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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

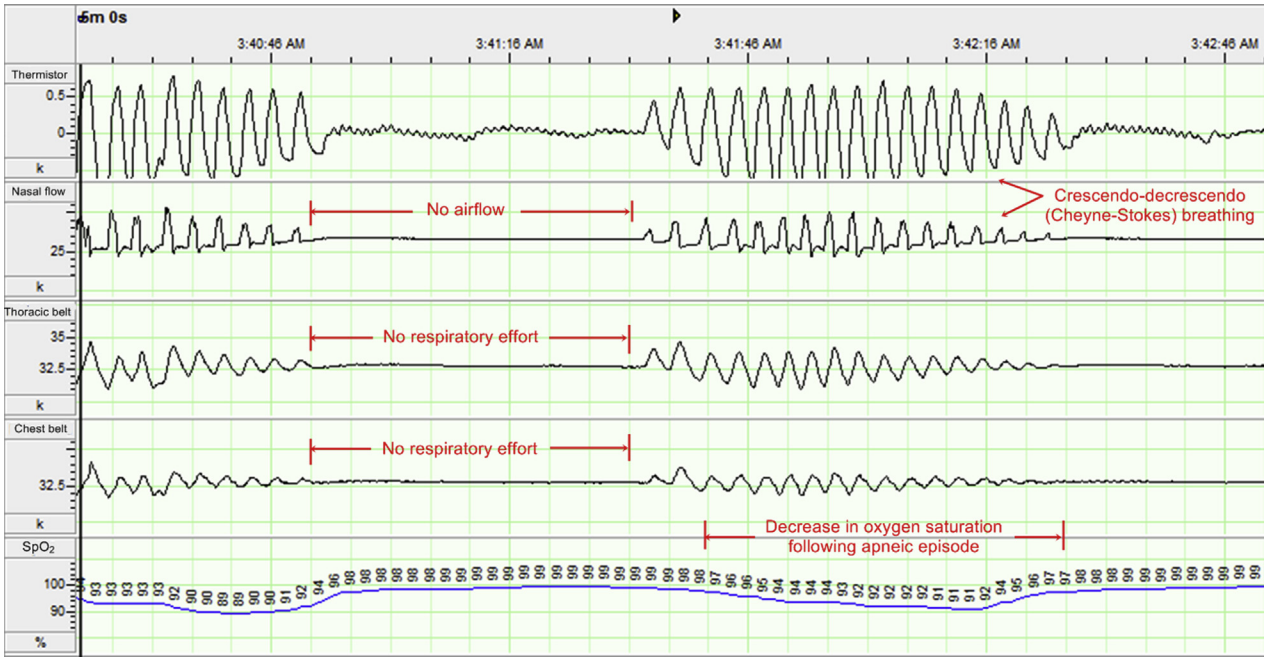
CPAP = continuous positive airway pressure

CSA = central sleep apnea

DSMB = Data and Safety Monitoring Board

PSG = polysomnography

FIGURE 1 Central Sleep Apnea With Cheyne-Stokes Breathing



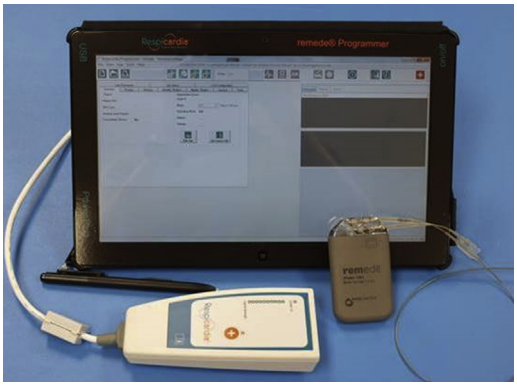
Selected channels of a polysomnogram of a patient with central sleep apnea with Cheyne-Stokes breathing.

stabilize gas exchange and maintain normal breathing. The use of phrenic nerve stimulation to regulate breathing has a long history of providing respiratory support in patients with respiratory paralysis from high cervical spinal cord injury (20). Temporary, transvenous, unilateral phrenic nerve stimulation has recently been shown to result in a more regular breathing pattern, fewer apneic events, improved oxygen saturation, and increased end-tidal carbon dioxide, without suppressing the intrinsic drive to breathe in patients with CSA (21). In a subsequent study, temporary unilateral phrenic nerve stimulation therapy reduced central apnea events and significantly improved important sleep parameters (22). A fully implantable system with transvenous leads was designed for the long-term application of transvenous phrenic nerve stimulation (The remedē System, Respicardia, Inc., Minnetonka, Minnesota). This implantable system is automated and requires no patient intervention to function, thus eliminating patient nonadherence. The 6-month results of a study evaluating the feasibility, safety, and efficacy of this system in a broad population of patients with CSA are presented here.

