Anthem

Clinical UM Guideline

Subject: Diaphragmatic/Phrenic Nerve Stimulation and Diaphragm Pacing Systems
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Description

This document addresses diaphragmatic/phrenic (D/P) nerve stimulation and diaphragm pacing systems with devices that have obtained approval or clearance from the U.S. Food and Drug Administration (FDA). Diaphragmatic/phrenic nerve stimulator devices and diaphragm pacing systems are indicated for certain ventilator-dependent individuals who lack voluntary control of their diaphragm muscles to enable independent breathing without the assistance of a mechanical ventilator.

Clinical Indications

Medically Necessary:

I. Diaphragmatic/Phrenic Stimulation

Diaphragmatic/phrenic nerve stimulation with an FDA-approved device is considered **medically necessary** as an alternative to invasive mechanical ventilation for individuals who are 18 years of age or older when ALL of the following criteria are met:

A. The individual has ventilatory failure from stable, high spinal cord injury **or** ventilatory failure from central alveolar hypoventilation syndrome; **and**
B. The individual cannot breathe spontaneously for 4 continuous hours or more without use of a mechanical ventilator; **and**
C. Diaphragm movement with stimulation is visible under fluoroscopy; **and**
D. Stimulation of the diaphragm either directly or through the phrenic nerve results in sufficient muscle activity to accommodate independent breathing without the support of a ventilator for at least 4 continuous hours a day; **and**
E. 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 the device; **and**
F. Bilateral clinically acceptable phrenic nerve function is demonstrated with electromyography recordings and nerve conduction times.

II. Diaphragmatic Stimulation

Diaphragm stimulation with an FDA approved diaphragm pacing system is considered **medically necessary** as an alternative to invasive mechanical ventilation in individuals who are 18 years of age or older when ALL of the following criteria are met:

A. The individual has ventilatory failure from stable, high spinal cord injury **or** ventilatory failure from central alveolar hypoventilation syndrome **or** ventilatory failure from motor neuron disease, for example amyotrophic lateral sclerosis; **and**
B. The individual cannot breathe spontaneously for 4 continuous hours or more without use of a mechanical ventilator; **and**
C. Diaphragm movement with stimulation is visible under fluoroscopy; **and**
D. Stimulation of the diaphragm directly results in sufficient muscle activity to accommodate independent breathing without the support of a ventilator for at least 4 continuous hours a day; **and**
E. 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 the device.

Not Medically Necessary:

Diaphragmatic/phrenic nerve stimulation devices and Diaphragm Pacing Systems are considered **not medically necessary** when:

- The individual can breathe spontaneously for 4 continuous hours or more without use of a mechanical ventilator; **or**
- The respiratory insufficiency is temporary.

Diaphragmatic/phrenic nerve stimulation and Diaphragm Pacing Systems are considered **not medically necessary** for all other indications including, but not limited to:

- 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 the phrenic nerve or diaphragm pacemaker device; **or**
- In individuals with intact phrenic nerve and diaphragm function; **or**
- For treatment of any other condition where the phrenic nerve and diaphragm are intact (for example, chronic obstructive lung disease, restrictive lung disease, singultus [hiccups], central sleep apnea); **or**
- For adolescents, children and infants; **or**
- When the above criteria are not met.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT	
64575	Open implantation of neurostimulator electrodes; peripheral nerve (excludes sacral nerve) [when specified as phrenic nerve stimulator]

64590	Insertion or replacement of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, requiring pocket creation and connection between electrode array and pulse generator or receiver [when specified as phrenic nerve stimulator]

HCPCS

C1778	Lead, neurostimulator (implantable) [for phrenic nerve stimulator]
C1816	Receiver and/or transmitter, neurostimulator (implantable) [for phrenic nerve stimulator]
L8680	Implantable neurostimulator electrode, each [for phrenic nerve stimulator]
L8682	Implantable neurostimulator radiofrequency receiver [for phrenic nerve stimulator]
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver [for phrenic nerve stimulator]

ICD-10 Procedure

0BHT0MZ-0BHT4MZ	Insertion of diaphragmatic pacemaker lead into diaphragm [by approach; includes codes 0BHT0MZ, 0BHT3MZ, 0BHT4MZ]

ICD-10 Diagnosis

G12.20-G12.29	Motor neuron disease
G47.35	Congenital central alveolar hypoventilation syndrome
G82.50-G82.54	Quadriplegia
G83.89	Other specified paralytic syndromes [respiratory]
J96.10-J96.12	Chronic respiratory failure
J96.20-J96.22	Acute and chronic respiratory failure
R06.81	Apnea, not elsewhere classified [respiratory muscle paralysis]
Z99.11	Dependence on respirator [ventilator] status

When services are Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed; or when the code describes a procedure or situation designated in the Clinical Indications section as not medically necessary.

