Phrenic (diaphragmatic) nerve stimulation

Clinical Policy ID: CCP.1041

Recent review date: 6/2024

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Policy contains: Central sleep apnea; diaphragm pacing; hypoventilation; phrenic nerve stimulation.

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Coverage policy

Phrenic nerve (diaphragmatic) stimulation is clinically proven and, therefore, may be medically necessary for the treatment of chronic hypoventilation, when implanted and managed by providers with expertise in phrenic nerve/diaphragm pacing and all of the following criteria are met (Perez, 2016; Trang, 2020; U.S. Food and Drug Administration, 2001, 2008):

- Either:
  - The Avery Breathing Pacemaker® (Avery Biomedical Devices Inc., Commack, New York) for adult and pediatric members with high cervical spinal cord injury or congenital central hypoventilation syndrome.
  - The NeuRx RA/4 Diaphragm Pacing System® (Synapse Biomedical Inc., Oberlin, Ohio) for members age 18 or older with high cervical spinal cord injury.
- The member meets all of the following criteria:
  - Cannot breathe spontaneously for more than four continuous hours without mechanical ventilation.
  - The phrenic nerves and diaphragm have sufficient function to accommodate electrical stimulation.
  - The member has relatively mild or no lung disease.

Diaphragm pacers may be used with bipolar cardiac pacemakers (Perez, 2016).

Limitations

All other uses of phrenic (diaphragmatic) nerve stimulation, including treatment of central sleep apnea or amyotrophic lateral sclerosis, are investigational/not clinically proven and, therefore, not medically necessary (Luni, 2020; Orr, 2021; Voigt, 2020; Woo, 2020).

Relative contraindications include (Perez, 2016; Trang, 2020):

- Presence of active infection.
- Chronic lung disease.
- Obstructive sleep apnea.
- Need for magnetic resonance imaging.
- Ability to breathe spontaneously for four continuous hours or more without a mechanical ventilator.
- Temporary respiratory insufficiency.
- Severe behavioral disorders.
- Obesity with excess fat tissue that can impair electrical signal transfer.

Alternative covered services

- Guideline-directed medical therapy.
- Positive airway pressure (e.g., mechanical ventilation and noninvasive respiratory assist devices).
- Oxygen therapy.

Background

Hypoventilation (a.k.a. respiratory depression or hypoventilation syndrome) is the inadequate exchange of carbon dioxide and oxygen within the lungs, creating abnormal retention of carbon dioxide in the blood. It is usually secondary to other medical problems and, if left untreated, can cause significant morbidity and become life threatening. A variety of conditions can cause hypoventilation, including conditions causing diaphragmatic dysfunction (Perez, 2016; Vashisht, 2022).

Both invasive and noninvasive mechanical ventilation can assist patients with diaphragmatic dysfunction to maintain adequate ventilation. Invasive ventilation requires a tracheostomy, and both ventilator types can restrict activity participation and speech. Diaphragmatic stimulation, also known as pacing, is an alternative to mechanical ventilation for improving hypoventilation and potentially quality of life (Perez, 2016).

Diaphragmatic pacing stimulates the diaphragm to contract and relax enabling the patient to breathe without mechanical ventilation. There are two types of diaphragmatic pacers (Vashisht, 2022):

- Diaphragmatic/phrenic nerve pacing systems involve electrodes surgically attached to the phrenic nerves at the cervical, thoracic, or diaphragmatic level. Pacing wires connect the electrodes to a receiver placed under the skin. An external transmitter, serving as the main control unit, is placed above the receiver on the surface of the skin and emits radiofrequency signals.
- Diaphragmatic pacing systems provide direct stimulation to the diaphragm through four electrodes laparoscopically implanted in the diaphragm (intramuscularly) and a fifth grounding electrode implanted under the skin. An electrode connector groups the five electrodes that exit the skin into a socket called an external pulse generator.

Respiratory rates are set in the transmitter. Surgical implantation is done under general anesthesia usually in an outpatient setting, and the equipment is tested during surgery. Approximately six to eight weeks after the procedure, when surgical incisions heal, diaphragm pacing starts. Initial pacing lasts 60 to 90 minutes per night, as diaphragms tire. By three months after surgery, as the diaphragm strengthens, patients achieve the maximum

of about eight to 12 hours each day. As 24-hour pacing is not recommended due to diaphragm fatigue, some may require another method of support such as home mechanical ventilation by tracheostomy or noninvasive positive pressure ventilation (Perez, 2016).

