

Diaphragmatic/Phrenic Nerve Stimulation and Diaphragm Pacing Systems



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DESCRIPTION

Diaphragmatic/Phrenic Nerve Stimulators for Ventilator-Dependent Conditions in Adults

Patients with high-level vertebrae C1-C3 spinal cord injuries typically experience respiratory muscle paralysis leading to chronic ventilatory insufficiency. The standard therapy for these patients is chronic mechanical ventilation via tracheostomy.

Diaphragmatic/phrenic nerve stimulation is an alternative to mechanical ventilation for a select subgroup of patients, common indications include patients with high quadriplegia (spinal cord injury) at or above C-3, chronic central alveolar hypoventilation syndrome. Diaphragmatic/phrenic nerve stimulation, also referred to phrenic pacing, phrenic nerve stimulation, diaphragm pacing, or electrophrenic respiration, is the electrical stimulation

of the diaphragm via the phrenic nerve, the major nerve supply to the diaphragm that controls breathing. Patients with partial or complete respiratory insufficiency who have an intact phrenic nerve and diaphragm may be eligible for diaphragmatic/phrenic nerve stimulation. The patient should be alert, mentally competent, motivated, and able to complete the training and rehabilitation needed for a successful outcome. Prior to implantation patients may undergo diaphragm electromyography, pulmonary function studies and/or polysomnography (i.e., sleep study).

Mark IV System

The Avery Breathing Pacemaker System (that is, the Mark IV™ Avery Biomedical Device, Inc., Commack, NY): This device is surgically implanted (e.g., thoracotomy approach) by placing an electrode behind the phrenic nerve, either in the neck or in the chest. The electrode is connected to a radiofrequency receiving (generator) which is implanted just under the skin which are connected to an external transmitter and antennas to send radiofrequency energy to the implanted receivers. The receivers then convert the radio waves into stimulation pulses. These pulses are then sent down the electrodes to the phrenic nerves, causing the diaphragm to contract. This contraction causes the patient to inhale. When the pulses stop, the diaphragm relaxes and the patient exhales. Repetition of this series of pulses produces a normal breathing pattern. For Mark IV pacing to be effective, candidates must have an intact phrenic nerve, a functional diaphragm, normal chest anatomy, and uncompromised lung function. The patient should be alert, mentally competent, motivated and able to complete the training and rehabilitation needed for a successful outcome.

Clinical Context and Therapy Purpose

The purpose of phrenic nerve stimulation (PNS) in ventilator-dependent conditions in adults who have to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations

The relevant population of interest is individuals with ventilator-dependent conditions in adults.

Interventions

The therapy being considered is diaphragmatic/peripheral nerve stimulation (PNS). This system stimulates the phrenic nerve in the chest, which sends signals to the diaphragm to restore a normal breathing pattern. The device activates automatically when the patient is in a sleeping position and suspends therapy when the patient sits up

Comparators

Patients with high-level, C1-C3 spinal cord injuries typically experience respiratory muscle paralysis leading to chronic ventilatory insufficiency and the standard therapy for these patients is chronic mechanical ventilation via tracheostomy.

Outcomes

Diaphragm stimulation devices are intended to lessen dependence on mechanical ventilators, increase mobility and independence, improve speech and sense of taste and smell, and reduce secretions and risks of infection.

Nonrandomized comparative studies, prospective case series and retrospective reviews have reported that the Mark IV device is a safe and effective alternative to invasive mechanical ventilation and is considered an established alternative therapy in appropriate candidates. Clinical trials with up to ten years follow-up reported success rates of 73% – 94% and included adult and pediatric patients with spinal cord injuries, congenital central alveolar hypoventilation syndrome and other causes of respiratory failure.

Diaphragmatic/Phrenic Nerve Stimulation for Central Sleep Apnea in Adults

Central sleep apnea (CSA) is characterized by sleep-disordered breathing due to diminished or absent respiratory effort. Central sleep apnea may be idiopathic or secondary (associated with a medical condition, drugs, or high altitude breathing). The use of positive airway pressure devices is currently the most common form of therapy for CSA. An implantable device (diaphragmatic/phrenic nerve stimulation) that stimulates the phrenic nerve in the chest is a potential alternative treatment. The battery-powered device sends signals to the diaphragm in order to stimulate breathing and normalize sleep-related breathing patterns.