When services are also Not Medically Necessary:
For the following procedure codes; or when the code describes a procedure designated in the Clinical Indications section as not medically necessary.

CPT

33276	Insertion of phrenic nerve stimulator system (pulse generator and stimulating lead[s]), including vessel catheterization, all imaging guidance, and pulse generator initial analysis with diagnostic mode activation, when performed
33277	Insertion of phrenic nerve stimulator transvenous sensing lead
33278	Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; system, including pulse generator and lead(s)
33279	Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; transvenous stimulation or sensing lead(s) only
33280	Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; pulse generator only
33281	Repositioning of phrenic nerve stimulator transvenous lead(s)
33287	Removal and replacement of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; pulse generator
33288	Removal and replacement of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; transvenous stimulation or sensing lead(s)
93150	Therapy activation of implanted phrenic nerve stimulator system, including all interrogation and programming
93151	Interrogation and programming (minimum one parameter) of implanted phrenic nerve stimulator system
93152	Interrogation and programming of implanted phrenic nerve stimulator system during polysomnography
93153	Interrogation without programming of implanted phrenic nerve stimulator system

HCPCS

C1823	Generator; neurostimulator (implantable), non-rechargeable, with transvenous sensing and stimulation leads

ICD-10 Diagnosis

	All diagnoses

Discussion/General Information

The NeuRx DPS™ RA/4 Respiratory Stimulation System (now known as the NeuRx® Diaphragm Pacing System [NeuRx DPS®], Synapse Biomedical, Inc., Oberlin, OH), an implantable electrical device that stimulates the diaphragm, was granted FDA approval under a Humanitarian Device Exemption (HDE) on June 17, 2008. On March 31, 2023, the FDA issued a premarket approval (PMA) for the NeuRx DPS. The FDA-approved indications are:

> For use in patients with stable, high spinal cord injuries with stimulatable diaphragms, but who lack control of their diaphragms. The device is indicated to allow the patients to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day. For use only in patients 18 years of age or older.

The NeuRx DPS is implanted through minimally invasive laparoscopic surgery and provides electrical stimulation to muscles and nerves that run through the diaphragm. This eliminates any direct contact with the phrenic nerve, allows all circuitry and electronics to remain outside the body, and provides direct, selective activation to each hemidiaphragm. According to manufacturer information,

when stimulated by the NeuRx DPS, the diaphragm contracts, mimicking natural breathing and allowing air to fill the upper and lower parts of the lungs, rather than forcing air in with a mechanical ventilator. The device uses four electrodes implanted in the muscle of the diaphragm to electronically stimulate contraction; this stimulation allows the user to inhale. The DPS is lightweight and battery powered, eliminating the need for an external power source.

FDA HDE approval of the NeuRx DPS device was primarily based on a prospective, nonrandomized, multicenter clinical trial that included 50 subjects throughout the U.S. and Canada (Onders, 2009). In the clinical trial, 98% of subjects with spinal cord injury were able to breathe normally for at least 4 hours following implantation of the device, while 50% have been able to completely eliminate their need for mechanical ventilation. The study inclusion criteria were:

- Age 18 years or older;
- Cervical spinal cord injury with dependence on mechanical ventilation;
- Clinically stable following acute spinal cord injury;
- Bilateral phrenic nerve function clinically acceptable as demonstrated with electromyography (EMG) recordings and nerve conduction times;
- Diaphragm movement with stimulation visible under fluoroscopy;
- Clinically acceptable oxygenation on room air (greater than 90% 0_2 saturation);
- Hemodynamically stable;
- No medical co-morbidities that would interfere with the proper placement or function of the device;
- Committed primary caregiver;
- Negative pregnancy test in females of child-bearing potential;
- Informed consent from the device user or designated representative.

Exclusion criteria were:

- Co-morbid medical conditions that preclude surgery;
- Active lung disease (obstructive, restrictive or membrane diseases);
- Active cardiovascular disease;
- Active brain disease;
- Hemodynamic instability or low oxygen levels on room air;
- Hospitalization for or a treated active infection, within the last 3 months;
- Significant scoliosis or chest deformity;
- Marked obesity;
- Anticipated poor compliance with protocol by either the device user or primary caregiver;
- Currently breastfeeding.

