
Diaphragmatic Pacing in Infants and Children with Congenital Central Hypoventilation Syndrome

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Abstract

Artificially supported ventilation is a mainstay of care for children with congenital central hypoventilation syndrome (CCHS). Determining the optimal type and duration of ventilatory support for each individual should proceed with careful consideration. Diaphragm pacing offers a number of advantages over positive pressure ventilation as an alternative method for providing artificial ventilatory support to children with chronic respiratory failure. With diaphragm pacing, the pacer sends electrical current directly

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to the phrenic nerves. Negative pressure ventilation is created by the child's diaphragm rather than by an external piston or blower of the mechanical ventilator. These benefits can substantially improve the quality of life of these patients and potentially optimize both behavioral and neurocognitive development in these children, especially in toddlers. This chapter explores important considerations including the pros and cons of diaphragmatic pacing.

Introduction

History of Congenital Central Hypoventilation Syndrome and Diaphragm Pacing

Understanding the etiology and treatment of individuals with a loss of *automaticity* of breathing is a long-standing but ongoing endeavor. The earliest description of this loss of *automatic* breathing while asleep was reportedly in 1955 [1]. The earliest clinical use of the literary misnomer Ondine's curse ("Undine's curse") was in an abstract published in 1962 by Severinghaus and Mitchell; therein, they described three adult patients with "loss of automatic breathing" demonstrated by severe central apnea during sleep following surgery for high cervical and brainstem surgery [1, 2]. It was not until 1970 that Mellins and his colleagues described the first infant with loss of automatic breathing and clinical features consistent with what is now widely termed congenital central hypoventilation syndrome (CCHS) [3]; that reference linked the term "Ondine's curse" with CCHS in reference to the described infant.

According to folklore, Ondine was a beautiful mermaid who lost her gift of immortality because she fell in love with a mortal named Hans. Though Hans promised that his every waking breath would be his pledge of love and faithfulness to Ondine, he was later unfaithful and left Ondine for another woman. This act of betrayal infuriated Ondine's father, Poseidon, ruler of the sea. Consequently, Poseidon placed a curse on Hans that none of his *automatic* bodily functions would occur unless he consciously willed them. The story ends with Hans about to fall asleep knowing that he will die because he will "forget to

breathe" [1]. Though compelling as a way to remember the nature of lost automaticity of breathing, the term "Ondine's curse" is considered an inappropriate comparison to CCHS and a literary misnomer for the following reasons: (1) Ondine did not place the curse on Hans, it was Poseidon's curse; (2) it would be inappropriate to suggest that children with CCHS are cursed or to suggest that they "forget" to breathe; and (3) the antiquated term has referred to individuals with altered control of breathing secondary to multiple etiologies, whereas CCHS is a well-defined genetic disorder due to mutations of the paired-like homeobox 2B (*PHOX2B*) gene resulting in dysregulation of *automatic* functions, which we now term autonomic nervous system dysregulation (ANS) [4, 5].

In individuals with CCHS, artificially supported ventilation is a mainstay of care, and determining the optimal type and duration of ventilatory support for each individual should proceed with careful consideration. Among the various types of artificial ventilatory support, diaphragm pacing can be an advantageous option in the appropriate patient. Electrical stimulation to cause diaphragmatic contraction was first reported in 1777 in a treatise by Carvallo [6]. In 1783, Hufeland utilized electrical stimulation of the phrenic nerve to induce contraction of the diaphragm in a dissertation entitled, *The Use of Electricity in Asphyxia* [7]. In 1818, Ure demonstrated the feasibility of galvanic stimulation of the phrenic nerve through a series of experiments on the cadaveric body of a criminal immediately following execution [8]. In 1871, Beard and Rockwell reported a practical treatise on the medical and surgical uses of electricity, with a devoted section entitled, "*Artificial Respiration by Electrization*" [9]. They described "the

Fig. 42.1 The minimally portable Avery Model S-242 was the first commercially distributed diaphragm pacemaker (Photo courtesy of Avery Biomedical Devices, Inc.)



process of exciting respiration by faradization” and the application of a current “firmly over the phrenic nerve at the outer borders of the sterno-leido-mastoid muscles.”

In 1872, Duchenne de Boulogne wrote, “It is apparent in all my experiments on men and on animals, alive and dead, that stimulation of the phrenic nerve by electrical current can produce contraction of the diaphragm” [10].

Progress in the clinical application of diaphragmatic pacing has been more apparent in the past century. The use of transcutaneous stimulation of six asphyxiated newborns, all of whom survived, was reported in 1927 by Israel [11]. In 1948, Sarnoff showed that in the absence of spontaneous respiratory activity, rhythmic stimulation of the phrenic nerve could duplicate minute volume, arterial blood oxygen, and carbon dioxide tensions [12]. Major advances in diaphragmatic pacing were made by Dr. William W. L. Glenn and his group at Yale University when in 1964 they reported the first results with diaphragm pacing via radio-frequency transmission [13]. Glenn, long considered the grandfather of modern diaphragmatic pacing, developed the methodology primarily for the care of quadriplegic patients. He and his colleagues then revealed in a large series of adult primarily quadriplegic

patients that diaphragm pacing is an effective and clinically useful modality [14].

In collaboration with Mr. Roger E. Avery, Dr. Glenn’s prototypes were brought into commercial distribution by Avery Laboratories, Inc. in the early 1970s. The first, and currently the only, commercially available diaphragmatic pacemaker in the USA approved for clinical use by the Food and Drug Administration (FDA) is produced by Avery Biomedical Devices, Inc (Commack, New York) [14]. Initially designed as a tabletop model that could allow for unilateral pacing (Fig. 42.1), the Avery system now is a portable model (Fig. 42.2) that fills a need for ambulatory, ventilator-dependent infants, children, and adults.

In the 1970s, Dr. Carl E. Hunt at Children’s Memorial Hospital (Northwestern University) introduced the use of diaphragm pacing into the pediatric population, targeting the ambulatory ventilator-dependent infants and children with CCHS [15]. Further reports of diaphragmatic pacing in infants and children soon followed. Taken together, this has now led to the development of a handful of centers in the USA and abroad with extensive clinical expertise in phrenic nerve stimulation to induce diaphragmatic pacing in children and adults.

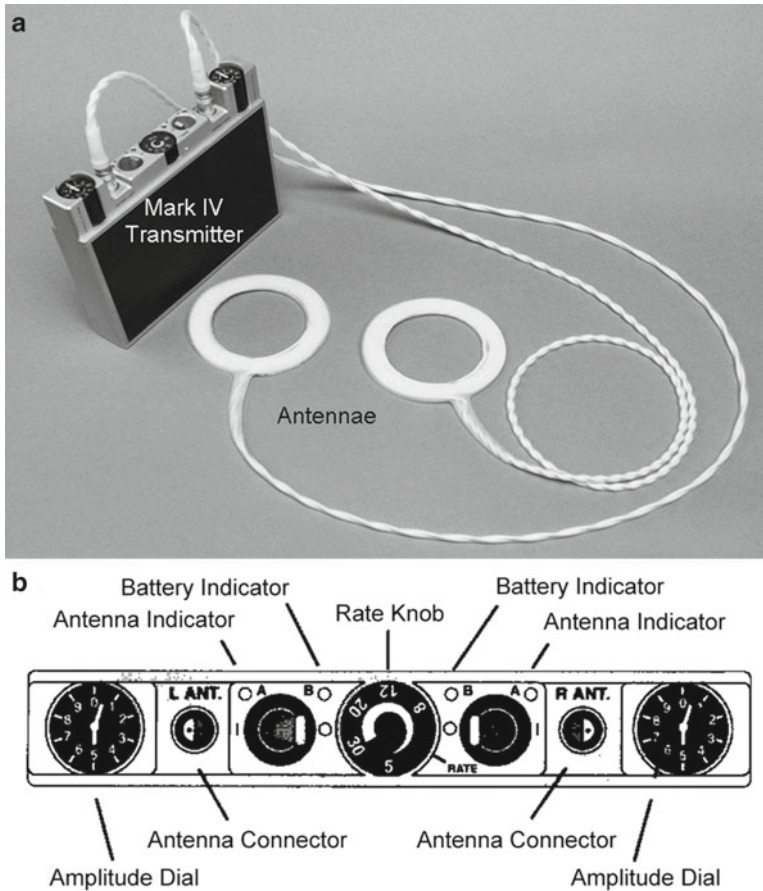


Fig. 42.2 (a) The Mark IV transmitter and antennae are shown. The ring is centered over the subcutaneously implanted receiver to optimize transmission of the signal. The transmitter and antenna are removed when the child is

not being paced. (Photo courtesy of Avery Biomedical Devices, Inc.) (b) Mark IV transmitter top panel (Schematic drawing courtesy of Avery Biomedical Devices, Inc.)

Rationale for Diaphragm Pacing in Pediatrics

Diaphragm pacing is an alternative method for providing ventilatory support to children with chronic respiratory failure. It offers a number of advantages over positive pressure ventilation as detailed later in this chapter. These benefits can substantially improve the quality of life of these patients and potentially optimize both behavioral and neurocognitive development in these children, especially toddlers who need to explore their environment in order to learn [16].

