Central Sleep Apnea: From Pathophysiology to Clinical Management

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ABSTRACT
Central Sleep Apnea (CSA) is one of the most common comorbidities in patients with systolic heart failure. CSA is a manifestation of respiratory control instability that occurs in advanced systolic dysfunction, and can negatively impact the prognosis of heart failure patients. Innovative therapeutic approaches have been introduced and are showing efficacy and positive effect on cardiac function. The increasing incidence of heart failure and its persistent economic and human burden require the cardiology clinician to maintain sufficient understanding of this common comorbidity in heart failure. In this review, we will discuss the treatment of CSA with focus on the most recent advances and therapeutic approaches.

Keywords — Central Sleep Apnea; Apnea-Hypopnea Index, Central Sleep Apnea, Heart Failure

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Abbreviations and Acronyms
CSR: Cheyne Stokes Respiration; CSA: central sleep apnea; OSA: Obstructive sleep apnea; ASV: Adaptive servo ventilation; LVEF: left ventricular ejection fraction.

I. INTRODUCTION

The increased occurrence of heart failure (HF) in recent years is likely due to survival of cardiovascular disease, increased prevalence of diabetes and hypertension, and aging of the population. The mortality of HF is largely unchanged despite advances in the management of cardiovascular disease. Sleep Disordered Breathing (SDB) is the most common comorbidity in HF patients. Central sleep apnea (CSA), a rare form of SDB in the general population, is most often encountered in patients with systolic HF with an estimated prevalence of 20–40% in this population. Recognition of the negative prognostic effect of CSA on HF and the advent of promising new therapeutic modalities, make it imperative for the HF-clinician to maintain sufficient understanding of CSA. Some of the important advances in the treatment of CSA and SDB are not pharmacological or technological breakthroughs; rather they are new approaches to delivery of care. These approaches include surveillance and disease management teams along with individualized care delivery of device treatment and follow up.

II. TERMINOLOGY

A pattern of breathing oscillation characterized by a crescendo-decrescendo ventilation followed by cessation of breathing was described by Hunter and by Cheyne and Stokes in the early to mid-19th century in patients with stroke, obesity and HF. This pattern is now termed Cheyne-Stokes Respiration (CSR) and is characterized by recurrent 60-90 second cycles of gradually increasing ventilation (crescendo), followed by a gradual decrease in ventilation (decrescendo) that culminates in a visually recognizable prolonged apnea. The occurrence of CSR in a given patient is a manifestation of an underlying oscillatory instability in the respiratory control system. CSR has been mainly observed in patients with systolic HF, where it is reported to occur even during restful wakefulness and exercise.

Polygraphic recording of sleep (polysomnography) became available in the 1960s. The first polysomnographic description of CSR was made in 1965. The definition of SDB includes both obstructive sleep apnea (OSA) and CSA. The abnormal respiratory events that constitute SDB are classified on the polysomnography into apneas, with complete cessation of airflow, and hypopneas, in which only a partial decrease in air flow occurs. SDB is diagnosed when more than 5 apneas or hypopneas are present per hour of sleep (Apnea-hypopnea index >5 events/hour). If the majority (more than half) of the events were obstructive, the SDB is classified as OSA. If more than half of the events are central, the SDB is classified as CSA. The polysomnographic diagnosis of CSA takes into account only the presence of central apnea or hypopnea and not necessarily the presence of the oscillatory pattern of ventilation characteristic of CSR. Patients with HF and CSA generally demonstrate the CSR pattern on the sleep study in association with their central respiratory events. However, the CSR pattern of respiration may be observed in the context of obstructive
events or without even meeting the definition of a respiratory event (no accompanying decrease in oxygen saturation). Therefore, CSR and CSA terms are not always interchangeable. It is accepted that patients who have predominantly central apneas and are classified as having CSA on their sleep studies have the same respiratory control instability that underlies CSR. In these patients the disorder is sometimes termed CSA-CSR to indicate the presence of the CSR breathing pattern and the sleep study diagnosed CSA. We will use the term CSA to refer to the polysomnographic classification of SDB with a majority of the respiratory events being central on a sleep study. Finally, it must be noted that at the end of a central apnea, a decrease in upper airway tone occurs. Thus, obstruction of the upper airway is part of the mechanism of central apnea, and one patient can manifest mixed, central, and obstructive events during a single night.

III. OVERVIEW OF THE MECHANISM OF CENTRAL SLEEP APNEA

The mechanism of respiratory control instability has been recently reviewed. We will focus in this overview on the most accepted mechanisms and on the therapeutic implications for the known pathways.