Central sleep apnea (CSA) is less common than obstructive sleep apnea (OSA). Based on analyses of a large community-based cohort of participants 40 years of age and older in the Sleep Heart Health Study, the estimated prevalence of CSA and obstructive sleep apnea are 0.9% and 47.6%, respectively. Risk factors for CSA include age (>65 years), male gender, history of heart failure (HF), history of stroke, other medical conditions (acromegaly, renal failure, atrial fibrillation, low cervical tetraplegia, and primary mitochondrial diseases), and opioid use. Individuals with CSA have difficulty maintaining sleep and therefore experience excessive daytime sleepiness, poor concentration, and morning headaches, and are at higher risk for accidents and injuries.

The goal of treatment is to normalize sleep-related breathing patterns. Because most cases of CSA are secondary to an underlying condition, central nervous system pathology, or medication side effects, treatment of the underlying condition or removal of the medication may improve CSA. Treatment recommendations differ depending on the classification of CSA as either hyperventilation-related (most common, including primary CSA and those relating to HF or high altitude breathing) or hypoventilation-related (less common, relating to central nervous system diseases or use of nervous system suppressing drugs such as opioids).

For patients with hyperventilation-related CSA, continuous positive airway pressure (CPAP) is considered first-line therapy. Due to CPAP discomfort, patient compliance may become an issue. Supplemental oxygen during sleep may be considered for patients experiencing hypoxia during sleep or who cannot tolerate CPAP. Patients with CSA due

to HF with an ejection fraction >45%, and who are not responding with CPAP and oxygen therapy, may consider bilevel positive airway pressure or adaptive servo-ventilation (ASV) as second-line therapy. Bilevel positive airway pressure devices have 2 pressure settings, 1 for inhalation and 1 for exhalation. Adaptive servo-ventilation uses both inspiratory and expiratory pressure and titrates the pressure to maintain adequate air movement. However, a clinical trial reported increased cardiovascular mortality with ASV in patients with CSA due to HF and with an ejection fraction <45% and therefore, ASV is not recommended for this group.

For patients with hypoventilation-related CSA, first-line therapy is bilevel positive airway pressure.

Pharmacologic therapy with a respiratory stimulant may be recommended to patients with hyper- or hypoventilation CSA who do not benefit from positive airway pressure devices, though close monitoring is necessary due to the potential for adverse effects such as rapid heart rate, high blood pressure, and panic attacks.

Currently there is one phrenic nerve stimulation device approved by the U.S. Food and Drug Administration (FDA) for CSA, the Remede System.

remede System

The remede System (Respicardia, Inc., Minneapolis, MN): Is an implanted nerve stimulator used to treat moderate to severe central sleep apnea (CSA) in adults. A cardiologist implants the system which includes a battery powered pulse generator that is implanted under the skin in the upper chest and thin wire leads that are threaded through veins (transvenous) near the nerve that stimulates breathing (phrenic nerve). The system is programmed using an external system programmer and programming wand. The remede System delivers a small electrical stimulus to the phrenic nerve while a patient is asleep. This stimulus makes the diaphragm muscle contract, which causes the patient to take a breath. The remede System has 2 modes, it can be set to generate pulses at a fixed rate (asynchronous therapy) or it can deliver a pulse only when it detects a pause in breathing (synchronous therapy). The physician is able to set the stimulator to deliver the most appropriate therapy for the patient. The system has safeguards to make sure that therapy is only delivered during sleep, for example it works only at the time of day when the patient is expected to be sleeping and it turns on only when the patient is inactive and lying down.

Clinical Context and Therapy Purpose

The purpose of phrenic nerve stimulation (PNS) in patients who have central sleep apnea (CSA) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations

The relevant population of interest is individuals with Central sleep apnea (CSA). Central sleep apnea is characterized by repetitive cessation or decrease in both airflow and

ventilatory effort during sleep. Individuals with CSA have difficulty maintaining sleep and therefore experience excessive daytime sleepiness, poor concentration, morning headaches, and are at higher risk for accidents and injuries.

Interventions

The therapy being considered is diaphragmatic/peripheral nerve stimulation (PNS). This system stimulates the phrenic nerve in the chest, which sends signals to the diaphragm to restore a normal breathing pattern. The device activates automatically when the patient is in a sleeping position and suspends therapy when the patient sits up.

Comparators

Current first-line therapy is positive airway pressure. There are several devices providing positive airway pressure.