Portability

For children with CCHS who require assisted ventilation while awake and asleep, the primary benefit of diaphragm pacing is portability and improved quality of life due to improved mobility. For these children, assisted ventilation via diaphragmatic pacing during wakefulness allows for unrestricted mobility without the “tether” of ventilator tubing and a bulky ventilator. During sleep, these children will continue with supported ventilation via mechanical ventilator and tracheostomy. The external equipment used

for diaphragm pacing includes a small, light-weight transmitter and bilateral antennae. The transmitter is battery-operated (does not require an electrical power outlet) and can easily fit into a small backpack or purse. In this scenario, these paced patients can better participate in relatively normal activities, such as attending school and family outings. In moderation and with certain clearly defined restrictions (described later), patients may even be able to participate in non-strenuous sports activities. Since children with CCHS are typically intellectually intact and ambulatory, use of diaphragm pacing to improve mobility permits an improvement of lifestyle not possible by other forms of ventilatory support.

Facilitating Speech

Speech is audible with air movement around the tracheostomy tube (cap or Passy-Muir one-way speaking valve on tube), up through the vocal cords on exhalation. Though clear speech is possible with mechanical ventilation, speaking with diaphragm pacing support may be easier for the individual with CCHS. Paced breaths stimulate inspiration, but do not have an active role in exhalation. This exhalation without the continuous flow of the ventilator or without constant pressure present with mechanical ventilation (PEEP) may facilitate speech. Another factor that may play a role in ease of speaking with diaphragm pacing is that the individual may be able to sense the start of the impulse to initiate inspiration and have a moment to adjust speech before the full pulse train is delivered. The individual can also override the diaphragm pacing impulse, as volitional control of breathing is not affected with diaphragm pacing. Though not studied systematically, diaphragmatic pacing may facilitate speech as compared to speaking with mechanical ventilator support.

Tracheostomy Decannulation

In children who will be using diaphragm pacing during sleep only, tracheostomy decannulation is a consideration. For these children, spontaneous

breathing is adequate during wakefulness, and assisted ventilation with diaphragmatic pacing is provided during sleep. Removal of the tracheostomy offers independent benefits (decreased, but yet unproven, likelihood of tracheal stenosis, malacia, tracheal-inominate fistula, and chronic infections). However, upper airway obstruction can occur during inspiration on paced breaths (diaphragm pacing induces negative pressure ventilation from the diaphragmatic contraction) and needs to be addressed before tracheostomy decannulation. An adenotonsillectomy should also be considered prior to decannulation to minimize airway resistance and optimize successful decannulation.

Negative Pressure Ventilation

Physiologic negative pressure ventilation (in contrast to positive pressure ventilation from a mechanical ventilator) is restored with diaphragm pacing. Though unproven, diaphragm pacing by negative pressure potentially reduces the risk of pulmonary barotrauma (from positive pressure ventilation) and lower lobe atelectasis (seen with long-term positive pressure ventilation). Negative pressure ventilation may potentially improve respiratory muscle function, arterial blood gases, and survival in patients with neuromuscular and chest wall disorders [17], though this has not been confirmed in CCHS patients with diaphragm pacers.

Diaphragm Pacing Technology

Over the past four decades, several systems have been developed with intention for clinical use to provide phrenic nerve stimulation and thereby diaphragmatic pacing. Currently, the Avery Mark IV Breathing Pacemaker (Avery Biomedical Devices, Inc., Commack, NY) is the only phrenic nerve stimulator with full premarket approval from the FDA for use in the USA (Fig. 42.2) [18]. Two other systems have been developed subsequent to the Avery system, but neither has FDA approval for use in children with CCHS in the USA.

The Atrostim phrenic nerve stimulation (PNS) device (Atrotech Ltd., Tampere, Finland), introduced in the USA in 1991, offered “multipole sequential stimulation” via a quadripolar phrenic nerve electrode system. This technology was successful in achieving pacing in some individuals in whom the Avery technology had not been [19]. The Atrostim PNS never achieved FDA approval and is no longer available in the USA.

The NeuRx Diaphragm Pacing System (Synapse Biomedical, Inc., Oberlin, Ohio) received FDA approval in June 2008 for use in ventilator-dependent spinal cord injury patients who lack voluntary control of their diaphragms. The device consists of four electrodes implanted underneath the diaphragm mapped in the distribution of the phrenic nerve and a fifth electrode under the skin [20]. All electrodes are connected to an external battery-powered pulse generator providing timing and control of the electrical stimulation, thereby regulating the movement of the diaphragm muscle bilaterally. This system is currently not approved for clinical use in CCHS patients or patients less than 18 years of age.

The Avery system has undergone upgrades and modifications with earlier models exhibiting premature failure due to limitations of receiver and/or electrode design. In March 1998, the US Food and Drug Administration gave premarket approval to the new Mark IV external transmitter, which is the current system in use by Avery Laboratories, Inc. Consequently, the primary focus of this chapter will be on the FDA-approved Avery diaphragm pacer system as it applies to children with CCHS.

The Mark IV Avery pacing system consists of (1) an external transmitter that supplies power to the pacing system via 9-V batteries, (2) external antennae, (3) small implanted radio-frequency receivers, and (4) single-contact, implanted platinum phrenic nerve electrodes (Figs. 42.2 and 42.3). The Mark IV transmitter (dimensions: 146 mm × 25 mm × 140 mm; weight with two 9-V batteries: 540 g) houses the “controls” used to adjust the stimulus parameters in order to optimize diaphragm pacing for the individual patient. The transmitter utilizes two independent stimulus generators that are electronically linked to allow

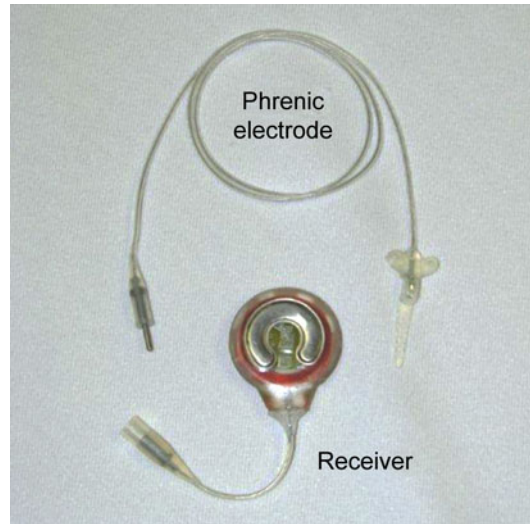


Fig. 42.3 The phrenic nerve electrode wire and receiver are shown. They are detached from one another during phrenic nerve electrode placement to facilitate passage of the male end of the electrode through the diaphragm. The long tab on the electrode can be reduced by half its length to facilitate insertion into the chest and positioning under the phrenic nerve. The long tab is *never* looped back over the electrode as that method would result in potential nerve entrapment (Photo courtesy of Avery Biomedical Devices, Inc.)

for simultaneous bilateral phrenic nerve stimulation at the respiratory rate determined to be optimal for the individual patient (these are “set” on the transmitter after careful physiologic assessment). The independent stimulus generators provide for distinctive unilateral settings of the stimulus amplitudes, stimulus pulse widths, pulse intervals, and slopes. Setting these variables independently with a digital oscilloscope and surface electromyogram electrodes allows for optimization of each diaphragmatic contraction and compensates for significant phrenic nerve differences or differences in scar tissue formation between the electrode and phrenic nerve on each side.

Each antenna (902A or 902AL) is a flat, donut-shaped, silicon-covered loop that is 80 mm in diameter and comes in a 1 or 2 m length. When placed over the subcutaneously implanted receiver, the antenna transcutaneously transfers the Mark IV transmitter-generated radio-frequency energy stimulus to the phrenic nerves.

The implanted receivers may be monopolar or bipolar (I-110A monopolar or I-110 bipolar). The choice of implanted receiver is based on the type of phrenic nerve electrode. Each small, disk-shaped receiver (30 mm in diameter, 9 mm thick, and 7.5 g in weight) contains electronic circuitry embedded in epoxy resin and coated with silicone rubber. The implanted monopolar receiver is composed of a single connector that employs an integrated anode plate, utilizing the patient's body tissue to complete the electrical stimulus circuit. The bipolar receiver is composed of two connectors that isolate the electrical stimulus circuit from the patient's internal body tissue. Each receiver converts the stimulus energy from the transmitter into very distinct stimulus pulses and transfers these pulses via a stainless steel wire to the platinum electrodes in contact with the thoracic phrenic nerves.

The implanted phrenic nerve electrodes may be monopolar or bipolar (E-377-05 monopolar or E-325 bipolar) and correspond to the implanted receivers. The implanted single-contact, platinum electrodes are attached to highly flexible, stainless steel fibers that are insulated by silicone rubber. The monopolar electrodes are composed of a single wire assembly and may only be used with the monopolar receivers. The bipolar electrodes are each composed of two separate wire assemblies and may only be used with the bipolar receivers. The authors' preference is bilateral implantation of monopolar electrodes and monopolar receivers; thereby, each hemidiaphragm is stimulated independently.

