ORIGINAL ARTICLE

Phrenic nerve stimulation in patients with central sleep apnea: a single-center experience from pilot and pivotal trials evaluating the remedē System

Dariusz Jagielski[1], Adam Kołodziej[1], Randy Westlund[2], Bartosz Biel[1], Krzysztof Nowak[1,3], Iwona Szemplińska[1], Irena Flinta[1,5], Magdalena Krawczyk[1,5], Katarzyna Kulej[1], Bartosz Krakowiak[1], Robin Germany[2], Antonis Panteleon[2], Scott McKane[2], Waldemar Banasiak[1], William T. Abraham[4], Piotr Ponikowski[1,3]

1 Department of Cardiology, Center for Heart Diseases, 4th Military Hospital, Wrocław, Poland
2 Respicardia Inc., Minnetonka, Minnesota, United States
3 Department of Heart Diseases, Wrocław Medical University, Wrocław, Poland
4 Division of Cardiovascular Medicine, Ohio State University, Columbus, Ohio, United States
5 Department of Physiology, Wrocław Medical University, Wrocław, Poland

KEY WORDS
central sleep apnea, heart failure, phrenic nerve stimulation

ABSTRACT

BACKGROUND Patients with central sleep apnea (CSA) have recently been shown to have improved sleep metrics and quality of life (QoL) with phrenic nerve stimulation (PNS).

AIMS The aim of this study was to report the results of a partnership between cardiology, sleep medicine, and electrophysiology in a single clinical center as well as the enrollment, implantation, and follow-up experience demonstrating both the safety and efficacy of PNS.

METHODS This analysis included data from the pilot and pivotal trials investigating the effect of PNS using an implantable transvenous system in patients with CSA. We present our experience and data on the enrollment processes, implantation feasibility and safety, sleep indices, and QoL at 6 and 12 months of follow-up.

RESULTS Between June 2010 and May 2015, cardiology patients were prescreened and 588 of them were sent for in-home sleep test. Ninety-six patients were referred for polysomnographic studies, and 33 were enrolled and had an implant attempt, with 31 successfully receiving an implant. The apnea–hypopnea index was reduced in the pilot trial (mean [SD] of 48.7 [15.5] events/h to 22.5 [13.2] events/h; P <0.001) and in the pivotal trial (mean [SD] of 48.3 [18.8] events/h to 26.0 [21.9] events/h; P <0.001). Improvement in QoL was also observed.

CONCLUSIONS We showed that PNS improved sleep metrics and QoL in patients with CSA, which is a result of multiple factors, including a comprehensive coordination between cardiology, sleep medicine, and electrophysiology. This ensures appropriate patient identification leading to safe implantation and full patient compliance during follow-up visits.

Correspondence to:
Dariusz Jagielski, MD, Department of Cardiology, Center for Heart Diseases, 4th Military Hospital, ul. Weigla 5, 50-981 Wrocław, Poland, phone: +48 26 166 02 37, email: dariuszjagielski@gmail.com
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INTRODUCTION Central sleep apnea (CSA) is a breathing disorder characterized by cessation of airflow in respiratory airways predominantly during sleep, accompanied by cessation of respiratory muscle contraction. This results in temporary withdrawal of activity from the respiratory control center.[1,2] The disorder often presents as Cheyne–Stokes respiration, a breathing pattern characterized by hyperpnea (cycles of deep, accelerating, crescendo–decrescendo breathing) followed by

WHAT'S NEW?

We present the results of a comprehensive partnership between cardiology, sleep medicine, and electrophysiology. Between June 2010 and May 2015, cardiology patients were screened for sleep-disordered breathing, and 588 of them were sent for overnight in-home sleep testing. Ninety-six patients were referred for polysomnographic studies based on a preliminary finding of central sleep apnea (CSA), and 33 were enrolled and underwent attempted implantation of a phrenic nerve stimulation (PNS) system. Thirty-one patients successfully received an implant. We showed that transvenous PNS improves sleep metrics, sleep quality, and quality of life in Polish patients with moderate to severe CSA both with and without heart failure. Of importance, device-related events were minimal after the 12-month follow-up, indicating long-term safety. Additionally, the therapy eliminates compliance issues experienced with traditional sleep apnea treatments. This manuscript summarizes the unique experience with the largest group of patients with the remedē® System in a single clinical center.

hypopnea (slower, shallower breathing) or apnea (no breathing at all with no respiratory effort from the diaphragm and intercostal muscles) (FIGURE 1).

