients.\textsuperscript{62} Based on a mean pretreatment LVEF
of 37%, which did not appreciably change with therapy, this study may have represented a population with milder HF than those studied in previous interventional trials. While there is evidence for the sustained efficacy of and adherence to ASV out to 6 months, more comprehensive, longterm studies will be needed to determine whether ASV yields benefits for CV outcomes or mortality. Besides ASV that is the rate-plus-volume-targeted device, BiPAP AutoSV (Respironics, USA) is the rate-plus-flow-targeted device. Arzt et al recently demonstrate its effectiveness suppressing CSR-CSA in patients with CHF. Ongoing large scale clinical trials using ASV and BiPAP autoSV in Europe and North America will give more answer for the efficacy of these new machines.

In patients with CHF, 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. The majority of the evidences indicates that CSR-CSA increases the mortality in CHF. Optimized medical therapy for CHF is the first-line therapy and the efficacy of PAP therapy is under active investigations.

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