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Review

Current treatment approaches and trials in central sleep apnea

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ABSTRACT

Central sleep apnea (CSA) is one of the most common comorbidities in patients with heart failure with reduced ejection fraction and is associated with negative consequences. Despite several recent advances, there are currently no widely accepted therapies for CSA. In this review we will discuss available therapies for CSA and review the published trials addressing treatment of CSA in HFrEF patients.

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Contents

1. Introduction

The mortality and morbidity of heart failure remain largely unchanged despite advances in the management of cardiovascular disease [1]. Sleep disordered breathing (SDB) is the most common comorbidity in heart failure (HF) patients [2]. Central sleep apnea (CSA), although infrequent in the general population, is most often encountered in patients with heart failure and reduced ejection fraction (HFrEF) with an estimated prevalence of 40% in this population [3]. It is also increasingly recognized in other cardiac populations including patients with heart failure with preserved ejection fraction, atrial fibrillation, stroke, and in opioid users. Recognition of the negative effects of CSA on HF [4–6] and the advent of promising new therapeutic modalities [7,8] underscores the need for cardiologists to develop and maintain sufficient understanding of CSA. In addition to new technological approaches for therapy, integration of different specialties (including

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sleep and cardiac physicians) may have the greatest impact in the delivery of care. Disease management teams, individualized treatment plans and continuous surveillance are needed to appropriately identify and treat CSA patients.

2. SDB classification and its implications to management

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 air flow, 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 (AHI) >5 events/h). If the majority (more than half) of the events is obstructive, the SDB is classified as OSA. If more than half of the events are central, the SDB is classified as CSA. Given the known difficulty in distinguishing central from obstructive hypopneas based on the clinical polysomnography, guidelines in the US recommend classification of SDB based only on apneas. However, many authorities in the field of sleep apnea further classify hypopneas into central and obstructive [9].

The implication of the current approach to classification of CSA and OSA is that patients classified as having CSA can have a large range of central apneas and a significant number of HF patients classified as CSA can have substantial component of obstructive apneas and hypopneas. In addition, a decrease in upper airway tone can occur at the end of a central apnea [10]. Thus, obstruction of the upper airway is part of the mechanism of central apnea in addition to the hypersensitivity to CO_2. Therefore, a single HF patient can manifest central, obstructive and mixed (events that demonstrate characteristics both central and obstructive properties) events during a single night. The distribution of these events may be important in choosing a specific treatment for a particular patient.

Cheyne–Stokes respiration (CSR) is an oscillatory breathing pattern found primarily in HF patients and is frequently seen during CSA (i.e. at night), but also can be seen during restful wakefulness and exercise [11,12]. The occurrence of CSR in a given patient is a manifestation of an underlying oscillatory instability in the respiratory control system. 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 waxing and waning 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 heart failure 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.

3. Consequences of CSA in HF patients

In CSA, as well as OSA, each respiratory event produces an episode of hypoxia followed by re-oxygenation when an arousal terminates the respiratory event. The recurrence of these respiratory events produces a characteristic pattern of nocturnal intermittent hypoxia seen only in SDB. Nocturnal intermittent hypoxia is a distinct physiologic state that is associated with a unique profile of respiratory, vascular and neuro-humoral responses [13,14]. Importantly, intermittent hypoxia upregulates the carotid chemoreceptors resulting in sustained stimulation in the ventilatory response consequently destabilizing the respiratory control system and propagating SDB [15]. In addition, activation of the chemoreceptors results in sustained sympathetic activation [13,16]. The negative impact of increased sympathetic tone is well established in heart failure patients [17]. These perturbations are inherently linked to the pathogenesis of cardiovascular disease; but are particularly detrimental to HF patients [17]. The consequences of SDB induced sympathetic activation to the failing heart include predisposition to tachyarrhythmia and possibly life threatening ventricular arrhythmias [18,19]. Treatment of both CSA and OSA decreases sympathetic activation in HF patients and improves myocardial work load [18,20–23].

Hospitalizations for decompensated heart failure are an important component of the progressive course of heart failure and indicate worse prognosis. CSA has the most negative consequences during and following decompensation episodes. Recently, a prospective cohort study addressed the effect of hospital-diagnosed CSA on discharge outcome of hospitalizations for decompensated heart failure. This study enrolled 889 consecutive patients with HF and reduced ejection fraction (HFrEF) who were hospitalized for decompensated HF and underwent in-hospital sleep testing during their admission. The multivariate modeling of readmission rates adjusted for a set of covariates were found in large HF registries to predict readmissions and mortality [24–26]. This study found that CSA is an independent predictor of post-discharge HF readmissions [5]. More recently, a large prospective study provided the first evidence that SDB is independently associated with post discharge cardiovascular mortality [4]. This study was a prospective cohort study of over a thousand HFrEF patients who were hospitalized with decompensated HF and were not previously diagnosed with SDB. These patients underwent in-hospital sleep testing and were followed for a median of 3 years post-discharge. Both CSA and OSA were independently associated with mortality. This study was the largest observational study to date evaluating the effect of CSA on HF related mortality [4]. These studies support the negative impact of CSA in HF and identify the HF decompensation as a critical phase in the progressive course of HF in which the patient is most susceptible to the consequences of CSA.

4. Should CSA be treated in HF patients?

Recently, a question was raised whether CSA in HFrEF patients should be treated [27]. To date, there has not been any adequately powered trial confirming such survival benefit [4,28,27]. A notion that CSA is a compensatory mechanism in HFrEF was based on the observation that CSR is associated with hyperventilation-related increases in end-expiratory lung volume, intrinsic positive airway pressure, and possible decrease of work of breathing associated with provision of periodic rest to the respiratory muscles in HF patients. The recent publication of a negative trial in HFrEF and CSA led renewed interest in this hypothesis [29].

This notion, not empirically tested in HF patients, stands in opposition to numerous studies over the past few decades demonstrating a negative impact of CSA in HFrEF patients. While the treatment of CSA with positive airway pressure devices has not been shown to improve mortality in heart failure patients in large randomized trials, the neuro-humoral consequences of CSA and their elimination with treatment are well documented in HF patients. Multiple randomized trials, albeit of small number of patients, showed that treatment of CSA decreases sympathetic activity, improves respiratory muscle strength and decreases work of breathing [21,30–32]. Interestingly, several of the hypothesized compensatory mechanisms of CSA would also be achieved by the application of positive airway pressure (PAP): CPAP or ASV which should have led to strongly positive outcomes in randomized trials utilizing these modalities. PAP stabilizes the airway by increasing the end-expiratory pressure and improves ventilation–perfusion matching and decreases work of breathing by increasing intra-thoracic volume [33].

Central events are associated with a similar pattern of hypoxia and sympathetic activation to that found with obstructive events [13,16]. The importance of treating OSA is firmly established in practice guidelines [33]. Many central events are associated with airway collapse

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