The Avery Breathing Pacemaker received initial U.S. Food and Drug Administration premarket approval as the Mark IV transmitter in March 1998, later renamed the Spirit transmitter, for phrenic nerve stimulation after approval and use in European nations (Avery Biomedical Devices, Inc., 2023). Transmitters are surgically attached to the phrenic nerve using a cervical or thoracic approach. It is indicated for patients (no age restriction) who require chronic ventilatory support because of upper motor neuron respiratory muscle paralysis or central alveolar hypoventilation, and whose remaining phrenic nerve, lung, and diaphragm function is sufficient to accommodate electrical stimulation (U.S. Food and Drug Administration, 2001).

The NeuRx DPS RA/4 Diaphragm Pacing System received a Humanitarian Device Exemption in June 2008 for patients age 18 years or older who have stable, high spinal cord injuries and diaphragms that can be stimulated, but who lack control of them (U.S. Food and Drug Administration, 2008). In 2011, they expanded the exemption to patients age 21 years or older with amyotrophic lateral sclerosis with stimulable hemidiaphragms who experience chronic hypoventilation that has not progressed to a forced vital capacity less than 45% of predicted (U.S. Food and Drug Administration, 2011a). The NeuRx system is implanted intramuscularly via a laparoscopic procedure.

In October 2017, the U.S. Food and Drug Administration issued premarket approval to the remedē® System (Respicardia, Minnetonka, Minnesota) for treatment of moderate-to-severe central sleep apnea in nonpregnant, adult patients. Remedē consists of an implantable pulse generator and transvenous leads that monitor the patient's respiratory signals and provide unilateral electrical stimulation to the left or right phrenic nerve (U.S. Food and Drug Administration, 2017). In 2023, the remedē® System received approval for use with 1.5T and 3T magnetic resonance imaging (U.S. Food and Drug Administration, 2023).

Findings

Phrenic nerve/diaphragmatic stimulation is a fairly uncommon procedure requiring multidisciplinary support. Several pacing systems are commercially available with varying regulatory requirements for clinical use. However, the evidence of safety and efficacy supporting the approved indications also varies in quality and consistency.

There is sufficient evidence to support the safety and efficacy of phrenic nerve/diaphragmatic stimulation for select patients with ventilatory failure due to high cervical spinal cord injury or congenital central hypoventilation syndrome. The optimal candidate requires at least 12 hours of mechanical ventilatory support daily and can gain freedom from the ventilator during the day; they have a condition for which the device has been approved, no or minimal lung disease, and sufficient phrenic nerve and diaphragm function to accommodate electrical stimulation. The implantation procedure and management of the pacing system should be carried out by specialists with expertise in the intervention. The supportive evidence is described below.

Guidelines

The American Thoracic Society recommends phrenic nerve/diaphragmatic stimulation for patients with congenital central hypoventilation syndrome or high cervical spine injury to optimize ventilation and oxygenation with the minimal amount of electrical stimulation. Low-quality evidence suggests phrenic nerve/diaphragmatic stimulation is feasible and safe in carefully selected children and adults, and may be used in patients with bipolar cardiac pacemakers. Obese persons with excess fat tissue that can impair signals between the antenna and receiver are typically not good candidates for the procedure. Main benefits are reduced need for mechanical ventilation and potential removal of the tracheostomy, which may improve speech, activity participation, and

overall quality of life. The main complications are related to the surgical procedure, device failure, and, for patients with a tracheostomy, obstructive apnea from desynchronization of upper airway skeletal muscle contraction, which is usually resolved by adjusting the settings (Perez, 2016).

According to an American Thoracic Society statement on future research priorities, evidence from one randomized controlled trial of the remedē system supported significant beneficial effects including reduction in the apnea-hypopnea index and near elimination of central apneas in patients with heart failure, but its effects on long-term heart failure and mortality outcomes were unclear. Upper airway collapse likely contributed to suboptimal response rates, and the apnea-hypopnea index thresholds for determining treatment success and predictors of response were not well established (Orr, 2021).

