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**Brief Title:** Phrenic Nerve Stimulation to Treat Central Sleep Apnea

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ABSTRACT
Objective: We evaluated chronic, transvenous, unilateral phrenic nerve stimulation to treat central sleep apnea (CSA) in a prospective, multi-center, non-randomized study.

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

Methods: Fifty-seven CSA patients underwent baseline polysomnography followed by transvenous phrenic nerve stimulation system implantation and follow-up. Feasibility was assessed by implant 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 (AHI) at 3 months. Quality of life (QoL) at 6 months was evaluated using a sleepiness questionnaire, patient global assessment, and in patients with HF at baseline, the Minnesota Living with Heart Failure (MLWHF) Questionnaire.

Results: The study met its primary endpoint, demonstrating a 55% reduction in AHI from baseline to 3 months (49.5±14.6 versus 22.4±13.6 episodes/hour of sleep, P<0.0001, 95% CI for change [-32.3, -21.9]). Central apnea index, oxygenation, and arousals significantly improved. Favorable effects on QoL and sleepiness were noted. In patients with HF, the MLWHF 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.

ClinicalTrials.gov Identifier: NCT01124370

KEYWORDS: apnea-hypopnea index, central sleep apnea, heart failure, phrenic nerve, sleep

CONDENSED ABSTRACT
Central sleep apnea (CSA) occurs predominantly in patients with heart failure (HF) and is associated with increased risk of morbidity and mortality. Established therapies for CSA are lacking, and those available may be limited by poor patient adherence with therapy. We evaluated chronic, transvenous, unilateral phrenic nerve stimulation to treat CSA in a prospective, multi-center, non-randomized study. Therapy resulted in a 56% reduction in AHI from baseline to 3 months. All other monitored sleep-disordered breathing parameters significantly improved. Favorable effects on quality of life and sleepiness were noted. Therapy was well tolerated. Efficacy was maintained at 6 months.

ABBREVIATIONS
AHI = apnea-hypopnea index
ASV = adaptive pressure support servoventilation
CPAP = continuous positive airway pressure
CSA = central sleep apnea
DSMB = data safety and monitoring board
ESS = Epworth sleepiness scale
MLWHF = Minnesota living with heart failure
OSA = obstructive sleep apnea
PGA = patient global assessment
PSG = polysomnography
Introduction

Central sleep apnea (CSA) occurs in approximately 35% of heart failure patients regardless of ejection fraction (1,2). It may also be seen in patients with atrial fibrillation, neurological disorders, and in chronic 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).

Central sleep apnea is characterized by temporary withdrawal of central respiratory drive resulting in cessation of 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.

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 (OSA), most notably continuous positive airway pressure (CPAP) therapy. While effective in treating OSA, CPAP failed to improve morbidity and mortality in a large trial of CSA perhaps due to its failure to improve CSA in some patients; however, survival improved in patients whose CSA was suppressed by CPAP (14,15,16). A major limitation with use of CPAP is patient non-adherence (17). A new type of positive airway pressure therapy, adaptive pressure support
servoventilation (ASV), has been introduced to treat CSA and is currently undergoing clinical evaluation. Early, small, nonrandomized studies of ASV in heart failure patients 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 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 CSA has been investigated utilizing unilateral, transvenous phrenic nerve stimulation to restore a physiological breathing pattern throughout sleep. This therapy stimulates the diaphragm during sleep to 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 CO$_2$ without suppressing the patient’s intrinsic drive to breathe in CSA patients (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 chronic application of transvenous phrenic nerve stimulation (the remede® System, Respicardia, Inc., Minnetonka, Minnesota). This implantable system is automated and requires no patient intervention to function, thus eliminating patient non-compliance. The 6-month results of a study evaluating the feasibility, safety, and efficacy of this system in a broad population of CSA patients 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 utilizes 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.

Study Overview and Patient Population

This is a prospective, international, multi-center, non-randomized, feasibility, safety, and efficacy study of patients with CSA before and after therapy using patients as their own control. The study was conducted under a U.S. Food and Drug Administration Investigational Device Exemption and registered on ClinicalTrials.gov (identifier: NCT01124370). Safety oversight was provided by an independent data and safety monitoring board (DSMB). Authors had full access
to study data and take full responsibility for the accuracy and completeness of the reported findings.

