Clinical Trials: Methods and Design

Design of the remedē System Pivotal Trial: A Prospective, Randomized Study in the Use of Respiratory Rhythm Management to Treat Central Sleep Apnea

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ABSTRACT

Background: Central sleep apnea is common in patients with cardiovascular disease and worsens outcomes. There is a lack of established therapies for central sleep apnea, and those available are limited by poor patient adherence and potentially adverse cardiovascular effects, at least in a subset of patients. The **rem**edē System (Respicardia, Minnetonka, Minnesota) is a new physiologic treatment that uses transvenous phrenic nerve stimulation to contract the diaphragm, thereby stabilizing gas exchange and restoring normal breathing throughout the sleep period.

Methods: This is a prospective multicenter randomized trial with blinded end points evaluating the safety and efficacy of the **rem**edē System. Up to 173 patients with central sleep apnea will be randomized 1:1 to **rem**edē System therapy initiated at 1 month after implantation (treatment) or to an implanted **rem**edē System that will remain inactive for 6 months (control). Primary efficacy end point is the percentage of patients who experience a reduction in apnea-hypopnea index by a ≥50% at 6 months (responder analysis). Primary safety end point is freedom from serious adverse events through 12 months. Secondary end points include sleep-disordered breathing parameters, sleep architecture, Epworth Sleepiness Scale score, and Patient Global Assessment.

Conclusions: This is the 1st randomized controlled trial of the safety and efficacy of the **rem**edē System for the treatment of central sleep apnea. (*J Cardiac Fail 2015;21:892−902*)

Key Words: Central sleep apnea, phrenic nerve stimulation, sleep, randomized controlled trial.

Central sleep apnea (CSA) occurs commonly in patients with cardiovascular disorders such as heart failure (HF) and atrial fibrillation.[1] The major mechanism underlying development of CSA is the increased sensitivity to changes in arterial blood carbon dioxide (PCO_2) levels resulting in periods of hyperventilation (hyperpnea) followed by periods of decreased (hypopnea) or lack of breathing (apnea).[2] Regardless of the associated comorbidities, acutely, episodes of apnea or hypopnea are associated with hypoxemia and changes in PCO_2 followed by arousals and autonomic dysfunction.[2] Over the long term, these acute changes result in increased sympathetic activity, which has adverse cardiovascular consequences. Multiple studies have demonstrated that HF patients with CSA have a significantly increased risk of ventricular arrhythmias, HF decompensations, and death.[2] Importantly, when CSA is effectively treated, the associated morbidities and

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mortality decrease.[3–5] Use of nocturnal oxygen, carbon dioxide, atrial pacing, theophylline, and acetazolamide have been evaluated in small numbers of CSA patients, but data on long-term efficacy and safety of these therapies are lacking.[6]

To date, CSA has been primarily treated with positive airway pressure (PAP) therapies. Designed to open closed airways, PAP therapies blow air into the lungs to increase airflow. Patients with CSA receiving PAP therapies have experienced improvement in sleep and cardiovascular variables.[3,7–10] However, 1 randomized trial of PAP therapy failed to reduce mortality in its overall CSA population with HF and reduced ejection fraction,[11] although survival improved in those patients in whom the apnea-hypopnea index (AHI) was effectively reduced by PAP.[3] Recently, however, a large randomized trial of another type of PAP therapy, adaptive pressure-support servoventilation (ASV), showed that, compared with control subjects, patients treated with ASV had a statistically significant 2.5% absolute increased annual risk of cardiovascular mortality.[12]

Recently, a new physiologic approach to treating CSA has been investigated. The **rem**edē System (Respicardia, Minnetonka, Minnesota) is a totally implantable lead-based device that delivers unilateral transvenous phrenic nerve stimulation to cause diaphragmatic contraction in a fashion mimicking a normal breathing pattern. The contraction of the diaphragm creates a negative intrathoracic pressure similar to that generated by normal breathing so that airflow is augmented and central apneas occurring during sleep are significantly decreased. Suppression of impending central apneas averts the increases in PCO_2 and decreases in PO_2 that trigger hyperventilation and reduction in PCO_2 below the apneic threshold.