METHODS

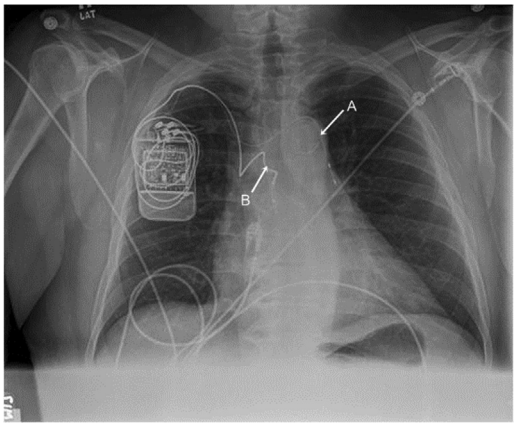
SYSTEM DESCRIPTION. The remedē System consists of a pulse generator, a stimulation lead, an optional sensing lead, and an external programmer used to adjust the settings on the pulse generator or to review diagnostic data via telemetry (**Figure 2**). The remedē pulse generator, similar in size and appearance to a standard pacemaker, is implanted in the right or left pectoral region (**Figure 3**). The system uses a transvenous lead implanted in the left pericardiophrenic or right brachiocephalic vein to provide neurostimulation to the adjacent phrenic nerve, resulting in diaphragmatic contraction. Previous evaluation of stimulation of the phrenic nerve demonstrated acute efficacy of unilateral stimulation, which resulted in bilateral contraction of the diaphragm (Respicardia, data on file). Sensing of respiration is accomplished either by the stimulation lead or a separate lead inserted in the azygos vein. Device-based sensors detect patient position and activity, aiding the device in determining appropriate therapy delivery times per the algorithm described in **Figure 4**. As shown in **Figure 5**, phrenic neurostimulation enables the resumption of normal breathing. By stabilizing carbon dioxide, the remedē System prevents apneic events and the subsequent periods of rapid breathing. An example of stimulation during sleep testing is shown in **Figure 6**.

FIGURE 2 The remedē System



The remedē System consists of an implantable pulse generator an implantable stimulation leads and an external system programmer.

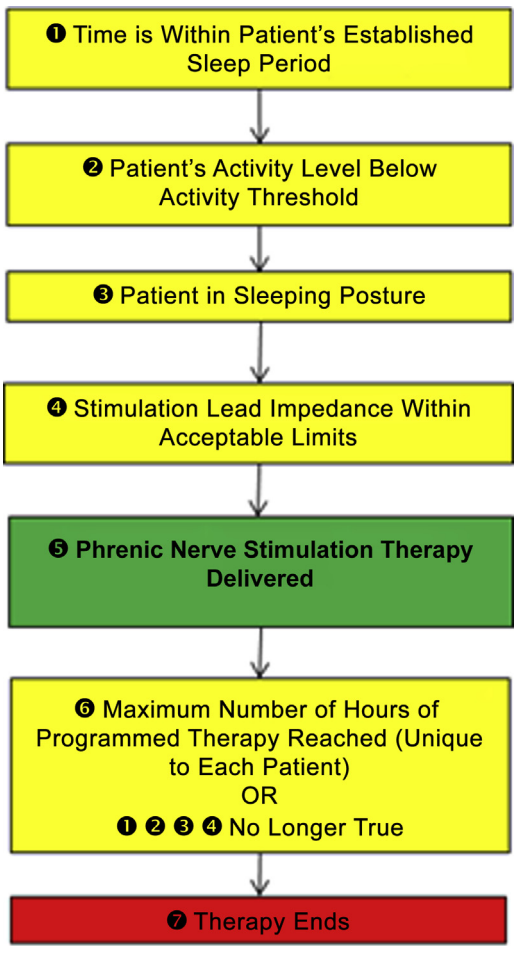
FIGURE 3 Implanted remedē System



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.

STUDY OVERVIEW AND PATIENT POPULATION. This was a prospective, international, multicenter, nonrandomized feasibility, safety, and efficacy study of patients with CSA before and after therapy, using patients as their own controls. The study was conducted under a U.S. Food and Drug Administration investigational device exemption and registered with ClinicalTrials.gov (NCT01124370). Safety oversight was provided by an independent Data and Safety Monitoring Board (DSMB). The authors had full access

FIGURE 4 Therapy Algorithm



The therapy algorithm used by The remedē System to provide phrenic nerve stimulation during sleep. The system uses time of day, activity level, and body position (upright or recumbent) to determine a potential sleeping state and therefore if stimulation should occur. All of these parameters are adjustable to tailor therapy to each patient's specific sleep routine.

to study data and take full responsibility for the accuracy and completeness of the reported findings.

