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DIAPHRAGMATIC PACING

SUMMARY

Diaphragmatic pacing is a valuable tool in liberating high cervical spinal cord injury and amyotrophic lateralizing sclerosis (ALS) patients from long-term mechanical ventilator dependence. This evidence-based medicine guideline describes the use of diaphragmatic pacing in such patients.

RECOMMENDATIONS

- **Level 1**
 - None
- **Level 2**
 - None
- **Level 3**
 - Diaphragmatic pacing reduces healthcare costs and improves quality of life for ventilator dependent quadriplegic patients and those with amyotrophic lateralizing sclerosis (ALS).
 - Quadriplegic patients should receive early consideration for diaphragmatic pacing to avoid respiratory muscle loss.
 - A non-stimulatable diaphragm should prompt no further weaning attempts and institution of permanent ventilator management.
 - Diaphragmatic pacing patients must always have a mechanical ventilator available in case of pacemaker malfunction.
 - If the patient does not feel that they are receiving adequate ventilation or pacemaker malfunction is suspected, diaphragmatic pacing should be discontinued, and the patient returned to their mechanical ventilator.
 - If patients develop new-onset shoulder or neck pain while pacing, diaphragmatic pacing should be discontinued, and the patient's surgeon notified.

INTRODUCTION

Spinal cord injury (SCI) represents a devastating traumatic event with over 11,000 patients sustaining such injuries in the United States each year (1). The etiology of acute SCI is variable with motor vehicle crash (25%), diving accidents (21%), gunshot wounds (14%), and athletic injuries (11%) representing the most common mechanisms. The severity of any residual deficit is dependent upon the level of SCI. Fifty-one percent of acute SCI occurs in the cervical region and approximately 4% of such patients will require long-term mechanical ventilation due to the presence of C1-C4 injury and inability to breathe spontaneously (1).

The primary muscle of inspiration is the diaphragm. The diaphragm is innervated by the phrenic motor neurons, which are supplied by cervical spinal nerves C3, C4, and C5. Upon contraction, the diaphragm creates a negative-pressure vacuum that draws air into the thoracic cavity. The stimulus to breathe during the day is a combination of volitional breathing initiated by the motor cortex and rhythmic autonomic

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

breathing initiated by the respiratory center in the medulla. At night, breathing is regulated by carbon dioxide levels sensed in the medulla. The stimulus travels from the brain down the upper and lower motor neurons resulting in transmission of a signal to the diaphragm via both the left and right phrenic nerves. These provide the only motor innervation to the diaphragm, which is essential for both coughing and breathing.

Spontaneous breathing normally maintains both respiratory muscle strength and endurance. Lack of spontaneous breathing rapidly results in atrophy of the diaphragmatic muscle fibers within 18 hours of disuse (2). Spontaneous patient breathing reduces the incidence of atelectasis, decreases pulmonary secretions, maintains alveolar recruitment, and reduces the risk of pneumonia. Fifty percent of acute quadriplegic SCI patients will develop acute bacterial pneumonia in the first week post-injury due to their reduced or absent ability to cough and deep breathe. Spontaneous breathing also increases cardiac output by maintaining normal negative intrathoracic pressure.

In the event of upper SCI, the normal motor pathways may be interrupted leading to respiratory paralysis. Dependence upon long-term mechanical ventilatory support significantly reduces life expectancy (1). Fifty-one percent of acute SCI patients will require mechanical ventilation at discharge and 81% will require tracheostomy to facilitate both clearance of pulmonary secretions and long-term mechanical ventilation. This typically requires chronic long-term acute care (LTAC) or skilled nursing facility (SNF) residence, prevents patients from resuming employment, and significantly increases their healthcare costs.