The study's primary endpoint was to assess the ability of the NeuRx DPS device to provide clinically acceptable tidal volume for at least 4 continuous hours of pacing. The safety endpoint was to qualitatively assess the adverse event reports and compare these to a similar population. Secondary endpoints included reduction of dependence on mechanical ventilation and surgical implementation site independence. The study provided an average follow-up of 1.7 ± 1.4 years (median, 1.4; range 0.2-7.7). Overall, a total of 48 out of 50 subjects enrolled have been able to pace for longer than 4 consecutive hours while achieving tidal volumes greater than their basal metabolic requirements. At the end of the study period, 44 subjects were using the device. A total of 4 subjects died in the course of the study, and there were 11 incidents of aspiration and 3 incidents of upper airway obstruction that occurred in 3 subjects.

The length of the conditioning phase was variable. It ranged from 1 week for 18-20 year olds on mechanical ventilation for less than 1 year, to 14 weeks for 40-50 year olds on a ventilator for greater than 5 years. Use of the device for periods greater than 4 continuous hours a day occurred after a period of diaphragmatic conditioning that ranged from 1 week to several months. The study investigators concluded that the use of the NeuRx DPS in individuals with high spinal cord injuries and stimulatable diaphragms may allow these subjects to be removed from the ventilator for at least 4 hours a day, provided that a mechanical ventilator is available at all times (as recommended in the labeling).

The most frequent adverse event attributable to this device was capnothorax. The capnothorax occurred as a consequence of the surgical implantation procedure. A total of 42% of the subjects enrolled in the clinical study experienced this complication in association with implantation of the electrodes in the diaphragm. While no subjects experienced compromised pulmonary gas exchange or hemodynamic instability as a result of the capnothorax, affected subjects required treatment with a chest tube, for up to 2 days in 1 individual, and an extended hospital stay of 5 days in 1 person. Synapse Biomedical Inc. has addressed this risk in the labeling and training procedure provided with this device. There have been few additional clinical studies of these devices, most of which were case series of small numbers with short-term outcomes data only.

On September 28, 2011, the FDA issued an HDE approval for use of the NeuRx DPS in:

> Amyotrophic lateral sclerosis (ALS) patients with a stimulatable diaphragm (both right and left portions) as demonstrated by voluntary contraction or phrenic nerve conduction studies, and who are experiencing chronic hypoventilation (CH), but not progressed to an FVC (forced vital capacity) less than 45% predicted. For use only in patients 21 years of age or older.

This approval was based on results of a multicenter, prospective study of the NeuRx DPS device of motor-point stimulation for conditioning the diaphragm of subjects with ALS, which showed the probable benefit to health from use of the device outweighed the risks of injury or illness from its use (FDA/HDE; SSPB, 2011).

Similar to the NeuRx DPS, the Avery Breathing Pacemaker System (that is, the Mark IV™, Avery Biomedical Devices, Inc., Commack, NY) is connected to the phrenic nerve by electrodes in the neck or chest area. The device consists of a surgically implanted receiver and electrodes that are connected to an external transmitter for transmitting the stimulating pulses across the skin to the implanted receiver. The pacemaker is classified as a Class III neurologic therapeutic device requiring 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).

In 2014, results of a retrospective review were published describing a multicenter, nonrandomized treatment protocol using a D/P system during the initial hospitalization phase following high (cervical) spinal cord injury. A total of 14 inpatient sites in the U.S. were included in this analysis, all of which used the same data collection tool. Twenty-nine subjects with an average age of 31.4 years (range, 17-65 years) were identified for this review; however, 7 subjects were subsequently disqualified due to pre-procedural findings from diaphragm motor point mapping that showed non-stimulatable diaphragms from either phrenic nerve damage or infarct. All subjects had experienced a traumatic high spinal cord injury with an elapsed time from injury to surgery of 40 days (range of 3-112 days). The post-procedure outcomes following laparoscopic D/P system implantation showed that 72.7% (16 of 22) were completely

free of ventilator support in an average of 10.2 days (mean SE of 10.2 ± 13.1 days [range, 1-45 days]). The remaining 6 subjects who had undergone D/P system implantation experienced delayed weaning of 180 days (in 2 trial participants), and partial weaning was achieved in 3 subjects, reflecting a total success rate of 82%. It was possible to remove the D/P wires from 8 of the 22 implanted subjects due to complete respiratory recovery. The last subject needed transfer to a long-term acute care hospital and subsequently had life-prolonging measures withdrawn. The authors concluded that laparoscopic diaphragm motor point mapping early after traumatic cervical spinal cord injury can assist with diagnosing those with complete phrenic motor neuron loss or phrenic nerve injury for whom D/P system implantation is not indicated. Also, in those with intact phrenic nerve systems following injury, D/P system implantation can successfully wean them from ventilator support, although it is acknowledged that these individuals may have been successfully weaned from ventilator dependence over time during the course of their recovery without the use of DP (Posluszny, 2014).

