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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

# Mechanisms and Clinical Consequences of Untreated Central Sleep Apnea in Heart Failure

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## ABSTRACT

Central sleep apnea (CSA) is a highly prevalent, though often unrecognized, comorbidity in patients with heart failure (HF). Data from HF population studies suggest that it may present in 30% to 50% of HF patients. CSA is recognized as an important contributor to the progression of HF and to HF-related morbidity and mortality. Over the past 2 decades, an expanding body of research has begun to shed light on the pathophysiologic mechanisms of CSA. Armed with this growing knowledge base, the sleep, respiratory, and cardiovascular research communities have been working to identify ways to treat CSA in HF with the ultimate goal of improving patient quality of life and clinical outcomes. In this paper, we examine the current state of knowledge about the mechanisms of CSA in HF and review emerging therapies for this disorder. (J Am Coll Cardiol 2015;65:72–84) © 2015 by the American College of Cardiology Foundation.


Congestive heart failure (HF) remains a major public health problem and continues to be associated with substantial morbidity and mortality. One factor now recognized as contributing to the excess morbidity and mortality in HF is sleep-disordered breathing. This condition is characterized by cycles of significant pauses in breathing and partial neurological arousals that ultimately have an impact on sleep quality and overall health. Sleep-disordered breathing is broadly classified into 2 types: obstructive sleep apnea (OSA) and central sleep apnea (CSA). The former is common and occurs in both the general and HF populations, whereas the latter is more uniquely associated with HF (1–3).

In OSA, repeated episodes of partial or complete upper airway obstruction occur during sleep. This obstruction causes loud snoring, repeated episodes of apnea and hypoxia, and arousals from sleep. These episodes of obstruction, hypoxia, and arousal lead to the development and progression of a number of cardiovascular disorders, including systemic hypertension, cardiac arrhythmias, myocardial ischemia and infarction, and HF (4,5). Because of its high prevalence in both the general and HF populations, OSA has been well studied, and effective methods to treat it have been developed (4,6). Of these therapies, continuous positive airway pressure (CPAP) is the primary therapeutic option, with several studies demonstrating that it significantly improves symptoms, such as snoring, morning headaches, and daytime sleepiness (7–9). CPAP has also been shown to significantly reduce blood pressure, and several

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studies suggest that it may reduce OSA-related mortality (10–12).

Most often seen in HF patients, CSA is distinguished by the temporary withdrawal of central (brainstem-driven) respiratory drive that results in the cessation of respiratory muscle activity and airflow. In HF patients, CSA commonly occurs in the form of Cheyne-Stokes respiration, a form of periodic breathing with recurring cycles of crescendo-decrescendo ventilation that culminates in a prolonged apnea or hypopnea. Like OSA, the presence of CSA in patients with HF is associated with a set of neurohumoral and hemodynamic responses that are detrimental to the failing heart (13–16). However, unlike OSA, the underlying pathophysiology of CSA and its consequences in HF have only more recently been recognized and understood. With this expanding knowledge base, clinicians have been working to identify ways to treat CSA in HF with the ultimate goal of improving patient quality of life (QOL) and clinical outcomes. Thus, in this paper, we will focus on the current state of knowledge about the mechanisms of CSA in HF and review emerging therapies for this disorder.

## CSA: PRESENTATION AND RISK FACTORS

Highly prevalent in HF, CSA occurs in 30% to 50% of patients (1–3). Clinically, HF patients with CSA may experience insomnia, fatigue, and/or daytime sleepiness, although the latter is often absent (17–19). Sometimes, a sleep partner may report witnessed apneas or the unusual breathing pattern of Cheyne-Stokes respiration. Patients may also report frequent awakenings, poor quality sleep, shortness of breath, paroxysmal nocturnal dyspnea, and nocturia (1). However, because these common findings can be due to HF itself, the presence of CSA is often overlooked by patients and clinicians, and failure to treat CSA potentially leads to a prognosis worse than that attributable to HF alone.

A number of risk factors have been identified for the development of CSA in HF, including male sex, higher New York Heart Association functional class, lower ejection fraction, waking hypocapnia (arterial partial pressure of carbon dioxide [$PaCO_2$] <38 mm Hg), higher prevalence of atrial fibrillation, higher B-type natriuretic peptide levels, and frequent nocturnal ventricular arrhythmias (3,18–20). No questionnaire-based screening tool has been validated to identify CSA in HF; therefore, a high index of suspicion for CSA should exist when 1 or more of these findings are present in a patient with HF (21).

**DIAGNOSTIC TESTING.** The gold standard test for diagnosing CSA is polysomnography, or overnight sleep study, which is performed in a sleep laboratory. Characteristic polysomnographic findings of CSA include: an onset near the transition into or out of stage 1, nonrapid eye movement sleep; cycles of deep, rapid, crescendo-decrescendo breathing followed by periods of hypopnea and/or apnea along with concomitant changes in blood oxygen saturation; and apneic periods accompanied by the absence of chest or abdominal wall activity (**Figure 1**) (22). A common measure of the severity of CSA is the apnea-hypopnea index (AHI), defined as the mean number of apnea and/or hypopnea episodes that occur during sleep divided by the number of hours of sleep, and is expressed in events per hour. According to 1 study, receiver-operating characteristic analysis of different AHI levels revealed that an AHI of 22.5 events/h had the greatest sensitivity and specificity in predicting mortality associated with CSA (23). Another study of ambulatory HF patients showed that mortality rose progressively with every 5 events/h increase in AHI (24). Because the detrimental effects of CSA increase with the increasing number of CSA events, reducing AHI should be the main focus of treatment.

**ABBREVIATIONS AND ACRONYMS**

**AHI** = apnea-hypopnea index
**ASV** = adaptive pressure support servo-ventilation
**CPAP** = continuous positive airway pressure
**CRT** = cardiac resynchronization therapy
**CSA** = central sleep apnea
**HF** = heart failure
**LVEF** = left ventricular ejection fraction
**NF-κB** = nuclear factor-kappa B
**OSA** = obstructive sleep apnea
**ROS** = reactive oxygen species

## PATHOGENESIS OF CSA IN HF

The pathogenesis of CSA in HF is complex and remains incompletely understood. However, a substantial body of research suggests that an increased respiratory control response to changes in $PaCO_2$ above and below the apneic threshold is central to the pathogenesis of CSA in HF (25–27). An understanding of normal respiratory control in both the awake and sleeping states can aid in understanding the current theories regarding CSA pathogenesis.

The respiratory control system consists of a complex matrix of peripheral and central receptors and rhythm generators interacting continuously with the lung, chest wall, and arterial blood gas content (28–31). This system operates in a negative feedback loop while performing its task of maintaining tightly regulated levels of $O_2$ and $CO_2$ under the numerous demands from human activity, disease, and aging. During wakefulness, normal breathing is influenced by both metabolic and behavioral factors. Metabolic factors (such as exercise-induced acidosis or diuretic-related alkalosis) alter the rate of production of $CO_2$ and modify breathing in response to input from central and peripheral chemoreceptors. On the basis of input from these receptors, tidal volume and breathing rate are modified to maintain $CO_2$ within a tight range. Behavioral factors also alter breathing