Since the first Avery system design, the receiver has been modified to decrease the diameter and improve the epoxy encapsulation to approach a hermetic seal. The electrode has also evolved from a bipolar 360° full-cuff design placed around the phrenic nerve to a preferred 180° monopolar half-cuff design placed underneath the nerve. This electrode design alleviates concerns for nerve entrapment from scar tissue formation and potential constriction and prevention of normal nerve growth with advancing age [21]. A bipolar electrode remains available for those patients implanted with other medical devices, such as a cardiac pacemaker, to provide

an additional margin of electrical isolation [22, 23]. For patients who have both diaphragmatic and cardiac pacemakers, the preference is the monopolar electrode for diaphragm stimulation and a bipolar electrode to pace the heart.

Candidate Selection

Patients who are candidates for diaphragmatic pacing may be ventilator dependent secondary to a high spinal cord injury at the level of C2–C3 or higher or due to central alveolar hypoventilation such as CCHS. To be considered for diaphragmatic pacing, patients must have little to no pulmonary parenchymal disease and must have intact phrenic nerves, a normal diaphragmatic muscle, and an intact phrenic nerve-diaphragm axis bilaterally.

The importance of an intact phrenic nerve is critical for successful diaphragm pacing. The integrity of the nerve must be confirmed prior to implantation of a pacing system. Evaluation of nerve integrity can be achieved with fluoroscopic evaluation of the diaphragm and the "sniff test." Under fluoroscopy, voluntary contraction of the diaphragm is confirmed. This evaluation is dependent upon the ability of the patient to cooperate and to momentarily breathe without ventilator support. The phrenic nerve may also be evaluated by percutaneous phrenic nerve stimulation and subsequent visualization of diaphragmatic contraction and validation on a digital oscilloscope. Diaphragmatic pacing has not been successful in younger children if there is diaphragm paralysis on one side. This may be secondary to either phrenic nerve injury or an abnormal diaphragmatic muscle, such as eventration. Infants and toddlers require bilateral pacing to achieve the necessary tidal volume to provide adequate ventilatory support. Unilateral pacing, however, may be considered in adults and in older children when pacing is capable of producing adequate tidal volumes with unilateral contraction, though this would not be considered an ideal long-term form of management.

When it is determined that a patient is not able to sustain adequate gas exchange by spontaneous

ventilation during wakefulness, thereby needing mechanical ventilation, discussion about the option of using diaphragm pacing should begin. For patients with CCHS, the likelihood of requiring continuous ventilation is suggested by assessing the specific *PHOX2B* mutation, the disease-defining gene for CCHS. The *PHOX2B* gene normally has a 20 alanine repeat region in exon 3. The most common *PHOX2B* mutations are heterozygous mutations in this area; polyalanine repeat expansion mutations (PARMs) represent 90–92% of individuals with CCHS; genotypes range from 20/24 to 20/33 (normal genotype is 20/20). Among the individuals with a PARM, nearly all of the children with 20/24 and 20/25 genotypes will require sleep-only ventilatory support, some with the 20/26 genotype will require continuous ventilatory support depending on their level of activity, and those with the 20/27 to 20/33 genotypes are likely to be full-time ventilator dependent. In the remaining 8–10% of individuals with CCHS, a non-PARM (NPARM) will be identified. Children with NPARMs are also likely to be full-time ventilator dependent. Again, it is essential that each child with CCHS be studied thoroughly and serially in a pediatric respiratory physiology center with expertise in CCHS—to ascertain and confirm the nature and severity of the awake and asleep ventilatory needs [5], thereby informing families of their options.

The full-time, continuous ventilator-dependent patients seeking mobility during wakefulness are the ideal candidates for diaphragm pacing, based on the combined experience of the authors. These candidates must have intact and functional phrenic nerves and diaphragms. They should not have truncal obesity or lung disease, thereby minimizing the potential respiratory load. These patients may be paced during the day to allow the full mobility benefit from the pacing system and returned to the ventilator during sleep when mobility is not a concern. Patients who are ventilator dependent only during sleep may also potentially benefit from implantation if they are seeking tracheostomy removal. There are many hurdles to overcome, and the role of diaphragmatic pacing for the purpose of decannulation is controversial. Ideally, the medical team should provide conservative care and fully inform the child and family

of the risks and benefits of diaphragm pacing. Diaphragm pacers may be implanted in infancy in centers with a highly trained surgeon. The authors, however, generally recommend implantation after 18–24 months of age, as children with CCHS often have mildly delayed motor milestones, and the pacers are most advantageous when the toddler has achieved adequate gross motor development to take advantage of the increased mobility.

Patients are *not candidates* for an Avery diaphragmatic system if they have a C3–C5 spinal injury that damaged the lower motor neurons of the phrenic nerve or if they have direct injury and/or paralysis of the phrenic nerve. They are also excluded if they have a muscular dysfunction such as myasthenia gravis or muscular dystrophy. Patients implanted with the phrenic nerve electrode/diaphragm pacers cannot undergo magnetic resonance imaging (MRI) studies, as the internal components (receiver, stainless steel wires, and electrodes) of the diaphragm pacer may be attracted to the MRI magnet. Therefore, patients who require frequent MRIs, such as those with Chiari II malformation, may be excluded from consideration for diaphragmatic pacing, though computerized tomography (CT) offers an alternative for imaging that does not impact the implanted diaphragm pacing components. Overweight or obese patients are not ideal candidates for diaphragmatic pacing for two reasons: (1) increased adipose tissue between the antenna on the skin and the subcutaneously implanted receiver may make it difficult to provide adequate voltage settings to ensure consistent support and (2) increased respiratory load may be too much for the diaphragm to work against to create adequate tidal volumes with each paced breath. Therefore, in the event of development of significant weight gain or obesity following implantation of the pacers, diaphragm pacing would need to be replaced by another form of ventilatory support until sufficient weight loss occurs. Patients with “twidder’s syndrome,” a behavior disorder that results in twisting and avulsing the receiver from the connecting wire, would also not be ideal candidates for pacer insertion [21, 24, 25]. This would render the pacers unusable until surgical intervention for component replacement can occur.

Factors that should be considered when determining ideal diaphragm pacer candidates for nighttime use with tracheal decannulation include the following: (1) candidates must only require ventilatory support while asleep, or no more than 14 h per day maximum; (2) they are not regularly taking daytime naps; (3) they have a stable medical course requiring infrequent hospitalizations; and (4) they do not require full-time ventilatory support during minor acute respiratory infections.

Clinicians, patients, and families should be aware of the risks and limitations of diaphragmatic placement prior to implantation. Though the authors continue to observe that diaphragmatic pacing has significant benefits in improving the quality of life of many of its patients, successful use of diaphragm pacing requires consistent teamwork between the surgeons, the centers with extensive experience in the management of children with CCHS and of implanting and electrophysiologically setting diaphragm pacers, the referring physicians, the children, the families, and the home nurses. The decision for surgical implantation is only the beginning of a carefully planned long-term patient care process. Relatively few centers perform significant numbers of diaphragm pacer implantations in the USA. Even fewer centers have teams dedicated to the ongoing care of the paced individual. In order for diaphragm pacing to be successful, there must be a committed pediatric pulmonologist and pediatrician locally, working in collaboration with and maintaining close communication with the physicians at the dedicated centers with diaphragm pacing expertise. Consolidation of patients to a limited number of centers allows each subject to benefit from the most extensive experience available. This extensive experience is vital to the success of diaphragm pacing due to the delicate nature of the implantation and the complexity of electrophysiologically setting the diaphragm pacers.

Diaphragm Pacemaker Implantation Techniques

The original idea for diaphragmatic pacing involved electrical stimulation of the phrenic nerve or diaphragm directly with a resultant

diaphragmatic contraction [9]. This contraction with subsequent pacing has been obtained using a variety of techniques, which have evolved over time. The different options, in terms of chronological development and anatomical location for stimulus, have included (1) placement of the electrode directly on the phrenic nerve in the neck, (2) placement of the electrode on the mediastinal portion of the phrenic nerve in the chest [26–28], and (3) placement of stimulating electrodes on the undersurface of the diaphragm [20].

Placement of the electrodes directly on the phrenic nerve in the neck had the advantage in that the nerve was relatively easy to identify as it overlies the anterior scalene muscle. This approach avoided the alternative, which at that time was a bilateral thoracotomy. This approach, however, proved to be less than desirable because the electrode left a large and visible lump on the neck of the patient, which was more obvious in children, and its proximity to the tracheostomy raised a potential risk for contamination during implantation. Further, in the active child, there was a risk for local trauma to the phrenic nerve/neck that would necessitate replacement of the component. Other factors of cervical implantation to consider include that the phrenic nerve typically derives from cervical roots 3, 4, and 5 merging into the phrenic nerve, so it does not form a single trunk until in the lower thorax; consequently, only 75% of the nerve fibers may be captured if the electrode is placed in the neck. With neck implantation of the phrenic nerve electrodes, stimulation of adjacent neck structures, such as the sternocleidomastoid muscle and brachial plexus, may result in undesirable twitching of the neck and arm simultaneous to the diaphragm stimulation [29].