Diaphragmatic/Phrenic Nerve Stimulators for Central Sleep Apnea

The Remedē® System (ZOLL® Medical Corporation, Minnetonka, MN) received an FDA PMA on October 6, 2017 for the treatment of moderate to severe central sleep apnea (CSA) in adult individuals. The manufacturer describes the device as:

> An implantable device designed to treat moderate to severe CSA. The system includes an implantable pulse generator (IPG) and transvenous leads for unilateral stimulation of the phrenic nerve and sensing respiration via transthoracic impedance. The remedē IPG is programmed via telemetry using the remedē System Programmer.

Abraham and colleagues (2015) performed a prospective, multicenter, international, nonrandomized feasibility study to evaluate unilateral phrenic nerve stimulation to treat CSA. Eligible subjects (n=57) had apnea-hypopnea index (AHI) values of 20 or higher and at least 50% of their events were CSA as confirmed by polysomnography. The subjects were implanted with the Remedē System and evaluated after 1, 2, 3 and 6 months, with the primary endpoint of the study being AHI reduction by 50% after 3 months. The Remedē System was successfully implanted in 49 out of 57 subjects (86%); however, 10 subjects did not complete the study. A total of 26% of subjects had serious adverse events (AE) that were related to the procedure or the device and included lead repositioning problems, migraine, hematoma and atypical chest pain the first night of therapy. For the 47 subjects that completed 3 months of therapy, there was a mean reduction in AHI of 27.1 ± 17.7 episodes/h (55%, p<0.0001) and a mean reduction in the central apnea index of 23.4 ± 15.3 episodes/h (84%, p<0.0001). After 6 months, subjects reported improvement in sleepiness, and 56% reported a marked or moderate improvement in how they felt since starting the therapy. A total of 36 subjects with heart failure showed an average improvement of 10 points on the Minnesota Living with Heart Failure Questionnaire (95% confidence interval [CI], –16 to –4; p=0.0009) at 6 months. Limitations of the study included a small sample size, lack of a control arm, short follow-up duration, and potential for referral bias. The authors concluded that unilateral phrenic nerve stimulation appears to be safe and effective for CSA, but large, prospective, randomized, controlled trials are needed.

In an analysis, Jagielski and colleagues (2016) reported on the 12-month outcomes of the study by Abraham and colleagues (2015). The researchers analyzed 41 out of 47 individuals who had been successfully implanted with the Remedē System. They found that the AHI was reduced from 49.9 ± 15.1 at baseline to 27.5 ± 18.3 (p<0.001). The central apnea index was reduced from 28.2 ± 15.0 to 6.0 ± 9.2 (p<0.001). They also noted improvements in the oxygen desaturation index, rapid eye movement, and sleep efficiency. On the quality of life assessment, 83% of subjects had a mild, moderate, or marked improvement at 12 months. A total of 3 subjects died before follow-up (2 from end-stage heart failure and 1 from sudden cardiac death); however, the deaths were adjudicated as unrelated to the procedure or the Remedē System. In addition to the adverse events already reported in the original study, 2 additional subjects had adverse events; 1 subject with impending pocket perforation and 1 subject with lead failure. Limitations of the study included loss to follow-up, the lack of a control group, open-label design, small sample size, and small number of female subjects. The researchers recommended large randomized controlled trials to confirm their results.

