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Phrenic Nerve Stimulation: Technology and Clinical Applications

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Abstract

Phrenic nerve stimulation is a technique used to reanimate the diaphragm of patients with central nervous system etiologies of respiratory insufficiency. Current clinical indications include congenital central hypoventilation syndrome, spinal cord injury above C4, brain stem injury, and idiopathic severe sleep apnea. Presurgical evaluation ensures proper patient selection by validating the intact circuit from the phrenic nerve through alveolar oxygenation. The procedure involves placing leads around the phrenic nerves bilaterally and attaching these leads to radio receivers in a subcutaneous pocket. The rate and amplitude of the current is adjusted via an external radio transmitter. After implantation, each patient progresses through a conditioning phase that strengthens the diaphragm and progressively provides independence from the mechanical ventilator. Studies indicate that patients and families experience an improved quality of life and are satisfied with the results. Phrenic nerve stimulation provides a safe and effective means for reanimating the diaphragm for certain patients with respiratory insufficiency, providing independence from mechanical ventilation.

History

In 1777, Cavallo was the first physician to claim that an electrical current could be used as a mechanism for artificial respiration. The modern-day concept of phrenic nerve stimulation began to take shape in 1818 when Andre Ure claimed to be able to restore ventilation in cases of suffocation, drowning, and hanging by direct stimulation of the phrenic nerve [1]. In 1872, Duchenne's seminal work on phrenic nerve stimulation in a patient showed that it was technically possible to conduct an electrical current through the phrenic nerve as a means of stimulating the diaphragm into a physiologically significant contraction [2]. Little technological advance with the

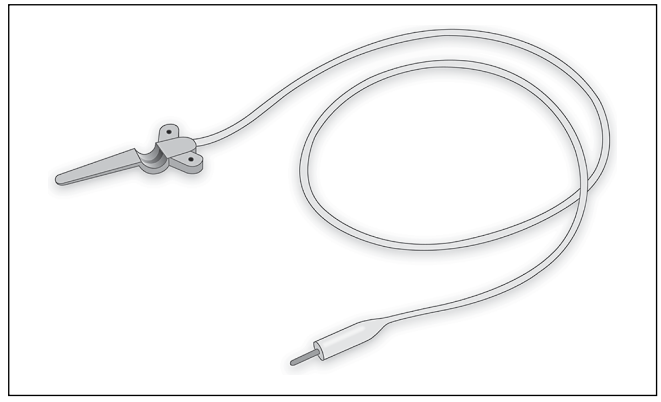

Fig. 1. Avery Mark IV Breathing Pacemaker System™ electrode lead and wire. The platinum lead is housed in silastic tubing that can be secured around the phrenic nerve. It is connected to a stainless steel wire with a connector terminus at the distal end (with permission from Avery Biomedical Devices).

technique was made over the following 150 years due to the advent and application of positive pressure ventilation or mechanical ventilation. Although the physiological aspects of electrical stimulation, muscle contraction, oxygenation, and carbon dioxide tension pressures were being elucidated, it was not until the pioneering work of William Glenn at Yale University that the intricacies of pacing and modulation began to be worked out. Meanwhile, battery technology improved, and the first implanted cardiac pacemaker was inserted in 1960. William Glenn used this newfound technology to stimulate the phrenic nerve in a patient on a long-term basis with much success [3]. Glenn partnered with Roger Avery to develop the first prototype that was brought to commercial distribution by Avery Laboratories Inc. (Commack, N.Y., USA) in the early 1970s [4].

Current Technology

Three major companies distribute phrenic nerve pacers throughout the world. Avery Laboratories distributes a pacemaker in the United States, the European Union, and several other countries. The Atrostim Phrenic Nerve Stimulator (PNS) V2.0 (Atrotech, Tampere, Finland) and Vienna Phrenic Pacemaker (MedImplant Biotechnisches Labor, Vienna, Austria) are the other two commercially available devices. Because the Avery Mark IV Breathing Pacemaker System™ is the only device approved for use in the United States and the European Union, it will be the focus of this discussion. The other systems differ from each other and the one discussed below, but these differences are not critical to the surgeon.