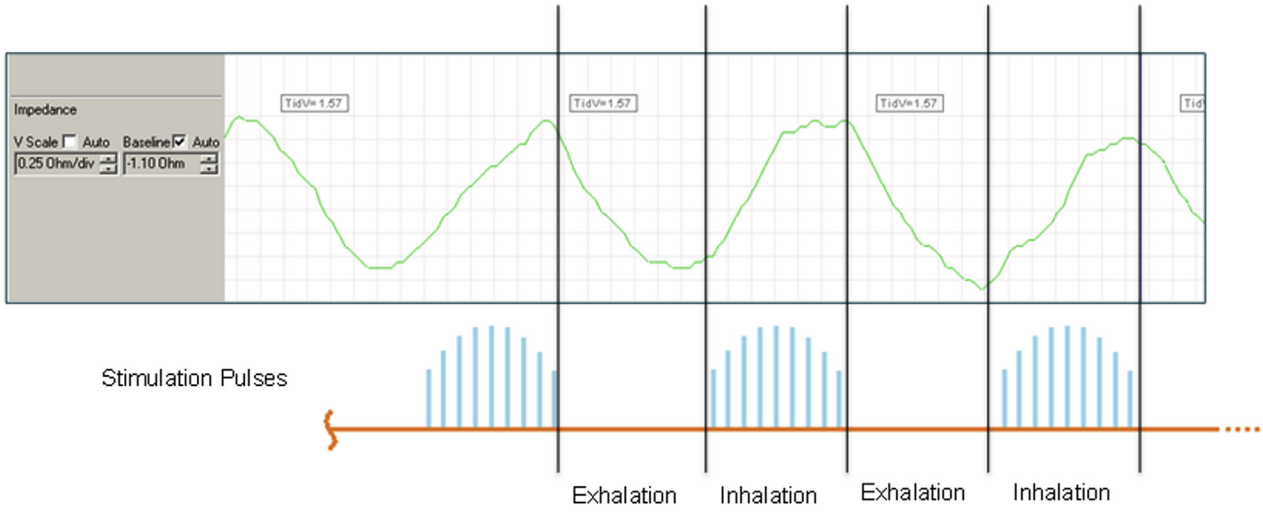
Patients were eligible if they had apnea-hypopnea index (AHI) values of at least 20 and at least one-half of their events were of central origin per polysomnography (PSG). Patients were excluded if ≥20% of their AHI was composed of obstructive apnea events. Patients were required to be on stable, optimal medical therapy for any comorbidity before enrollment. Additional exclusion criteria included phrenic nerve palsy, baseline hypoxia (oxygen saturation <90% on room air), severe chronic obstructive pulmonary disease, creatinine >2.5 mg/dl, and any cardiac procedure in the 3 months before the baseline study. Ethics committees at participating centers approved the study, and patients provided written informed consent before study procedures.

STUDY PROCEDURES. Baseline sleep assessment. Eligible patients underwent overnight, attended PSG scored by a core laboratory (Registered Sleepers, Inc., Leicester, North Carolina) according to the 2007 American Association of Sleep Medicine guidelines (23). Respiratory effort was measured by respiratory inductive plethysmography, and airflow was assessed using thermal and pressure transducers. Obstructive apnea was defined as the absence of airflow in the presence of respiratory effort for >10 s. Central apnea was defined as the absence of respiratory effort and airflow for >10 s. Mixed apnea was defined as a minimum of 3 respiratory efforts with absent inspiratory effort at the beginning of the episode. Hypopnea was defined as a ≥30% reduction in airflow lasting at least 10 s, associated with at least a 4% decrease in arterial oxyhemoglobin saturation and was not further classified. An electroencephalographic arousal was defined as the appearance of alpha waves or a shift to a greater frequency for at least 3 s after at least 10 s of sleep. The AHI was defined as the number of episodes of apnea and hypopnea per hour of sleep.

System implantation. After completing baseline assessment, patients underwent implantation of the remedē System. Venous access was obtained via the axillary or subclavian vein. On the basis of the patient's anatomy and the implanting physician's preference, the transvenous stimulation lead was placed in either the left pericardiophrenic or the right brachiocephalic vein. Differences in the size and angle of the vessel and location and presence of valve structures may make lead placement variable for each patient. Therefore, leads were available for both the left pericardiophrenic vein and the right brachiocephalic vein. Response to neurostimulation was assessed by external palpation of diaphragmatic contraction and/or by observing movement of the diaphragm during fluoroscopy. An additional sensing lead was placed in the azygos vein as necessary at the time of implantation. All leads were secured to the pectoralis muscle, connected to the remedē neurostimulator, and secured in a subcutaneous pocket in the pectoral area.

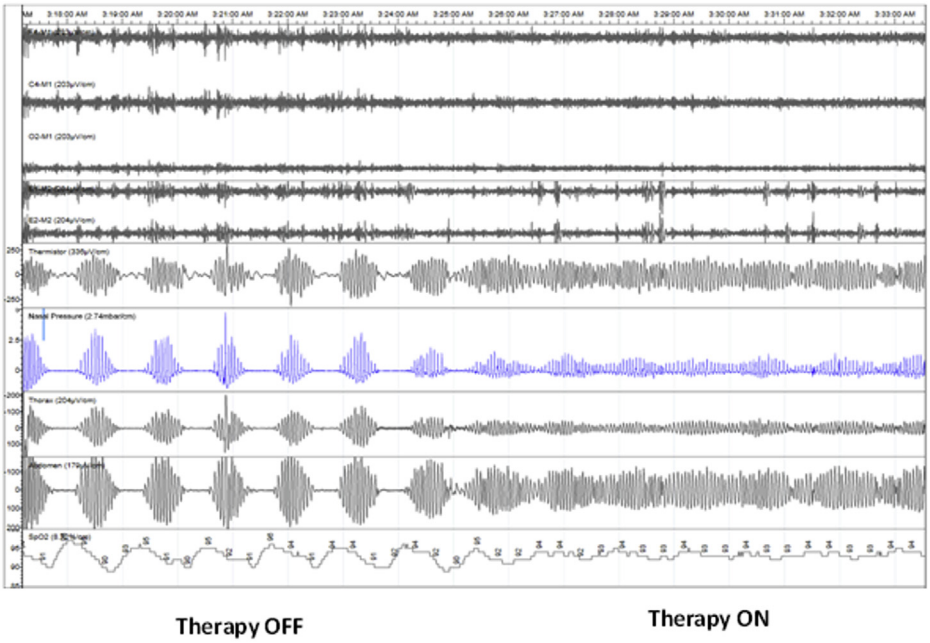
After a 1-month healing period, patients underwent PSG for therapy initiation. Therapy was programmed to begin when the patient was in a sleeping position and at rest during normal sleep hours. Individualized device settings, including therapy start

