



**SANDHILLS
CENTER**



Phrenic (diaphragmatic) nerve stimulation

Clinical Policy ID: CCP.1041

Recent review date: 6/2021

Next review date: 10/2022

Policy contains: Alveola hypoventilation syndrome, diaphragm function, phrenic nerve stimulation.

This policy is a Sandhills Center Clinical Coverage Policy adopted from AmeriHealth Caritas of North Carolina. These clinical policies are used to assist with making coverage determinations. Sandhills Center's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Sandhills Center when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Sandhills Center clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Sandhills Center's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Sandhills Center will update its clinical policies as necessary. Sandhills Center clinical policies are not guarantees of payment.

Coverage policy

Phrenic (diaphragmatic) nerve stimulation with a Food and Drug Administration-approved device, such as NeuRx DPS® RA/4 respiratory stimulation system (Synapse Biomedical Inc., Oberlin, Ohio) is clinically proven and, therefore, medically necessary when all of the following criteria are met:

- The member is 18 years of age or older.
- The member has been diagnosed with hypoventilation, including congenital central hypoventilation syndrome, chronic pulmonary disease with ventilatory insufficiency, and respiratory paralysis from lesions of the brain stem and cervical spinal cord (Centers for Medicare & Medicaid Services, 2021).
- There is a normal diaphragm muscle function.
- The phrenic nerves are intact and able to send a signal when stimulated.
- The member has relatively mild or no lung disease.
- The member cannot breathe spontaneously for more than four hours without mechanical ventilation (Perez, 2016; Sieg, 2016).

Limitations

All other uses of phrenic (diaphragmatic) nerve stimulation, including for treating sleep apnea, are investigational/not clinically proven, and therefore not medically necessary (Centers for Medicare & Medicaid Services, 2019).

Alternative covered services

Mechanical ventilation.

Background

The two phrenic nerves (left and right) originate in the neck, in cervical nerves C3 – C5, and continue between the lung and heart before they attach into the diaphragm, which is a large muscle critical in breathing. The nerves play an important role in breathing, as they send information to the diaphragm signaling it to breathe, and the diaphragm returns sensory information.

Some persons with lesions of the brain stem or cervical spinal cord (Centers for Medicare & Medicaid Services, 2021) have difficulties breathing due to the inability to send proper signals between the diaphragm, lungs, and phrenic nerves. While mechanical ventilators can assist these patients, phrenic nerve stimulation, also known as pacing, is another, sometimes preferable method of improving breathing (Perez, 2016).

Persons who only need mechanical ventilators during sleep may be good candidates for phrenic nerve stimulation. Even in those who require support 24 hours a day, improved speech and activities are possible after phrenic nerve stimulation as opposed to ventilators. Other candidates for diaphragmatic pacing include those with normal diaphragm muscle function, intact phrenic nerves that can send signals, and mild or no lung disease. Obese persons, with excess fat tissue that can impair signals between the antenna and receiver, are typically not good candidates for the procedure.

Diaphragmatic nerve stimulation involves electrodes surgically attached to the phrenic nerves; receivers surgically implanted in the abdomen or chest; antennae taped on the chest over the receivers; and a portable external transmitter machine. When turned on, the transmitter signals the receivers, and the receiver converts the signal to an electric current that is conducted to the phrenic nerves. This conduction is a stimulant enabling the diaphragm muscles to contract, and a breath to be taken. Respiratory rates are set in the transmitter. Surgery is done under general anesthesia, and the equipment is tested during surgery (Perez, 2016).

About 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 require another method of support such as home mechanical ventilation by tracheostomy or noninvasive positive pressure ventilation.

The Food and Drug Administration gave premarket approval for the Mark IV transmitter for phrenic nerve stimulation in adults and children in March 1998, after approval and use in European nations (Avery Biomedical Devices, 2021). The Administration also approved the NeuRx Diaphragm Pacing System in June 2008 for patients with stable, high spinal cord injuries with diaphragms that can be stimulated, but who lack control of their diaphragms (Food and Drug Administration, 2011).

In addition, the Food and Drug Administration gave approval to the Remede® System, an implantable phrenic nerve stimulator device for treatment of moderate-to-severe central sleep apnea in adult patients, in October 2017 (Food and Drug Administration, 2017). Remede addresses central sleep apnea, which occurs in 40% of patients with heart failure, plus those with stroke history, opioid use, or neurological conditions (Joseph, 2016).