Heart failure (HF) is associated with CSA in up to 40% of patients, but it can be found in other comorbidities including atrial fibrillation, neurologic disorders, chronic renal diseases, and long-term opioid use.[3,4] Increased rehospitalizations and deterioration in cardiac function have been correlated with CSA.[5,6] Pathological mechanisms include hypoxia, hypercapnia, oxidative stress, systemic inflammation, endothelial dysfunction, sympathetic nervous system activation, and cardiac arrhythmias accompanied by increased therapies from an implanted cardioverter-defibrillator (ICD).[7-9] Arrhythmias in patients with HF and CSA occur independently of the time of day, which makes the need for treatment even more relevant.[10]

Treatment options for CSA are very limited. Several methods, such as continuous positive airway pressure and adaptive servoventilation, have been used to treat CSA in patients with systolic HF. These therapies have shown improvements in sleep metrics; however, adaptive servoventilation has shown unfavorable effects in patients with HF with reduced ejection fraction (≤45%).[11-14]

Recently, transvenous PNS was approved by the US Food and Drug Administration for the treatment of moderate to severe CSA in adult patients.[15] Phrenic nerve stimulation contracts the diaphragm and modulates respiration. The anatomical bases for the concept were described previously.[16] Our center is unique in that it is one of a few institutions that participated both in the pilot and pivotal trials.

METHODS

The analysis included patients at our center who were enrolled in the pilot and pivotal clinical trials. The remedē System pilot trial (ClinicalTrials.gov, NCT01124370) was a prospective, nonrandomized safety and efficacy study, in which patients served as their own controls. We attempted to insert implants in 12 patients (from a total of 57 implant attempts worldwide). The Respicardia, Inc. Pivotal Trial of the remedē System (ClinicalTrials.gov, NCT01816776) was a prospective randomized controlled trial assessing the safety and effectiveness of PNS. We inserted implants in 21 patients (from a total of 151 implant attempts worldwide). The inclusion and exclusion criteria for both trials as well as definitions of the sleep metrics were described previously.[17,18] Studies were performed in compliance with the Declaration of Helsinki, Good Clinical Practice, and ISO-14155:2011. The local ethics committee approved the study protocols for both studies. Serious adverse events (SAEs) related to the implant procedure, device, and delivered therapy

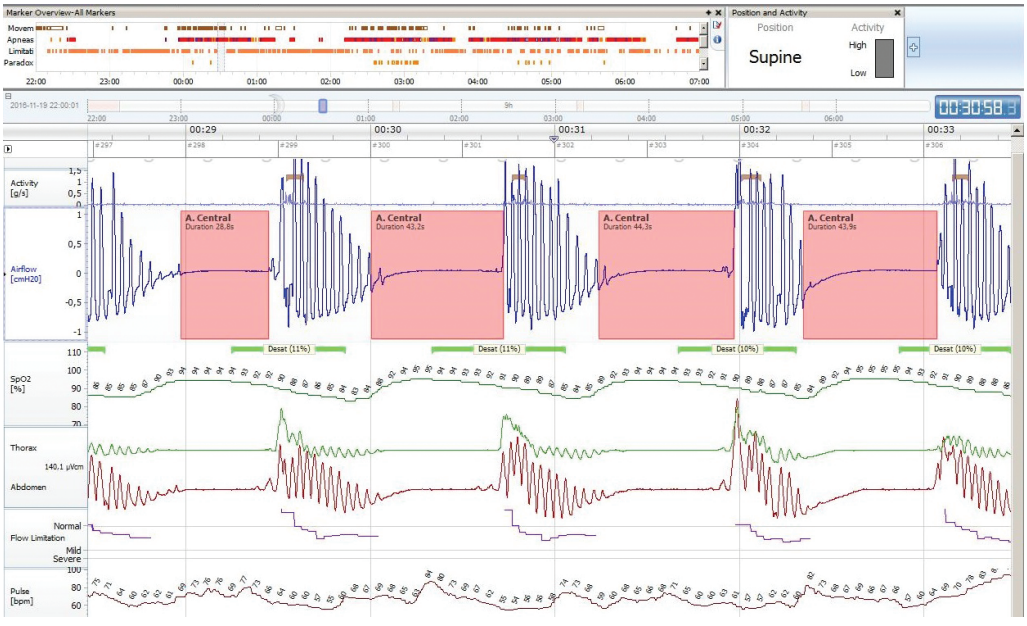

FIGURE 1 Selected metrics of a polysomnographic study in a patient with central sleep apnea and Cheyne–Stokes respiration