FIGURE 5 Graphical Representation of Phrenic Nerve Stimulation Delivered by the remedē System During Sleep



Phrenic neurostimulation stimulates the diaphragm during sleep to stabilize gas exchange and maintain normal breathing. Typical pulse stimulation characteristics are 0.1 to 10 mA for 60 to 300 μs at 20 to 40 Hz.

FIGURE 6 Polysomnogram Demonstrating the Effect of Phrenic Nerve Stimulation



The tracing shows respiratory stabilization of a patient with central sleep apnea with Cheyne-Stokes respiration after transvenous, unilateral phrenic nerve stimulation therapy.

and stop times and programmed maximal stimulation parameter, were determined by interviewing the patient regarding sleep habits and then monitoring response to overnight stimulation. Programmed maximal stimulation parameter is the stimulation setting that maximizes the reduction in AHI while minimizing sleep disruptions.

Follow-up visits. Patients returned for follow-up at 1, 2, 3, and 6 months post therapy initiation. At the 1- and 2-month visits, patients were assessed for therapeutic response and comfort. Stimulation settings were adjusted if necessary. At the 3- and 6-month visits, patients were assessed for study end points, and no changes were made to the programming of the device during the end point study night. PSG was performed at each of the 4 follow-up visits. Patients will continue to be followed through 24 months as part of the ongoing study.

STUDY ENDPOINTS. The primary end point of the study was change in the AHI after 3 months of therapy. The expected reduction in the AHI due to treatment with the remedē System was 50%. This value was chosen on the basis of an understanding that a 50% reduction in AHI is achievable, clinically meaningful, and associated with a reduced risk for mortality (9,24). Components of the AHI (i.e., central apnea index, obstructive apnea index, mixed apnea index, and hypopnea index) along with other standard sleep parameters were analyzed to characterize the full impact of phrenic nerve stimulation therapy. Secondary end points included the feasibility and safety of transvenous, unilateral phrenic nerve stimulation therapy. Feasibility was assessed by the lead implantation success rate and ability to deliver therapy. Safety was evaluated by continuous monitoring of adverse events related to the device or therapy. Additionally, changes in quality of life at 6 months were evaluated using the Epworth Sleepiness Scale (25), a patient global assessment (26), and the Minnesota Living With Heart Failure Questionnaire (for patients with heart failure at baseline) (27).

STATISTICAL ANALYSIS. A minimal sample size of 40 patients was chosen on the basis of prior experience with transvenous, unilateral phrenic nerve stimulation (22) and to provide reasonable confidence in the estimates of feasibility, safety, and efficacy.

Baseline demographic and outcome results were summarized using standard summary statistics for continuous and categorical data. Differences in outcome measures between baseline and 3 months were tested with paired Student *t* tests. If there was evidence of non-normality (Shapiro-Wilk test) in the distribution of these paired outcome data, differences were tested with the nonparametric Wilcoxon signed rank test.