Respiratory control in HF:

The respiratory control system consists of a complex matrix of receptors, rhythm generators, and signal effectors. This system functions in a negative feedback loop and is tasked with maintaining a tight level of O_2 and CO_2 under the varying conditions of the organism’s life. The system includes two main sets of controllers. One set is located behind the blood brain barrier at the level of the brainstem (the central chemoreceptors); the second set is in close proximity to the lungs at the carotid bodies (the peripheral chemoreceptors). The two controllers integrate chemical and mechanical signals arising from the lung parenchyma, the upper airways, the chest wall and the blood content of gas, along with various other proprioception and behavioral signals. It is generally accepted that the central chemoreceptors are primarily responsible for the maintenance of background regular breathing rhythm, while the peripheral chemoreceptors are tasked with immediate response to sudden perturbations to the system such as acute drops in the fractional inspired O_2 (hypoxia). The two peripheral and central controllers are likely linked directly with neural pathways as well as indirectly through the circulation. In addition, the two controllers are linked in series to the same receptors in the chest wall, the lung, and the upper airways to maintain redundancy and integration of the afferent signals along with smoothing of the efferent signal. There are several implications to these characteristics of the respiratory control system. One is that the in the presence of circulatory delay, such as in the case of the systolic HF, an additional lag time occurs between the output signal from the central chemoreceptors and the peripheral chemoreceptors. Another implication is that, since the central chemoreceptors are located behind the blood brain barrier, they are subject to the disorders that affect cerebrovascular function.

During sleep, the behavioral control of breathing is abolished, and the arterial carbon dioxide level (PaCO_2) becomes the main stimulus for ventilation. Respiration ceases if PaCO_2 falls below a tightly regulated level called the apnea threshold. Patients with HF have a unique pattern of chronic hyperventilation, characterized by close proximity between baseline sleep level of PaCO_2 and apnea threshold. Any slight increase in ventilation during sleep, as occurs with arousal or changes in sleep stages, will result in a drop in PaCO_2 below the apnea threshold precipitating apneic events. Several factors produce a delay in resumption of breathing until an excessive chemical stimulus (hypercapnea) has accumulated producing an “overshoot” of ventilation that is likely to drop PaCO_2 again below the apnea threshold and create periodic breathing and CSA.

The ventilatory response to hypercapnea is increased in HF patients causing an exaggerated response to the increased PaCO_2 following apnea.

Therapeutic targets contributing to respiratory control instability

a. Systolic dysfunction

As described above, patients with systolic HF have a specific pattern of respiratory control instability that underlines the mechanism of CSA. HF patients have increased baseline ventilation, along with proximity of the baseline PaCO_2 level to the apnea threshold level of PaCO_2. The mechanism of this chronic hyperventilation in patients with systolic HF is thought to be related to pulmonary interstitial congestion providing stimulatory feedback to the peripheral chemoreceptors. In animal models respiratory control instability and central apnea were induced in response to increased left atrial pressure. This may explain in part why CSA is more common in the supine position in HF patients. Therefore, any transient increase in ventilation such as during arousals or sleep stage shifts can cause sufficient drops in PaCO_2 to cross the apnea threshold. The predisposition of HF patients to fluid retention and increased venous pressures is a likely contributor. The activation of pulmonary interstitial stretch receptors due to venous congestion can upregulate the ventilatory drive. Patients with more severe systolic HF have prolonged circulation time that correlates with the duration of the central apneas. This abnormality alone does not independently cause sufficient respiratory control instability to produce CSA, however. The difference in signal time, amplitude, and direction between the peripheral and central chemoreceptors may be increased by this circulatory delay contributing to further instability.

b. Impaired cerebrovascular reactivity

Changes in cerebral perfusion (cerebrovascular reactivity) in response to changes in PaCO_2 play an important role in the central chemoreceptors’ function. Normally, an increase in PaCO_2 (such as during an apnea) produces cerebrovascular dilation; while a decrease in PaCO_2 (as during hyperventilation following an apnea) produces cerebrovascular constriction. The normal decrease in cerebral perfusion with hypocapnea (the hyperventilation phase of CSR) allows for more accumulation.
of CO₂ at the level of central chemoreceptors creating increased stimulus to breathe during the hyperventilation stage of CSR. This counteracts the inhibitory input from the peripheral chemoreceptors (which is about to decrease its ventilatory output due to the hypocapnea at the end of hyperventilation); this can shorten the duration of the subsequent apnea. Similar events, but in opposite directions, occur during the apnea. The cerebrovascular dilation induced by the increase in PaCO₂ has a wash-out effect decreasing the accumulation of CO₂ at the level of the chemoreceptors and dampening the stimulus to breathe. This inhibitory effect counteracts the vigorous stimulatory input from the peripheral chemoreceptors and can shorten the duration of the post-apnea hyperventilation (ventilatory overshoot) 20. HF patients have reduced cerebral blood flow response to changes in PaCO₂, which impairs the ability of the central chemoreceptors to dampen the overshoot and undershoot in the peripheral chemoreceptors’ response to CO₂21. The mechanism of this impaired reactivity may be a manifestation of the endothelial dysfunction typical to HF.