The National Institute for Health and Care Excellence guidelines on intramuscular diaphragmatic stimulation for ventilator-dependent chronic respiratory failure from spinal cord injuries or motor neuron disease notes that evidence on efficacy is limited, and that safety is a concern. Thus, the Institute recommends using the procedure only in research (National Institute for Health and Care Excellence, 2017, 2023).

An American Academy of Sleep Medicine guideline, based on a literature review and meta-analysis of adaptive servo-ventilation for adult central sleep apnea, did not mention phrenic nerve/diaphragmatic stimulation (Aurora, 2016). A guideline update is in progress (American Academy of Sleep Medicine, 2024).

The European Congenital Central Hypoventilation Syndrome Consortium Project Guideline Development Group considers phrenic nerve stimulation a mode of daytime ventilatory support in patients with congenital central hypoventilation syndrome needing more than 16 hours per day of ventilation and older than one year of age. In patients younger than six years of age, pacing with a tracheostomy provides greater stability of tidal volume, oxygen saturation, and blood partial pressure of carbon dioxide than pacing without tracheostomy (Trang, 2020).

Research findings

A systematic review of 10 studies (n = 281) assessed phrenic nerve/diaphragmatic stimulation; of the 10 articles, seven were case studies. Safety outcomes were rarely the primary outcome measure and were inconsistently reported across studies. Two were randomized trials of amyotrophic lateral sclerosis (n = 148); one found no difference in complication rates between cases and controls, while the other found a 78% versus 3% gap. In one study of cervical spine injury (n = 55), cases and controls had similar survival rates. Authors did not support phrenic nerve/diaphragmatic stimulation for these two disorders based on observed efficacy and safety results (Woo, 2020).

A systematic review of phrenic nerve/diaphragmatic stimulation for high spinal cord injuries and central hypoventilation syndromes yielded 420 studies from the literature dating back to the 1980s. The procedure was a safe and effective option for decreasing ventilator dependence in high spinal cord injuries and central hypoventilation. However, there were no Class I, II, or III studies, and just 18 relevant Class IV (lowest quality) articles. Authors assessed the quality of the studies as “very poor” and could not complete a meta-analysis of efficacy or safety (Sieg, 2016).

A systematic review of 12 studies revealed that intramuscular diaphragmatic stimulation using an abdominal laparoscopic approach for patients with traumatic high cervical injuries appears as effective and as safe as traditional phrenic nerve stimulation, based on indirect comparison. The percent of patients independent of ventilator support post-procedure ranged from 40% to 72%, and most could use the diaphragm stimulator instead of the ventilator for several hours per day. In one case series (n = 88), capnothorax was observed in 42% of patients, which was managed successfully with simple aspiration, drainage, or observation (Garara, 2016).

A study of 101 cervical spinal cord injury patients, 40 of whom received diaphragm pacing and 61 who did not, showed that those with the procedure had significantly lower length of hospital stay and mortality (Kerwin, 2018).

In a study of 151 persons with central sleep apnea given transvenous phrenic nerve stimulation using the remedē system, 97% were successfully implanted with the system; 62% of stimulation leads were placed in the left pericardiophrenic vein and 35% in the right brachiocephalic vein. Procedures took an average of 2.7 hours, and 94% were free from implant-related serious adverse events through six months (Augostini, 2019).

In the same study population, the percentage of subjects with at least a 50% improvement in apnea-hypopnea index was greater in the treatment group (51%) than in the control group (11%), significant at $P < .0001$. Assessing the 96 (of 151) patients in the study with heart failure, the average Minnesota Living with Heart Failure Questionnaire score improved significantly after 12 months ($P = .005$). After six months, heart failure hospitalization was lower in treated patients compared to controls (4.7% versus 17%, $P = .065$) (Costanzo, 2018).

In 2022, we updated the reference list and added new information addressing the effectiveness of phrenic nerve/diaphragmatic stimulation for central sleep apnea, amyotrophic lateral sclerosis, and congenital central hypoventilation syndrome. We added professional guidance from the European Congenital Central Hypoventilation Syndrome Consortium Project Guideline Development Group(Trang, 2020) and an American Thoracic Society statement on future research priorities (Orr, 2021). The results of two meta-analyses confirmed these findings (Luni, 2020; Voigt, 2020).

