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Phrenic Nerve Stimulation for the Treatment of Central Sleep Apnea

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate chronic, transvenous, unilateral phrenic nerve stimulation to treat central sleep apnea (CSA) in a prospective, multicenter, nonrandomized study.

BACKGROUND CSA occurs predominantly in patients with heart failure and increases the risk for morbidity and mortality. Established therapies for CSA are lacking, and those available are limited by poor patient adherence.

METHODS Fifty-seven patients with CSA underwent baseline polysomnography followed by transvenous phrenic nerve stimulation system implantation and follow-up. Feasibility was assessed by implantation success rate and therapy delivery. Safety was evaluated by monitoring of device- and procedure-related adverse events. Efficacy was evaluated by changes in the apnea-hypopnea index at 3 months. Quality of life at 6 months was evaluated using a sleepiness questionnaire, patient global assessment, and, in patients with heart failure at baseline, the Minnesota Living With Heart Failure Questionnaire.

RESULTS The study met its primary end point, demonstrating a 55% reduction in apnea-hypopnea index from baseline to 3 months (49.5 ± 14.6 episodes/h vs. 22.4 ± 13.6 episodes/h of sleep; $p < 0.0001$; 95% confidence interval for change: −32.3 to −21.9). Central apnea index, oxygenation, and arousals significantly improved. Favorable effects on quality of life and sleepiness were noted. In patients with heart failure, the Minnesota Living With Heart Failure Questionnaire score significantly improved. Device- or procedure-related serious adverse events occurred in 26% of patients through 6 months post therapy initiation, predominantly due to lead repositioning early in the study. Therapy was well tolerated. Efficacy was maintained at 6 months.

CONCLUSIONS Transvenous, unilateral phrenic nerve stimulation appears safe and effective for treating CSA. These findings should be confirmed in a prospective, randomized, controlled trial. (Chronic Evaluation of Respicardia Therapy; NCT01124370) (J Am Coll Cardiol HF 2015;3:360–9) © 2015 by the American College of Cardiology Foundation.

Central sleep apnea (CSA) occurs in approximately 35% of patients with heart failure regardless of ejection fraction (1,2). It may also be seen in patients with atrial fibrillation, in those with neurological disorders, and in long-term opioid users (1–5). An uncommon idiopathic form of CSA may also be found in the general population (6). In patients with heart failure, multiple studies have demonstrated that the presence of CSA is an independent predictor of morbidity and mortality (7–10).

CSA is characterized by temporary withdrawal of central respiratory drive, resulting in cessation of

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respiratory muscle activity and airflow. Commonly presenting as Cheyne-Stokes breathing, the CSA breathing pattern is recognizable by cycles of deep, rapid, crescendo-decrescendo breathing (hyperpnea), followed by slower, shallower breathing (hypopnea) or no breathing at all with no respiratory effort from the diaphragm (apnea) (**Figure 1**). These repeated cycles during sleep impart significant cardiovascular insults, including hypoxemia (11), sympathetic nervous system activation (12), acute pulmonary and systemic hypertension (11), and arrhythmias (1,13). Each individual episode contributes a discrete hypoxic episode and a release of norepinephrine (12). As the cycle continues, these insults continue to adversely affect the heart and contribute to the downward cycle of heart failure.

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Despite optimal therapy of underlying disorders (e.g., heart failure), CSA persists in many patients. Treatment for CSA has used existing approaches for obstructive sleep apnea, most notably continuous positive airway pressure (CPAP) therapy. Although effective in treating obstructive sleep apnea, CPAP failed to diminish morbidity and mortality in a large trial of CSA, perhaps because of its failure to alleviate CSA in some patients; however, survival improved in patients whose CSA was suppressed by CPAP (14–16). A major limitation with the use of CPAP is patient nonadherence (17). A new type of positive airway pressure therapy, adaptive pressure support servoventilation, has been introduced to treat patients with CSA and is currently undergoing clinical evaluation. Early, small, nonrandomized studies of adaptive pressure support servoventilation in patients with heart failure demonstrated favorable effects on cardiac function (18). However, patient adherence to this mask-based therapy may still be suboptimal (19). A number of other therapies, including nocturnal oxygen administration, theophylline, and acetazolamide, have been evaluated to treat patients with CSA but are limited either by lack of demonstrated long-term efficacy or potential side effects (5). Given the limited options for treating CSA, there is clearly a need for alternative therapeutic approaches.