Intrathoracic phrenic nerve stimulation avoids the bulky electrode in the neck and extraneous stimulation of the neck muscles during pacing. Implantation initially required surgeons to perform bilateral thoracotomies to place the electrodes directly on the mediastinal portion of the phrenic nerves. This technique has the potential to be moderately painful, with up to four incisions: two thoracotomy incisions for implantation of the electrodes and two additional incisions for the subcutaneously implanted receivers. This approach required several days of hospitalization

and often required bilateral chest tubes. This technique has been modified and is described later in this chapter.

Direct stimulation of the diaphragm has been advocated by others with placement of the stimulating electrodes on the undersurface of the diaphragm using a minimally invasive laparoscopic approach [20]. It is currently promoted in adult patients with respiratory failure caused by spinal cord injury and amyotrophic lateral sclerosis. Electrodes are not placed directly on the phrenic nerve. With this technique, the undersurface of each hemi-diaphragm is mapped and stimulated to identify two maximal motor points to which pacemaker electrodes are sutured. Then, the ends of the electrodes are tunneled externally and connected to a four-channel external stimulator. The goal of this pacing method is to provide pacing for 4-h periods, a duration that would be of limited value in the active child with CCHS. This technology, NeuRx Diaphragm Pacing System (Synapse Biomedical Inc., Oberlin, Ohio), is not FDA approved for use in children with CCHS.

In 1998, Shaul et al. described the first thoracoscopic implantation of phrenic nerve electrodes for diaphragmatic pacing in children [27]. The use of thoracoscopy potentially decreases perioperative morbidity, pain, and scarring that is typically associated with bilateral thoracotomies. It has encouraged wider utilization of diaphragmatic pacing in children, and this technique is the preferred approach today in patients with CCHS. The anesthesia considerations, positioning of the patient, and technique for implantation are described as follows:

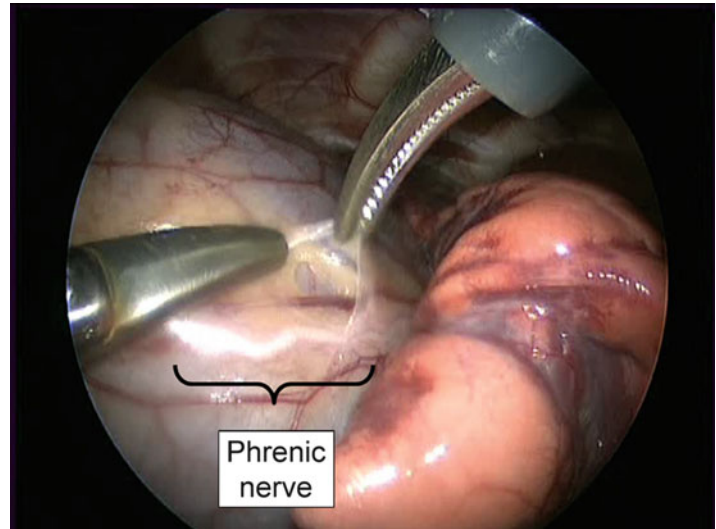
Anesthesia must be carefully administered to patients with CCHS as they are at high risk for bradycardia and asystoles [30] due to their autonomic dysfunction. Atropine should be readily available and given when necessary, though its effectiveness in CCHS has not been systematically considered. Muscle paralysis must be avoided to prevent interference with intraoperative testing of the electrodes, following placement on the phrenic nerves. Single lung ventilation is essential for visualization and the ability to retract the lung away from the mediastinum so that the phrenic nerve may be appreciated. Single

lung ventilation may be best achieved using contralateral main stem intubation with an appropriately sized cuffed endotracheal tube in children 10 years of age and below. In the authors' experience, this is almost always best achieved by standard orotracheal intubation, rather than intubation of the existing tracheostomy stoma, which is covered with an occlusive dressing during the procedure. In older patients, single lung ventilation may be accomplished with a double lumen endotracheal tube. A fiber-optic bronchoscope aids the placement and proper positioning of these tubes. The balloon should be carefully inflated to create a seal, which prevents ventilation of the desired lung during the thoracoscopic implantation. An arterial pressure monitoring line is optional. Bladder catheterization is recommended as the procedure lasts between 3 and 6 h, depending upon the experience of the surgical team.

Positioning of the patient should be done with the chest in a nearly full lateral position and the hip posteriorly inclined at a 45° angle. Simultaneous access to the chest and the upper abdomen is necessary for electrode placement in the thorax and receiver implantation in a subcutaneous pocket in the upper abdomen under the costal margin. The lower thoracic and upper lumbar spine may need to be rotated to allow the abdomen to be in a semilateral position. The use of a vacuum-extractable bean bag with padding facilitates this task. The surgeon and camera holder stand at the back of the patient. The scrub nurse and first assistant stand across from the surgeon. Two monitors should be utilized to allow surgeons, assistant, and scrub nurse to visualize the procedure. The patient is further prepared preoperatively with a dose of parenteral antibiotics, preferably vancomycin, administered in the standard dosages and continued postoperatively for 24 h.

The technique typically requires three trocars (3 or 5 mm) to be placed in the anterior axillary line in approximately the 5th, 7th, and 9th intercostal spaces. A fourth trocar may be inserted as an additional lung retractor if needed. The lung is deflated, with the assistance of single lung ventilation, and reflected posteriorly. The phrenic nerve is identified as cephalad as it can be

Fig. 42.4 A thoracoscopic view of the phrenic nerve. A parallel incision is made along the phrenic nerve in preparation for electrode placement



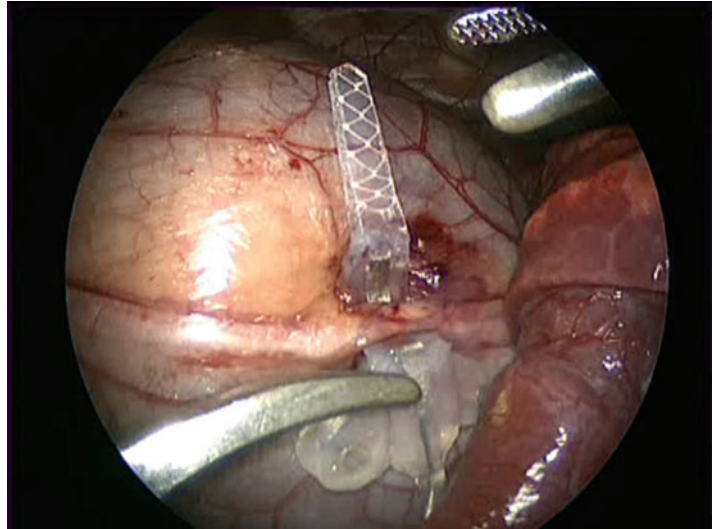
effortlessly accessed. The initial location of electrode implantation on the phrenic nerve is on the pericardium in the mediastinum as the pulmonary hilum typically prevents accessing the nerve more cephalad. Proximal placement of the electrode leaves the distal phrenic nerve available should future electrode replacement be required. Small parallel incisions are made on the mediastinal pleura anterior and posterior to the phrenic nerve (Fig. 42.4). These should be kept to a length of 1 cm or less to help stabilize the electrode. The distal “male end” of the electrode wire assembly is passed into a 2-in. length, quarter-inch width penrose drain and held in position with a circumferential externally applied tie. The use of the penrose facilitates passage of the electrode wire in and out of the chest without having to handle the electrode wire and potentially damage the wire or its insulation, which may result in failure. The entire electrode wire assembly is then placed into the chest through the inferior-most trocar site, which should be enlarged slightly to prevent damage to the delicate electrode. The electrode is passed through the incisions in the mediastinal pleura and positioned under the phrenic nerve so that the nerve rests comfortably in the groove on the platinum electrode (Fig. 42.5). The electrode is held in that position with 2 or 3 nonabsorbable 4–0 sutures using intracorporeal knots.

In preparation for implantation of the receivers, a 4–5-cm subcostal incision is then made on the upper abdomen. When inserting bilateral receivers, the receivers are ideally placed 6 in. (15.2 cm) from the center of one receiver to the center of the second receiver.¹ For cosmetic purposes, the incisions and receivers are also ideally placed at the same distance distal to the rib cage inferior margin and at the same distance lateral to the umbilicus. A 4×4-cm subcutaneous pocket is then created inferiorly to house the receiver and a SILASTIC® pouch containing the electrode-receiver connection. A large tonsil clamp is passed through the upper edge of the pocket under the costal margin, through the periphery of the diaphragm and into the chest. The end of the penrose is grasped with the clamp, and the distal end of the electrode wire is pulled carefully down into the subcutaneous pocket. The penrose is removed, and the electrode wire’s male connector is exposed and connected to the female connector of the receiver. The receiver is placed into the subcutaneous pocket with its functioning side down.

In the presence of the surgical and medical pacing team and an Avery engineer, the transmitter is turned on. A sterile antenna is placed over

¹Personal communication, Ken Aron, Vice President, Sales and Marketing, Avery Biomedical Devices.