Device	Description	Comments
CPAP	Continuous positive airway pressure	Considered first line therapy for patients with hyperventilation-related CSA
BPAP	Bilevel positive airway pressure (2 pressure settings - 1 for inhalation and 1 for exhalation)	Considered first line therapy for patients with hypoventilation-related CSA
ASV	Adaptive servo-ventilation (titrates the inspiratory and expiratory pressure)	Not recommended for patients with CSA with HF and a left ventricular ejection fraction <45%

CSA: central sleep apnea; HF: heart failure.

For patients who do not benefit from positive airway pressure devices, pharmacologic therapy with a respiratory stimulant may be recommended. Close monitoring is necessary due to the potential of adverse effects such as rapid heart rate, high blood pressure, and panic attacks.

Outcomes

Outcomes of interest include sleep quality metrics and quality of life measures. The Apnea-Hypopnea Index (AHI) is the number of apnea and hypopnea (events per hour of sleep, in which the apnea events last at least 10 seconds and are associated with decreased blood oxygenation. In adults, the AHI scale is: < 5 AHI (normal); 5 > AHI < 15 (mild); 15 ≥ AHI < 30 (moderate); and ≥ 30 AHI (severe) per hour of sleep. Additional sleep metrics include the central apnea index (CAI, number of central apnea events per hour of sleep) and obstructive apnea index (OAI, number of obstructive apnea events per hour of sleep).

Subjective sleepiness can be measured by the Epworth Sleepiness Scale (ESS). The ESS is a short, self-administered questionnaire that asks patients how likely they are to fall asleep (0 = "no chance" to 3 = "high chance") in 8 different situations (e.g., watching TV, sitting quietly in a car, or sitting and talking to someone). The scores are added, ranging from 0 to 24, with scores over 10 indicating excessive sleepiness and recommendation to seek medical attention. Quality of life can be measured by Patient Global Assessment, which consists of a 7-point scale (1 = "markedly improved" to 7 = "markedly worsened").

The FDA approval of the remede System is based on an industry-supported, multicenter, prospective, randomized controlled sham study that aimed to determine the safety and effectiveness for treatment central sleep apnea (CSA) (Costanza et. al., 2016). A total of 151 adult subjects were randomized to receive either medical management and the remede System (n=73), or medical management and inactive sham remede System (n=78). The subjects in the study were an average of 65 years old and predominately Caucasian (95%) and males (89%). The primary endpoint was a 50% or greater reduction in AHI from baseline at 6 months, and the AHI was determined using polysomnography. Subjects were evaluated regularly until the end of the trial. After 6 months, the remede System was activated in the sham group. Effectiveness was based on modified intention to treat (ITT) data at 6 months (n=141). A significant higher number of subjects in the active remede System group had a 50% or better reduction in AHI from baseline to 6 months post-procedure (p<0.0001). The success rate for the active remede System group was 51% compared to 11% in the sham group for a total difference of 41% (95% CI, 25% to 51%; p<0.0001). A total of 76% of subjects in the remede System group reported improvement in quality of life. Safety results were based on intention to treat (ITT) data for 12 months (n=151). There were 7 deaths, but none found to be related to the device or treatment. The number of subjects free from serious adverse events (AEs) was 91% (95% CI, 86% to 95%); however, 13 subjects had serious AEs including impending pocket erosion, implant site infection, lead dislodgement, concomitant device interaction, elevated transaminase, extra-respiratory stimulation, implant site hematoma, lead component failure, lead displacement, and non-cardiac chest pain. The number of subjects who experienced non-serious AEs were 48%. Implants were unsuccessful in 5 subjects, and the rate of explants was 5.3% (8/151). The authors concluded that transvenous neurostimulation could provide a treatment option for central sleep apnea. Limitations of the study included low percentage of female subjects and potential referral bias.

In 2015, Abraham et al. evaluated transvenous unilateral phrenic nerve stimulation to treat central sleep apnea (CSA) in a prospective, multicenter, nonrandomized study. 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. 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. The authors concluded, transvenous unilateral phrenic nerve stimulation appears safe and effective for treating CSA, and these findings should be confirmed in a prospective randomized, controlled trial (NCT01124370).