For patients with amyotrophic lateral sclerosis, an American Academy of Neurology practice guideline does not mention phrenic nerve/diaphragmatic stimulation as a treatment modality (Miller, 2009, reaffirmed 2023). The contradictory evidence of the safety and clinical benefit of phrenic nerve/diaphragmatic stimulation for this indication does not support routine use outside of clinical trials (U.S. Food and Drug Administration, 2011b; Woo, 2020).

Based on this new information, we modified the coverage section to consider phrenic nerve/diaphragmatic stimulation clinically proven and medically necessary for the following indications when carried out by providers with expertise in phrenic nerve/diaphragmatic stimulation consistent with device approval requirements (Perez, 2016; Trang, 2020):

- The Avery Breathing Pacemaker for use in adult and pediatric patients (no age limits) who have hypoventilation caused by high cervical spinal cord injury and congenital central hypoventilation syndrome.
- NeuRx RA/4 Diaphragm Pacing System for adult patients with high spinal cord injuries to allow freedom from mechanical ventilation for at least four hours daily.

There is insufficient evidence of safety and efficacy to support diaphragmatic pacing for other indications, including central sleep apnea and amyotrophic lateral sclerosis.

In 2023, we added two systematic reviews of transvenous phrenic nerve stimulation for central sleep apnea. No policy changes are warranted.

In participants with heart failure with reduced ejection fraction, compared to guideline-directed medical therapy, positive airway pressure modalities and transvenous phrenic nerve stimulation produced statistically significant reductions in the apnea-hypopnea index (eight randomized controlled trials, n = 648), with no inter-treatment differences found. Only transvenous phrenic nerve stimulation was associated with a statistically significant decrease in daytime sleepiness (Epworth sleepiness score, six randomized controlled trials, n = 374). Based on two ranking schemes (Hasse diagram and P-scores), adaptive servo-ventilation and transvenous phrenic nerve stimulation were the most effective treatments, although adaptive servo-ventilation is often contraindicated in this population. However, only one randomized control trial of transvenous phrenic nerve stimulation met criteria for inclusion. Comparisons of quality of life metrics, changes in left ventricular ejection fraction, and mortality across interventions are needed (Iftikhar, 2022).

Another systematic review included 13 articles (n = 232), of which 12 included overlapping populations from the remedē pilot and/or pivotal trial studies. The majority of participants were men with an average age ≥ 60 years and an average body mass index ≥ 29 kg/m^2. The most common complications were implant site infections, lead displacements, and discomfort. The results suggest remedē improves sleep and respiratory parameters with few complications in adults with moderate-to-severe central sleep apnea, including a minority with heart failure, with some improvement in quality of life. Additional research is needed to assess device effectiveness in patients with heart failure who may have orthopnea or daytime Cheyne-Stokes respirations, as the remedē system is only active at night when patients are supine (Sagalow, 2022).

In 2024, we added a new meta-analysis and results from the remedē System Pivotal Trial investigator group that addressed participants with central sleep apnea, with no policy changes warranted.

The pivotal trial results (n = 134) suggest transvenous phrenic nerve pacing may improve the nocturnal hypoxemic burden due to sleep-disordered breathing, normalize nocturnal heart rate perturbations, alter cortical activity underlying the disorder, and improve sleep quality, daytime sleepiness, and fatigue/weakness (Baumert, 2023a, 2023b; Hartman, 2024; Hill, 2023).

A meta-analysis of 10 randomized and observational studies, including Costanzo (2018), found significant reductions in the apnea-hypopnea index ($P < .00001$), central apnea index ($P < .00001$), and Arousal Index ($P = .0002$), but not in the percent of sleep with oxygen saturation < 90% or in the Epworth Sleepiness Scale. While phrenic nerve stimulation appears to be safe and feasible in this population, several of the included studies were conducted by the same investigator group, resulting in overlapping study populations. The authors called for larger, independent randomized controlled trials to evaluate the efficacy and long-term outcomes (Wang, 2023).

References

On April 16, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “phrenic nerve” (MeSH), “diaphragm” (MeSH), “electrical stimulation” (MeSH), “sleep apnea, central/therapy” (MeSH), and “phrenic nerve stimulation.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

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