c. Upper airway instability
Systolic HF can promote upper airway instability due to cerebral venous congestion which can worsen or unmask latent OSA22. A recent study examined the correlation between lower extremity volume shifts during sleep and the apnea hypopnea index (AHI) in HF patients with either OSA or CSA 23. The study showed a correlation between the AHI and leg volume shifts in both OSA and CSA patients. Furthermore, the nightly fluid shift from the legs was found to correlate with a nightly relative decrease in PaCO₂ levels in CSA patients. These data suggest that fluid not only accumulates in cervical venous vessels but also in pulmonary interstitium in CSA patients. This increase in intrapulmonary volume may cause activation of irritant receptors resulting in hyperventilation and decrease PaCO₂ and worsening the respiratory control instability and subsequently CSA events, as described above. The results of this study suggest minimizing peripheral edema in HF patients may further decrease apneic episodes in HF patients by minimizing OSA and CSA episodes.

Central events are often accompanied by a secondary decrease in respiratory motor output to the upper airway musculature causing obstructive type events from collapse of the upper airway. It has also been postulated tonic output to pharyngeal constrictors during apneic episodes can further narrow the upper airway during apneic episodes 24. Either of these mechanisms would cause increased resistance upon resumption of breathing worsening subsequent ventilatory overshoot. Exacerbation of OSA can also occur in HF patients by the mechanisms described above from lower extremity fluid shifts. Furthermore, weight loss in HF patients can also lead to a decrease in pharyngeal fat pad volume, which was recently found to be significantly increased in patients with OSA 24. Obstructive apneas, probably through intermittent hypoxia, can increase the ventilatory response to subsequent apneas and produce central apneas 25. Therefore, worsening of HF may lead to both increased central and obstructive apneas.

d. Intermittent hypoxia

Each respiratory event in CSA produces an episode of hypoxia followed by re-oxygenation when an arousal terminates the respiratory event. The recurrence of these respiratory events and their respective recovery phases produces a characteristic pattern of intermittent hypoxia during sleep unique to SDB. The intermittent hypoxic pattern results in upregulation of the chemoreceptor response to subsequent episodes of hypoxia and propagation of the “ventilatory overshoot” characteristic of CSR 25. This upregulation of chemoreceptor response has been shown to be increased in patients with HF and CSA versus HF patients without CSA with these patients having an increased sensitivity to PaCO₂ 26. Furthermore, higher altitudes with lower partial pressures of oxygen have been known to induce CSA episodes in patients with and without HF 27. As not all HF patients with CSA are hypoxic at baseline, intermittent hypoxia may not be the primary cause of CSA episodes. However, this cannot discount the role hypoxia can play in exacerbating the vicious cycle of cyclical breathing in these patients. It is therefore theoretically reasonably to target this stimulus with supplemental oxygen. In addition ventilatory assistance devices decrease hypoxia and can ameliorate the ventilator overshoot as one of their therapeutic effects.

IV. TREATMENT OF CENTRAL SLEEP APNEA

Does treatment of CSA modify its cardiovascular consequences?

CSA is a manifestation of respiratory control instability in patients with systolic dysfunction. However, once present, CSA produces a profile of neurocirculatory responses that are detrimental for the failing heart. Sympathetic activation 28, arrhythmia 29, and ventricular irritability 30, 31 occur due to CSA in patients with HF. Initial reports suggested efficacy of continuous positive airway pressure (CPAP) in decreasing the AHI 32, 33 and increasing left ventricular ejection fraction in patients with systolic HF and CSA 32, 34. Later, a large adequately powered trial of CPAP in patients with systolic HF and CSA found partial improvement of the AHI with CPAP and no survival benefit 35. Post hoc analysis of this study revealed that cardiac and survival benefit occurred in a subgroup of treated patients in whom the AHI was normalized. Therefore, treatment of CSA was associated with cardiovascular benefit only when the AHI was normalized 36 rather than just decreased. Newer pressure devices are able to accomplish this normalization in AHI readily as discussed below.