In 2016, Jagielski et al. evaluated the 12- month clinical outcomes of patients with central sleep apnea (CSA) treated with unilateral transvenous phrenic nerve stimulation in the prospective, multi-center, non-randomized remede System pilot study. Forty-seven patients with CSA were treated with the remede System for a minimum of 3 months. Sleep disordered breathing parameters were evaluated by polysomnography (PSG) as 3, 6 and 12- month follow-up. Sleep symptoms and quality of life were also evaluated, Forty-one patients completed all follow-up PSGs and were included in the analysis. At 12 months, there was sustained improvement compared with baseline in the apnea-hypopnea index, central apnea index and there was sustained improvement in the oxygen desaturation index, rapid eye movement sleep and sleep efficiency. There were continued favorable effects on sleepiness and quality of life. Three deaths unrelated to remede System therapy and five serious adverse events occurred over 12 months of follow-up. The authors noted the main limitations of the study were the non-randomized, open-label nature of the trial, the small sample size, the small number of women enrolled in the study, and the fact that many of the parameters studied were only exploratory and hypothesis-generating and the results should be confirmed with future larger, randomized, controlled studies.

In 2018, Costanza et al. reported the 12- month results from remede System pivotal trial (see above) to evaluate the benefits of this therapy for central sleep apnea (CSA). Reproducibility of treatment effect was assessed in the former control group in whom the implanted device was initially inactive for the sixth month and subsequently activated when the randomized control assessments were complete. Patients with moderate-to-severe central sleep apnea implanted with the remede System were randomized to therapy activation at 1 month (treatment) or after 6 months (control). Sleep indices were assessed from baseline to 12 months in the treatment group and from 6 to 12 months in former controls. In the treatment group, a $\geq 50\%$ reduction in apnea-hypopnea index occurred in 60% of patients at 6 months (95% confidence interval [CI] 47% to 64%) and 67% (95% CI 53% to 78%) at 12 months. After 6 months of therapy, 55% of former controls (95% CI 43% to 67%) achieved $\geq 50\%$ reduction in apnea-hypopnea index. Patient Global Assessment was markedly or moderately improved at 6 and 12 months in 60% of treatment patients. Improvements persisted at 12 months. A serious adverse event within 12 months occurred in 13 patients (9%). Phrenic nerve stimulation produced sustained

improvements in sleep indices and quality of life to at least 12 months in patients with central sleep apnea. The similar improvement of former controls after 6 months of active therapy confirms benefits are reproducible and reliable.

In 2021, Costanza et al. reported on the Post Approval Study (PAS) that collected clinical evidence regarding long-term safety and effectiveness in adults with moderate to severe CSA through five years post implant regarding the remede System Pivotal Trial, which was a prospective, multi-center, randomized trial evaluating the safety and effectiveness of transvenous phrenic nerve stimulation (TPNS) therapy for the treatment of central sleep apnea (CSA). Patients remaining in the Pivotal Trial at the time of FDA approval were invited to enroll in the PAS and consented to undergo sleep studies (scored by a central laboratory), complete the Epworth Sleepiness Scale (ESS) questionnaire to assess daytime sleepiness, and safety assessment. All subjects (treatment and former control group) receiving active therapy were pooled; data from both trials were combined for analysis. Fifty-three of the original 151 Pivotal Trial patients consented to participate in the PAS and 52 completed the 5-year visit. Following TPNS therapy, the apnea-hypopnea index (AHI), central-apnea index (CAI), arousal index, oxygen desaturation index, and sleep architecture showed sustained improvements. Comparing 5 years to baseline, AHI and CAI decreased significantly (AHI baseline median 46 events/hour vs 17 at 5 years; CAI baseline median 23 events/hour vs 1 at 5 years), though residual hypopneas were present. In parallel, the arousal index, oxygen desaturation index and sleep architecture improved. The ESS improved by a statistically significant median reduction of 3 points at 5 years. Serious adverse events related to implant procedure, device or delivered therapy were reported by 14% of patients which include 16 (9%) patients who underwent a pulse generator reposition or lead revision (primarily in the first year). None of the events caused long-term harm. No unanticipated adverse device effects or related deaths occurred through 5 years. Currently, a large, prospective single-arm post-market study (The remede System Therapy [rēST] Study) of TPNS is collecting real-world experience in adult patients with moderate to severe CSA (NCT03884660).