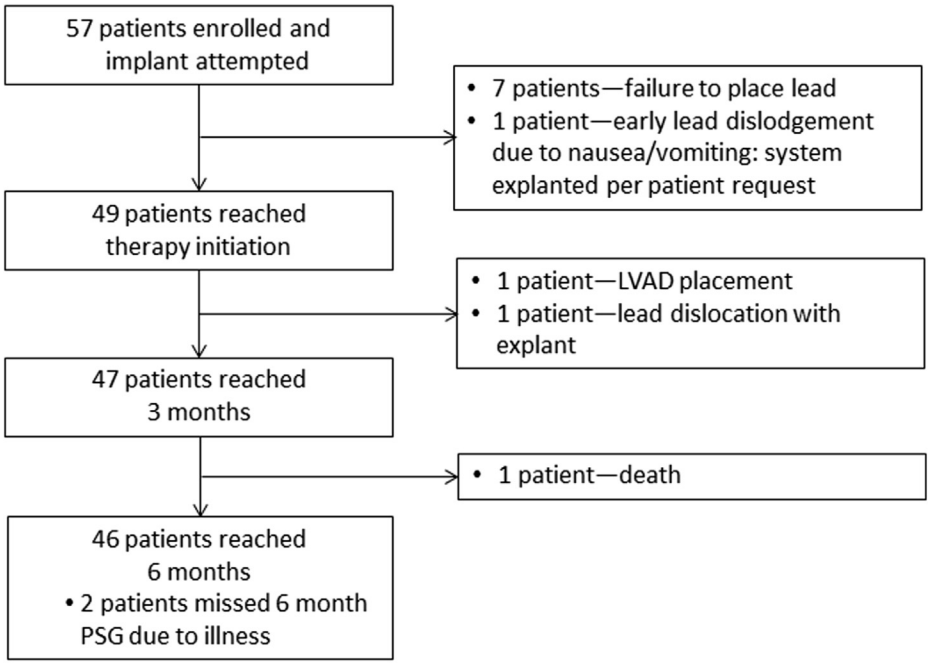
The primary end point (AHI change from baseline at 3 months) was considered statistically significant if the p value was ≤0.05. Nominal p values associated with other statistical tests are reported without adjustment for multiple testing or assignment of statistical significance levels. Differences among baseline, 3 months, and 6 months were tested with a repeated-measures analysis of variance. If there was evidence of non-normality in the distribution of these repeated measures, the differences across the 3 visits were tested with the nonparametric Friedman test. Statistical analyses were performed with SAS version 9 (SAS Institute Inc., Cary, North Carolina).

RESULTS

PATIENTS. Between June 2010 and August 2012, 57 patients were enrolled in the study (Figure 7). Of the enrolled patients, 8 (14%) left the hospital without implanted systems: 7 had anatomical issues that prevented lead placement, and 1 had a severe reaction to anesthesia resulting in dislodgement of the stimulation lead. Before the 3-month follow-up visit, 2 patients were withdrawn from the study: 1 for placement of a left ventricular assist device and another after a mechanical fall resulting in system explantation. The DSMB judged these 2 events as unrelated to phrenic nerve stimulation therapy or the system implantation procedure. Forty-seven patients were available for end point assessment at 3 months (Table 1). The mean baseline AHI was in the severe range at 49.5 ± 14.6 episodes/h. Heart failure was the predominant etiology of CSA in the patient population, followed by other cardiac causes, chronic opiate use, atrial fibrillation, and idiopathic causes. Follow-up continued out to 24 months.

PRIMARY OUTCOME. At 3 months, there was a mean reduction in AHI of 27.1 ± 17.7 episodes/h (55%, $p < 0.0001$) accompanied by a mean reduction in the central apnea index of 23.4 ± 15.3 episodes/h (84%, $p < 0.0001$) (Table 2). The AHI reduction was not different for stimulation of the right (mean reduction 26.8 ± 17.5) or left (mean reduction 27.3 ± 18.2) phrenic nerve. Significant improvement in sleep efficiency, rapid eye movement sleep, arousals, and oxygenation also occurred. Two of 47 patients (4%) were unable to complete valid PSG at 6 months but did complete the office visit. In the 44 patients available for 6-month assessment, improvements in sleep parameters were maintained (Table 3).

FIGURE 7 Patient Disposition



Flow diagram indicating progress of eligible patients through the study. LVAD = left ventricular assist device; PSG = polysomnography.

SECONDARY OUTCOMES. Feasibility. The remedē System neurostimulator and stimulation lead were successfully implanted in 49 of 57 enrolled patients (86%). Of the 47 patients who reached the 3-month primary and secondary study end point analyses, 29 (61%) had the lead implanted in the left pericardiophrenic vein and 18 (39%) in the right brachiocephalic vein. In 37 of 47 patients (79%), a sensing lead was implanted in the azygos vein to sense respiration. After implantation, 11 of 47 patients (23%) required lead repositioning, and an additional patient had a lead dislodgement and was unable to have the lead repositioned, resulting in explantation. The majority (8 of 12) of cases in which repositioning of the stimulation lead was required occurred early in the study, when only the left pericardiophrenic stimulation lead was available for implantation. Variable venous anatomy made implanting a lead securely in the left pericardiophrenic vein difficult in some cases, and subsequently a lead designed for the right brachiocephalic vein was introduced. This new lead and implantation location, along with improved operator experience with the left pericardiophrenic lead, resulted in a first-attempt implantation success rate of 100% for the last 20 patients enrolled in the study (15 left pericardiophrenic vein leads, 5 right brachiocephalic vein leads). During the course of the study, none of the patients requested that therapy be discontinued. Patients received 5.4 ± 1.2 h of therapy during 5.8 ± 1.2 h of sleep every night, on the basis of the algorithm in Figure 4.

The presence of additional leads in the vasculature did not result in failure to implant the remedē System. In addition, there was no difference in complications or the length of the procedure in patients with successful implants.