The severity of a patient's SCI is graded using the American Spinal Injury Association (ASIA) score:

- A - Complete: No motor or sensory function in S4-S5
- B - Incomplete: Sensory, but no motor function below neurologic level
- C - Incomplete: Motor function below neurologic level with more than half of key muscle groups having a muscle grade less than 3
- D - Incomplete: Motor function below neurologic level with at least half of the key muscle groups having a muscle grade > 3
- E - Normal: Sensory and motor function normal

Electrical innervation of the phrenic nerves can be employed in appropriate patients to stimulate the diaphragm and replace the absent drive to breathe. This technique allows approximately 50% of previously ventilator-dependent SCI patients to be freed from mechanical ventilation and improve their quality of life (3). Diaphragmatic pacing can be performed by either stimulating the diaphragm directly or stimulating the phrenic nerve. Pacing improves quality of life, reduces nocturnal hypoventilation, and improves survival (3-5). Diaphragmatic pacing is also FDA-approved for the treatment of amyotrophic lateralizing sclerosis (ALS). The remainder of this evidence-based medicine guideline will focus on direct diaphragmatic stimulation using the Synapse Biomedical Neu-Rx[®] system.

The Neu-Rx[®] diaphragmatic pacing system, developed by Case Western Reserve University, employs four laparoscopically placed intramuscular diaphragmatic electrodes (two in each hemidiaphragm) and an external pulse generator to help patients breathe by electrical stimulation of their diaphragm muscles. The resulting negative intrathoracic pressure results in a breath, the volume and rate of which can be adjusted by altering the clinician programmed parameters of pulse amplitude, pulse duration, pulse frequency, pulse ramp, inspiration time, and respiratory rate. Each of the four electrodes can be individually programmed to achieve appropriate contraction of each hemidiaphragm. The requirements for diaphragmatic pacing include the presence of a stimulatable diaphragm (determined by a fluoroscopic "sniff" test, phrenic nerve electromyography study, or intra-operative stimulation), potential for rehabilitation, and appropriate family support structure. The benefits of diaphragmatic pacing include decreased pulmonary secretions, decreased risk of pulmonary infection, lower healthcare costs, and better quality of life.

LITERATURE REVIEW

Onders et al. performed a multi-center trial in 50 full-time ventilator dependent patients with intact phrenic nerves (a requirement for successful diaphragmatic pacing) who had been on mechanical ventilation for an average of 5.6 years (longest duration was 28 years) (3). The authors reported a 100% success rate in achieving adequate tidal volumes (3). In follow-up six months after implantation of the NeuRx[®] system, 50%

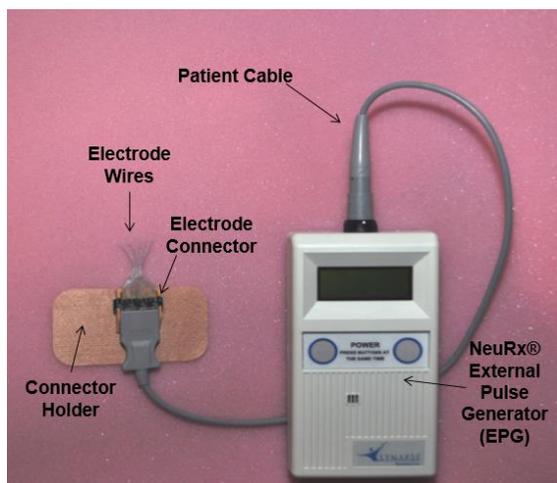
of patients no longer required mechanical ventilation, >66% had eliminated the need for specialized attendants by pacing over 12 hours/day, two patients had regained volitional breathing, and no patients remained on full-time ventilation.

In a subsequent multi-center trial of eight centers and 29 ventilator-dependent acute SCI patients who had been on mechanical ventilation for 42 ± 30 days, 28% of patients were found to have non-stimulatable diaphragms indicating that permanent ventilator management would be necessary (4). Eighty-one percent of patients with a stimulatable diaphragm were completely weaned from mechanical ventilation in 22 ± 45 days. Thirty-three percent recovered sufficient respiratory function to no longer need diaphragmatic pacing long-term.

