Phrenic Nerve Stimulation for Central Sleep Apnea
Wiping Out Apnea or Whipping the Muscles?*

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Central sleep apnea (CSA) occurs in about one-third of patients with advanced heart failure (HF) (1). It is characterized by a waxing and waning respiratory pattern, usually of about 60 s cycle length during non-rapid eye movement sleep (2). In contrast to most sleep-related breathing disorders, CSA is associated with hyperventilation (3).

Underlying CSA in HF is the triad of low cardiac output, high sympathetic activation, and pulmonary congestion. The sympathetic activation and congested lungs lead to hyperventilation and increased work of breathing, resulting in a fall in arterial CO₂ to a level below the apneic threshold. Hyperventilation becomes "periodic" because of low cardiac output and circulatory delay of arterial CO₂ reaching the brain stem’s respiratory control center. A waxing and waning pattern of ventilation occurs as a result of the arterial CO₂ level oscillating above and below the apneic threshold. Such patients report orthopnea, exertional dyspnea, insomnia, and fatigue.

Whether CSA is a cause of, or simply associated with, increased morbidity and mortality in HF is controversial (4). Whereas obstructive sleep apnea is recognized as a cause of various cardiovascular sequelae, mainly due to the hypoxemia, large swings in negative intrathoracic and positive pulmonary and systemic blood pressure, sympathetic bursts, and the release of proinflammatory proteins, the same cannot be said for CSA. Usually CSA is not associated with large intrathoracic pressures nor hypoxemia; moreover, the increased sympathetic activity can be explained by cardiac failure rather than CSA per se (5). Some evidence exists that the cyclic nature of breathing in CSA may assist cardiac output (6). Nevertheless, whether CSA is a cause of, or associated with, HF morbidity and mortality, it has heralded a greater understanding of HF symptoms and an opening for novel therapeutic options for this subgroup of patients with HF.

Leading this charge have been positive airway pressure (PAP) devices via masks worn mainly during sleep, the rationale being that it works for obstructive sleep apnea and acute cardiogenic pulmonary edema. Via the mechanisms of upper airway splinting, increasing lung volume, and reducing left ventricular afterload, initial single-center studies of PAP in patients with HF indicated improvements in cardiac function, exercise capacity, and sympathetic activity, but the investigators were unable to confirm improved survival in the entire group (9). Of note, a subgroup of patients (~57%) who had decreases in apnea-hypopnea index to <15 at 3 months did have a clear-cut survival benefit (10). Larger multicenter trials, CANPAP (Canadian Continuous Positive Airway Pressure for Patients With Central Sleep Apnea and Heart Failure), over 2 years confirmed improvements in cardiac function, exercise capacity, and sympathetic activity, but the investigators were unable to confirm improved survival in the entire group (9). From the Department of Allergy, Immunology and Respiratory Medicine and the Department of Medicine, Monash University, Melbourne, Australia. Dr. Naughton has reported that he has no relationships relevant to the contents of this paper to disclose.

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treatment was suboptimal (mean usage 3.6 h/night), with mask type and leaks not reported. Nevertheless, larger and longer PAP trials are currently under way, which hopefully will address some of these anomalies (NCT00733343 and NCT01128816).

Alternative therapies shown to be effective in “before and after” clinical trials include optimizing pharmacological therapy, biventricular and atrial overdrive pacemakers, left ventricular assist devices, and cardiac transplantation. Body position (elevation and/or sleeping in the lateral position) has also been shown to alleviate CSA. Thus, the optimal treatment for patients with CSA is dependent upon the patient and the cause of HF.

In this setting, unilateral phrenic nerve pacing has emerged to treat CSA. A small pulse generator, a stimulator lead, and an optional sensing lead are inserted transvenously, on either side in the subclavicular area, with an external control programmer. The theory is that unilateral phrenic nerve stimulation will result in bilateral diaphragmatic activation during episodes of central apnea.

Following the collection of pilot data (11,12), the present industry-sponsored study was a prospective, nonrandomized study of the feasibility, safety, and efficacy of unilateral phrenic nerve stimulation in 57 patients with CSA at 12 hospitals across 4 countries over 6 months (13). The population studied had mainly systolic dysfunction (New York Heart Association functional classes II and III and left ventricular ejection fractions of approximately 30%), although a small number of subjects had HF with preserved ejection fraction, and a few were taking narcotics, a known cause of CSA. As with most reports of CSA, the majority of the subjects were male, an interesting and recurring observation.

Of 57 patients enrolled, 8 were unable to have the stimulator implanted and were excluded from further analysis. A further 11 required changes to the lead. Three patients were further lost to follow-up because of the insertion of left ventricular assist devices, a mechanical fall damaging the stimulator, and 1 death, thus explaining the serious adverse event rate of 26% (14 of 57) and having 44 patients complete the 6-month testing.

In the 6-month review of 44 patients, there was a significant fall in the central apnea index (from 28 to 5 events/h), although the obstructive AHI did not change. The overall AHI and oxygen desaturation index dropped by about 50% (from 49 to 23 events/h and from 46 to 23 events/h, respectively). Sleep efficiency and the duration of rapid eye movement sleep improved. Quality of life improved, and sleepiness and HF were alleviated. Details about ventilation, partial pressure of CO₂, heart function, body position, and weight are not included in the report.

The study raises several interesting issues. Should we treat the CSA or the underlying HF? What effect does phrenic nerve stimulation have on objective cardiac function and the associated morbidity and mortality of HF? What effect does it have on minute volume of ventilation, and accordingly the work of breathing? Is it possible to increase ventilation and decrease CO₂ to such levels that laryngeal closure may occur? Could inspiratory dyssynchrony between respiratory pump and upper airway muscles occur, as seen in the polio era of external negative-pressure iron-lung ventilators?

Some investigators have suggested that CSA is simply a compensatory response to advanced HF (4). Part of this story is that episodes of central apnea provide periodic rest for periodically overworked respiratory muscles. What will happen with removal of the periodic rest because of ongoing stimulation? The histopathology and function of the respiratory muscles have been reported to differ in patients with HF. This effect is potentially reversible if rest is provided (14).

The investigators are to be congratulated for undertaking this difficult study. However, they should be encouraged to continue and attempt to answer whether the underlying cardiac function improves, which this editorialist believes is the linchpin to CSA management.

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