The Management of Co-Morbidities In Patients with Heart Failure – Central Sleep Apnoea

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Abstract

Despite many therapeutic advances, heart failure (HF) remains challenging to treat and continues to be associated with high rates of morbidity and mortality. There is an ongoing need to identify co-morbidities that either contribute to the progression of heart failure or limit the therapeutic response to treatment. One area under active investigation is the treatment of central sleep apnoea (CSA). CSA has consistently been shown to be associated with a worse prognosis in HF patients. Thus, understanding how to diagnose and treat CSA is of paramount importance to the HF clinician. Without treatment, HF patients continue to be at risk for the devastating consequences of CSA. Prognosis is very poor with studies consistently demonstrating poor outcomes among HF patients with CSA. Over the course of the night, each discrete event contributes to increased nor-epinephrine levels and hypoxia which are associated with progressive heart failure and arrhythmias. Initial therapeutic options utilized therapies which were developed for obstructive sleep apnoea with limited success or even harm. ASV is now contraindicated in HF patients with an EF < 45% leaving only 2 potential treatment options: CPAP and transvenous phrenic nerve stimulation. Data from the recently presented (post ESC guidelines) trial on transvenous phrenic nerve stimulation demonstrated efficacy without the need for patient compliance or any safety concerns. It is expected that additional studies in CSA will continue to demonstrate the full impact of treating this important co-morbidity on patients with HF.

Keywords: Heart failure; Sleep Apnoea; Guidelines

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Background

Despite many therapeutic advances, heart failure (HF) remains challenging to treat and continues to be associated with high rates of morbidity and mortality. There is an ongoing need to identify co-morbidities that either contribute to the progression of heart failure or limit the therapeutic response to treatment. One area under active investigation is the treatment of central sleep apnoea (CSA). CSA has consistently been shown to be associated with a worse prognosis in HF patients.[1–6] Thus, understanding how to diagnose and treat CSA is of paramount importance to the HF clinician.

CSA is a chronic respiratory disorder characterized by fluctuations in central, brainstem-driven respiratory drive that results in the cessation of respiratory muscle activity and airflow during sleep. [7] CSA is a common finding in HF, occurring in up to 40% of patients, and is seen in both HF with reduced ejection fraction and HF with preserved ejection fraction.[8–14] CSA in patients with HF is usually in the form of Cheyne-Stokes respiration [15–18] which is characterized by cycles of deep, rapid, crescendo-decrescendo breathing (hyperpnoea) followed by a period of slower, shallower

Figure 1. The pathophysiological consequences of CSA in heart failure

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breathing (hypopnoea) or no breathing at all (apnoea). The mechanism underlying the development of CSA in HF is respiratory control system instability due to oscillation of the arterial blood carbon dioxide level (PaCO₂) above and below the central threshold of ventilation termed the apnoeic threshold.[19–21] Multiple factors appear to contribute to respiratory control system instability and predispose HF patients to fluctuations in the PaCO₂, including lung congestion, elevation in sympathetic activation and reduced cardiac output leading to prolonged circulation time. [22–28] Often these factors lead to hyperventilation which drives the PaCO₂ below the apnoeic threshold, the brainstem-driven respiratory drive is suppressed, and cessation of respiratory muscle activity and airflow (i.e., CSA) ensues. Resumption of breathing after an apnoeic episode does not occur until the chemical stimuli accumulate to relatively hypercapnic levels leading to a period of rapid breathing (hyperpnea) and triggering the next apnoeic event.

Pathophysiology
Each CSA cycle of apnoea and hypopnoea is associated with significant pauses in breathing or shallow breathing, with consequent hypoxia and arousals that cause severe disruption to the architecture of sleep and a surge in sympathetic activity (Figure 1). Repeated cycles of apnoea, hypoxia, and arousal during sleep impart significant cardiovascular insults such as additional sympathetic nervous system activation, acute pulmonary and systemic hypertension, plaque rupture and arrhythmias,[1,29–31] As the cycles continue, these insults continue to adversely affect the heart and contribute to the downward cycle of HF including an increased risk for recurrent HF hospitalizations, ventricular arrhythmias and mortality (Figure 1).[3,6]

Identifying heart failure patients with CSA
Given the pathophysiological and prognostic significance of CSA in patients with HF, clinicians must maintain a high suspicion for CSA in HF patients. Additionally, patients should be evaluated for the presence of CSA when admitted to the hospital with acute decompensated HF, since signs of CSA such as shortness of breath at night often emerge with worsening HF. HF patients commonly have CSA risk factors including male gender, higher New York Heart Association class, lower left ventricular ejection fraction, waking hypocapnia, presence of atrial fibrillation, higher brain natriuretic peptide (BNP) levels, and frequent nocturnal ventricular arrhythmias.[8,10] Symptoms for CSA are more difficult to assess in patients with HF as many of the symptoms overlap with symptoms of HF such as fatigue or gasping at night. Additional signs and symptoms consistent with the presence of CSA include unusual daytime or night-time breathing patterns, disrupted sleep, nocturia, morning headaches, and diminished concentration and memory.[32] If possible, the patient’s sleep partner should also be questioned about the patient’s sleep habits, especially regarding episodes of apnoea, frequent arousals, or changes in behaviour or mood, which might signal the presence of CSA.