The Avery Mark IV Breathing Pacemaker System™ is comprised of two internally implanted electrodes and two radio receivers. The electrodes are manufactured from flexible stainless steel wire insulated by a silastic coating. The stainless steel wire is connected to a platinum nerve contact at the proximal end, and the distal end connects easily to the radio receiver (fig. 1, 2). An alternative configuration that contains

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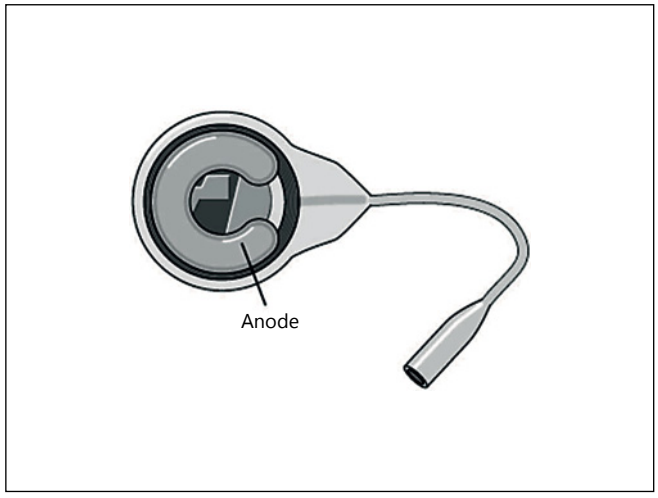

Fig. 2. Avery Mark IV Breathing Pacemaker System™ radio receiver. This internally implanted radio receiver connects to the lead and wire depicted in fig. 1. When connected, the radio receiver captures radiofrequency data that are sent by the radio transmitter and converts the data into an electrical signal that is propagated to the platinum lead connected to the phrenic nerve (with permission from Avery Biomedical Devices).

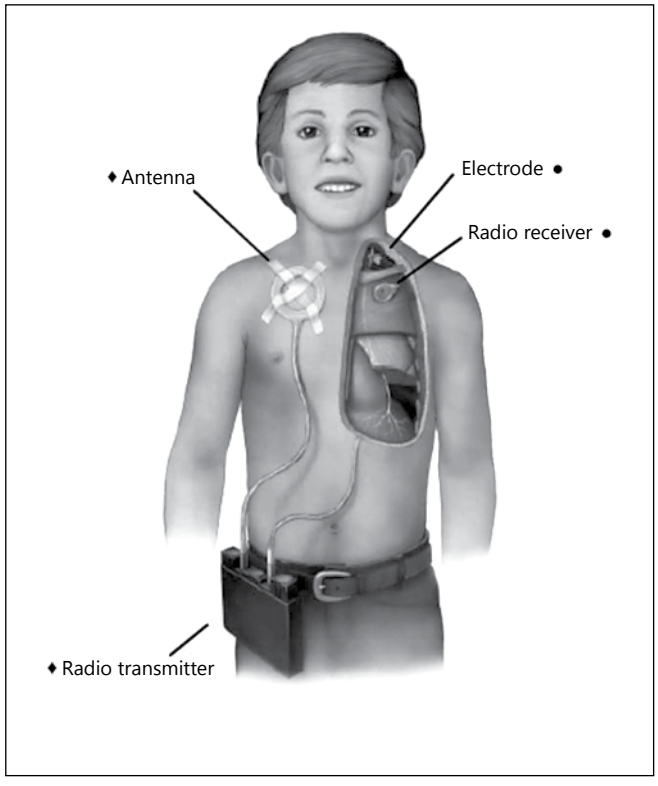

Fig. 3. Internal and external components that comprise the Avery Mark IV Breathing Pacemaker System™. This sketch depicts all components of the system, both internal (●) and external (◆) (with permission from Avery Biomedical Devices).

twin platinum contacts that connect directly to one receiver is also available. The smallest receiver has a 2.5-cm diameter and 0.55-cm thickness. All implanted elements are coated in silicon. An external antenna and radio transmitter are applied to the patient, as shown in figure 3. The manufacturer suggests that the antenna be replaced regularly every 6 months to avoid failure.

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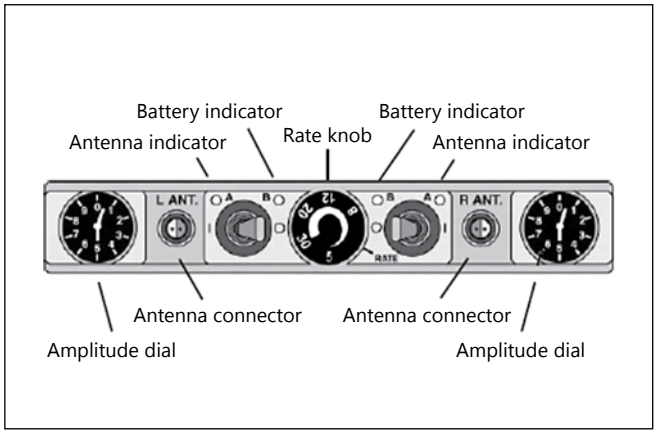

Fig. 4. Avery Mark IV Breathing Pacemaker System™ superior view radio transmitter. The external radio transmitter contains power-hungry battery functions, such as adjustment dials for the amplitude and rate output. Battery and antenna indicators help alert the patient or caregiver to impending maintenance that must occur for proper functioning (with permission from Avery Biomedical Devices).