Fig. 42.5 A thoracoscopic view of the phrenic nerve following placement of a pacing electrode. Note how the nerve rests comfortably in the groove on the platinum electrode



the implanted receiver and a current is applied, testing the function of the receiver. The subsequent diaphragm contraction is verified. If the phrenic nerve electrode is properly positioned, the pacing team will demonstrate that the diaphragm contracts at a relatively low threshold. If necessary, the electrode can be repositioned until minimal electrical threshold to elicit a diaphragm contraction is documented. Once the testing is completed and successful contraction confirmed, the connection between the receiver and the electrode and excess wire is placed in a 3×3-cm SILASTIC® pouch. The pouch is made by folding over a sheet of SILASTIC® and suturing closed the edges, with the connection inside. The SILASTIC® pouch is important because it prevents direct scar tissue formation around the excess electrode wire, receiver wire, and their connection, which, in the event of an electrode or receiver failure, permits subsequent electrode and/or receiver replacement. This also allows redundant wire to be pulled into the chest during growth and prevent traction on the phrenic nerve. The receiver is placed in the subcutaneous pocket, conducting side down, and the pouch containing the connection is placed over it. The signal transmission and electrical thresholds are again confirmed by the medical pacing team before the incisions are closed. A small chest tube is

placed in the apex of the chest through the inferior-most trocar site and connected to a pleural suction device. The patient is then repositioned to complete the procedure on the contralateral side. If necessary, the endotracheal tube is also repositioned.

Upon completion of the second side of pacemaker implantation, the patient is returned to the supine position and a chest X-ray is taken. This is to evaluate for a pneumothorax and to document the baseline location of the electrodes. If there is no air leak from the chest tubes and the lungs are well inflated on the chest X-ray, the chest tubes are removed at the end of the procedure. Otherwise, they are left on suction and are removed in the postoperative period using standard chest-tube protocol.

In the authors' experience, postoperative atelectasis is very common following the procedure. To alleviate this, it is necessary to provide positive pressure ventilation using a standard mechanical ventilator in the intensive care unit for the initial 1–3 postoperative days. It is also important to make sure that adequate inspiratory pressures can be achieved using the patient's tracheostomy, often requiring a cuffed endotracheal or tracheostomy tube. Transition to the home ventilator settings should be made on the day before hospital discharge.

Medical Management and Setting of Diaphragmatic Pacing

Timing

The initial evaluation to set the diaphragmatic pacers occurs 6–8 weeks following surgical implantation of the internal components, with follow-up every 6 months for the first 18 months, and then annually. More frequent follow-up is necessary in children younger than 3 years of age. It is important for medical management to occur in a center that is dedicated and experienced with care of individuals with CCHS and diaphragmatic pacing. At this type of center, the transmitter is set during mild sedation or while the child is sleeping, allowing for accurate determination of initial settings without the interference of volitional breaths or the patient's resistance to stimulated diaphragm contraction, as may occur with increased anxiety. This technique has been published previously [21] and is briefly described later.

Determining Diaphragm Pacer Settings

The methodology for electrophysiologic setting of the pacers is a time-consuming and arduous process that requires use of a digital oscilloscope. Specifically, the antenna wire is looped through an Inductive Antenna Coupler (Avery SK549, Commack, NY), then placed over the implanted receiver to synchronize the oscilloscope sweep with the stimulating pulse output. Surface electromyogram (EMG) electrodes are positioned at the costal margin bilaterally to record the stimulus pulse and the diaphragmatic action potential. The EMG signals are amplified (Grass P15, 1,000 \times , 10–1,000 Hz; Grass Instruments, Quincy, MA) and displayed on an oscilloscope (Tektronix DPO7054 Digital Phosphor, Beaverton, OR).

The transmitter is adjusted to optimize the diaphragmatic contraction and minimize the electrical stimulation of the phrenic nerves. The amplitude, pulse interval, slope, pulse width, and range are set to obtain a stimulating “pulse train” over the inspiratory period to generate a forceful

diaphragmatic contraction and a subsequent effective tidal volume. The recurring pulse train to trigger an inspiration is determined by the respiratory rate setting. Collectively, the effect is optimization of minute ventilation. Passive exhalation occurs between each pulse train stimulus.

Each phrenic nerve and hemi-diaphragm is set independently. The Mark IV transmitter external controls consist of an on/off switch, an amplitude dial, and a rate knob (Fig. 42.2). The amplitude dial controls the electrical stimulus output level, which will determine the force of the diaphragm contraction. The amplitude knob should be set to zero before turning on the transmitter. Once the transmitter is turned on, the amplitude dial is slowly adjusted to higher values until a visible diaphragm contraction is detected on the patient and an action potential is visualized on the oscilloscope. The dial should then be further turned to higher values until a maximum diaphragm contraction is reached. This is the point at which an increase in electrical output will not elicit a stronger diaphragm contraction or a further increase in diaphragm action potential amplitude on the oscilloscope. When the optimal amplitude setting has been determined, the Mark IV internal controls are adjusted. This is crudely accomplished with a screwdriver and a flashlight on the “inside” of the transmitter (this aspect has not been modernized since the earliest pacers, reportedly due to financial incentives that restrict advancement of this technology). The initial “inspiratory time” is determined by the patient's age and respiratory rate. This is then adjusted based upon the effectiveness of the settings and the anticipated activity level of the patient. The aim is typically for an inspiratory time range of 600–1,000 ms and an interpulse interval range of 80–120 ms delivered during the entirety of the inspiratory duration. An “interpulse interval” will determine the space between each pulse in the pulse train. A shorter pulse interval will result in more electrical pulses per inspiration and a more impactful breath, while a longer pulse interval will result in fewer pulses per breath and a less impactful breath. The “slope” modifies the amplitude of the individual stimulating pulses of the pulse train. It is adjusted to allow for a smoother contraction and is typically left at a factory default

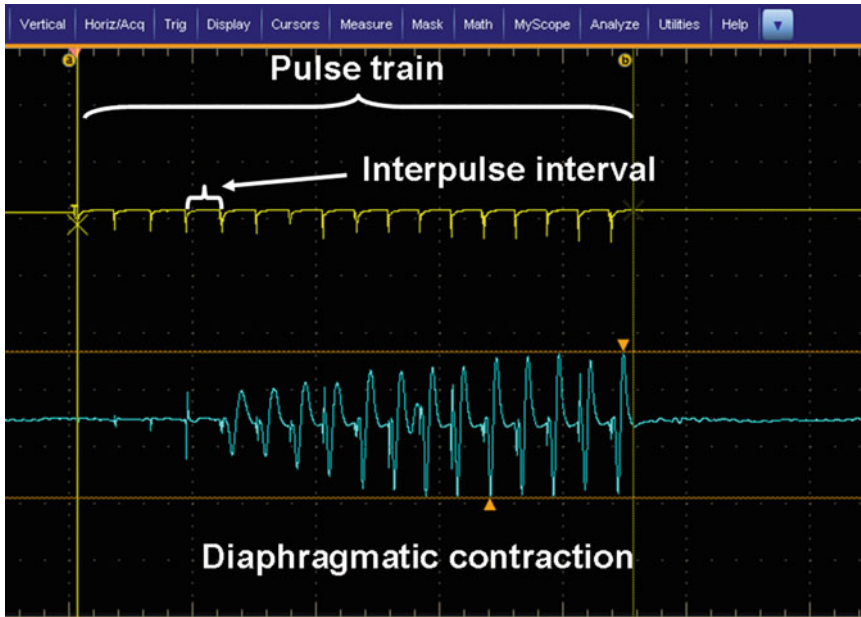


Fig. 42.6 A pulse train given over a set inspiratory time is demonstrated on a Tektronix DPO7054 Digital Oscilloscope. The distance between each stimulus signal is the interpulse interval

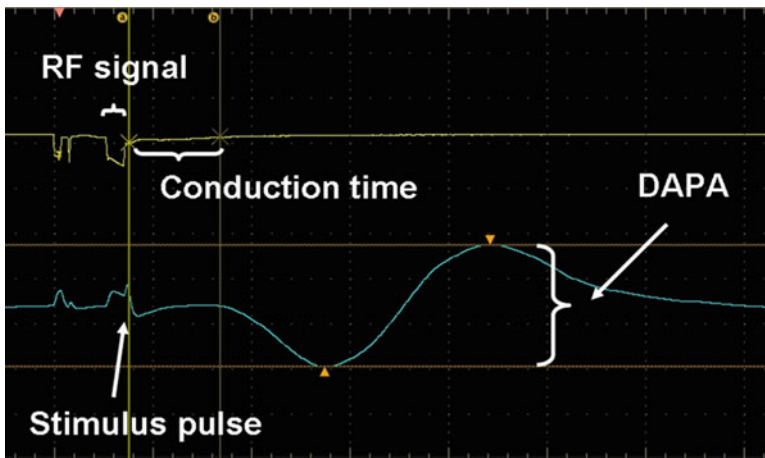


Fig. 42.7 A radio-frequency (RF) signal produced by the implanted receiver produces a stimulus pulse that travels to the phrenic nerve electrode. The time interval of signal transfer to the phrenic nerve is the phrenic nerve

conduction time (PNCT). This results in diaphragmatic contraction and generation of diaphragmatic action potential amplitude (DAPA), as measured on the digital oscilloscope

of zero. The “pulse width” is also factory set at 150 μ s, and the “range” is factory set with a maximum of 9.5 V (Figs. 42.6 and 42.7).