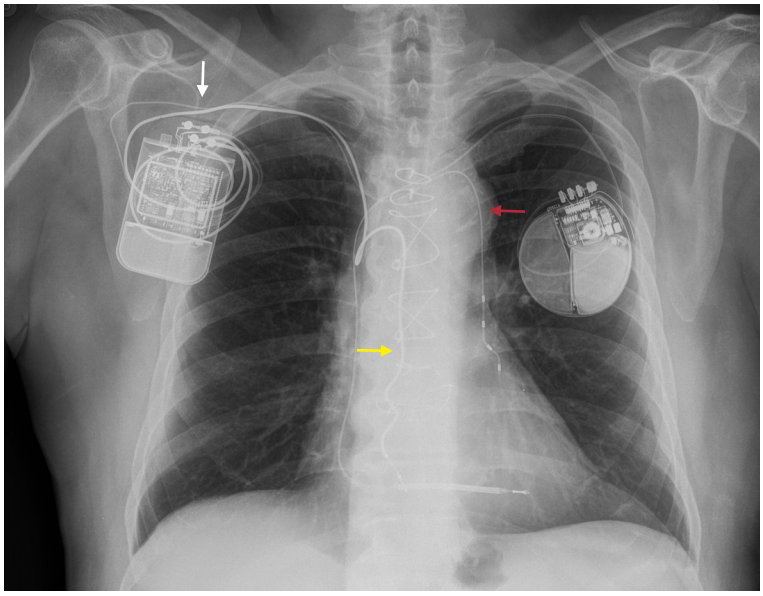

FIGURE 2 The localization of the remedē® System pulse generator (white arrow) under the right clavicle and the stimulating electrode in the left pericardiophrenic vein (red arrow) and the respiration sensing electrode in the azygous vein (yellow arrow)[26]

were collected over 12 months and adjudicated by an independent Clinical Events Committee. All patients gave written informed consent for participation in the study.

Patient identification Potential study candidates were identified by screening the patient database at the 4th Military Hospital in Wrocław, Poland. The following risk factors were used during the prescreening process: obesity, diabetes mellitus, history of tobacco use, arterial hypertension, coronary artery disease, HF (ischemic and nonischemic cardiomyopathy), and atrial fibrillation. Patients were asked about the following symptoms: chronic fatigue, daytime somnolence, somnolence while driving or watching television, and witnessed apneas. A NOX-T3 (Nox Medical Inc., Reykjavík, Iceland) polygraph was used for the in-home sleep test. Sleep tests with at least moderate sleep apnea and evidence of central events were sent to a central core laboratory (Registered Sleepers, Leicester, North Carolina, United States). If the core laboratory identified significant CSA, patients were referred to a local sleep laboratory (EMC-sa.pl) to attend in-lab polysomnography with an electroencephalogram. These polysomnographies were sent to the core laboratory for evaluation. Patients in both trials were eligible if they met the following criteria: apnea–hypopnea index (AHI) ≥20 events/h, >50% of apneas were of central origin, and ≤20% of the AHI were possible obstructive apneas. For the pivotal trial, an additional criterion was 30 central apneas or more through the night.

Implantation technique and phrenic nerve stimulation All implantations were performed in the Electrophysiological Laboratory of the Department of Cardiology of the 4th Military Hospital by one operator. Implantation of the remedē® System (Respicardia, Inc., Minnetonka, Minnesota, United States) is similar to cardiac implantable electronic device (CIED) procedures. Briefly, a transvenous stimulation lead is introduced to the vascular system and placed in either the left pericardiophrenic vein or the right brachiocephalic vein following venous access by way of the cephalic, subclavian, or axillary vein. A sensing lead is introduced into the azygos vein. The leads are connected to the remedē® System implantable pulse generator and then secured in a subcutaneous pocket in the pectoral area (FIGURE 2).