Onders et al. subsequently reported on 92 patients with traumatic spinal cord injury who underwent implantation of the NeuRx® system (5). 81% of patients were able to achieve four consecutive hours of pacing and 61% utilized diaphragmatic pacing 24 hours a day and avoided the need for mechanical ventilation. 5.4% of patients could not be weaned from their ventilator. Overall median survival was significantly increased compared to expected survival times.

CARE AND MAINTENANCE (6)

The following are important points in the maintenance of the NeuRx® diaphragmatic pacing system (DPS).



The external components of the NeuRx® DPS include the External Pulse Generator (EPG) or stimulator, the patient cable, and the implanted diaphragmatic electrode wires which are connected to the patient cable via the electrode connector or “block”. The electrode connector is attached to the chest wall using an adhesive connector holder.



A DPS patient with stimulator, patient cable, and electrode connector in use.



The stimulator can only be programmed by a clinician using a separate programming station. The only settings on the stimulator are two “power” buttons which must both be pushed simultaneously to either “turn on” or “turn off” the stimulator (a safety feature to guard against inadvertent inactivation).



The DPS Patient Kit consists of a black plastic briefcase containing the backup stimulator, spare batteries, a screwdriver (to replace the battery in the stimulator), and spare connector holders. The spare stimulator should be available at all times should the stimulator in use develop problems. The two stimulators are typically programmed with the same settings and should be alternated to maintain the charge on the internal batteries



The stimulator screen indicates the Breath-per-Minute (BPM) rate and when the individual electrodes are active. During the inspiration phase, a letter ‘A’, ‘B’ or ‘C’ is shown below each electrode number indicating the quality of the diaphragmatic stimulation. “A” indicates a good stimulation, while “C” denotes a poor stimulation. During the expiration phase, a ‘-’ character is shown below each output number indicating that the stimulator is not active. A “?” mark indicates a weak electrical signal.



If ‘X’ appears below one or more output numbers, one or more electrode wires may be loose or broken, the patient cable may be broken or not connected properly, or the stimulator may be broken. The stimulator should be changed, and the patient’s surgeon notified.

Powering the stimulator

- To turn the stimulator ON: Depress the two buttons on the front of the stimulator simultaneously.
- To turn the stimulator OFF: Depress the two buttons on the front of the stimulator simultaneously.
- The buttons must be depressed simultaneously as a safety feature to guard against inadvertent activation/deactivation of the stimulator.
- The batteries that power the stimulator will each last for approximately 500 hours (3 weeks) under normal use. They must be specially ordered. Spare batteries must always be available.
- The device contains a permanently installed back-up lithium-ion battery that is not replaceable. The internal backup battery will power the stimulator for approximately 24 hours after the replaceable battery is fully depleted.
- The stimulator will initially display “REPLACE BATT” when the battery needs to be replaced.
- If the stimulator displays “LOW BATTERY”, replace the battery immediately.
- To replace the external battery:
 - Ensure that the stimulator is turned OFF prior to battery replacement.
 - Use the provided flat blade screwdriver to remove the battery cover located on the back bottom of the stimulator.
 - Remove old battery and replace with a new battery.
 - Replace the battery cover and secure with mounting screws.
 - Dispose of depleted batteries according to local regulations.



Cables

- The cable connects the exit site connector (electrode wires) to the stimulator.
- Do not cut, kink or pull on the cable.
- Do not manipulate the metal pins in the end pieces of the cable.
- Do not immerse the cable in water.
- Keep extra cables in a dry secure location.
- When in use, the cable should fit securely into the exit site connector and the stimulator.
- The length of the cable should be long enough to provide comfort and allow range of motion without pulling on the exit site connector.
- Notify the patient's surgeon if the cable gets cut, kinked, falls in water, or has a loose connection to the exit site connector or stimulator.