Safety. One of 47 patients (2%) died between the 3- and 6-month follow-up visits because of end-stage heart failure. The DSMB adjudicated this death as not related to the procedure or to phrenic nerve stimulation therapy. Three of 47 patients (6%) were adjudicated by the DSMB as having serious adverse events related to the device, implantation procedure, or therapy but not related to lead dislodgement. Two patients had serious adverse events (hematoma and migraine) related to the implantation procedure. An additional patient had a serious adverse event on the night when therapy was originally initiated, and the stimulation sensation

TABLE 1 Baseline Patient Demographics (n = 47)

Age, yrs	65.9 ± 9.6
Body mass index, kg/m^2	29.3 ± 4.4
Men	89%
Atrial fibrillation	30%
AHI, episodes/h of sleep	50 ± 15
CAI, episodes/h of sleep	28 ± 14
OAI, episodes/h of sleep	3 ± 3
History of hypertension	74%
CSA etiology	
Atrial fibrillation	2%
Opiate use	4%
Idiopathic	2%
Other cardiac	13%
Heart failure	79%
New York Heart Association functional class	
I	9%
II	47%
III	21%
IV	2%
Heart failure with ejection fraction >40%	9%
Coronary artery disease	66%
Systolic blood pressure, mm Hg	123 ± 21
Diastolic blood pressure, mm Hg	73 ± 11
Creatinine, mg/dl	1.2 ± 0.4
Ejection fraction	30.5 ± 11.6
Concomitant cardiac device	53%
Cardiac resynchronization + defibrillation device	19%
Implantable cardioverter-defibrillator	28%
Pacemaker	6%
Medications in patients with heart failure and reduced ejection fraction (n = 31)	
Aldosterone antagonist	48%
Beta-blocker	100%
ACE inhibitor or ARB	100%

Values are mean ± SD or %.

ACE = angiotensin-converting enzyme; AHI = apnea-hypopnea index; ARB = angiotensin II receptor blocker; CAI = central apnea index; CSA = central sleep apnea; OAI = obstructive apnea index.

was associated with atypical chest discomfort. Therapy was reinitiated on the following night without further discomfort.

Quality of life. Sleepiness was alleviated, as evidenced by a reduction in the mean Epworth Sleepiness Scale score in patients at 6 months (from 8.0 ± 3.9 to 6.1 ± 4.6, p = 0.0034) and in patients with Epworth Sleepiness Scale scores >10 at baseline (from 12.4 ± 1.9 to 8.5 ± 5.2, p = 0.0023). All 46 patients completed the 6-month patient global assessment, which asked the patient to reply, on a 7-point scale, to the question "How do you feel today as compared to how you felt before having your device implanted?" (27). Twelve (26%) reported marked improvement, 14 (30%) moderate improvement, 9 (20%) mild improvement, and 10 (22%) no change, and 1 (2%) reported being slightly worse. No patients reported being moderately worse or markedly worse. The Minnesota Living With Heart Failure Questionnaire, completed by the 36 patients with heart failure at 6 months, also showed improvement by an average of 10 points (p = 0.0009; 95% confidence interval: −16 to −4).

DISCUSSION

The present study demonstrates the feasibility, safety, and efficacy of long-term, transvenous, unilateral phrenic nerve stimulation as a treatment for patients with CSA using an implantable system. Results showed improvement in AHI, central apnea index, arousals, sleep efficiency, and rapid eye movement sleep after 3 months of treatment. These improvements were sustained at 6 months and were accompanied by alleviation of both sleepiness and heart failure symptoms. The mean obstructive apnea index was unchanged, suggesting that therapy

TABLE 2 Effects on Sleep-Disordered Breathing Parameters at 3 Months With the remede System (n = 47)

Parameter	Baseline	3 Months	Difference	(95% CI)	p Value
AHI, episodes/h of sleep	49.5 ± 14.6	22.4 ± 13.6	−27.1 ± 17.7	(−32.3 to −21.9)	<0.0001*
CAI, episodes/h of sleep	28.0 ± 14.2	4.7 ± 8.6	−23.4 ± 15.3	(−27.8 to −18.9)	<0.0001*
OAI, episodes/h of sleep	3.0 ± 2.9	3.9 ± 4.7	0.9 ± 5.4	(−0.7 to 2.4)	0.2816*
MAI, episodes/h of sleep	3.4 ± 4.5	0.3 ± 0.6 ± 1.0	−3.0 ± 4.5	(−4.4 to −1.7)	<0.0001†
HI, episodes/h of sleep	15.1 ± 12.1	13.5 ± 9.0	−1.5 ± 14.8	(−5.9 to 2.8)	0.4809*
ODI4, episodes/h of sleep	45.2 ± 18.7	21.6 ± 13.7	−23.7 ± 21.2	(−29.9 to −17.4)	<0.0001*
Arousal index, episodes/h of sleep	36.2 ± 18.8	23.7 ± 10.6	−12.5 ± 16.9	(−17.5 to −7.6)	<0.0001*
Sleep efficiency, %	68.3 ± 17.2	76.6 ± 15.4	8.4 ± 20.2	(2.4 to 14.3)	0.0066*
REM sleep, %	11.1 ± 6.8	15.6 ± 8.2	4.5 ± 11.2	(1.2 to 7.8)	0.0086*

Values are mean ± SD. *Paired Student *t* test. †Wilcoxon signed rank test.