Therapy initiation and follow-up Therapy was initiated approximately 30 days after implantation to allow for healing. The exception to this was the control group in the pivotal trial, who had therapy initiated after the assessment of 6-month effectiveness.

In the case of concomitant CIED interactions, testing between the remedē® System and CIED was performed. If an interaction was deemed to pose a clinical risk, the stimulation settings of the remedē® System were changed and the process was repeated in order to demonstrate no further interactions.

After therapy initiation, titration office visits were scheduled. Therapy effectiveness was assessed by patient interview, examination of remedē® System diagnostics, and sleep study data. If the programmed remedē® System settings were determined to be suboptimal, the energy output was usually increased and another titration office visit was scheduled 2 to 4 weeks later. The patient's sleep quality was also assessed by patient symptoms or polygraphy. This titration process facilitated patient acclimation to remedē® System therapy. Follow-up visits were scheduled at every 3 months; in-lab polysomnography studies (scored by the core laboratory) and assessment of QoL using a 7-point patient global assessment scale were done every 6 months.[19] Stimulation of the phrenic nerve during sleep in a patient with CSA and the termination of apnea episodes are demonstrated in FIGURE 3.

Statistical analysis Differences in baseline characteristics between studies were assessed using the Fisher exact test for categorical data and the analysis of variance for continuous data. Data are presented as mean (SD) or median (IQR) for continuous variables and number (percentage) for categorical variables.

Changes in continuous outcome measures from baseline to 6 and 12 months were tested with the paired *t* test or nonparametric Wilcoxon signed-rank test if distributional assumptions were not met. Outcome differences between studies were not tested. If the nominal *P* value was lower than 0.05, the result was considered

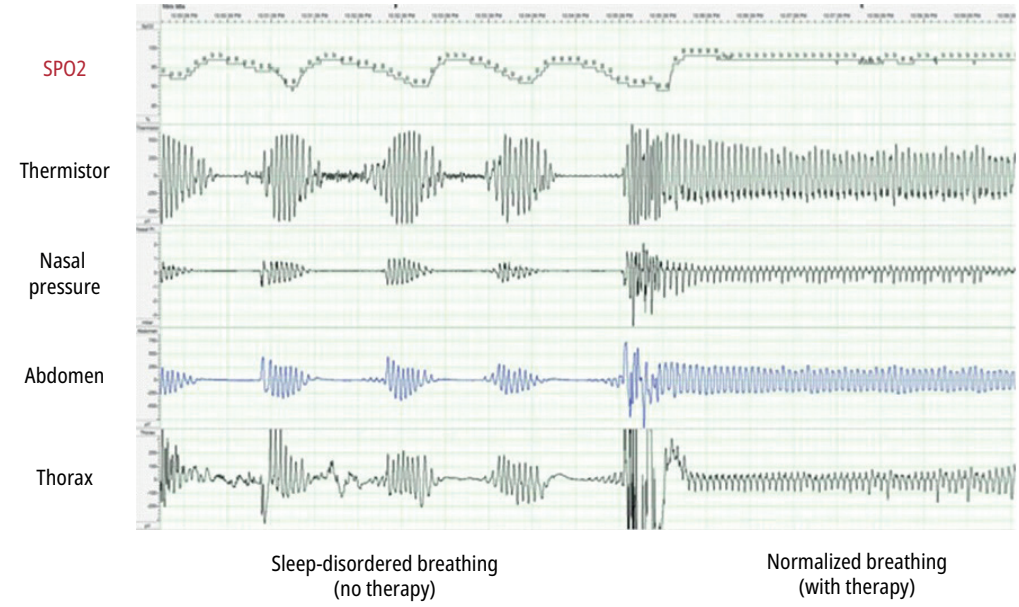

FIGURE 3 Termination of apnea episodes during unilateral phrenic nerve stimulation during sleep in a patient with central sleep apnea

significant. For the effectiveness analysis, pivotal trial participants randomized to the control group, who had the therapy initiated following the 6-month randomized portion of the trial, were pooled with the treatment group participants based on the number of months of active therapy. All follow-up results shown are for months of active therapy. Statistical analyses were performed with SAS (version 9.4, SAS Institute Inc., Cary, North Carolina, United States).