Care of exit sites

- Keep the skin at the exit sites clean and dry.
- Clean the exit sites with an alcohol wipe, allow alcohol to dry, and place a gauze dressing over the exit site. Be sure to cover all the wires with the gauze. Place a transparent dressing over the gauze (Tegaderm™ and Op-Site™ are examples of transparent dressings).
- Change the dressings every 3 days or more often if the dressing becomes wet or otherwise soiled. The adhesive connector holder dressing should be changed weekly or if it becomes soiled or no longer sticks to the skin.
- If the area becomes red, swollen, painful, or drainage appears, notify the patient's surgeon.
- The exit site connector should lie flat against the surface of the skin.
- Observe that the electrode leads are properly positioned within the connector.
- The connector will snap into the adhesive connector holder.
- Notify the patient's surgeon if there is a change in the appearance of the connector.
- Patients may cover the entire exit site and connector with an occlusive transparent dressing to shower, bathe, or undergo rehabilitation therapy in a pool. Diaphragmatic pacing must be discontinued during these times.

Care of the stimulator

- The surfaces of the stimulator may be cleaned and disinfected with a solution of ¼ teaspoon of household bleach (3-6% bleach) to 1 pint of water. Rubbing alcohol (isopropanol) may be used in place of bleach. Typical cleaners such as glass or multi-surface spray cleaners are adequate. Do NOT use these cleaners on parts that will contact the skin (for example, electrodes at the exit sites).
- The surfaces of the patient cables may be cleaned with a mild anti-bacterial hand soap solution.

Alarms

The stimulator initiates an audible alarm if it detects any of the following problems:

- If the connection from the cable to the stimulator or the cable to the electrode wires becomes loose or disconnects, a beep lasting the duration of an inhaled breath will sound. The alarm will repeat at each programmed inhalation until the cable is reconnected.
- A 10-second-long audible alarm will sound when the stimulator switches to the internal backup battery. The 10 second alarm repeats once every hour.
- A 20-second-long audible alarm will sound when the internal backup battery is low. The 20 second alarm repeats once every minute.

VENTILATOR WEANING USING THE DPS SYSTEM

Once the DPS system has been implanted, diaphragm pacing can begin immediately. The DPS stimulator will initially be programmed by the Synapse Biomedical technician in conjunction with the patient's surgeon. The stimulator settings are programmed to achieve pain-free electrical stimulation of the patient's diaphragm. Many quadriplegic patients will develop significant diaphragmatic atrophy and respiratory muscle weakness following their injury. This atrophy must generally be reversed through serial "conditioning sessions" before they can be liberated from mechanical ventilation for any significant portion of time. The stimulator settings are increased over time to achieve larger tidal volumes once the diaphragmatic muscle regains function. Multiple repetitions of small tidal volumes rebuilds respiratory muscle strength so that larger tidal volumes and endurance are eventually possible, similar to weight lifting in a gym.

Conditioning Sessions

The following describes the process of one conditioning session:

- Secretions should be cleared prior to conditioning and managed throughout the conditioning session.
- Connect the patient cable to the electrode connector block and to the stimulator.
- Place a pulse oximeter on the patient and continuously monitor throughout conditioning session.
- Turn the stimulator on by depressing the two buttons at the same time.
- Remove the patient from their ventilator.

- Allow the patient to become comfortable on the stimulator for several minutes and measure tidal volumes with a respirometer. Make note of tidal volume, pulse oximeter reading and any comments, complaints, or discomforts.
 - **If the patient develops new-onset shoulder or neck pain while pacing, turn off the patient's diaphragmatic pacemaker and notify the patient's surgeon.** Such pain is generally referred from the diaphragm and may require a temporary decrease in stimulator settings to improve patient comfort.
- At the midway point of a timed conditioning session, measure tidal volumes with a respirometer. Compare to initial readings and, using the BORG scale below, determine the effort to breathe. Make note of the patient's tidal volume, pulse oximeter reading and any comments, complaints, or discomforts in the patient's medical record. If the effort to breathe on the Borg scale is 4 or greater, or the patient's pulse oximeter reads below 90%, discontinue the conditioning session and return the patient to the mechanical ventilator.