An alternative approach to treating patients with CSA has been investigated using unilateral, transvenous phrenic nerve stimulation to restore a physiological breathing pattern throughout sleep. This therapy stimulates the diaphragm during sleep to

ABBREVIATIONS AND ACRONYMS

AHI = apnea-hypopnea index

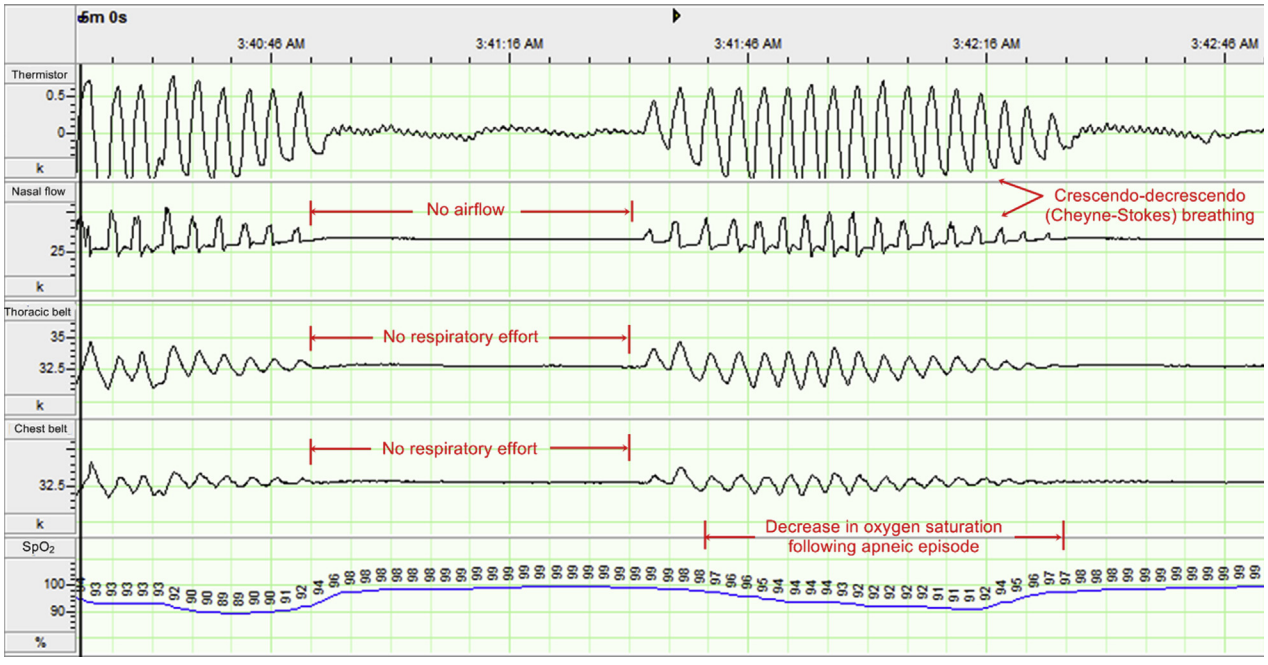
CPAP = continuous positive airway pressure

CSA = central sleep apnea

DSMB = Data and Safety Monitoring Board

PSG = polysomnography

FIGURE 1 Central Sleep Apnea With Cheyne-Stokes Breathing



Selected channels of a polysomnogram of a patient with central sleep apnea with Cheyne-Stokes breathing.