The FDA PMA of the Remedē System was based on a multicenter, prospective, randomized, controlled sham study that aimed to determine the safety and effectiveness for treating CSA (Costanzo, 2016). A total of 151 adult subjects were randomized to receive either medical management and the Remedē System (n=73), or medical management and an inactive sham Remedē System (n=78). The subjects in the study were an average of 65 years old and predominately Caucasian (95%) and male (89%). The primary endpoint was a 50% or greater reduction in AHI from baseline to 6 months, and the AHI was determined using polysomnography. Subjects were evaluated regularly until the end of the trial. After 6 months, the Remedē System was activated in the sham group. Effectiveness was based on modified intention-to-treat (ITT) data at 6 months (n=141). A significantly higher number of subjects in the active Remedē 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 Remedē System group was 51% compared to 11% in the sham group for a total difference of 41% (95% CI, 25% to 54%; p<0.0001). A total of 76% of subjects in the active Remedē System group reported improvement in quality of life. Safety results were based on ITT data for 12 months (n=151). There were 7 deaths but none were found to be related to the device or treatment. The number of subjects free from serious 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 was 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 a low percentage of female subjects, potential referral bias, and a loss to follow-up.

Costanzo and colleagues (2018a) reported on the 12-month outcomes of the 2016 Costanzo study. At 12 months post Remedē System implantation, the treatment group had an active device for 12 months (n=54), and the control group had an active device for 6 months (n=65). After 12 months, 67% of the treatment group had a ≥ 50% reduction in AHI from baseline (36 of 54; 95% CI, 53% to 78%). Subjects continued to have improvements in sleep metrics, oxygenation, and quality of life. For the control group with an active device for 6 months, 55% of subjects had a ≥ 50% reduction in AHI from baseline (36 of 65; 95% CI, 43% to 67%). At 12 months follow-up, there were 7 reported deaths, but they were not related to the procedure or device. The freedom from serious adverse events at 12 months for the intent-to-treat population was 91% (138 of 151; 95% CI, 86% to 95%). The authors concluded that the Remedē System improves sleep metrics and quality of life for at least 12 months without safety concerns.

In addition, Costanzo and colleagues (2018b) performed a post-hoc analysis of a subset of participants from the 2016 Costanzo study to determine if there was an association between treating CSA with the Remedē System and changes in heart failure (HF) metrics for individuals with CSA and HF. A total of 96 individuals with HF were included in the analysis, and 75/96 completed a 12-month follow-up visit. Metrics evaluated at baseline and at 6 and 12 months included the Epworth Sleepiness Scale, health-related quality of life, the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and echocardiographic parameters. There was a ≥ 50% reduction in AHI at 6 months for 41/77 individuals (53%) and at 12 months for 40/70 (57%) individuals. All respiratory and sleep metrics improved from baseline to 12-month follow-up (p<0.05). At 12 months, the MLHFQ score changed by –6.8 ± 20.0 (p=0.005). The researchers found that phrenic nerve stimulation reduces CSA severity in individuals with HF, but further studies in HF populations are needed to confirm the results.

Follow-up safety data was published at 3 years for the Costanzo study of the Remedē System unilateral phrenic nerve stimulation for

treatment of moderate to severe CSA, along with optimal medical management, compared to optimal medical management alone (implanted with an inactive Remedē device). Sleep metrics (by polysomnography) and echocardiographic parameters were reported at baseline, 12, 18, and 24 months, in addition to available 36-month sleep results from polygraphy. Safety was assessed through 36 months; however, analysis focused through 24 months and available 36-month results. Trial participants were assessed at 24 months (n=109) and 36 months (n=60). Baseline characteristics included mean age of 64 years, 91% male, and mean AHI of 47 events per hour. Sleep metrics, central apnea index, arousal index, oxygen desaturation index, and rapid eye movement sleep were reported as improved through 24 and 36 months with continuous use of the phrenic nerve therapy. At least 60% of subjects in the treatment group achieved at least 50% reduction in AHI through 24 months. Serious adverse events (SAEs) related to the Remedē system implant procedure, device, or therapy through 24 months were reported by 10% of subjects with no unanticipated adverse device effects or deaths (Fox, 2019).

Additional authors also published results of this study data and found improvements at 6, 12 and 18 months of therapy: AHI decreased by 25, 25 and 23 events/hour ($p<.001$ at each visit), central apnea index decreased by 22, 23 and 22 events/hour ($p<.001$ at each visit), and arousal index changed by 12 ($p=0.005$), 11 ($p=0.035$) and 13 events/hour ($p<.001$). Quality of life (QoL) instruments demonstrated clinically meaningful improvements in daytime somnolence, fatigue, general and mental health, and social functioning. The only related SAE was reported as lead component failure in 1 subject (Javaheri, 2020). However, 27% of trial subjects experienced an AE during the first year (23 in the device-treated group and 18 in the sham control group).