Optimization of HF Therapy

Systolic dysfunction causes the respiratory control instability underlying CSA. 3, 37. Hence, optimization of HF therapy is the most important first step in treatment. Angiotensin converting enzyme inhibitors and beta-blockers were reported to improve CSA 38, 39. This may be due to a direct effect on improving the cerebrovascular response to changes in PaCO₂ and restoration of the important protective role of the brain extracellular fluid PaCO₂ and [H+] 41. Optimization of HF therapy also leads to decreased preload. Subsequently, decreased interstitial pressure in the lung tissue would result in decreased ventilatory drive. The same decrease in preload will decrease cervical venous congestion and result in less instability of the upper airway.
Most of the interventions that improve cardiac systolic function result in improvement in CSA (but not necessarily in OSA). These interventions include atrial overdrive pacing and cardiac resynchronization. The pathophysiologic relationship between systolic dysfunction and CSA is substantiated by these studies. Additionally, the therapeutic feedback relationship between HF and CSA is supported by the improvement in CSA with the optimization of pharmacological or electromechanical therapy in underlying HF. Nevertheless, many patients will be diagnosed with CSA despite a HF regimen that is already optimal. These patients are likely to benefit from additional treatment targeted to the CSA. Positive airway pressure and CSA

a. Continuous Positive Airway Pressure in the treatment of CSA

As noted above, HF patients can have upper airway instability that may contribute to CSA. Multiple studies have shown improvement in cardiac parameters with continuous positive airway pressure CPAP therapy. The earlier small trials in patients with HF and CSA suggested that CPAP improved sympathetic activity, gas exchange, and left ventricular ejection fraction (LVEF) and central apneas and central sleep apnea. These studies prompted a large adequately powered multicenter trial of CPAP in patients with systolic HF and CSA. They found partial improvement of the AHI with CPAP and no survival benefit. Post hoc analysis of this study revealed that cardiac and survival benefit occurred in a subgroup of treated patients in whom the AHI was normalized. Therefore, treatment of CSA was associated with cardiovascular benefit only when the AHI is normalized rather than just decreased. Since the obstructive and central sleep disordered breathing often co-exist in patients with HF, it is likely these patients who had profound improvement in their respiratory events with CPAP actually had more obstructive than central disorder to begin with. Although the studies above showed improvement in AHI with CPAP therapy, there was a heterogeneous response in the AHI levels among the patients undergoing therapy. Two possible hypotheses have been described by Jaffuel et al. The first is that higher pressures used in some of the patients described in the studies may affect the cardiac output. It is has been established that higher pressures used in CPAP can decrease the cardiac output and ultimately exacerbate central apneic episodes. The second hypothesis is the timing of central apneic episodes may affect the response to CPAP. Central episodes occurring at the end of the night, versus episodes throughout the night, are usually induced by obstructive episodes in the beginning of the night. Amelioration of the obstructive events by CPAP can decrease the number of central apneic episodes. Further randomized trials are needed to help elucidate the factors that cause this heterogeneous response to CPAP. At this time, CPAP should be considered in patients with co-existent OSA and CSA when sleep laboratory titration demonstrates benefit. If a sleep demonstrated complete normalization of the AHI in a patient with CSA, it is possible to accept CPAP as a treatment device for this patient.

b. Adaptive servo-ventilation (ASV)

In addition to providing baseline positive pressure to stabilize and maintain the patency of the airway (similar to CPAP), these devices adapt to deliver additional breaths when central apneas or hypopneas are detected to counteract the hyperventilation and “ventilatory undershoot”. During a hyperventilation phase, these devices adapt to stop supplying additional ventilatory support to prevent further exacerbation of the hyperventilation. Therefore, ASV can be considered to have upper airway stabilizing effects of CPAP with additional ability to treat respiratory control instability, the primary abnormality in CSA. Thus, by preventing the increase in PaCO2 during the apnea, and subsequently preventing the hyperventilation that follows the apnea, the periodic breathing cycle is broken. ASV devices are FDA approved for the treatment of CSA. These devices have shown advantage to CPAP at immediately normalizing the AHI in patients with HF and CSA, and have become routinely used for the treatment of CSA and periodic breathing. ASV has demonstrated efficacy in supporting normalization of the AHI and improving LVEF. In addition, the device is effective for treatment of combined obstructive and central sleep apnea, a common occurrence in HF patients. A recent study compared the efficacy of ASV against CPAP in mild-to-moderate HF patients with coexisting CSA and OSA. Although both modalities improved major indices, ASV significantly improved AHI and BNP levels after 12 months when compared to CPAP and was found to be superior in the study. Further studies need to be conducted to determine if similar results are found in patients with severe HF.