RESULTS Patients' baseline characteristics A total of 200 polygraphy studies followed by 31 polysomnographies were performed between June 2010 and August 2012, resulting in the enrollment of 13 patients in the pilot trial. Between December 2013 and May 2015, 388 polygraphy studies followed by 65 polysomnographies were performed, resulting in the enrollment of 21 patients in the pivotal trial. One patient in the pilot trial voluntarily withdrew consent prior to implantation. Heart failure (defined as a New York Heart Association class I or higher according to the investigator) was present in 12 of the 12 patients (100%) and 14 of the 21 patients (67%) in the pilot and pivotal trials (P = 0.032). There were no significant differences in age, sex, hypertension, atrial fibrillation, diabetes, and body mass index between the trials. The baseline characteristics of patients in each trial are presented in TABLE 1.

Implantation procedure Implantation was successful in all except 2 patients (94%). Of the 31 successfully implanted patients, the stimulation lead was placed in the left pericardiophrenic vein in 22 patients (71%) (6 of 10 patients in the pilot and 16 of 21 patients in the pivotal trial) and in the right brachiocephalic vein in 9 patients (29%) (4 of 10 patients in the pilot and 5 of 21 in the pivotal trial). The sensing lead was placed in 22 patients (71%). There were 2 implantation failures in the pilot trial due to anatomical issues: one due to an old thrombosis in the left subclavian vein from a previous procedure and one due to lack of success in achieving acceptable stimulation threshold of the phrenic nerve. Four patients required lead repositioning or replacement, including 3 in the pilot trial and 1 in the pivotal trial. The mean (SD) length of the implantation procedure, from skin to skin was 3.7 (0.8) hours in the pilot trial and 2.7 (0.8) hours (P = 0.003) in the pivotal trial. Pulse generators were exchanged due to normal battery depletion after a mean period of 4 years in 2 patients without any sequelae, which is comparable to the experience of Fox et al.[20]

Sleep indices Follow-up assessments were conducted in 28 patients at 6 months and in 27 patients at 12 months. At 6 months, there was a mean (SD) reduction in the AHI of 25.5 (15.8) events/h (within-group change from baseline, P <0.001) and at 12 months, a mean (SD) reduction of 29.0 (15.3) events/h (P <0.001), in the pilot trial. Similar AHI reductions of 24.6 (22.9) events/h (P <0.001) at 6 months and of 22.7 (22.7) events/h (P <0.001) at 12 months were observed in the pivotal trial (FIGURE 4).

Improvements in AHI were accompanied by a mean reduction in the CAI and oxygen desaturation index (TABLE 2). We also observed an improvement in the arousal index at 6 months in the pilot trial and at 6 and 12 months in the pivotal trial.

Improvements in the percentage of rapid eye movement sleep ranged from 4.3 to 9.1 at 6 and 12 months (P ≤0.03 at each visit for each study). The percentage of sleep with O_2 saturation of less than 90% decreased more in the pivotal trial than in the pilot trial (approximately

TABLE 1 Baseline characteristics of patients from the pilot and pivotal trials

Variable		Pilot trial (n = 12)	Pivotal trial (n = 21)	*P* value
Age, y	Mean (SD)	60 (6)	64 (9)	0.22
	Median (IQR)	61 (51–68)	65 (41–78)	
	Min – max	56–66	61–68	
Male sex, n (%)		12 (100)	21 (100)	1
Coronary artery disease, n (%)		8 (67)	14 (67)	1
Hypertension, n (%)		8 (67)	13 (62)	1
Heart failure, n (%)		12 (100)	14 (67)	0.03
NYHA class, n (%)	I	1 (8)	4 (19)	0.02
	II	11 (92)	9 (43)	
	III	0 (0)	1 (5)	
Atrial fibrillation, n (%)		3 (25)	9 (43)	0.46
Diabetes, n (%)		1 (8)	7 (33)	0.21
BMI, kg/m^2, mean (SD)		29.4 (4.3)	32.3 (5.1)	0.11
Ejection fraction, %, mean (SD)		23.6 (7.2)	32.6 (12.7)	0.05
β-Blockers, n (%)		12 (100)	18 (86)	0.28
ACEIs/ARBs, n (%)		12 (100)	19 (90)	0.52
Loop diuretics, n (%)		8 (67)	10 (48)	0.47
CIED, n (%)		4 (33)	13 (62)	0.16
ICD, n (%)		3 (25)	9 (43)	0.46
CRT-D, n (%)		1 (8)	3 (14)	1
Pacemaker, n (%)		0 (0)	1 (5)	1
AHI, events/h, mean (SD)		48.7 (15.5)	47.8 (18.7)	0.85
CAI, events/h, mean (SD)		20.2 (11.9)	27.0 (14.9)	0.23
OAI, events/h, mean (SD)		3.5 (2.4)	2.3 (2.0)	0.2
MAI, events/h, median (IQR)		2.2 (1.1–7.8)	1.3 (0.5–3.4)	0.28