This long-term, single-arm follow-up study has limitations that include the following. First, it is an observational study that followed the randomized, controlled Pivotal Trial and all patients received active therapy, so the study lacked a control group or external control similar enough to meaningfully assess impact of long-term outcomes such as survival. However, change from baseline assessments were able to be analyzed for some endpoints. Another limitation is the lack of availability of data for some eligible participants who completed the Pivotal Trial. This was due to the interval between closure of the Pivotal Trial and initiation of the 5-year PAS as a separate study. In addition, not all Pivotal Trial sites and patients chose to participate in the PAS, a fact which may have led to underestimation of adverse events. However, the decision to participate in the PAS study was independent of and unrelated to issues with stimulation discomfort, or therapy effectiveness. The authors conclude the results of this prospective long-term 5-year study suggest TPNS is a safe and effective therapy, resulting in clinically meaningful improvements in sleep and excessive daytime sleepiness for patients with CSA. The consistent safety and effectiveness of the remede System through

5 years provides further evidence that TPNS is a viable therapy for adult patients with moderate to severe CSA and particularly those lacking alternative treatment options or unable to tolerate mask-based therapies.

In 2021, Schwartz et al. analyzed transvenous phrenic nerve stimulation (TPNS) responses among PAP-naive and prior PAP-treated patients from the remede System Pivotal Trial. Of 151, 56 (37%) used PAP therapy before enrolling in the trial. Patients were implanted with a TPNS device and randomized to either active or deferred (control) therapy for 6-months before therapy activation. Apnea-hypopnea index (AHI) and patient-reported outcomes (PRO) were assessed at baseline, and 6 and 12- months following active therapy. Patients had moderate-severe CSA at baseline, which was of greater severity and more symptomatic in the PAP-treated versus PAP-naive group (median AHI 52/h versus 38, central apnea index (CAI) 32/h versus 18, Epworth Sleepiness Scale 13 versus 10, fatigue severity scale 5.2 versus 4.5). Twelve months of TPNS decreased AHI to <20/h and CAI to \leq 2/h. Both groups showed reductions in daytime sleepiness and fatigue, improved well-being by patient global assessment, and high therapeutic acceptance with 98% and 94% of PAP-treated and PAP-naive patients indicating they would undergo the implant again. Stimulation produced discomfort in approximately one-third of patients, yet <5% of prior PAP-treated participants discontinued therapy. Several limitations should be considered when interpreting the current findings. First, they reflect a post hoc, exploratory subgroup analysis that might not predict therapeutic responses prospectively. Nonetheless, the subgroups' responses are consistent with the responses observed in the parent pivotal trial and suggest that TPNS can provide effective initial and salvage therapy for patients with moderate to severe CSA. Second, while head-to-head trials of PAP-based versus TPNS therapy would allow direct comparisons of therapeutic modalities, these trials would of necessity be unblinded and would exclude patients with reduced left ventricular ejection fraction. Other than ASV, PAP modalities are not specifically indicated to treat CSA, and trials of these therapies were generally compared to an untreated rather than an active comparator group. Third, we acknowledge that no data were collected to determine the reason(s) that patients stopped PAP therapy, since these were not the primary focus of the parent clinical trial from which the current sub-analysis was derived. Specifically, the parent protocol did not collect information on PAP treatment withdrawal date or treatment response. Lacking this information, we could not determine whether our subgroups differed in sleep apnea characteristics while on PAP therapy, or whether PAP was ineffective rather than simply poorly tolerated. Despite protocol-related constraints in collecting pre-baseline treatment records, we still found that clinically meaningful responses to TPNS occurred in both groups, suggesting TPNS to be effective, tolerable, and safe. Fourth, we recognize that we were not adequately powered to compare treatment responses across all polysomnographic and clinical symptom domains between groups, but instead note that clinically meaningful improvements of similar magnitude were consistently achieved in both the PAP-naive and PAP-treated groups across both the 6 and 12- month time points after TPNS therapy activation. Further research is needed to examine effects of demographic/anthropometric parameters, co-morbidities, baseline sleep apnea characteristics, PAP treatment responses, and the time since withdrawal of

PAP therapy on TPNS responses between the groups. Such work would ultimately allow us to optimize patient selection criteria, characterize titration responses, and address questions about comparative effectiveness and tolerability.

In June 2021, ECRI updated their product brief regarding the remede System for treating moderate to severe central sleep apnea (CSA). The focus of their report was regarding the remede System 's safety and effectiveness for treating moderate to severe CSA and how it compares with other CSA treatments. While this review showed the evidence to be somewhat favorable, they noted the following evidence limitations:

- Studies in the systematic review (SR) are at high risk of bias due to one or more of the following: small sample size, single-center focus, subjective outcomes in unblinded patients, and lack of randomization. The SR included two publications that used a prototype (i.e., Eupnea System) to deliver TPNS, and results may not fully generalize to patients treated with the commercially available remede System.
- The randomized controlled trial (RCT) is at risk of bias from reporting of subjective measures in nonblinded patients to assess quality of life (QOL) and daytime sleepiness. The pre-/post-treatment study is at risk of bias from small size, use of subjective outcome measures, and lack of controls and randomization. Furthermore, the RCT allowed patients in the control arm to cross over to active stimulation six months after enrollment; therefore, the study was no longer an RCT after six-month follow-up, which increases the potential bias for findings reported after six months. Controlled trials that compare remede with alternative treatment options for patients with moderate to severe CSA and report on long-term (>5 year) outcomes are needed to assess remede's comparative safety and effectiveness.

