Novel Therapies for the Treatment of Central Sleep Apnea

Shahrokh Javaheri, MD[a,*], Robin Germany, MD[b], John J. Greer, PhD[c]

KEYWORDS

• Congestive heart failure • Opioids • Ampakines • CPAP • Adaptive servo ventilators • Apnea

KEY POINTS

- Central sleep apnea (CSA), rare in general population, is a common polysomographic finding in patients with heart failure and chronic opioid users.
- Adaptive servoventilation devices have been successfully used to treat central sleep apnea in both heart failure and with opioids.
- A recent study using an out dated adaptive servoventilation failed to show benefits in treating CSA in heart failure.

INTRODUCTION

Neurophysiologically, central sleep apnea (CSA) is due to a temporary failure of respiratory rhythmogenesis. CSA occurs in a number of disorders across all age groups and both genders.[1] The most common causes of CSA are cardiocerebrovascular disorders, such as congestive heart failure, atrial fibrillation, and stroke, and chronic use of opioids to treat pain. In this article, the authors concentrate on the treatment of CSA in heart failure (HF) and in association with opioids. There have been important advances in the therapy of CSA in these 2 conditions.

At the outset, it is emphasized that the patterns of breathing associated with CSA due to HF versus opioids are distinctly different from each other, as shown in **Figs. 1** and **2** and later discussed. This distinction is diagnostically important because the therapeutic options are distinctly different for these 2 conditions.

CENTRAL SLEEP APNEA AND PERIODIC BREATHING IN HEART FAILURE

CSA in HF, with both reduced and preserved ejection fraction (HFrEF and HFpEF, respectively), occurs in the background of a unique periodic breathing referred to as Hunter-Cheyne-Stokes breathing (HCSB)[2] (see **Fig. 1**). The pattern was first recognized by John Hunter several decades before John Cheyne noted it (see Ref.[2] for details). This crescendo-decrescendo pattern of breathing occurs primarily in non-rapid eye movement (REM) sleep and is related to increased loop gain, which is present in a subset of patients with HF.[1,3,4] Central apneas and hypopneas frequently occur between the crescendo-decrescendo arms of periodic breathing. These events are associated with arterial oxyhemoglobin desaturation, changes in partial pressure of carbon dioxide, and arousals. These pathophysiological consequences of HCSB eventually result in a hyperadrenergic state, which is a

[a] Bethesda North Hospital, 10535 Montgomery Road, Suite 200, Cincinnati, OH 45242, USA; [b] Section of Cardiology, University of Oklahoma College of Medicine, Oklahoma City, OK, USA; [c] University of Alberta, Edmonton, Alberta, Canada
* Corresponding author.
E-mail address: shahrokhjavaheri@icloud.com

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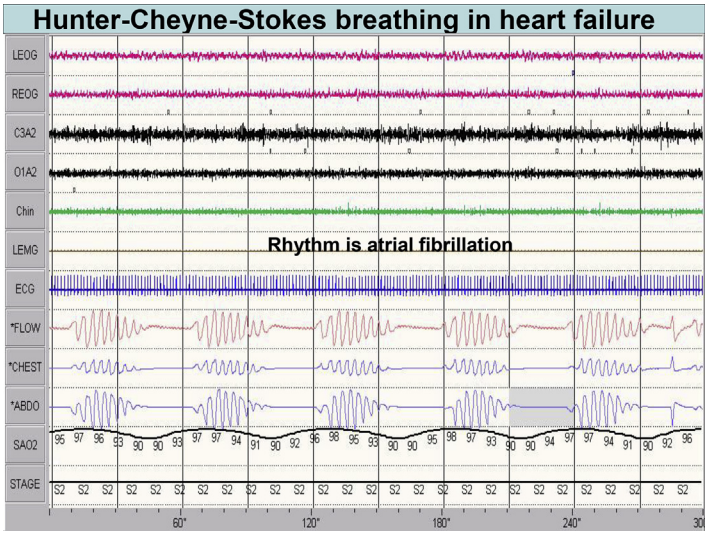