Patients were eligible if they had an apnea-hypopnea index (AHI) of at least 20 and at least half of the events were of central origin per polysomnography (PSG). Patients were excluded if ≥20% of their AHI was comprised of obstructive apnea events. Patients were required to be on stable, optimal medical therapy for any co-morbidity prior to enrollment. Additional exclusion criteria included phrenic nerve palsy, baseline hypoxia (SpO2 < 90% on room air), severe chronic obstructive pulmonary disease, creatinine >2.5 mg/dl, and any cardiac procedure in the 3 months prior to the baseline study. Ethics committees at participating centers approved the study, and patients provided written informed consent prior to 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 seconds. Central apnea was defined as the absence of respiratory effort and airflow for >10 seconds. 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 ≥30% reduction in airflow lasting at least 10 seconds, 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 seconds after at least 10
seconds 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. Based on 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 implant. All leads were secured to the pectoralis muscle, connected to the remedē neurostimulator, and secured in a subcutaneous pocket in the pectoral area.

Following 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/stop time and programmed maximum stimulation parameter, were determined by interviewing the patient regarding sleep habits and then monitoring response to overnight stimulation. Programmed maximum 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 endpoints and no changes were made to the programming of the device during the endpoint 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 endpoint of the study was change in the AHI following 3 months of therapy. The expected reduction in the AHI due to treatment with the remedē System was 50%. This value was chosen based on an understanding that a 50% reduction in AHI is achievable, clinically meaningful, and associated with a reduced risk of mortality (24,25). 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 endpoints included the feasibility and safety of transvenous, unilateral phrenic nerve stimulation therapy. Feasibility was assessed by the lead implant 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 (ESS) (26), a Patient Global Assessment (PGA) (27), and the Minnesota Living With Heart Failure Questionnaire (MLWHF; for patients with heart failure at baseline) (28).

**Statistical Analysis**
A minimum sample size of 40 patients was chosen based on 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’s 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 endpoint (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 (ANOVA). 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.).

Results

Patients

Between June 2010 and August 2012, 57 patients enrolled in the study (Figure 7). Of the enrolled patients, 8 (14%) did not leave the hospital with an implanted system: 7 had anatomical issues that prevented lead placement and 1 had a severe reaction to anesthesia resulting in dislodgement of the stimulation lead. Prior to the 3-month follow-up visit, 2 patients were withdrawn from the study: 1 for placement of a left ventricular assist device and another
following a mechanical fall resulting in system explant. The DSMB judged these 2 events as unrelated to phrenic nerve stimulation therapy or the system implantation procedure. Forty-seven patients were available for endpoint assessment at 3 months (Table 1). The mean baseline AHI was in the severe range at 49.5±14.6 episodes/hour. 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/hour (55%, p<0.0001) accompanied by a mean reduction in the central apnea index of 23.4±15.3 episodes/hour (84%, p<0.0001) (Table 2). 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 (REM) sleep, arousals, and oxygenation also occurred. Two of the 47 (4%) patients were unable to complete a valid PSG at 6 months, but did complete the office visit. In the 44 patients available for 6-month assessment, improvement in sleep parameters was maintained (Table 3).

**Secondary Outcomes**

**Feasibility**

The remedē System neurostimulator and stimulation lead were successfully implanted in 49 of the 57 (86%) enrolled patients. Of the 47 patients who reached the 3-month primary and secondary study endpoint analyses, 29 (61%) had the lead implanted in the left pericardiophrenic vein, and 18 (39%) in the right brachiocephalic vein. In 37 of the 47 (79%) patients, a sensing lead was implanted in the azygos vein to sense respiration. Following implantation, 11 of the 47 (23%) patients required lead repositioning, and an additional patient had a lead dislodgement and
was unable to have the lead repositioned, resulting in explant. The majority (8/12) of cases where 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 implant location, along with improved operator experience with the left pericardiophrenic lead, resulted in a first-attempt implant 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 hours of therapy during 5.8±1.2 hours of sleep every night based on 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 the 47 (2%) patients died between the 3- and 6-month follow-up visits due to end-stage heart failure. The DSMB adjudicated this death as not related to the procedure or to phrenic nerve stimulation therapy. Three of the 47 (6%) patients were adjudicated by the DSMB as having serious adverse events related to the device, implant 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 was associated with atypical chest discomfort. Therapy was re-initiated on the following night without further discomfort.
Quality of Life

Sleepiness improved as evidenced by a reduction in the ESS score in patients at 6 months (8.0±3.9 to 6.1±4.6; p=0.0034) and in patients with an ESS greater than 10 at baseline (12.4±1.9 to 8.5±5.2; p=0.0023). All 46 patients completed the 6-month PGA, which asked the patient to rank on a 7-point scale, “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, 10 (22%) no change, and 1 (2%) reported being slightly worse. No patients reported being moderately worse or markedly worse. The MLWHF questionnaire, completed by the 36 heart failure patients at 6 months, also showed improvement by an average of 10 points (p=0.0009, 95% CI [-16, -4]).