ECRI concluded the following: Available evidence suggests transvenous phrenic nerve stimulation (TPNS) with remede improves sleep quality and quality of life (QOL) in patients with moderate to severe CSA for up to five years. No published studies are available to determine how well remede works compared with other CSA treatment. Controlled trials that compare remede with alternative treatment options for patients with moderate to severe CSA and report on long-term (> 5 year) outcomes are needed to assess remede's comparative safety and effectiveness. Two ongoing trials will not provide comparative data.

In a patient education and information series by the American Thoracic Society (ATS) regarding central sleep apnea in adults which states the following regarding phrenic nerve stimulation: "This may be an option for select people who have CSA and are unable to tolerate PAP therapy or have persistent CSA despite using PAP therapy. It is a surgically implanted device that stimulates the phrenic nerve and results in contraction of the diaphragm. This is performed in specialized centers. Currently, long term success and outcomes with this treatment is being studied."

The Heart Failure Association of the European Society of Cardiology (ESC) Seferovic et al. 2019 published a clinical practice update on heart failure that included pharmacotherapy, procedures, devices, and patient management. The HFA of the ESC recognized the need to review and summarize recent developments in a consensus document. This expert consensus report is neither a guideline update nor a position statement, but rather a summary and consensus view in the form of consensus recommendations.

The consensus recommendation for the treatment of central sleep apnea (CSA) states:

- In patients with predominantly CSA and concomitant heart failure with reduced ejection fraction (HFrEF), evidence is insufficient to recommend CSA therapy for any putative benefit in the heart failure itself, and treatments directed at the CSA should be reviewed and avoided, unless compelling symptomatic indications for treatment of the CSA exist, in which case positive pressure airway mask therapy should be avoided and phrenic nerve stimulation (PNS) may be considered as an alternative.

The supporting evidence states that HFrEF patients with predominantly CSA suffered an increase in mortality in SERVE-HF, so that it is essential to know if such patients have CSA prior to starting positive airway pressure therapy. One small trial (Pivotal trial) showed promise for PNS for the treatment of severe central sleep apnea. However, the randomized trial included only 151 patients (73 assigned to PNS) of whom only 96 had HF (48 assigned to PNS – and perhaps only half of these had HFrEF) and follow-up was for only six months. PNS improved AHI and symptoms, although blinding may have been imperfect; two deaths occurred in each group.

The practical comments state that PNS received FDA approval in 2018 and is also reimbursed in a number of European countries. Further clinical trials are required before making positive recommendations.

Summary of Evidence

remede System

Based on review of the peer reviewed medical literature on phrenic nerve stimulation (PNS) (remede System) for central sleep apnea (CSA), while the evidence may show promise related to the following: the PNS with the remede System results in a statistically significant reduction in CSA-related events as measured by the apnea-hypopnea index; however, the clinical significance of this reduction remains uncertain. PNS is associated with improved patient quality of life and daytime sleepiness. PNS in the treatment of adults with CSA has a moderate safety profile, with nonserious abdominal discomfort near the diaphragm being the most commonly associated treatment-related adverse events. However, the clinical significance and longer-term efficacy and safety of CSA need further evaluation. Further, studies that compare the efficacy, safety and patient acceptance of PNS with other noninvasive, available therapies for CSA (e.g., PAP therapies) are needed. In addition, studies with longitudinal data are needed to assess the

effect of PNS on CSA-related morbidity and mortality. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Diaphragmatic/ phrenic nerve stimulation in Pediatric Population

Diaphragmatic/ phrenic nerve stimulation has been proposed in the pediatric population (i.e., individuals < 18 years of age) for a variety of conditions including tetraplegia, congenital central alveolar hypoventilation syndrome (CCAHS), cervical spinal cord injury, acute flaccid myelitis, and central neurological cause. The available studies in the peer-reviewed published scientific literature are primarily in the form of case series, case reports, and retrospective studies. The studies are limited by the small patient populations, and lack of a control or comparator group. The clinical effectiveness and long-term safety of diaphragmatic pacing in the pediatric population needs to be further assessed. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Other Indications

Diaphragmatic/phrenic nerve stimulation has been proposed for respiratory support in other diagnostic conditions to delay the need for mechanical ventilation. Further large, randomized, comparative, controlled studies are needed to determine the safety and efficacy, and the further studies also need to help define optimal patient selection and assess long term outcomes, because the evidence is insufficient to determine the effects of the technology on net health outcomes.