Fig. 1. A 5-minute epoch of a polysomnogram of a patient with systolic HF showing HCSB with central apneas in N2 non-REM sleep. Note the gradual decrease in ABD and chest tracings followed by a gradual symmetric increase in these tracings out of central apnea sandwiched between the thoracoabdominal excursions. ABDO, abdomen; ECG, electrocardiogram; EEG, electroencephalogram; EOG, electro-oculogram; thermocouple tracing representing airflow, SaO_2, arterial oxyhemoglobin saturation. (*Adapted from* Javaheri S. Heart failure. In: Kryger MH, Roth T, Dement WC, editors. Principles and practices of sleep medicine. 6th edition. Philadelphia: WB Saunders, in press; with permission.)

known predictor of premature mortality in patients with HF. HF patients with CSA have excess hospital readmission,[5] and mortality, when compared with HF patients without CSA.[6] Therefore, the hope has been that treatment of CSA in HF would attenuate the number of hospital readmissions and premature mortality. However, as will be noted later, a recent phase 3 randomized clinical trial using the old generation adaptive servoventilation (ASV), to treat CSA in HFrEF failed to show any improvement in either hospitalization or all-cause mortality.

PREVALENCE OF CENTRAL SLEEP APNEA IN HEART FAILURE

There are many studies from different laboratories and from many countries that have consistently shown high prevalence of CSA in patients with HF with both reduced and preserved in left ventricular ejection fraction (LVEF) (for reviews see Refs.[1,2]). In these studies, the prevalence of predominant CSA as a disorder varies from 20% to 50% of the consecutive patients enrolled. These

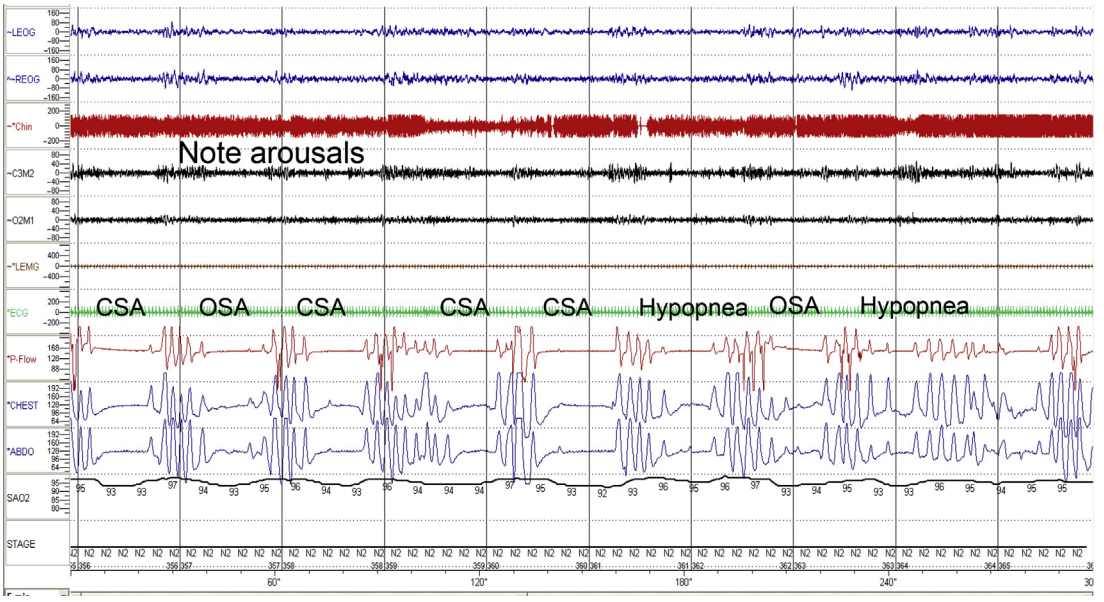

Fig. 2. A typical 5-minute epoch of various disordered breathing events associated with the use of opioids. Note central apneas of variable duration (contrast Fig. 1), large breaths out of apnea (contrast Fig. 1). Tracings similar to Fig. 1. (*Adapted from* Javaheri S, Malik A, Smith J, et al. Adaptive pressure support servoventilation: a novel treatment for sleep apnea associated with use of opioids. J Clin Sleep Med 2008;4(4):305–10; with permission.)