Borg Scale (breathing effort)

0 = No breathlessness at all
 1 = Very slight breathlessness
 2 = Slight breathlessness
 3 = Moderate breathlessness
 4 = Somewhat severe breathlessness
 5 = Severe breathlessness
 7 = Very severe breathlessness
 10 = Maximum breathlessness

- Prior to ending a conditioning session, measure tidal (breath) volumes with a respirometer. Make note of tidal volume measurements, pulse oximeter reading, breathing effort, and any comments, complaints, or discomforts.
- If the patient remains comfortable and shows no signs / symptoms of tiring, the conditioning session can be continued unless otherwise ordered by the patient's physician.
- When a conditioning session is over, place the patient back on the ventilator and turn the stimulator off by depressing the two buttons at the same time.
- Allow an approximately 45-60-minute rest period between sessions.
- Conditioning notes should be reviewed with the physician to determine increases in conditioning time.

Conditioning while in a wheel chair / recliner:

- Place an abdominal binder on the patient and make sure it does not constrict the rib cage.
- Ensure that the stimulator is secured to the patient so that it cannot fall out of the chair; this can dislodge the electrode wires and/or break the patient cable.
- Be aware that the duration of a conditioning session the patient tolerates may initially be shorter than that of a conditioning session performed while in bed.
- Sessions should last as long as the patient can tolerate (initially, 1-2 minutes is acceptable)
- While up in a chair, condition as frequently as possible with 45-60 minutes rest periods between sessions.

STOP the conditioning session and place the patient back on the ventilator:

- If you notice any change in heart rate or feeling of chest discomfort.
- If signs of shortness of breath or any discomfort persists or worsens.
- If oxygen level drops below 90%.
- If management of secretions becomes difficult.
- If the patient's Borg scale is 4 or greater.

TROUBLESHOOTING (6)

The following guide can be helpful in troubleshooting potential problems with the DPS system:

Problem	Action
Pacing of the diaphragm stops	<ol style="list-style-type: none"> 1. Check the connection of the electrode leads to the connector holder 2. Check the connection of the patient cable to the connector holder 3. Check the connection of the patient cable to the stimulator
Patient is not receiving adequate ventilation	Disconnect the stimulator and return the patient to a ventilator
Patient discomfort during pacing	Contact the patient's surgeon
Bleeding, bruising, or infection of the electrode implantation site(s)	Contact the patient's surgeon
Patient feels pain at the electrode site	Disconnect the stimulator and contact the patient's surgeon
Skin irritation or hypersensitivity to stimulation	Contact the patient's surgeon
"B"s or "C"s appear on the stimulator display	Diaphragmatic pacing is still occurring. Notify patient's surgeon if "A"s were present previously.
Four "X"s appear on the stimulator display	Disconnect the patient cable from the stimulator and insert the test plug. If the problem persists, contact Synapse Biomedical as the stimulator may need to be replaced. If the problem resolves with the test plug, replace the patient cable.
One or more "X"s appear on the stimulator display	Contact the patient's surgeon to evaluate the electrode block for possible electrode repair
The stimulator is exposed to substantial amounts of water or fluid	Disconnect the stimulator first, then contact Synapse Biomedical
A continuous audio alarm is heard during inspiration	<ol style="list-style-type: none"> 1. Check the connection of the electrode leads to the connector holder 2. Check the connection of the patient cable to the connector holder 3. Check the connection of the patient cable to the stimulator
The stimulator beeps every hour	The stimulator is running on its internal battery. Replace the main battery as described.
The stimulator beeps every minute	The stimulator is running on its internal battery and the internal battery is getting low. Replace the main battery immediately.

Adapted from the Synapse Biomedical Caregiver Manual. https://www.synapsebiomedical.com/wp-content/uploads/2017/09/2017_SCI_Caregiver_Manual.pdf

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