Intramuscular diaphragm stimulation has been used for ventilator-dependent chronic respiratory failure in people with high spinal cord injuries (National Institute for Health and Clinical Excellence, 2017).

Findings

The American Thoracic Society statement on diaphragm pacing phrenic nerve stimulation includes a description of the procedure, along with criteria for which persons are candidates for the procedure, including some with congenital central hypoventilation syndrome (Perez, 2016).

The National Institute for Health and Care Excellence guideline on intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure from spinal cord injuries notes that evidence on efficacy is limited, and that safety is a concern. Thus, the Institute recommends the procedure be used only in research (National Institute for Health and Care Excellence, 2017).

The Centers for Medicare & Medicaid Services has a long-standing National Coverage Determination for phrenic nerve stimulation. The Centers state that the procedure is proven for hypoventilation from 1) respiratory paralysis from lesions of the brain stem and the cervical spinal cord, and 2) chronic pulmonary disease with ventilator insufficiency (Centers for Medicare & Medicaid Services, 2021).

In 2017, the Food and Drug Administration approved the Remede® phrenic nerve stimulator for treating central sleep apnea in adults. However, a Local Coverage Determination from Medicare considers research on efficacy for transvenous phrenic nerve stimulation for sleep apnea “in beginning stages” and does not cover it (Centers for Medicare & Medicaid Services, 2019).

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 stimulation (Aurora, 2016).

A systematic review of 10 studies (n = 281) assessed diaphragm pacing systems; of the 10 articles, seven were case 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 diaphragm pacing systems for these two disorders based on observed efficacy and safety results (Woo, 2020).

A systematic review of phrenic nerve stimulators for high spinal cord injuries and central hypoventilation syndromes dating back to the 1980s yielded 420 studies from the literature, and concluded that 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. The percent of patients independent of ventilator support post-procedure ranged from 40% to 72% (Garara, 2016).

In a survey of 54 Canadian long-term mechanical ventilator facilities covering 428 patients, 13% offered phrenic nerve stimulation, compared to diaphragmatic pacing (21%), negative pressure (15%), and positive pressure ventilators (100%) (Rose, 2014).

A review of cervical spinal cord injury treatment noted that phrenic nerve function is preserved and tolerated after exogenous pacing of the diaphragm through electrical stimulation directly to the phrenic nerves. Benefits include a lower rate of pulmonary complications, improved venous return, improved breathing and speech, facilitation of eating, cost-effectiveness, and increased patient mobility. The article suggests that the same nerve function preservation may be accomplished less invasively by using percutaneous stimulation of the diaphragm (Dalal, 2014).

In a study of 112 intensive care unit patients, estimators of diaphragm thickness after phrenic nerve stimulation was much more accurate after initiation of mechanical ventilation than after switch to pressure support ventilation (Dube, 2017).

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).

A study of patients on permanent respiratory support ($n = 126$) compared 38 on phrenic nerve pacing with 88 who were mechanically ventilated. Paced patients were younger but had a longer survival, even after adjustment for age. Phrenic nerve-supported patients had better results in health-related quality of life using SF-36 scores (Romero, 2012).

A study of 76 patients found that values under 11 cm H₂O of twitch tracheal pressure in response to magnetic phrenic stimulation in a spontaneous breathing trial predicted with 89% accuracy the likelihood of failure to wean from mechanical ventilation (Dres, 2018).

In a study of 151 persons with central sleep apnea given transvenous phrenic nerve stimulation using the Remede 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, 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 $P < .0001$ (Costanzo, 2018).

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 4.7% in treatment patients, nearly significantly lower ($P = .065$) than the 17% in controls (Costanzo, 2018).

References

On March 24, 2021, 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” and “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.

Augostini RS, Afzal MR, Costanzo MR, et al. How to implant a phrenic nerve stimulator for treatment of central sleep apnea? *J Cardiovasc Electrophysiol*. 2019;30(5):792-799. Doi: 10.1111/jce.13898.

Aurora RN, Bista SR, Casey KR, et al. Updated adaptive servo-ventilation recommendations for the 2012 AASM guideline: "The treatment of central sleep apnea syndromes in adults: Practice parameters with an evidence-based literature review and meta-analyses." *J Clin Sleep Med*. 2016;12(5):757-761. Doi: 10.5664/jcsm.5812.

Avery Biomedical Devices Inc. System Information. <https://www.averybiomedical.com/diaphragm-pacing-systems/system-information/>. Published 2021.