When the transmitter is ideally set, the goal will be to provide support to obtain end-tidal carbon dioxide values of 35–45 mmHg and

hemoglobin oxygen saturation values $\geq 95\%$. It is essential that each child receives two transmitters and that a backup transmitter is available in the event of transmitter damage/failure. Recognizing that a child’s ventilatory demands vary with activity, one transmitter is set to provide support

for rest or quiet activity and the other “backup” transmitter is set to provide optimal ventilation and oxygenation during high exertion/activity or exercise. These latter settings are determined during comprehensive testing and careful observation in a center dedicated to the care of children with CCHS and with expertise in diaphragm pacing.

Initiating Diaphragm Pacing

It is essential that the child is studied in the condition in which he or she will be using the diaphragm pacers. So if the child will be using the pacers during wakefulness, it is essential that comprehensive studies are performed during activities of daily living (with full physiologic recording). If the child will be using pacers during sleep, it is essential that comprehensive studies are performed during several nights of sleep (with full physiologic recording). Diaphragm fatigue will not be observed with the conservative settings described previously and with the shortest interpulse interval of 50 ms. During the course of the inpatient evaluation to set and initiate diaphragm pacing, the authors typically begin with 2–4 h, then gradually increase the duration with careful physiologic recording until the time of discharge. By the end of the 4-day admission, the child will typically be able to pace 8–10 continuous hours each day. Once home, the child can typically gradually increase by 1–2 h/week until reaching 12–15 h/day of continuous pacing. Flow sheets are provided for the families and home nurses to complete to confirm the success of diaphragm pacing in the home and compliance with the recommendations. Families are instructed that the diaphragm pacer transmitter must be “off” when the child is receiving positive pressure mechanical ventilation or when the child is being suctioned.

Other Considerations for the Diaphragmatically Paced Individual

There are several risks to be measured when considering diaphragmatic pacer implantation. This is delicate surgery, performed by a limited

number of surgeons in the world. Along with the usual risks associated with surgery and anesthesia, there is a potential risk that the phrenic nerve may be injured. This is a serious complication, but especially critical for the patient who only requires ventilation during sleep but relies on intact phrenic nerves for awake, spontaneous ventilation. As with any surgical procedure and implantation of foreign material into the body, there is also the risk that the implanted pacing system may become infected. This risk is reduced by having completely enclosed internal components. In the event of development of infection, it would likely necessitate surgical removal of the electrode, wires, and receiver [21] and prolonged antibiotics before consideration of reimplantation.

Diaphragm pacing uses mechanical equipment, and just as with any other mechanical equipment, it is subject to deterioration or technical problems. The internal components of the pacing system can break or malfunction. This may require a repeat operation for component replacement [21]. Likewise, external components may also break or malfunction and require replacement. Recognition of such component breakage/malfunction is the result of vigilance in management and close monitoring of the individual with diaphragm pacers.

The authors collectively have more than 100 years of experience in pacing patients with CCHS for 12–15 h a day, without evidence of irreparable nerve or muscle damage [21]. However, in spite of this experience, there are no data evaluating the lifelong effects of diaphragmatic pacing on the phrenic nerve or diaphragmatic muscle.

As stated previously, the diaphragmatic pacer is an alternative mode of artificial ventilation with the added benefit of enhanced mobility. The work of breathing is performed by the child’s diaphragm rather than by an external piston or blower of the mechanical ventilator. The care and vigilance needed to support these patients do not change. Clinicians need to proactively resist the insurance companies that advise withdrawing in-home nursing care, “because the child is now off the ventilator.” Observation and comprehensive physiologic monitoring of a child using diaphragm pacing is as important as for a child on

home mechanical ventilation. They will continue to require home end-tidal carbon dioxide monitoring and pulse oximetry in addition to the highly trained registered nurse during, at the minimum, all sleep time and ideally during all time that diaphragmatic pacing or mechanical ventilation is in use. It would be prudent for more independent individuals, such as adolescents and adults, who have chosen decannulation to invest in a medical alert bracelet so that in the event of development of loss of consciousness, they would be given respiratory support.

When diaphragm pacing is being considered for use during sleep in a patient seeking removal of the tracheostomy, it has been the collective experience of the authors that it is generally not possible to remove the tracheostomy and still perform diaphragm pacing under 6–9 years of age because of the high risk of development of upper airway obstruction and concern for development of midface hypoplasia in the growing child that requires chronic noninvasive (mask) ventilation. With normal, spontaneous breathing, synchronous neuronal impulses are sent to upper airway skeletal muscles, causing them to contract in order to maintain upper airway patency. Physiologically, the upper airway skeletal muscle tone decreases during sleep, especially during rapid eye movement sleep. With diaphragm pacing, one bypasses the brainstem respiratory centers. The diaphragm pacer sends electrical current directly to the diaphragm, and there is no synchronous neuronal activity to the upper airway skeletal muscles. This resultant upper airway obstruction is nearly universal in diaphragm pacer patients without a tracheostomy. Only with careful setting of the diaphragm pacers is support during sleep achievable, and even then, it seems that the children will experience some level of upper airway obstruction if the tracheostomy is removed (Fig. 42.8). Infants and toddlers have such severe obstructive apnea under these conditions that it is not possible to pace without a tracheostomy. Therefore, if the goal of pacing is to remove the tracheostomy, we do not generally consider diaphragmatic pacing implantation until patients are over 6–9 years of age and ideally much later [31].

A patient with CCHS and their family who consider decannulation must be willing to accept that diaphragm pacing without a tracheostomy is not as secure of a method of ventilatory support as tracheostomy and positive pressure ventilation. They are at risk, as described and illustrated previously, for respiration decompensation from airway obstruction when decannulated. The largest concern is that if damage occurs to the phrenic nerve, it may render a part-time ventilator-dependent patient into a full-time ventilator-dependent patient. Some damage to the phrenic nerve may be reversible with time, but transection of the phrenic nerve requires reanastomosis and regeneration to resume pacing [21, 32]. These concerns lead the authors to preferentially consider full-time ventilator-dependent patients as candidates for diaphragm pacing during the day for its mobility benefits and placement back on the ventilator in the evening for sleep. In contrast, diaphragmatic pacing in patients who require artificial ventilation during sleep only, and who are seeking tracheostomy removal, is only considered by the authors in extenuating circumstances. Once adulthood is reached, and the individual with CCHS can more actively participate in the decision, then diaphragm pacing during sleep with decannulation becomes a more reasonable consideration.

Troubleshooting Pacer Malfunction

In our experience, most of the diaphragm pacer failures involve the external components. A subset of failures will require replacement of the internal components of the diaphragm pacer system [21]. The following maneuvers would help confirm that external components of the system are functional; continued failure to obtain a diaphragmatic contraction suggests a problem with internal components.

Parents are instructed to examine the external diaphragm pacer components and the child daily for appropriate diaphragmatic contraction. Ideally, they hold the antenna over a transistor radio to confirm that the transmitter is generating a radio-frequency signal and the antenna is functional (the pulse train is audible over the radio). They

