Sleep, the dreams and the heart. Emphasis on central sleep apnea

Author
Shahrokh Javaheri
Professor Emeritus, University of Cincinnati, College of Medicine. Cincinnati, Ohio
Adjunct Professor of Medicine, The Ohio State Medical School. Columbus, Ohio
Sleep Physician, Bethesda North Hospital

Correspondence
Shahrokh Javaheri
200 Bethesda North Hospital10535 Montgomery Road, Suite Cincinnati, OH 45242
Phone: (513) 3770595. E-Mail: shahrokhjavaheri@icloud.com

Normally as sleep deepens from N1 to N3, there is an orchestrated progressive reduction in central nervous system sympathetic outflow associated with an increase in parasympathetic activity. The hemodynamic manifestations of these favorable changes in autonomic activity are a clinically significant reduction in systemic blood pressure and a reduction in heart rate. For these reasons, non-REM sleep which accounts for 80% of total sleep time is peaceful for the cardiovascular system. Not surprisingly, multiple studies have shown decreased acute cardiovascular events during sleep compared to wakefulness, although other factors also contribute to these temporal associations.

Meanwhile sleep could be disrupted by the number of sleep disorders including sleep-related breathing disorders, specifically sleep apneas and hypopneas, both obstructive and central disordered breathing events. The repetitive cycles of apnea and the following compensatory hypopnea are associated with overnight adverse cardiovascular consequences which include altered blood gas chemistry with recurrent episodes of hypoxia-reoxygenation and ups and downs in arterial PC02, arousals, and augmented swings in negative intrathoracic pressure. These sleep-related breathing disorders consequences are qualitatively similar for both phenotypes of sleep apnea, with acute and chronic hemodynamic, inflammatory and oxidative stress on the cardiovascular system.

Sleep related breathing disorders are quite common in patients with left ventricular systolic and diastolic dysfunction with or without heart failure syndrome. Worldwide, many laboratories have reported on the prevalence of sleep apnea in patients with various cardiovascular disorders. In regard to heart failure, 52% of those with reduced ejection fraction and 48% of those with preserved ejection fraction suffer from obstructive and central sleep apnea. Frequently these 2 phenotypes are observed in the polysomnogram of the patients.

As noted above, long-term pathobiological derangements of sleep apnea including up-regulation of neurohormonal activity, oxidative stress and inflammation result in endothelial dysfunction. Both obstructive and central sleep apnea could result in a vicious bidirectional cycle between heart failure and sleep apnea with important consequences of hospital readmissions and premature mortality.

That treatment of sleep-related breathing disorders in heart failure is multifaceted and includes optimization of pharmacological therapy with the aim of optimizing cardiovascular function, avoidance of smoking and alcoholic beverages, improved sleep hygiene, exercise and weight loss when applicable. A specific therapy of sleep apnea depends primarily on the phenotype. For obstructive sleep apnea the use of continuous positive airway pressure is the choice among multiple positive airway pressure devices available globally. Although no randomized clinical trial has yet been reported, observational studies consistently show that treatment of OSA with continuous positive airway pressure devices improves left ventricular ejection fraction (in heart failure with reduced ejection fraction), improves diastolic dysfunction (in those with preserved ejection fraction), readmission to the hospital and mortality. This was best observed in a US study of a large cohort of Medicare beneficiaries in which those who were diagnosed with OSA and treated had reduced hospitalization and improved survival. The field however is hungry for randomized clinical trials, involving heart failure patients with both reduced and preserved ejection fraction.

The initial approach to the treatment of central sleep apnea is appropriate evidence-based pharmacological therapy and CRT when applicable. Improvement in cardiopulmonary function has been shown to improve central sleep apnea. Regarding CRT multiple studies have shown that in those individuals in whom CRT improves cardiac function central sleep apnea improves. This is in contrast to lack of improvement in obstructive sleep apnea with CRT in most studies.
SPECIFIC THERAPY OF CENTRAL SLEEP APNEA. PHARMACOLOGICAL THERAPY

The author has performed randomized clinical trials using acetazolamide and theophylline to treat central sleep apnea in heart failure with reduced ejection fraction. Both medications improve central sleep apnea. However long-term studies are not available. Oxygen is also a potent medication for treatment of central sleep apnea and is discussed later.