CSA traditionally has been diagnosed through polysomnography (PSG), or the overnight sleep study, which is performed in a sleep laboratory with a sleep technician in attendance. Based on current guidelines, the PSG is diagnostic for CSA if respiratory monitoring demonstrates at least three consecutive cycles of crescendo-decrescendo change in breathing amplitude and one or both of the following: 1) five or more central sleep apnoeas or hypopnoeas per sleep hour and/or 2) cyclical crescendo-decrescendo breathing ≥ 10 consecutive minutes.[33] CSA severity commonly is described by the apnoea-hypopnoea index (AHI), defined as the number of apnoea and hypopnoea events per hour of sleep with an AHI > 15 events/hour indicating moderate to severe CSA. While patients may have both CSA and OSA, the predominant form typically classifies the disorder.

While many patients go to the sleep laboratory for diagnosis, portable sleep monitors are designed to be used in an unattended, home-based setting. A number of different types of portable monitors are commercially available, with each device differing in the number and type of sleep-related variables they monitor. Level 3 portable monitors, which record at least 3 channels of data (e.g., oximetry, airflow, respiratory effort), have been shown to offer accurate diagnostic performance in HF patients and can distinguish obstructive from central events based on belt movement.[34] It is important for the clinician, however, to account for possible underestimation of the number of apnoea events/hour with portable monitors as they are not able to monitor sleeping time.

Treatment options for CSA
Optimum treatment for HF patients with CSA has been limited. Current treatment options for CSA include medications, oxygen, positive airway pressure and neurostimulation of the phrenic nerve.[35] While a number of medications have been studied in small trials with acetazolamide and theophylline demonstrating some improvement in randomized trials, none are currently recommended due to lack of larger and longer term trials.[36] Oxygen has been used and improves symptoms in some studies, but no long term randomized trials have been completed.[36] Until recently, due to the diagnosis of CSA primarily occurring in the sleep lab, positive airway pressure therapies historically used for the treatment of OSA were tested in the treatment of CSA. A very different approach using neurostimulation to stimulate the phrenic nerve and move the diaphragm to restore normal breathing has been developed.

Positive airway pressure therapies were initially utilized to open closed airways in patients with obstructive sleep apnoea. There are currently three primary types of these therapies: continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP) in which pressure levels decrease during exhalation, and BiPAP-adaptive servoventilation (ASV) in which the two pressures change due to sensors in the device.[37] The use of CPAP to treat CSA was studied in a large randomized, controlled trial, the Canadian Positive Airway Pressure Study (CANCAP). This trial was stopped early due to slow enrollment and safety concerns as the treatment group initially had a higher mortality than the treatment group.[38] However, over time, no difference in morbidity or mortality was seen. CPAP did improve the number of events per hour (40 to 19) and ejection fraction, but compliance with the therapy was low with an average use of 3.6 hours/night.

A newer form of positive airway pressure therapy, ASV, was designed specifically for the heart failure patient. It was expected that ASV would be able to deliver lower airway pressure to patients and adjust automatically to increase or lower pressure to maintain airflow. A large randomized study, the SERVE-HF
trial, demonstrated that the AHI was greatly reduced while the patient wore the device. However, the trial also showed a surprising increase in both overall and cardiovascular mortality. While there is debate on the cause of the increased mortality, the pressure delivered was quite elevated in some patients and compliance remained an issue with patients utilizing therapy 3.2 hours/night.[39] Based on this data, ASV is now a Class III contraindication in the HF guidelines for patients with an ejection fraction less than 45%.

A novel physiologic approach to the treatment of CSA is now available using transvenous stimulation of the phrenic nerve. This system, the remedi® System, was developed to physiologically address the treatment of CSA. As there is a delay in the signal from the brain to the phrenic nerve to stimulate the diaphragm in CSA, this system stimulates the phrenic nerve to prevent the apnoea or shallow breathing and is designed to normalize the breathing pattern.® Clinical data from the randomized controlled clinical trial was presented at the ESC-HFA meeting in May 2016. The trial met its primary endpoint; a greater proportion of patients in the treatment group having a ≥ 50% reduction in AHI compared to the control group at 6 months. In addition, pre-specified test improvements in both respiratory metrics (AHI, central apneas, oxygenation, arousals and % of time in REM sleep) and in patient reported outcomes (Patient Global Assessment and Epworth Sleepiness Scale) were demonstrated. There were no safety concerns with 91% freedom from device related serious adverse events. While not powered, it was encouraging that no difference in either all-cause or cardiovascular mortality was noted. It is possible that a stronger recommendation for this therapeutic approach could have been included in recent guidelines had the data been available earlier.[41]

**The future of CSA therapy**

Central sleep apnoea is of paramount importance to the HF clinician. Without treatment, HF patients continue to be at risk for the devastating consequences of CSA. Prognosis is very poor with studies consistently demonstrating poor outcomes among HF patients with CSA. Over the course of the night, each discrete event contributes to increased nor-epinephrine levels and hypoxia which are associated with progressive heart failure and arrhythmias. Initial therapeutic options utilized therapies which were developed for obstructive sleep apnoea with limited success or even harm.

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**Declaration of Interest**

AJSC and WTA declare consultancy fees from Respicardia. LGS has no conflicts of interest to declare.

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The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals” [42].

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