The evidence in the published peer-reviewed scientific literature does not support the Mark IV stimulation systems for any other indications because the evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

American Academy of Sleep Medicine (AASM)

In 2016, the American Academy of Sleep Medicine (AASM) issued an updated guideline on the treatment of central sleep apnea syndromes in adults with an evidence-based literature review and meta-analysis. This guideline does not include diaphragmatic/phrenic nerve stimulation or diaphragm pacing as a recommended treatment for this condition.

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA)

In 2017, ACC/AHA/HFSA issued a focused update of the 2015 ACCP/AHA guideline for the management of heart failure which includes the following recommendations regarding sleep disordered breathing:

- In patients with NYHA class II-IV heart failure and suspicious of sleep disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable.

- In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness.
- In patients with NYHA class II-IV heart failure with reduced ejection fraction (HFrEF) and central sleep apnea, adoptive servo-ventilation causes harm.

This guideline does not include diaphragmatic/phrenic nerve stimulation or diaphragm pacing as a recommended treatment for heart failure management.

Regulatory Status

The Avery Breathing Pacemaker System (that is, the Mark IV™ Avery Biomedical Device, Inc., Commack, NY) is the only other diaphragmatic/phrenic stimulator system cleared for use by the FDA in the United States for ventilator-dependent individuals. The pacemaker is classified as a Class III neurologic therapeutic device requiring premarket approval (PMA). The device is approved “for persons who require chronic ventilatory support because of upper motor neuron respiratory muscle paralysis (RMP) or because of central alveolar hypoventilation (CAH) and whose remaining phrenic nerve, lung, and diaphragm function is sufficient to accommodate electrical stimulation” (FDA, 2003). Clinical trials that have studied the efficacy of this device have been very limited and included small numbers of subjects.

The remede System was approved by the FDA on October 6, 2017, for the treatment of moderate to severe central sleep apnea in adult individuals. The manufacturer describes the device as:

- An implantable pacemaker-like device that was designed for improving central sleep apnea (CSA) using Respidrive™, a Respiratory Rhythm Management™ algorithm. The remede System delivers electrical pulses via a proprietary, novel transvenous implantable lead to one of the body’s two phrenic nerves. The remede System therapy is intended to stimulate the diaphragm to restore a more natural, less disrupted, breathing pattern.

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policy

- [10.01.14 Humanitarian Use Devices](#)

Medically Necessary: Mark IV System

Diaphragmatic/phrenic nerve stimulation with the Mark IV system as an alternative to mechanical ventilation is considered **medically necessary** when **ALL** of the following criteria is met:

- The individual has chronic central alveolar hypoventilation syndrome/congenital central hypoventilation syndrome; **OR** High quadriplegia at or above C-3; **AND**
- 18 years and older; **AND**
- Diaphragm movement with stimulation visible under fluoroscopy or ultrasound; **AND**
- Have intact phrenic nerve function; **AND**
- Individual has normal chest anatomy, a normal level of consciousness, and has the ability to participate in and complete the training and rehabilitation associated with the use of this device; **AND**
- Diaphragmatic/phrenic nerve stimulation will allow the individual to breath without the assistance of a mechanical ventilator for at least 4 continuous hours a day.

Replacement and Revisions

Replacement or revisions of diaphragm/phrenic nerve stimulation and diaphragm pacing systems (generator and/or leads) is considered **medically necessary** if the individual meets the above criteria and is no longer under warranty or cannot be repaired.

Investigational

Diaphragm/phrenic nerve stimulation and diaphragm pacing systems are considered **investigational** for all other indications including but not limited to the following because the evidence is insufficient to determine the effects of the technology on net health outcomes:

- When the above criteria is not met
- In individuals whose phrenic nerve or diaphragm function is not sufficient to achieve adequate diaphragm movement from the electrical stimulation
- For treatment of any other condition where the phrenic nerve and diaphragm are intact including:
 - Obstructive lung disease
 - Restrictive lung disease
 - Singultus (hiccups)
 - Central sleep apnea (remede System)
 - Management of heart failure and treatment of sleep related disorders including but not limited to central sleep apnea
- Underlying cardiac, pulmonary or chest wall disease is present which is significant enough to prevent spontaneous breathing off a ventilator for more than 4 hours even with the use of phrenic nerve or diaphragm pacemaker device.