A prospective multicenter nonrandomized pilot study of chronic transvenous phrenic nerve stimulation with the **rem**edē System in CSA patients[13] showed that implantation of the **rem**edē System was uneventful in 86% of patients. From baseline to 3 months, chronic **rem**edē System therapy improved the AHI by 55% ($P < .001$), central apnea index (CAI) by 83% ($P < .001$), 4% oxygen desaturation index (ODI4) by 52% ($P < .001$), arousal index by 35% ($P < .001$), rapid eye movement (REM) sleep by 41% ($P < .001$), Patient Global Assessment (PGA) by 45%, and Minnesota Living With Heart Failure score by an average of 10 points ($P < .001$). Efficacy was maintained at 6 and 12 months' follow-up, and therapy was well tolerated. Serious adverse events related to the device, implantation procedure, or therapy are listed in Supplemental Table 1. These adverse events are consistent with those occurring with other cardiac devices, such as cardiac resynchronization therapy devices, at a similar stage of development.[14]

Given the adverse effects CSA has on morbidity and mortality, the disappointing outcomes of PAP therapies, and the encouraging results of the pilot study of phrenic nerve stimulation, a prospective randomized trial has been designed to evaluate the safety and effectiveness of the **rem**edē System in patients with various etiologies of CSA. The **rem**edē System has received an investigational device exemption from the United States Food and Drug Administration (FDA), and the FDA endorses the study's design and planned analysis.

The **rem**edē System Pivotal Trial successfully completed enrollment in May 2015. To date the Data Safety and Monitoring Board (DSMB) has not detected or reported to the Steering Committee or the Sponsor any signals of lack of safety. Data will be analyzed when the enrolled patients have completed 6 months of follow-up. The primary results are expected in 2016.

Materials and Methods

System Description

The **rem**edē System consists of a neurostimulator, a stimulation lead, and a sensing lead. The neurostimulator is similar in appearance to a standard pacemaker and is implanted in either the left or the right pectoral region (Fig. 1). The stimulation lead is designed to transvenously stimulate the phrenic nerve. Although only a single phrenic nerve is stimulated, both diaphragms move in response to this stimulation during sleep, which restores a full breath (Respicardia data on file). Two types of stimulation leads are available: a 4-French lead that is designed to be implanted in the left pericardiophrenic vein, and a 7-French lead designed for implantation in the right brachiocephalic vein. Clinical experience has shown that both the left pericardiophrenic vein and the right brachiocephalic vein are suitable sites for effective chronic phrenic nerve stimulation.[13] In addition, the implanting physician chooses a commercially available small cardiac pacing lead, which is placed in the azygos vein and connected to the device to sense respiration.

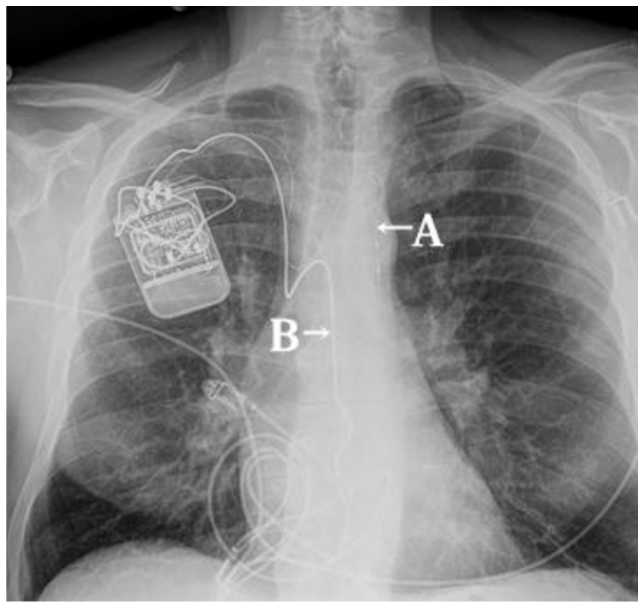

Fig. 1. Implanted **rem**edē System. In this patient, the neurostimulator was implanted in the right pectoral area. The right subclavian approach was used to place the stimulation lead (*A*) in the left pericardiophrenic vein and to place the sensing lead (*B*) in the azygos vein.