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AHI, apnea–hypopnea index; ARB, angiotensin receptor blocker; BMI, body mass index; CAI, central apnea index; CIED, cardiac implantable electronic device; CRT-D, cardiac resynchronization therapy-defibrillator; ICD, implantable cardioverter–defibrillator; IQR, interquartile range; MAI, mixed apnea index; NYHA, New York Heart Association; OAI, obstructive apnea index

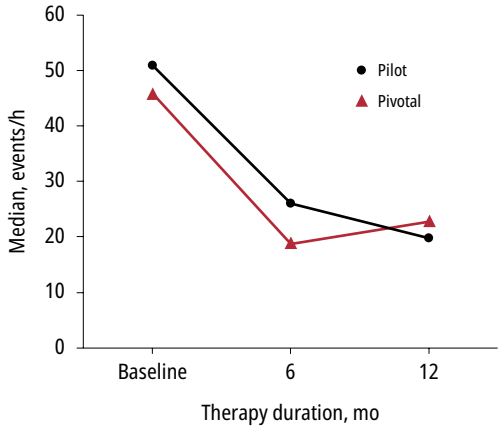

FIGURE 4 Mean apnea–hypopnea index of all patients from the pilot and pivotal trials implanted in Wrocław after 6 and 12 months of phrenic nerve stimulation with the remedē® System

6% improvement at each visit in the pivotal trial, within-group change $P \leq 0.02$ for each visit, and approximately 3% improvement at each visit in the pilot trial, $P = 0.03$ and 0.2 at 6 and 12 months, respectively). The OAI after 6 and 12 months of follow-up was stable in both studies. Sleep metrics from the pilot and pivotal trials are presented in TABLE 2.

Quality of life assessment Following 6 months of therapy, 68% of patients combined across the trials described a marked or moderate improvement, and 11% described a mild improvement in patient global assessment. The results were maintained at 12 months (63% and 19%, respectively; FIGURE 5).

Adverse events No deaths were associated with the implantation procedure. One patient

TABLE 2 Sleep metrics of the patients from the pilot and pivotal trials after 6 and 12 months of phrenic nerve stimulation