POSITIVE AIRWAY PRESSURE DEVICES

Continuous positive airway pressure (CPAP) devices have been used to treat central sleep apnea in patients with heart failure and reduced ejection fraction. In the post hoc analysis of the Canadian CPAP trial, survival improved in those patients with heart failure and reduced ejection fraction who responded to CPAP. In these patients the average AHI decreased from about 40/h of sleep at baseline to a mean of 6 per hour of sleep after 3 months of use of CPAP. In contrast, in those patients in whom CPAP failed to attenuate central sleep apnea, mortality increased early on with the use of CPAP.

The author has reported that in those heart failure patients whose sleep apnea responds to CPAP there was a considerable reduction in nocturnal arrhythmias which was in contrast to those who did not respond to CPAP.

It is noted that the number of CPAP-nonresponders is significant varying from 40-50% of patients with heart failure reduced ejection fraction with central sleep apnea.

For these reasons a new device called adaptive servo ventilation was created. This device has gone through generations with improved algorithms. In the most recent generation, the positive end expiratory pressure automatically changes in response to the dynamics of upper airway obstruction. Furthermore, the algorithm of inspiratory pressure support has become much more friendly. The other virtues include an automatic breath nuit, providing a mandatory breath if breathing ceases for a few seconds, aborting any impending apnea. The inspiratory pressure support is variable and anti-cyclic to the pattern of breathing of the patient, with the pressure support increasing when the patient’s ventilation decreases, and in contrast, the inspiratory pressure support with decrease when the patient’s ventilation increases. With all these virtues, multiple observational, and a few small randomized trials and meta-analyses show the superiority of adaptive servo ventilation when compared to other devices.

It was with the greatest surprise, when a large randomized trial showed that treatment with adaptive servo ventilation did not improve hospitalization and mortality of patients with heart failure and reduced ejection fraction and central sleep apnea. It was most surprising that ASV use was associated with excess cardiovascular mortality. Following these results, the manufacturers of ASV devices declared that ASV use should be contraindicated in this population. This single the study changed the practice of sleep medicine for thousands of patients with heart failure and reduced ejection fraction suffering from central sleep apnea.

The author along with several other individuals analyzed the above trial carefully and concluded that there were major pitfalls in the study. Most importantly the device used was the old generation adaptive Servo ventilation which is no longer manufactured by the company who supported the study.

Currently, there is another randomized trial in progress, the advent heart failure using an upgraded adaptive Servo ventilation device with a different algorithm and equipped with automatic end expiratory positive pressure responding to upper airway obstruction.

NON-MASK THERAPY OF CENTRAL SLEEP APNEA IN HEART FAILURE AND REDUCED EJECTION FRACTION

One of the reasons that adaptive servo ventilation might have failed to improve survival could have been due to the increased intrathoracic pressure associated with use of the device, a scenario similar to that observed in the Canadian CPAP trial. The notion here is that the increased intrathoracic pressure imposed by the device could have resulted in adverse hemodynamic effects involving the right ventricle, increasing the afterload while decreasing preload.

Consequently, interest has risen in two other therapeutic options. The first is phrenic nerve stimulation, a transvenously placed lead stimulating a hemidiaphragm resulting in normal breathing during sleep. The results of a randomized trial has been published. The study involved 31 centers in Europe and the USA. 151 eligible patients were randomly assigned to the treatment (n=73) or control groups. The primary effectiveness outcome was a comparison of the proportion of patients in the treatment versus control groups achieving a reduction in AHI of 50% or greater from baseline to 6 months. These patients suffered from severe central sleep apnea. The average AHI decreased from 50 per hour of sleep to 26, a reduction of a magnitude to that of the CANPAP trial, with the difference that these patients suffered from a more severe sleep apnea compared to those in the CANPAP trial (average AHI=40). Consequently to the reduction in AHI, arousal index and desaturation during sleep decreased and importantly patient global assessment improved significantly. Additional analysis is in progress to determine any differences in the rate of hospitalization between the two arms.

The other therapeutic option that has attracted attention is the use of nocturnal oxygen which has been shown to be effective in the treatment of central sleep apnea. Multiple studies, both observational and randomized have shown improvement in central sleep apnea, arousals and most importantly in virtual elimination of hypoxic burden. In two randomized trials, left ventricular ejection fraction increased in association with treatment of central sleep apnea in patients with heart failure and reduced ejection fraction. A large randomized trial powered to detect differences in hospital admission-readmission and mortality is necessary.

References