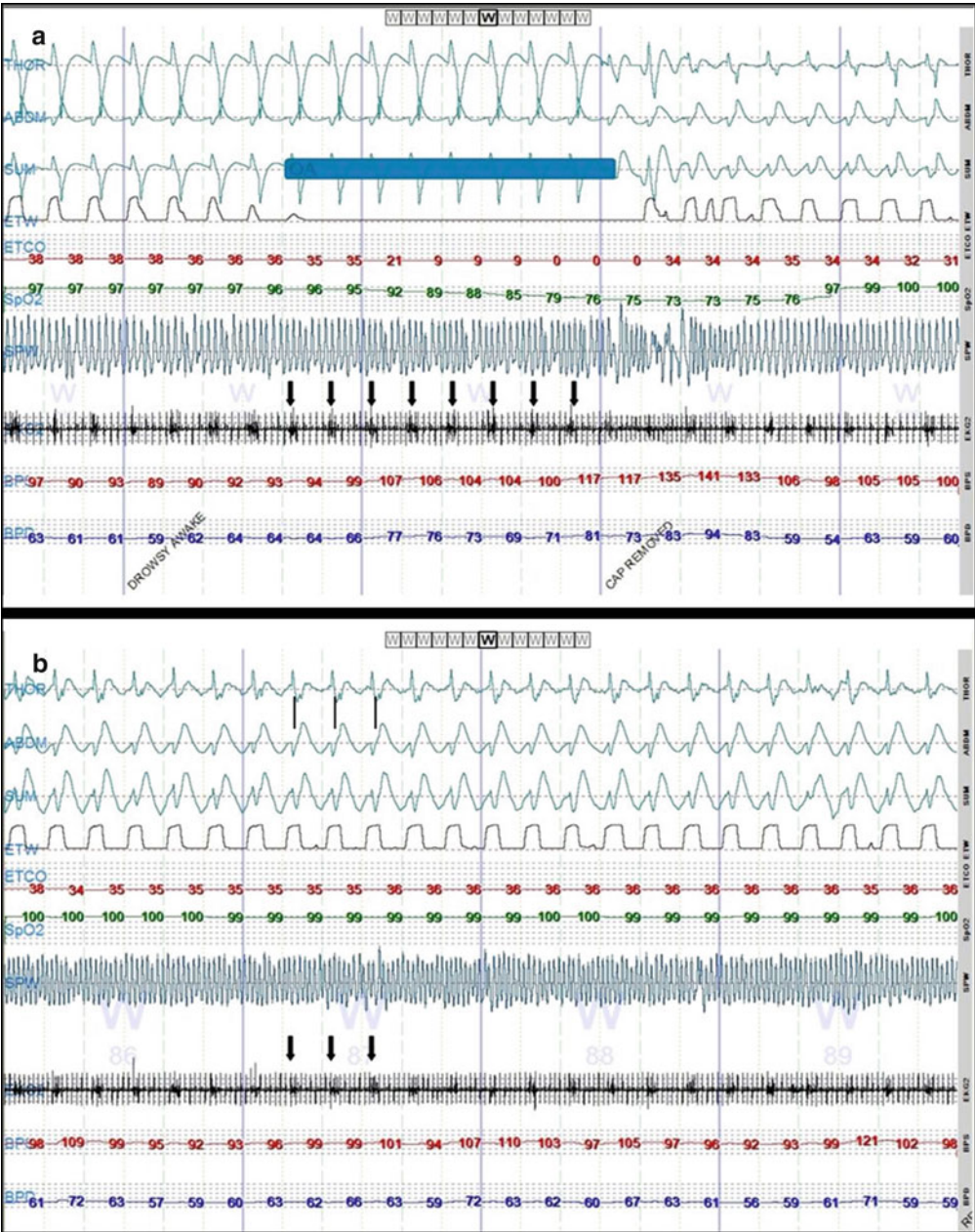


Fig. 42.8 Diaphragm pacing impulses can be visualized on the ECG channel, indicated by vertical arrows in **a** and **b**. **(a)** This recording was obtained during an overnight recording of an adolescent with CCHS in a state of drowsy wakefulness, lying supine, with her tracheostomy tube capped. It demonstrates complete airway obstruction (blue horizontal bar) and rapid development of hypoxemia (hemoglobin saturation nadir 73%) during 8 paced breaths. Note how abruptly this event occurs, making it easily missed by a caregiver until the hemoglobin saturation plummets. Recovery is rapid once the tracheostomy cap is removed. **(b)** This recording was obtained from the same adolescent shown in **a**, but early in the evening while awake, sitting upright, with her tracheostomy tube capped. It demonstrates paradoxical inward

movement of the chest on inspiration with delivery of each diaphragm pacing-induced breath (indicated by vertical arrows and bars). Note that paradoxical movement occurs during the delivery of the paced impulse, then breathing on the inductance plethysmography bands becomes inphase for the remainder of the breath. Collectively, these figures demonstrate the typical findings of airway obstruction during even drowsy wakefulness in the paced tracheostomy-capped child (not even sleep), with rapid development of severe physiologic compromise—symptoms that would be expected to be even more severe during sleep in the child whose tracheostomy was removed, hence the rationale for not recommending tracheal decannulation in the child who will be using diaphragm pacing during sleep

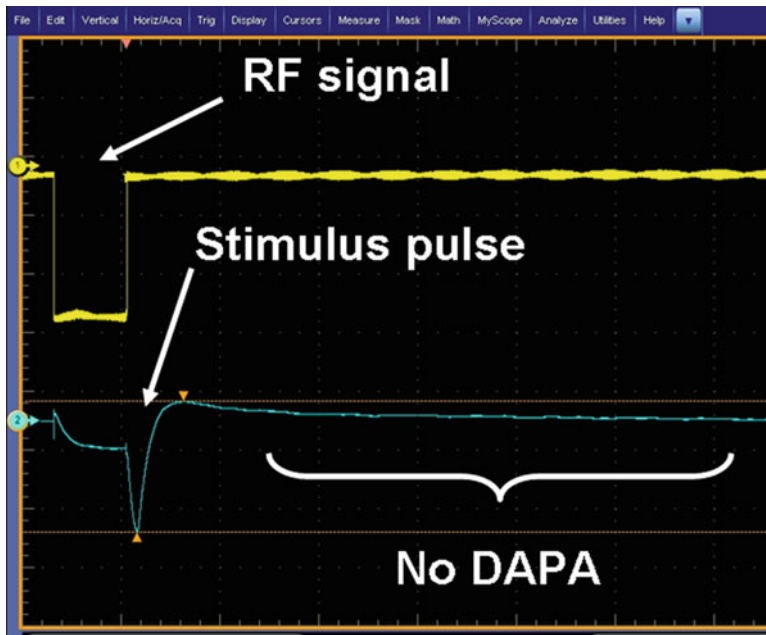


Fig. 42.9 Oscilloscope image of a failed electrode or damaged phrenic nerve. The radio-frequency (RF) signal and stimulus pulse are present, but a diaphragmatic action

potential (DAPA) is not seen. This indicates that the electrical signal is generated but does not reach the diaphragm

are instructed to assess each hemi-diaphragm independently and then together. If either diaphragm is not pacing, the parent is instructed to contact the team that implanted and maintains the diaphragm pacers. The parent is advised to sequentially (1) replace the battery, (2) replace the antenna, and (3) increase the amplitude setting by 1–2 U on the transmitter dial. If the child is only paced while awake and receives positive pressure ventilation via tracheostomy while asleep, then the child can be placed on the ventilator full time until the failure can be addressed. If the child uses pacing full time and had their tracheostomy decannulated, unilateral pacing may be able to provide adequate gas exchange in older children until the child can be seen by the diaphragm pacing team. However, if adequate gas exchange cannot be achieved with unilateral pacing, then the child needs to be immediately admitted to the hospital for an alternative form of ventilatory support. Frequently, this can be achieved with noninvasive positive airway pressure ventilation, avoiding the need for endotracheal intubation.

However, proper settings will need to be ascertained with comprehensive physiologic studies.

During an inpatient pacemaker evaluation to determine the cause of the dysfunction, the radio-frequency signal (from the transmitting antenna), stimulus pulse (from the electrode on the phrenic nerve), and the action potential (from the diaphragm) are assessed with a digital oscilloscope and surface electromyogram (EMG) electrodes at the costal margin. If neither a stimulus pulse nor an action potential is seen on the oscilloscope, the receiver has malfunctioned or a wire has broken, but its insulation has remained intact [21]. The receiver in this situation would need to be replaced. This requires operative repair, but does not require entry into the chest for replacement of the damaged component. If the radio-frequency signal and stimulus pulse are present, but a diaphragmatic action potential is not seen, this indicates that the electrical signal is generated but not reaching the diaphragm (Fig. 42.9). This may indicate that the wire insulation is disrupted, the electrode is no longer in contact with the phrenic nerve, or

that the phrenic nerve is injured. A break in a wire prevents transmission of the electrical impulse to the phrenic nerve. A chest radiograph is taken to evaluate for electrode position and a potential wire breakage. The patient will require general anesthesia with the thorax reexplored and a new electrode implanted in order to reestablish signal transmission. This is more involved than receiver replacement; scarring as a result of the initial electrode implantation may cause an exploratory evaluation for a broken or a damaged wire to be very difficult, especially if the initial placement was performed via open thoracotomy. In the single instance in which an electrode required replacement following initial thoracoscopic placement, minimal scarring was noted and the procedure was straightforward. When a malfunctioned electrode is replaced, a new electrode is typically placed distal to the previous electrode on the phrenic nerve. This potential for electrode replacement is why it is recommended that the initial electrode placement be as proximal as possible. The previous electrode wire is then severed while the actual electrode is left in situ. Attempts to remove the phrenic nerve electrode may damage the phrenic nerve and should not be pursued.

Diaphragm Pacer Outcomes

There has only been one life-table analysis published in children utilizing the Avery pacing system [21]. These data are more than two decades old but describe experience totaling 192 system years and 96 patient years of pacing. The internal component problems were classified into four categories: receiver failure, electrode wire or insulation breakage, infection, or mechanical nerve injury.

Receiver Failure and Electrode Wire or Insulation Breakage

In this analysis, 15 of 26 component failures were due to receiver failure. The receivers may have failed from fluid penetration of the epoxy encapsulation, component failure, or receiver wire

breakage occurred in one child with “twiddler’s syndrome” who twisted the receiver in the subcutaneous pocket, with subsequent wire breakage [24, 25]. Six of the 26 internal component failures were due to wire malfunction or breakage.

Infection

Infection is a known complication for all implantation surgery. In this series, four component infections occurred in 33 patients and 66 internal systems. Three of these patients required component removal and subsequent replacement [21].