Endpoint	Study	Baseline	6 months of therapy			12 months of therapy		
			Result	Paired change	*P* value	Result	Paired change	*P* value
AHI, events/h, mean (SD)[a]	Pilot	48.7 (15.5) n = 12	26.2 (10.5) n = 10	–25.5 (15.8) n = 10	<0.001	22.5 (13.2) n = 9	–29.0 (15.3) n = 9	<0.001
	Pivotal	48.3 (18.8) n = 20	24.1 (21.1) n = 18	–24.6 (22.9) n = 18	<0.001	26.0 (21.9) n = 18	–22.7 (22.7) n = 18	<0.001
CAI, events/h, mean (SD)/ median (IQR)[a]	Pilot	20.2 (11.9) n = 12	5.7 (8.6) n = 10	–15.9 (8.5) n = 10	<0.001	2.1 (1.0–11.6) n = 9	–13.7 (13.7) n = 9	0.02
	Pivotal	23.7 (14.8) n = 20	1.3 (0.7–4.0) n = 18	–19.8 (15.5) n = 18	<0.001	(0.0–2.9) n = 18	–20.1 (13.9) n = 18	<0.001
OAI, events/h, median (IQR)[b]	Pilot	3.7 (1.1–5.5) n = 12	1.4 (0.6–4.4) n = 10	0.2 (–3.3 to 0.8) n = 10	0.865	1.0 (0.8–1.6) n = 9	–0.5 (–2.1 to 0.1) n = 9	0.55
	Pivotal	2.2 (1.2–3.7) n = 20	1.9 (0.7–6.7) n = 18	0.5 (–1.6 to 1.0) n = 18	0.865	3.7 (1.1–9.9) n = 18	0.9 (–1.1 to 5.5) n = 18	0.19
ODI4, events/h, mean (SD)/ median (IQR)[a]	Pilot	50.8 (24.8) n = 12	25.7 (10.7) n = 10	–30.6 (20.8) n = 10	0.001	22.4 (12.8) n = 9	–33.3 (30.0) n = 9	0.01
	Pivotal	43.9 (18.9) n = 20	23.9 (21.2) n = 18	–20.8 (19.8) n = 18	<0.001	25.6 (22.9) n = 18	–17.7 (–34.9 to –2.1) n = 18	0.001
ArI, events/h, mean (SD)/ median (IQR)[a]	Pilot	39.5 (17.1) n = 12	26.6 (12.0) n = 10	–11.1 (–19.4 to –8.0) n = 10	0.025	33.2 (10.1) n = 9	–12.2 (–17.9 to –3.2) n = 9	0.22
	Pivotal	51.5 (19.6) n = 20	27.8 (18.5) n = 18	–24.3 (22.1) n = 18	<0.001	25.5 (14.2) n = 18	–26.6 (21.9) n = 18	<0.001
REM sleep, %, mean (SD)[a]	Pilot	12.0 (5.4) n = 12	20.5 (5.1) n = 10	9.1 (7.0) n = 10	0.003	19.2 (6.3) n = 9	6.7 (6.5) n = 9	0.02
	Pivotal	8.6 (5.8) n = 20	13.2 (6.3) n = 18	5.3 (–2.2 to 10.5) n = 18	0.025	16.0 (8.0) n = 18	7.2 (7.3) n = 18	<0.001
Sleep with O_2 saturation <90%, %, median (IQR)[b]	Pilot	6.1 (1.6–9.4) n = 12	1.4 (0.7–4.4) n = 10	–3.8 (–5.8 to –0.7) n = 10	0.027	1.2 (0.5–1.8) n = 9	–1.4 (–6.6 to 0.4) n = 9	0.2
	Pivotal	9.8 (3.3–19.0) n = 20	3.2 (0.1–6.8) n = 18	–4.9 (–8.5 to –0.5) n = 18	0.002	4.4 (0.9–7.1) n = 18	–4.5 (–9.1 to 0.0) n = 18	0.02

a Nominal 2-sided *P* value from the paired *t* test for change from baseline to visit

b Nominal 2-sided *P* value from the Wilcoxon signed-rank test for change from baseline to visit

Abbreviations: ArI, arousal index; ODI4, oxygen desaturation index; REM, rapid eye movement; others, see TABLE 1

(3%) died within 12 months, and this event was judged by the Clinical Events Committee as unrelated to the remedē® System implant, device, or therapy. There were 7 reported related SAEs during the implant procedure, the related hospitalization period, or during the 12-month follow-up. Adverse events from the pilot and pivotal trials are presented in TABLE 3.

Long-term follow-up data Twelve patients (6 from the pilot and 6 from the pivotal trial) have died since the first implant in 2010, mostly due to advanced HF. To the best of our knowledge, none of the deaths were related to the remedē® System implantation. Five patients had the entire system extracted for various reasons, without any complications.

DISCUSSION This single-center experience describing a comprehensive hospital-based screening, implantation, and follow-up program

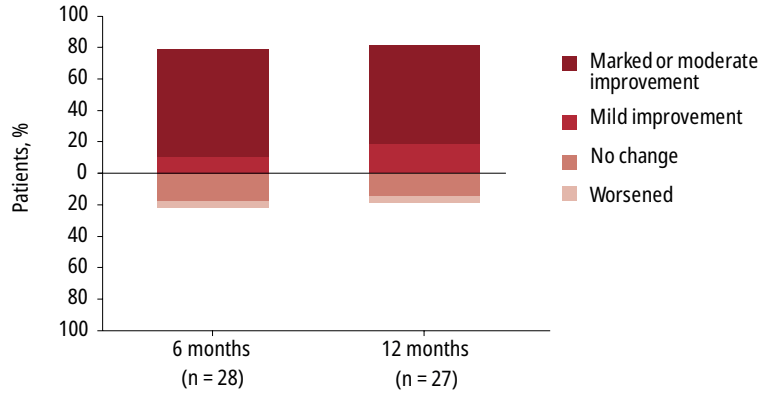

FIGURE 5 Patient global assessment from pooled pilot and pivotal trial cohorts after 6 and 12 months of phrenic nerve stimulation