Discussion

The present study demonstrates the feasibility, safety, and efficacy of chronic, transvenous, unilateral phrenic nerve stimulation as a treatment for CSA using an implantable system. Results showed improvement in AHI, central apnea index, arousals, sleep efficiency, and REM sleep following 3 months of treatment. These improvements were sustained at 6 months and were accompanied by improvement in both sleepiness and heart failure symptoms. The mean obstructive apnea index was unchanged, suggesting that therapy did not induce or contribute to upper airway obstruction.

Results from the PGA showed the majority of patients experienced improvement in symptoms following 6 months of phrenic nerve stimulation therapy. Heart failure patients showed significant improvement in MLWHF questionnaire score at 6 months, comparable to that seen with cardiac resynchronization therapy (29). If this finding is confirmed in future
randomized controlled trials, treatment with the remedē System may offer significant symptomatic improvement 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 chronic (3-month) feasibility of pacing the phrenic nerve while assessing safety and efficacy. While quality of life indicators are subject to influence, especially in an un-blinded open label, uncontrolled study, the AHI is an unbiased endpoint lending credibility to the statistically significant reduction achieved. Reduction in AHI has been shown to improve outcomes for patients with OSA, and similar findings have been seen in small studies of CSA. Further, it has been demonstrated that mortality is related to the severity of the AHI (24,25), suggesting reduction in AHI by the remedē System may reduce risk of 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) (30). 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 (30).

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 implant technique, technology, and tools available to the implanter. The profile is similar to early development of
cardiac resynchronization implant techniques and tools. Coupled with increased experience, improvements made to the implant 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 of 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 (1,13,31). Sleep apnea also induces a pro-inflammatory milieu, and it has been associated with increased risk for dementia and worsening of diabetes control (31).

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.
remedē Pilot Study Investigators

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References


Figure Titles and Legends

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.

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.

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.

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 0.1-10 mA for 60-300 µsec at 20-40 Hz.
**Figure 6: Polysomnogram demonstrating the effect of phrenic nerve stimulation.** The above tracing shows respiratory stabilization of a patient with central sleep apnea with Cheyne-Stokes respiration following transvenous, unilateral phrenic nerve stimulation therapy.

**Figure 7: Patient Disposition.** Flow diagram indicating progress of eligible patients through the study. LVAD indicates left ventricular assist device. PSG indicates polysomnography.
Table 1: Baseline Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=47</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>65.9±9.6</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>29.3±4.4</td>
</tr>
<tr>
<td>Male (%)</td>
<td>89</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>30</td>
</tr>
<tr>
<td>Apnea-hypopnea index (AHI), episodes/hr of sleep</td>
<td>50±15</td>
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<tr>
<td>Central apnea index (CAI), episodes/hr of sleep</td>
<td>28±14</td>
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<tr>
<td>Obstructive apnea index (OAI), episodes/hr of sleep</td>
<td>3±3</td>
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<tr>
<td>History of hypertension (%)</td>
<td>74</td>
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<tr>
<td>Central sleep apnea etiology</td>
<td></td>
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<tr>
<td>Atrial fibrillation (%)</td>
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<tr>
<td>Opiate use (%)</td>
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<td>Idiopathic (%)</td>
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<td>Other cardiac (%)</td>
<td>13</td>
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<td>Heart failure (%)</td>
<td>79</td>
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<td>New York Heart Association classification</td>
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<tr>
<td>I (%)</td>
<td>9</td>
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<tr>
<td>II (%)</td>
<td>47</td>
</tr>
<tr>
<td>III (%)</td>
<td>21</td>
</tr>
<tr>
<td>IV (%)</td>
<td>2</td>
</tr>
<tr>
<td>Heart failure with ejection fraction &gt; 40% (%)</td>
<td>9</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>66</td>
</tr>
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</table>
Systolic blood pressure (mmHg) & 123±21 \\
Diastolic blood pressure (mmHg) & 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 \\