Policy Guidelines

- **Diaphragm Fluoroscopy (Sniff Test):** a diaphragm fluoroscopy (sniff test) checks how the diaphragm (the muscle that controls breathing) moves when an individual breathes normally and when they inhale quickly. The diaphragm normally moves down when a person inhales, and up when a person exhales. Both the right and left sides of the diaphragm should move in the same direction at the

same time. This test shows if there are problems with the phrenic nerve, which controls movement of the diaphragm.

- Normal Diaphragmatic Motion:
 - The diaphragm contracts during inspiration: moves downward
 - The diaphragm relaxes during expiration: moves upwards
 - Both hemi-diaphragms move together
- Abnormal Diaphragmatic Motion
 - The affected hemi-diaphragm does not move downwards during inspiration
 - Paradoxical motion can occur (diaphragm moves opposite to the normal direction of its movements)
 - Weak response to phrenic nerve stimulation or there is unilateral movements
- Stimulation of the phrenic nerve may be performed by percutaneously stimulating the phrenic nerve in the neck and assessing diaphragmatic movements.
- A provider may utilize electromyography (EMG) or nerve conduction studies to assess phrenic nerve function.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 0424T Insertion or replacement of neurostimulator system for treatment of central sleep apnea; complete system (transvenous placement of right or left stimulation lead, sensing lead, implantable pulse generator)
- 0425T Insertion or replacement of sensing lead only for treatment of central sleep apnea
- 0426T Insertion or replacement of stimulation lead only for treatment of central sleep apnea
- 0427T Insertion or replacement of pulse generator only for treatment of central sleep apnea
- 0428T Removal of neurostimulator system for treatment for central sleep apnea; pulse generator only
- 0429T Removal of sensing lead only for treatment of central sleep apnea
- 0430T Removal of stimulation lead only for treatment of central sleep apnea
- 0431T Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only
- 0432T Repositioning of neurostimulator system for treatment of central sleep apnea; stimulation lead only

- 0433T Repositioning of sensing lead only for treatment of central sleep apnea
- 0434T Interrogation device evaluation implanted neurostimulator pulse generator system for central sleep apnea
- 0435T Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session
- 0436T Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; during sleep study
- 64575 Open implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
- 64580 Open implantation of neurostimulator electrode array; neuromuscular
- 64585 of peripheral neurostimulator electrode array
- 64590 Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling
- 64595 Revision or removal of peripheral or gastric neurostimulator pulse generator or receiver
- 95970 Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g. contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycle, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve neurostimulator pulse generator/transmitter without programming
- 95971 Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g. contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple spinal cord or peripheral nerve (e.g. sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
- 95972 Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g. contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with complex spinal cord or peripheral nerve (e.g. sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
- C1767 Generator neurostimulator (implantable) non-rechargeable
- C1778 Lead, neurostimulator (implantable)
- C1787 Patient programmer, neurostimulator
- C1816 Receiver and/or transmitter, neurostimulator (implantable)
- C1820 Generator, neurostimulator (implantable), non-high-frequency with rechargeable battery and charging system

- C1822 Generator, neurostimulator (implantable), high frequency, with rechargeable battery and charging system
- C1823 Generator, neurostimulator (implantable), non-rechargeable, with transvenous sensing and stimulation
- C1897 Lead, neurostimulator test kit (implantable)
- L8679 Implantable neurostimulator, pulse generator any type
- L8680 Implantable neurostimulator electrode, each
- L8681 Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
- L8682 Implantable neurostimulator radiofrequency receiver
- L8683 Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
- L8685 Implantable neurostimulator pulse generator, single array, rechargeable includes extension
- L8686 Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
- L8687 Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
- L8688 Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension
- L8689 External recharging system for battery (internal) for use with implantable neurostimulator, replacement only

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POLICY HISTORY

Date	Reason	Action
October 2022	Annual Review	Policy Revised
October 2021	Annual Review	Policy Renewed
October 2020	Annual Review	Policy Renewed
October 2019	Annual Review	Policy Renewed
October 2018		New Policy Created

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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 Medical Policy Analyst
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