This prospective data is hampered by several limitations including the fact that the study was not blinded and the authors themselves acknowledge that, “In our study, subjective patient assessments of health status could be biased by the knowledge of treatment assignment.” Additional concerns include small sample size and substantial drop-out rates (13 of 73; 21%) which were not considered in the outcomes analysis. Generalizability is limited due to a study population that was predominantly male (89%) and white (95%); and the possibility of observer bias regarding the metrics is apparent, since the device manufacturer participated in the study design, data collection and analysis. Additional large randomized controlled trials are needed to confirm these results and support use in a broader population in accordance with generally accepted standards of medical practice.

Definitions

Alveolar Hypoventilation Syndrome: Insufficient ventilation leading to an increase in $PaCO_2$ (that is, hypercapnia). Alveolar hypoventilation is caused by several disorders that are collectively referred to as hypoventilation syndromes. The term, central alveolar hypoventilation, is used to describe alveolar hypoventilation secondary to an underlying neurologic disease. Alveolar hypoventilation is a cause of hypoxemia. The presence of hypoxemia, along with hypercapnia, aggravates the clinical manifestations seen with hypoventilation syndromes.

Amyotrophic Lateral Sclerosis (ALS): A form of motor neuron disease that is caused by the progressive degeneration of upper and lower neurons in the spinal cord and brain that results in respiratory compromise and central alveolar hypoventilation syndrome due to muscle weakness and atrophy.

Capnothorax: A respiratory condition related to the implantation of device electrodes whereby air enters the pleural cavity. This condition is caused by the inflation of the abdomen with CO_2 during laparoscopic surgical procedures.

Central Sleep Apnea (CSA): A type of sleep apnea that occurs when the brain periodically fails to communicate with the muscles that are necessary for breathing.

References

Peer Reviewed Publications:

1. Abraham WT, Jagielski D, Oldenburg O, et al. Phrenic nerve stimulation for the treatment of central sleep apnea. JACC Heart Fail. 2015; 3(5):360-369.
2. Ali A, Flageole H. Diaphragmatic pacing for the treatment of congenital central alveolar hypoventilation syndrome. J Pediatr Surg. 2008; 43(5):792-796.
3. Alshekhlee A, Onders RP, Syed TU, et al. Phrenic nerve conduction studies in spinal cord injury: applications for diaphragmatic pacing. Muscle Nerve. 2008; 38(6):1546-1552.
4. Costanzo MR. Central sleep apnea in patients with heart failure-how to screen, how to treat. Curr Heart Fail Rep. 2020; 17(5):277-287.
5. Costanzo MR, Javaheri S, Ponikowski P, et al; remede® System Pivotal Trial Study Group. Transvenous phrenic nerve stimulation for treatment of central sleep apnea: Five-year safety and efficacy outcomes. Nat Sci Sleep. 2021; 13:515-526.
6. Costanzo MR, Ponilowski P, Coats A, et al. Phrenic nerve stimulation to treat patients with central sleep apnea and heart failure. Eur J Heart Fail. 2018b; 20(12):1746-1754.
7. Costanzo MR, Ponikowski P, Javaheri S, et al. Transvenous neurostimulation for central sleep apnea: a randomized controlled trial. Lancet. 2016; 388(10048):974-982.
8. Contanzo MR, Ponikowski P, Javaheri S, et al. Sustained 12 month benefit of phrenic nerve stimulation for central sleep apnea. Am J Cardiol. 2018a; 121(11):1400-1408.
9. DiMarco AF, Onders RP, Ignagni A, et al. Phrenic nerve pacing via intramuscular diaphragm electrodes in tetraplegic subjects. Chest. 2005; 127(2):671-678.
10. DiPALS Writing Committee. Safety and efficacy of diaphragm pacing in patients with respiratory insufficiency due to amyotrophic lateral sclerosis (DiPALS): a multicenter, open-label, randomized controlled trial. Lancet. 2015; 14(9):883-892.
11. Elefteriades JA, Quin JA, Hogan JF, et al. Long-term follow-up of pacing of the conditioned diaphragm in quadriplegia. Pacing Clin Electrophysiol. 2002; 25(6):897-906.
12. Fox H, Oldenburg O, Javaheri S, et al. Long-term efficacy and safety of phrenic nerve stimulation for the treatment of central sleep apnea. Sleep. 2019; 42(11).
13. Garrido-Garcia H, Mazaira Alvarez J, Martin Escribano P, et al. Treatment of chronic ventilatory failure using a diaphragmatic pacemaker. Spinal Cord. 1998; 36(5):310-314.
14. Gonzalez-Bermejo J, Morélot-Panzini C, Salachas F, et al. Diaphragm pacing improves sleep in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2012; 13(1):44-54.
15. Gonzalez-Bermejo J, Morélot-Panzini C, Tanguy ML, et al. Early diaphragm pacing in patients with amyotrophic lateral sclerosis (RespiStimALS): a randomized controlled triple-blind trial. Lancet Neurol. 2016; 15(12):1217-1227.
16. Hirschfeld S, Exner G, Luukkaala T, Baer GA. Mechanical ventilation or phrenic nerve stimulation for treatment of spinal cord injury-induced respiratory insufficiency. Spinal Cord. 2008; 46(11):738-742.
17. Jagielski D, Ponikowski P, Augostini R, et al. Transvenous stimulation of the phrenic nerve for the treatment of central sleep apnea: 12 months' experience with the Remedē® System. Eur J Heart Fail. 2016; 18(11):1386-1393.
18. Javaheri S, McKane S. Transvenous phrenic nerve stimulation to treat idiopathic central sleep apnea. J Clin Sleep Med. 2020;