c. Bilevel positive airway pressure with preset back up rate

This modality has been used effectively in small trials to treat CSA. Bilevel provides upper airway stability support by the same mechanism as CPAP. The disparate inspiratory and expiratory pressures can assist with PaCO2 regulation and patient tolerance at higher airway pressures. In this setting, bilevel was administered with a back-up rate effectively as a form of ventilation with predetermined minute ventilation that corresponds with the patient’s minute ventilation during stable breathing.

Oxygen Therapy

CSA can result in intermittent hypoxia which is an exacerbating factor for HF. Nocturnal oxyhemoglobin desaturations can result in sympathetic activation. Moreover, depleted oxygen stores in patients with HF may compound the ventilatory response to the increase in PaCO2 during apnea. Supplemental oxygen in these patients should blunt the sympathetic activation and perhaps lessen the hyperventilatory response. Another possible mechanism of action would be a direct effect on the peripheral chemoreceptors decreasing their background chemosensitivity to PaCO2 and thereby dampening the ventilatory overshoot following apnea induced hypercapnea. Some small studies suggest that nocturnal oxygen can reduce CSA, benefit LVEF, and reduce sympathetic tone. These effects are supported by longer term trials that have shown efficacy for nocturnal oxygen in HF patients with CSA. It should be noted that nocturnal oxygen alone
cannot eliminate the upper airway obstruction that so often coexists in HF patients with central apneas62.

Pacing therapy
A novel investigational treatment is the use of transvenous unilateral phrenic nerve stimulation (PNS) devices. The device was recently investigated in a small multicenter prospective, non-randomized acute study. 16 male HF patients had a two-lead PNS device inserted transvenously. Participants underwent a two day polysomnography study comparing one night of control sleep with no PNS and a second night with PNS. The investigators observed a significant improvement in the major indices of CSA severity, including AHI, central apnea index, arousal index, and oxygen desaturation index 4%. The study did not address the effect of phrenic nerve stimulators in women, as all study participants were male, interactions of the implantable device with other devices, the long-term safety of the devices, and did not address the effect PNS devices with concurrent OSA. PNS devices are known to exacerbate and worsen symptoms of OSA in children with central alveolar syndrome 65. A second Chinese study also looked at the efficacy of PNS in patients with HF and CSR 66. Participants underwent insertion of single lead PNS device and were monitored for a single night. Investigators found a significant improvement in AHI. The interactions of the PNS devices with preexisting implantable devices and long-term safety were also not addressed in the second study.

The unilateral implantable phrenic nerve stimulator was tested and may benefit67. Phrenic nerve stimulation may work by ventilating throughout the central apnea episode with unilateral lung inflation preventing the precipitous drop in CO2 and dampening the subsequent ventilatory overshoot. This is reviewed elsewhere in this issue. This therapy may be a promising option for those who do not tolerate pressure therapy. In addition, the integration of this implantable stimulator in other implantable devices with possibly on-demand treatment may be another direction. Further randomized control trials are needed to further investigate the long-term efficacy and safety of the devices.

V. NEW MANAGEMENT APPROACHES TO CENTRAL SLEEP APNEA IN HF PATIENTS
One of the most important recent advances in health care delivery is the introduction of disease management teams. These multidisciplinary teams include various types of providers specializing in the delivery of several aspects of care to patients with chronic disease such as renal failure or HF. In this latter case, disease management programs have been shown to have a positive impact on heart outcomes71, 72.

SDB is by far the most common comorbidity in patients with HF and is also the least diagnosed. HF patients with SDB present with different symptoms from the general population with SDB. Also these patients deal with the burden of HF and its consequences of limited functional status, disturbed sleep, and recurrent hospitalizations affecting acceptance and adherence to device treatment. These patients are often already established in a HF management team and have regular engagement with this team. In addition, these patients are often already receiving device management for pacemakers and implantable defibrillators. All these considerations support the integration of surveillance and management of SDB in HF within the HF management team. These integrative approaches have been increasingly recognized in the U.S. The natural course of HF includes periods of decompensation and stabilization with variable degree of improvement in the systolic function. These profound physiological changes impact respiratory control stability and upper airway tone accounting for shift in the type of severity in SDB. There is a paucity of data addressing the prospective management of SDB in HF patients.

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