Centers for Medicare & Medicaid Services. Transvenous Phrenic Nerve Stimulation in the Treatment of Central Sleep Apnea. Local Coverage Determination L37929. <https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=37929>. Revision effective October 24, 2019.

Centers for Medicare & Medicaid Services. Phrenic Nerve Stimulator. National Coverage Determination 160.19. <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=244&ncdver=1&bc=AgAAgAAAAAAAAA%3d%3d&>. Posted 2021.

Costanzo MR, Ponikowski P, Coats A, et al. Phrenic nerve stimulation to treat patients with central sleep apnoea and heart failure. *Eur J Heart Fail*. 2018;20(12):1746-1754. Doi: 10.1002/ejhf.1312.

Dalal K, DiMarco AF. Diaphragmatic pacing in spinal cord injury. *Phys Med Rehabil Clin N Am*. 2014;25(3):619-29, viii. Doi: 10.1016/j.pmr.2014.04.004.

Dres M, Goligher EC, Dube BP, et al. Diaphragm function and weaning from mechanical ventilation: an ultrasound and phrenic nerve stimulation clinical study. *Ann Intensive Care*. 2018;8(1):53. Doi: 10.1186/s13613-018-0401-y.

Dube BP, Dres M, Mayaux J, Demiri S, Similowski T, Demoule A. Ultrasound evaluation of diaphragm function in mechanically ventilated patients: comparison to phrenic stimulation and prognostic implications. *Thorax*. 2017;72(9):811-818. Doi: 10.1136/thoraxjnl-2016-209459.

Food and Drug Administration. Premarket Approval: Remede System. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160039>. Notice date October 23, 2017.

Food and Drug Administration. Summary of Safety and Probable Benefit. https://www.accessdata.fda.gov/cdrh_docs/pdf10/H100006b.pdf. Published September 28, 2011.

Garara B, Wood A, Marcus HJ, Tsang K, Wilson MH, Khan M. Intramuscular diaphragmatic stimulation for patients with traumatic high cervical injuries and ventilator dependent respiratory failure: A systematic review of safety and effectiveness. *Injury*. 2016;47(3):539-544. Doi: 10.1016/j.injury.2015.12.020.

Joseph S, Costanzo MR. A novel therapeutic approach for central sleep apnea: Phrenic nerve stimulation by the remedē® system. *Int J Cardiol*. 2016;206 Suppl:S28-34. Doi: 10.1016/j.ijcard.2016.02.121.

Kerwin AJ, Yorkgitis BK, Ebler DJ, Madbak FG, Hsu AT, Crandall ML. Use of diaphragm pacing in the management of acute cervical spinal cord injury. *J Trauma Acute Care Surg*. 2018;85(5):928-931. Doi:

10.1097/TA.0000000000002023.

National Institute for Health and Care Excellence. Intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by high spinal cord injuries. <https://www.nice.org.uk/guidance/ipg594>. Published September 27, 2017.

Perez IA, Kun S, Keens TG. Patient Education | Information Series. Diaphragm Pacing by Phrenic Nerve Stimulation. *Am J Respir Crit Care Med*. 2016;193(8):P13-4. Doi: 10.1164/rccm.1938P13.

Romero FJ, Gambarrutta C, Garcia-Forcada A, et al. Long-term evaluation of phrenic nerve pacing for respiratory failure due to high cervical spinal cord injury. *Spinal Cord*. 2012;50(12):895-898. Doi: 10.1038/sc.2012.74.

Rose L, McKim D, Katz S, et al. Institutional care for long-term mechanical ventilation in Canada: A national survey. *Can Respir J*. 2014;21(6):357-362. Doi: 10.1155/2014/538687.

Sieg EP, Payne RA, Hazard S, Rizk E. Evaluating the evidence: is phrenic nerve stimulation a safe and effective tool for decreasing ventilator dependence in patients with high cervical spinal cord injuries and central hypoventilation? *Childs Nerv Syst*. 2016;32(6):1033-1038. Doi: 10.1007/s00381-016-3086-2.

Woo AL, Tchoe HJ, Shin HW, Shin CM, Lim CM. Assisted breathing with a diaphragm pacing system: A systematic review. *Yonsei Med J*. 2020;61(12):1024-1033. Doi: 10.3349/ymj.2020.61.12.1024.

Policy updates

6/2013: initial review date and clinical policy effective date: 12/2013

6/2014: Policy references updated.

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