16(12):2099-2107.
19. Krieger LM, Krieger AJ. The intercostal to phrenic nerve transfer: an effective means of reanimating the diaphragm in patients with high cervical spine injury. Plastic and Recon Surg. 2000; 105(4):1255-1261.
20. Luni FK, Daniels J, Link MS, et al. Meta-analysis of usefulness of phrenic nerve stimulation in central sleep apnea. Am J Cardiol. 2020; 125(11):1738-1744.
21. Mahajan KR, Bach JR, Saporito L, Perez N. Diaphragm pacing and noninvasive respiratory management of amyotrophic lateral sclerosis/motor neuron disease. Muscle Nerve. 2012; 46(6):851-855.
22. McDermott CJ, Bradburn MJ, Maguire C, et al. DiPALS: Diaphragm pacing in patients with amyotrophic lateral sclerosis - a randomised controlled trial. health technol assess. 2016; 20(45):1-186.
23. Oldenburg O, Costanzo MR, Germany R, et al. Improving nocturnal hypoxemic burden with transvenous phrenic nerve stimulation for the treatment of central sleep apnea. J Cardiovasc Transl Res. 2021; 14(2):377-385.
24. Onders RP, Elmo MJ, Ignagni AR. Diaphragm pacing stimulation system for tetraplegia in individuals injured during childhood or adolescence. J Spinal Cord Med. 2007; 30 Suppl 1:S25-S29.
25. Onders RP, Elmo M, Khansarinia S, et al. Complete worldwide operative experience in laparoscopic diaphragm pacing: results and difference in spinal cord injured patients and amyotrophic lateral sclerosis patients. Surg Endosc. 2009; 23(7):1433-1440.
26. Onders RP, Khansarinia S, Weiser T, et al. Multicenter analysis of diaphragm pacing in tetraplegics with cardiac pacemakers: positive implications for ventilator weaning in intensive care units. Surgery. 2010; 148(4):893-897; discussion 897-898.
27. Onders RP, Ponsky TA, Elmo M, et al. First reported experience with intramuscular diaphragm pacing in replacing positive pressure mechanical ventilators in children. J Pediatr Surg. 2011; 46(1):72-76.
28. Posluszny JA Jr, Onders R, Kerwin AJ, et al. Multicenter review of diaphragm pacing in spinal cord injury: successful not only in weaning from ventilators but also in bridging to independent respiration. J Trauma Acute Care Surg. 2014; 76(2):303-309.
29. 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.
30. Schwartz AR, Goldberg LR, McKane S, Morgenthaler TI. Transvenous phrenic nerve stimulation improves central sleep apnea, sleep quality, and quality of life regardless of prior positive airway pressure treatment. Sleep Breath. 2021 Mar 20. [Epub ahead of print].
31. Shaul DB, Danielson PD, McComb JG, Keens TG. Thorascopic placement of phrenic nerve electrodes for diaphragmatic pacing in children. J Pediatr Surg. 2002; 37(7):974-978.
32. Woo A, Tchoe HJ, Shin HW, et al. Assisted breathing with a diaphragm pacing system: A systematic review. Yonsei Med J. 2020; 61(12):1024-1033.
33. Zhang X, Ding N, Ni B, et al. Safety and feasibility of chronic transvenous phrenic nerve stimulation for treatment of central sleep apnea in heart failure patients. Clin Respir J. 2017; 11(2):176-184.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Centers for Medicare and Medicaid Services. National Coverage Determination for Phrenic Nerve Stimulators. NCD 160.19. Longstanding coverage determination; Effective date not posted. Available at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=244&ncdver=1&bc=AAAAQAAAAAAA&. Accessed on November 13, 2023.
2. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: The care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology (AAN). Neurology. 2009; 73(15):1218-1226.
3. U.S. Food and Drug Administration (FDA). Part 882 Neurological devices. Sec. 882.5830. Implanted diaphragmatic/phrenic nerve stimulator. April 8, 1986. Revised April 1, 2020. Current as of July 20, 2022. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=882.5830. Accessed on November 13, 2023.
4. U.S. Food and Drug Administration. Humanitarian Device Exemption Database. NeuRx DPS RA/4 Respiratory Stimulation System (Synapse Biomedical, Inc., Oberlin, OH). Summary of Safety and Probable Benefit. No. H070003. Rockville, MD: FDA. June 17, 2008. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=375540. Accessed on November 13, 2023.
5. U.S. Food and Drug Administration (FDA). Humanitarian Device Exemption Database. NeuRx DPS Diaphragm Pacing System (Synapse Biomedical, Inc., Oberlin, OH). Summary of Safety and Probable Benefit. No. H100006. Rockville, MD: FDA. September 28, 2011. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=375558. Accessed on November 13, 2023.
6. U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health (CDRH) Premarket Approvals for the Avery Breathing Pacemaker System Mark IV (Avery Biomedical Devices, Inc., Commack, NY). Summary of Safety and Effectiveness. No. P860026. Rockville, MD: FDA. February 25, 1987; updated 2000. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P860026S006. Accessed on November 13, 2023.
7. U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health (CDRH). Premarket Notification Database. NeuRx Diaphragm Pacing System (NeuRx DPS) (Synapse Biomedical, Inc., Oberlin, OH). Summary of Safety and Effectiveness. No. P200018. Rockville, MD: FDA. March 31, 2023. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf20/P200018B.pdf. Accessed on November 13, 2023.
8. U.S. Food and Drug Administration (FDA). Center for Devices and Radiological Health (CDRH). Premarket Notification Database. Remedē System (Respicardia, Inc., Minnetonka, MN). Summary of Safety and Effectiveness. No. P160039. Rockville, MD: FDA. October 6, 2017. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160039b.pdf. Accessed on November 13, 2023.
9. Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, et al. American Thoracic Society (ATS). ATS clinical policy statement: congenital central hypoventilation syndrome: genetic basis, diagnosis and management. Am J Respir Crit Care Med. 2010; 181:626–644.