Mechanical Injury to Phrenic Nerve

Two cases of mechanical injury to the phrenic nerve were reported. Although not strictly a component failure, this is undoubtedly the most serious “failure” that can occur. In one patient, the phrenic nerve was entrapped within a bipolar cuff electrode. Phrenic nerve function recovered by 4 months after removal of the bipolar electrode and placement of a more distal unipolar electrode. A second patient developed phrenic nerve dysfunction from traction on the nerve by the tethered electrode wire, which severed the edge of the nerve, leaving only a few fibers of the phrenic nerve intact. The phrenic nerve was reanastomosed and the nerve recovered. This patient has also subsequently resumed pacing. Surgical technique was modified to minimize these complications, including the use of a SILASTIC® pouch and monopolar electrodes as described in previous sections. No further cases of mechanical nerve injury have been observed since instituting these modifications [21].

Taken collectively, the life-table analysis was completed when the only method of implantation was an open thoracotomy. As experience grows with the thoracoscopic technique and with use of the smaller Avery receiver, it will be essential to repeat the life-table analysis project to more closely estimate the success of the current technique and technology and update the analysis from two decades prior.

Current Outcome Information

Currently, we estimate that more than 400 Avery breathing pacemaker systems have been implanted in infants and children over the last four decades in the USA, of which a subset are in patients with CCHS. The authors are aware of individuals who have been successfully paced with the Avery system for more than 30 years. Specifically, the longest use of diaphragm pacing in a quadriplegic patient who initiated diaphragm pacing as an adult is nearly 39 years; a pediatric patient (initiated at 15 years of age) is 36 years old, and a pediatric patient with CCHS (initiated at 2 years of age) is 34 years.² This information is reassuring regarding use of diaphragmatic pacing for long-term management, but also emphasizes the importance of development of an updated outcome review.

Summary: Future Directions

The volume of patients and low potential for financial gain has significantly limited advancement of the technology for diaphragmatic pacing. In spite of this, Avery Biomedical, Inc. is in active development of the next-generation transmitter. With an all-digital design that is smaller than the Mark IV, it will replace and feature improved mechanical and functional reliability. This includes improved battery life and the ability to store multiple parameter settings for enhanced functionality.³ While this promises to be an improvement over current technology, the long-term goal is a totally implantable biofeedback diaphragm pacer system that will be capable of sensing the patient's ventilatory needs and automatically adjust ventilatory demands of the patient.

²Personal communication with Ken Arons, Vice President, Sales and Marketing, Avery Biomedical Devices.

³Personal communication, Ken Aron, Vice President, Sales and Marketing, Avery Biomedical Devices.

References

1. Sugar O. In Search of Ondine's Curse. *JAMA*. 1978;240(3):236–37.
2. Severinghaus JW, Mitchell RA. Ondine's curse—failure of respiratory center automaticity while awake. *Clin Res*. 1962;10:122.
3. Mellins RB, Balfour Jr HH, Turino GM, Winters RW. Failure of automatic control of ventilation (Ondine's curse). Report of an infant born with this syndrome and review of the literature. *Medicine*. 1970;49(6):487–504.
4. Weese-Mayer DE, Shannon DC, Keens TG, Silvestri JM. American Thoracic Society Statement. Idiopathic congenital central hypoventilation syndrome: Diagnosis and management. *Am J Respir Crit Care Med*. 1999;160:368–73.
5. Weese-Mayer DE, Berry Kravis EM, Ceccherini I, et al. On behalf of the ATS Congenital Central Hypoventilation Syndrome Subcommittee. An Official ATS Clinical Policy Statement: Congenital Central Hypoventilation Syndrome. Genetic basis, diagnosis and management. *Am J Respir Crit Care Med*. 2010;181:626–44.
6. Beard GM, Rockwell AD. History of electro-therapeutics. In: A practical treatise on the medical and surgical uses of electricity including localized and general electrization. New York, NY: William Wood; 1871. p. 102.
7. Hufeland CW. *Usum uis electriciae in asphyxia experimentis illustratum*. *Dissertatio Inauguralis Medica*, Göttingen, Germany, 1783.
8. Ure A. An account of some experiments made on the body of a criminal immediately after execution, with physiological and practical observations. *J Sci Arts (Lond)*. 1819;6:283.
9. Beard GM, Rockwell AD. Artificial respiration by electrization. In: A practical treatise on the medical and surgical uses of electricity including localized and general electrization. New York, NY: William Wood; 1871. pp. 591–593.
10. Duchenne GBA. *De l'électrisation localisée et de son application à la pathologie et à la thérapeutique par courant induits et par courants galvaniques interrompus et continus* par le Dr. Duchenne. Paris, Baillière, 1872.
11. Israel F. *Über die wiederbelebung sheintoter neugeborener mit hilfe des elektrischen stroms*. *Z Geburtshilfe Perinatal*. 1927;91:601–22.
12. Sarnoff SJ, Hardenbergh E, Whittenberger JL. Electrophrenic respiration. *Science*. 1948;108:482.
13. Glenn WW, Hageman JH, Mauro A, et al. Electrical stimulation of excitable tissue by radiofrequency transmission. *Ann Surg*. 1964;160:338–50.
14. Glenn WW, Judson JP. Radio-frequency electrophrenic respiration. Long-term application to a patient with primary hypoventilation. *JAMA*. 1968;203(12):1033–7.
15. Hunt CE, Matalon SV, Thompson TR, et al. Central hypoventilation syndrome. Experience with bilateral

- phrenic pacing in 3 neonates. *Am Rev Respir Dis.* 1978;118:23.
16. Elefteriades JA, Weese-Mayer DE. The diaphragm: dysfunction and induced pacing. In: Baue AE, Geha AS, Laks H, Hammond GL, Naunheim KS, editors. *Glenn's thoracic and cardiovascular surgery.* 6th ed. Stamford: Appleton & Lange; 1996. p. 623–42.
 17. Corrado A, Gorini M. Long-term negative pressure ventilation. *Respir Care Clin N Am.* 2002;8:545–57.
 18. Mark IV Breathing Pacemaker System | Avery Biomedical Devices, Inc. <http://www.averylabs.com/breathing-pacemakers/markiv-system.html>. Accessed 6 Sept 2010.
 19. Weese-Mayer DE, Silvestri JM, Kenny AS, et al. Diaphragm pacing with a quadripolar phrenic nerve electrode: an international study. *Pacing Clin Electrophysiol.* 1996;19:1311–9.
 20. Onders RP, Elmo M, Khansarinia S, et al. Complete worldwide operative experience in laparoscopic diaphragm pacing: results and differences in spinal cord injured patients and amyotrophic lateral sclerosis patients. *Surg Endosc.* 2009;23:1433–40.
 21. Weese-Mayer DE, Morrow AS, Brouillette RT, et al. Diaphragm pacing in infants and children: a life-table analysis of implanted components. *Am Rev Respir Dis.* 1989;139:974–9.
 22. Kolb C, Eicken A, Zrenner B, Schmitt C. Cardiac pacing in a patient with diaphragm pacing for congenital central hypoventilation syndrome. *J Cardiovasc Electrophysiol.* 2006;17:789–91.
 23. Movahed MR, Jalili M, Kiciman N. Absence of device-device interaction (DDI) in a patient with cardiac and diaphragmatic pacemakers for congenital central hypoventilation syndrome. *Pacing Clin Electrophysiol.* 2005;28:1238–9.
 24. Ellis GL. Pacemaker twiddler's syndrome: a case report. *Am J Emerg Med.* 1990;8:48–50.
 25. Fitzgerald D, Davis GM, Gottesman R, et al. Diaphragmatic pacemaker failure in congenital central hypoventilation syndrome: a tale of two twiddlers. *Pediatr Pulmonol.* 1996;22:319–21.
 26. Glenn WWL, Phelps ML. Diaphragm pacing by electrical stimulation of the phrenic nerve. *Neurosurgery.* 1985;17:974–84.
 27. Shaul DB, McComb JG, Keens TG. Thoracoscopic placement of phrenic nerve electrodes for diaphragm pacing. *Pediatr Endo Innov Techn.* 1998;2:101–5.
 28. Shaul DB, Danielson PD, McComb JG, et al. Thoracoscopic placement of phrenic nerve electrodes for diaphragmatic pacing. *J Pediatr Surg.* 2002;37:974–8.
 29. Ali A, Flageole H. Diaphragmatic pacing for the treatment of congenital central alveolar hypoventilation syndrome. *J Pediatr Surg.* 2008;43:792–6.
 30. Gronli JO, Santucci BA, Leurgans SE, et al. Congenital central hypoventilation syndrome: *PHOX2B* genotype determines risk for sudden death. *Pediatr Pulmonol.* 2008;43:77–86.
 31. Chen ML, Keens TG. Congenital central hypoventilation syndrome: not just another rare disorder. *Paediatr Respir Rev.* 2004;5(3):182–9.
 32. Hunt CE, Brouillette RT, Weese-Mayer DE, et al. Diaphragm pacing in infants and children. *PACE.* 1988;11:2135–41.