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker
Table 2: Effect on Sleep-Disordered Breathing Parameters at 3 Months with the remedē® System (N=47)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline*</th>
<th>3 Months*</th>
<th>Difference*</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea-hypopnea index (AHI), episodes/hr of sleep</td>
<td>49.5±14.6</td>
<td>22.4±13.6</td>
<td>-27.1±17.7</td>
<td>(-32.3, -21.9)</td>
<td>&lt; 0.0001†</td>
</tr>
<tr>
<td>Central apnea index (CAI), episodes/hr of sleep</td>
<td>28.0±14.2</td>
<td>4.7±8.6</td>
<td>-23.4 ± 15.3</td>
<td>(-27.8, -18.9)</td>
<td>&lt; 0.0001†</td>
</tr>
<tr>
<td>Obstructive apnea index (OAI), episodes/hr of sleep</td>
<td>3.0±2.9</td>
<td>3.9±4.7</td>
<td>0.9±5.4</td>
<td>(-0.7, 2.4)</td>
<td>0.2816†</td>
</tr>
<tr>
<td>Mixed apnea index (MAI), episodes/hr of sleep</td>
<td>3.4±4.5</td>
<td>0.3±0.6±1</td>
<td>-3.0±4.5</td>
<td>(-4.4, -1.7)</td>
<td>&lt; 0.0001‡</td>
</tr>
<tr>
<td>Hypopnea index (HI), episodes/hr of sleep</td>
<td>15.1±12.1</td>
<td>13.5±9.0</td>
<td>-1.5±14.8</td>
<td>(-5.9, 2.8)</td>
<td>0.4809‡</td>
</tr>
<tr>
<td>4% Oxygen desaturation index (ODI4), episodes/hr of sleep</td>
<td>45.2±18.7</td>
<td>21.6±13.7</td>
<td>-23.7±21.2</td>
<td>(-29.9, -17.4)</td>
<td>&lt; 0.0001†</td>
</tr>
<tr>
<td>Arousal index, episodes/hr of sleep</td>
<td>36.2±18.8</td>
<td>23.7±10.6</td>
<td>-12.5±16.9</td>
<td>(-17.5, -7.6)</td>
<td>&lt; 0.0001†</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>68.3±17.2</td>
<td>76.6±15.4</td>
<td>8.4±20.2</td>
<td>(2.4, 14.3)</td>
<td>0.0066†</td>
</tr>
<tr>
<td>Rapid eye movement (REM) sleep, %</td>
<td>11.1±6.8</td>
<td>15.6±8.2</td>
<td>4.5±11.2</td>
<td>(1.2, 7.8)</td>
<td>0.0086†</td>
</tr>
</tbody>
</table>

*All values expressed as mean±SD.

† Paired Student's t-test.
‡ Wilcoxon signed rank test.
Table 3: Effect on Sleep Parameters at Six Months with the remedē® System (N=44)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline*</th>
<th>3 Months*</th>
<th>6 Months*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea-hypopnea index (AHI), no./hr of sleep</td>
<td>49.4±14.9</td>
<td>22.8±13.6</td>
<td>23.3±13.3</td>
<td>≤0.0001†</td>
</tr>
<tr>
<td>Central apnea index (CAI), no./hr of sleep</td>
<td>28.1±14.7</td>
<td>5.0±8.8</td>
<td>4.5±7.2</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Obstructive apnea index (OAI), no./hr of sleep</td>
<td>3.0±2.8</td>
<td>3.9±4.8</td>
<td>3.8±5.2</td>
<td>0.0223‡</td>
</tr>
<tr>
<td>Mixed apnea index (MAI), no./hr of sleep</td>
<td>3.0±3.7</td>
<td>0.3±0.6</td>
<td>0.6±1.5</td>
<td>&lt;0.0002†</td>
</tr>
<tr>
<td>Hypopnea index (HI), no./hr of sleep</td>
<td>15.4±12.4</td>
<td>13.5±9.0</td>
<td>14.4±8.3</td>
<td>0.0179‡</td>
</tr>
<tr>
<td>4% Oxygen desaturation index (ODI4), no./hr of sleep</td>
<td>46.0±18.8</td>
<td>22.0±13.8</td>
<td>22.9±13.3</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Arousal index, no./hr of sleep</td>
<td>35.5±18.4</td>
<td>23.4±10.9</td>
<td>24.7±12.3</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>69.3±16.8</td>
<td>76.9±15.6</td>
<td>81.4±12.5</td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Rapid eye movement (REM) sleep, %</td>
<td>11.2±6.3</td>
<td>16.2±8.1</td>
<td>17.4±6.9</td>
<td>&lt;0.0001†</td>
</tr>
</tbody>
</table>

*All values expressed as mean±SD.
†Repeated measures ANOVA.
‡Friedman test.
Time is within patient's established sleep period

Patient's activity level below activity threshold

Patient in sleeping posture

Stimulation lead impedance within acceptable limits

Phrenic nerve stimulation therapy delivered

Maximum number of hours of programmed therapy reached (unique to each patient) OR

No longer true

Therapy ends.
Therapy OFF  Therapy ON
57 patients enrolled and implant attempted

49 patients reached therapy initiation

47 patients reached 3 months

46 patients reached 6 months
• 2 patients missed 6 month PSG due to illness

• 7 patients—failure to place lead
• 1 patient—early lead dislodgement due to nausea/vomiting: system explanted per patient request

• 1 patient—LVAD placement
• 1 patient—lead dislocation with explant

• 1 patient—death