CI = confidence interval; HI = hypopnea index; MAI = mixed apnea index; ODI4 = 4% oxygen desaturation index; REM = rapid eye movement; other abbreviations as in Table 1.

TABLE 3 Effects on Sleep Parameters at 6 Months With the remedē System (n = 44)

Parameter	Baseline	3 Months	6 Months	p Value
AHI, episodes/h of sleep	49.4 ± 14.9	22.8 ± 13.6	23.3 ± 13.3	≤0.0001*
CAI, episodes/hr of sleep	28.1 ± 14.7	5.0 ± 8.8	4.5 ± 7.2	<0.0001*
OAI, episodes/hr of sleep	3.0 ± 2.8	3.9 ± 4.8	3.8 ± 5.2	0.0223†
MAI, episodes/h of sleep	3.0 ± 3.7	0.3 ± 0.6	0.6 ± 1.5	<0.0002*
HI, episodes/h of sleep	15.4 ± 12.4	13.5 ± 9.0	14.4 ± 8.3	0.0179†
ODI4, episodes/hr of sleep	46.0 ± 18.8	22.0 ± 13.8	22.9 ± 13.3	<0.0001*
Arousal index, episodes/h of sleep	35.5 ± 18.4	23.4 ± 10.9	24.7 ± 12.3	<0.0001*
Sleep efficiency, %	69.3 ± 16.8	76.9 ± 15.6	81.4 ± 12.5	<0.0001*
REM sleep, %	11.2 ± 6.3	16.2 ± 8.1	17.4 ± 6.9	<0.0001*

Values are mean ± SD. *Repeated-measures analysis of variance. †Friedman test.
Abbreviations as in Tables 1 and 2.

did not induce or contribute to upper airway obstruction.

Results from the patient global assessment showed that the majority of patients experienced alleviation of symptoms after 6 months of phrenic nerve stimulation therapy. Patients with heart failure showed significant improvement in Minnesota Living With Heart Failure Questionnaire score at 6 months, comparable to that seen with cardiac resynchronization therapy (28). If this finding is confirmed in future randomized controlled trials, treatment with the remedē System may offer significant symptomatic alleviation for this patient group.

This study represents the largest cohort of subjects to be implanted with The remedē System to date with the intent to determine the long-term (3-month) feasibility of pacing the phrenic nerve while assessing safety and efficacy. Although quality-of-life indicators are subject to influence, especially in an unblinded, open-label, uncontrolled study, the AHI is an unbiased end point lending credibility to the statistically significant reduction achieved. Reduction in AHI has been shown to improve outcomes for patients with obstructive sleep apnea, and similar findings have been seen in small studies of CSA. Furthermore, it has been demonstrated that mortality is related to the severity of the AHI (9,24), suggesting that a reduction in AHI by the remedē System may reduce the risk for mortality.

System implantation was successful in 86% of patients, which is similar to that seen in early trials of new transvenous lead technologies (e.g., cardiac resynchronization therapy) (29). The success rate improved throughout the study, particularly with the introduction of a right brachiocephalic vein lead better suited for some anatomies and improved implantation techniques. Twenty-six percent of patients had serious adverse events related to the device or procedure. Although this number may initially appear high, it is similar to other newly introduced cardiac devices, such as cardiac resynchronization therapy, at this stage of development (29).

Benefit and risk need to be considered together. The benefit to the patient from this significant reduction in AHI is clinically meaningful and associated with improved symptoms. The adverse event profile noted is representative of early experience with the implantation technique, technology, and tools available to the implanter. The profile is similar to early development of cardiac resynchronization implantation techniques and tools. Coupled with increased experience, improvements made to the implantation tools and techniques are expected to reduce the rate of device- and procedure-related adverse events in the future. The benefit of AHI improvement demonstrated by the remedē System is clinically meaningful and outweighs the risk for adverse events seen in this trial.

Given the prevalence of CSA and its association with increased morbidity and mortality in certain clinical disorders, there is a need for better therapies. The pathophysiologic mechanisms responsible for the deleterious effects of CSA are now increasingly understood. Cyclical episodes of apnea and arousal are associated with hypoxia and norepinephrine release, which may contribute to myocardial ischemia and fibrosis, progressive worsening of cardiac function, and increased risk for atrial and ventricular arrhythmias (1,13,30). Sleep apnea also induces a proinflammatory milieu, and it has been associated with increased risk for dementia and worsening of diabetes control (30).

The present study is limited by its size, the lack of a parallel control arm, and the diversity of the patient population. Because no parallel control arm was included, some of the effect could be due to regression to the mean. However, longitudinal studies of CSA have not shown significant improvements in sleep-disordered breathing parameters without effective treatment (15). Thus, the efficacy seen in the present study likely represents a treatment rather than a placebo effect.

In summary, transvenous, unilateral phrenic nerve stimulation appears to be a safe and effective approach for the treatment of CSA. By directly stimulating the phrenic nerve, this approach may restore a more natural breathing pattern, resulting in additional improvements in cardiac symptoms, sympathetic surges, and outcomes. The present observations should be confirmed in a larger prospective, randomized, controlled trial.