Websites for Additional Information

1. National Institute of Neurological Disorders and Stroke. National Institute of Health (NIH). Amyotrophic Lateral Sclerosis (ALS) Fact Sheet. Last reviewed October 17, 2023. Available at: https://www.ninds.nih.gov/amyotrophic-lateral-sclerosis-als-fact-sheet?search-term=National%20Institute%20of%20Health%20(NIH).%20Amyotrophic%20Lateral%20Sclerosis%20(ALS)%20Fact%20Sheet. Accessed on November 13, 2023.

Index

NeuRx DPS
Remedē System
Respidrive™, Respiratory Rhythm Management™

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised Description, Discussion/General Information, References, Websites for Additional Information, and Index sections. Updated Coding section with 01/01/2024 CPT changes; added 33276, 33277, 33278, 33279, 33280, 33281, 33287, 33288, 93150, 93151, 93152, 93153 replacing 0424T-0436T deleted as of 01/01/2024, also revised descriptor for 64590.
Reviewed	11/10/2022	MPTAC review. Updated References section.
Reviewed	11/11/2021	MPTAC review. Updated References section. Updated Coding section with 01/01/2022 CPT descriptor change for 64575.
Reviewed	11/05/2020	MPTAC review. The Discussion and References sections were updated. Reformatted Coding section.
Reviewed	11/07/2019	MPTAC review. Discussion/General Information, References, and Websites sections updated.
	03/19/2019	Updated Coding section with 01/01/2019 HCPCS changes; added C1823.
New	11/08/2018	MPTAC review. Initial document development. Moved content of MED.00100 Diaphragmatic/Phrenic Nerve Stimulation and Diaphragm Pacing Systems to new clinical utilization management guideline document with the same title.