demonstrates how a novel therapy can be incorporated into a hospital system for the benefit of patients participating in the 2 clinical trials. We developed a screening process to identify patients, showed improvement in implant procedure time between trials, and patients experienced clinically meaningful improvements in sleep and QoL outcomes during the 12-month follow-up, with minimal risk. The results at our site were concordant with the results from the full trials.[21,22]

The deleterious cardiovascular effects of CSA mediated through intermittent episodes of hypoxia, arousals, activations of the sympathetic nervous system, and other injurious mechanisms lead to increased mortality, particularly in patients with the most severe (≥30 events/h of AHI) sleep-disordered breathing.[23] In our cohort, the reduction in the mean baseline AHI provides evidence that unilateral PNS may influence long-term outcomes (>12 months). Our cohort demonstrated stable OAI at 6 and 12 months, allowing us to conclude that unilateral PNS does not contribute to upper airway collapse.

TABLE 3 Summary of related serious adverse events from the pilot and pivotal trials during 12 months of phrenic nerve stimulation

Event	Pilot trial (n = 12)		Pivotal trial (n = 21)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Any event	4	3 (25)	3	3 (14)
Implant site infection	0	0 (0)	1	1 (5)
Inadequate lead position	1	1 (8)	0	0 (0)
Lead component failure	0	0 (0)	1	1 (5)
Lead dislodgement[a]	3	3 (25)	0	0 (0)
Lead displacement[b]	0	0 (0)	1	1 (5)

a When the stimulation lead was pulled out of the target vessel and required repositioning or replacement to deliver therapy.

b When the lead remained in the target vessel but the electrode position did not allow effective delivery of therapy.

Implant success improved to 100% in the pivotal trial. Additionally, the implantation procedure time decreased by 1 hour (27%) between the pilot and pivotal trials. This is not surprising considering the increasing knowledge of pericardiophrenic vein anatomy and general experience. A shorter duration is clinically important because it reflects a lower risk of infection and reduced fluoroscopy time and anesthesia.

The number of patients experiencing related SAEs remained at an acceptably low level throughout both studies and was comparable with early cardiac resynchronization therapy studies.[24] The rate improved from 25% in the pilot trial to 14% in the pivotal trial, probably due to improved implant tools and more experience.

Limitations The pilot trial was a nonrandomized and open-label study. There were small differences in study protocols. For example, accepted baseline oxygen saturation was 90% or lower in the pilot trial but lower than 92% in the pivotal trial, and the pivotal trial excluded patients with new ICD or any CIED change 30 days prior to baseline testing. Despite recruitment attempts to include women in the trials, only men were enrolled at our center. However, we believe that this had a minor influence on the results because CSA occurs predominantly in men.[25] Owing to stringent enrollment criteria, only 6% of patients undergoing home sleep testing were enrolled in the clinical trial; however, it is likely that many more suffered from some degree of CSA. Finally, the subjective measures of health status and symptoms could be a source of bias.

Conclusions Our center successfully developed and implemented a screening program to identify patients within the cardiology department, with close collaboration between sleep medicine and electrophysiology. Our implant metrics improved over the 2 trials, demonstrating that the technique is feasible and safe as a therapeutic method to treat patients with CSA, and improvements in sleep and QoL were observed. While PNS for the treatment of CSA seems promising, further long-term studies should be performed to assess outcomes such as survival, especially in the HF population.

ARTICLE INFORMATION

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CONFLICT OF INTEREST DJ received speaker honoraria, grants funding the project, and consulting fees from Respicardia, Inc. AK received grants funding the project, consulting fees, and personal fees from Respicardia, Inc. RW, RG, AP, and SM are employees of Respicardia, Inc. BB, KN, IS, IF, KK, and BK received personal fees from Respicardia, Inc. MK and WD declare no conflict of interest. WTA received speaker honoraria and consulting fees from Respicardia, Inc. PP received grants funding the project, speaker honoraria and consulting fees from Respicardia, Inc.

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