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REFERENCES

1. Lanfranchi P, Somers V, Braghiroli A, Corra U, Eleuteri, Giannuzzi P. Central sleep apnea in left ventricular dysfunction: prevalence and implications for arrhythmic risk. Circulation 2003;107:727–32.

2. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure. A contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail 2007;9:251–7.

3. Somers V, White D, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation scientific statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing in collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation 2008;118:1080–111.

4. Javaheri S, Parker TJ, Liming JD, et al. Sleep apnea in 81 ambulatory male patients with stable heart failure: types and their prevalences, consequences and presentations. Circulation 1998;97:2154–9.

5. Aurora RN, Chowdhuri S, Ramar K, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with and evidence-based literature review and meta-analyses. Sleep 2012;35:17–40.

6. Solin P, Jackson DM, Roebuck T, Naughton MT. Cardiac diastolic function and hypercapnic ventilatory responses in central sleep apnea. Eur Respir J 2002;20:717–23.

7. Lanfranchi PA, Braghiroli A, Bosimini E, Mazzuero G, Colombo R, Donner CF, et al. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. Circulation 1999;99:1435–40.

8. Hanly PJ, Zuberi-Khokhar NS. Increased mortality associated with Cheyne-Stokes respiration in patients with congestive heart failure. Am J Resp Crit Care Med 1996;153:272–6.

9. Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction and low diastolic blood pressure are predictors of mortality in systolic heart failure. J Am Coll Cardiol 2007;49:2028–34.

10. Andreas S, Hagenah G, Moller C, Werner GS, Kreuzer H. Cheyne-Stokes respiration and prognosis in congestive heart failure. Am J Cardiol 1996;78:1260–4.

11. Javaheri S, Dempsey JA. Central sleep apnea. Compr Physiol 2013;3:141–63.

12. Naughton MT, Benard DC, Liu PP, Rutherford R, Rankin F, Bradley TD. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. Am J Respir Crit Care Med 1995;152:473–9.

13. Bitter T, Westerheide N, Prinz C, et al. Cheyne-Stokes respiration and obstructive sleep apnoea are independent risk factors for malignant ventricular arrhythmias requiring appropriate cardioverter-defibrillator therapies in patients with congestive heart failure. Eur Heart J 2011;32:61–74.

14. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. Circulation 2000;101:392–7.

15. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med 2005;353:2025–33.

16. Arzt M, Floras JS, Logan AG, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). Circulation 2007;115:3173–80.

17. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy. The challenge to effective treatment. Proc Am Thorac Soc 2008;5:173–8.

18. Takama N, Kurabayashi M. Effect of adaptive servo-ventilation on 1-year prognosis in heart failure patients. Circ J 2012;76:661–7.

19. Harris N, Javaheri S. Advanced PAP therapies. In: Mattice C, Brooks R, Lee-Chiong T, editors. Fundamentals of Sleep Technology. Philadelphia, PA: Lippincott, Williams & Wilkins, 2012:444–52.

20. Glenn WWL, Phelps ML. Diaphragm pacing by electrical stimulation of the phrenic nerve. Neurosurgery 1985;17:974–84.

21. Zhang X-L, Ding N, Wang H, et al. Transvenous phrenic nerve stimulation in patients with Cheyne-Stokes respiration and congestive heart failure. Chest 2012;142:927–34.

22. Ponikowski P, Javaheri S, Michalkiewicz D, et al. Transvenous phrenic nerve stimulation for the treatment of central sleep apnea in heart failure. Eur Heart J 2012;33:889–94.

23. Iber C, Ancoli-Israel S, Chesson AL Jr., Quan SF, for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine, 2007.

24. Jilek C, Krenn M, Sebah, et al. Prognostic impact of sleep disordered breathing and its treatment in heart failure: an observational study. Eur J Heart Fail 2011;13:68–75.

25. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14:540–5.

26. Tate CW III, Robertson AD, Zolty R, et al. Quality of life and prognosis in heart failure: results of the Beta-Blocker Evaluation of Survival Trial (BEST). J Card Fail 2007;13:732–7.

27. Rector TS, Kubo SH, Cohn JN. Patients' self-assessment of their congestive heart failure. Part 2: content, reliability and validity of a new measure, the Minnesota Living With Heart Failure Questionnaire. Heart Fail 1987;3:198–209.

28. McAlister FA, Ezekkowitz J, Hooton N, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction. A systematic review. JAMA 2007;297:2502–14.

29. Alonso C, Leclercq C, d'Allones FR, et al. Six year experience of transvenous left ventricular lead implantation for permanent biventricular pacing in patients with advanced heart failure: technical aspects. Heart 2001;86:405–10.

30. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. Physiol Rev 2010;90:47–112.

KEY WORDS apnea-hypopnea index, central sleep apnea, heart failure, phrenic nerve, sleep

APPENDIX For a list of the remedē Pilot Study investigators and the members of the Data and Safety Monitoring Committee, please see the online version of this article.