The radio transmitter is the programmable element in the circuit and consumes standard alkaline batteries. Because surgically implanted materials do not contain power-hungry programmable components, patients can typically go for many years without needing revision surgery for impulse generator purposes. Figure 4 depicts the relevant components of the radio transmitter. The radio transmitter can be adjusted with respect to the amplitude and rate. That information is transmitted to the implanted radio receivers bilaterally, and electrical stimulation of the phrenic nerve ensues. With an intact nerve and diaphragm, simultaneous right- and left-sided contraction of the diaphragm takes place and a negative inspiratory pressure ensues, providing the force needed to expand the thoracic cavity and oxygenate the alveoli.

Clinical Indications

Phrenic nerve pacers are implantable devices that provide an electrical current to the nerve, resulting in diaphragmatic contraction. This mechanism contributes support for patients with chronic ventilatory insufficiency whose phrenic nerve, diaphragm, and lungs demonstrate adequate independent function. To meet these requirements, patients need to have intact C4 anterior horn cells, phrenic nerves, diaphragm, and alveolar function. While C3, C4, and C5 all contribute to the phrenic nerve, C4 forms the largest contribution. Thus, patients with a central lesion above the C4 anterior horn cells comprise the majority of the patients who can currently benefit from the procedure. Alternatively, patients with lesions that include the C4 anterior horn cells may be candidates for direct diaphragmatic pacing or the other procedures discussed at the conclusion of this chapter. Although not the focus of this chapter, it should be noted that there are similar methods for direct pacing of the diaphragm. However, properties of the muscular contraction will differ when compared to physiological stimulation via an intact phrenic nerve.

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Physicians have attempted to place stimulators in conjunction with phrenic nerve grafts in the setting of spinal cord stimulation [spinal cord injury (SCI)] below C3 and in cases of phrenic nerve injury from prior radiation or other causes. Although there are case reports of successful pacing and subsequent diaphragm conditioning, these are not typical indications. The current clinical indications include congenital central hypoventilation syndrome, SCI rostral to C4, brain stem injury, and idiopathic severe sleep apnea.

To date, congenital central hypoventilation syndrome and SCI comprise more than 75% of the patients who have received phrenic nerve pacers. Both populations, when appropriately selected, appear to benefit equally from the device. Patients have had phrenic nerve pacers placed for other indications with varying success, which is primarily due to patient selection. Patients with stroke, encephalitis, meningitis, and Shy-Drager syndrome may thus be candidates, although clinical decisions have to be strictly individualized in these cases.

Presurgical Evaluation

Candidates for the procedure must be carefully evaluated to ensure they meet the indications for implantation and successful pacing. Patients must be diagnosed with severe chronic respiratory insufficiency requiring mechanical ventilation or significant positive pressure support for more than 3 months. The viability of motor neurons should be confirmed prior to the procedure. Failure of diaphragmatic contraction after electrical stimulation is a contraindication. There may be exceptions to this dictum, as discussed in the last section of this chapter.

The viability of the phrenic nerve is critical and deserves a bit more attention. The best current means of testing its viability is by percutaneous electrical stimulation under fluoroscopy. The nerve is accessed in the neck where it passes over the anterior scalene muscle. When some axons in the nerve are viable, a brief low-amplitude contraction will occur. This is quite similar to a hiccup. A stronger contraction is desirable, and a more vigorous contraction will take place when all axons in the nerve are properly functioning [5]. The best means of assessing the strength of the contraction is on fluoroscopy. The unaided eye is not reliable due to patient factors such as age and body habitus.

The timing of these electrodiagnostic evaluations are critical and still a matter of controversy. A study in 2007 found that when tested in the acute phase after injury or insult, phrenic nerves tended to be responsive, although this response to external stimulus was not necessarily enduring. Conversely, the study also showed that patients whose phrenic nerves were not responsive in the subacute phase could become responsive to external stimulus up to a year later [6]. The current best recommendation is to perform percutaneous phrenic nerve electrical stimulation trials under fluoroscopy at 3 months after injury. Because some

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patients can recover phrenic nerve function after 3 months, it is reasonable to repeat the study at 12 months if the first trial did not show intact phrenic nerve conduction.

Surgical Technique

The cervical technique first described by Glenn et al. in 1976 [7] has undergone minor modifications over the last 40 years. The thoracic approach was initially developed for children whose necks were too small to accommodate the leads. With the size and technology of the current devices, this is rarely a concern. The following section will review both the thoracic and cervical approaches. It should be noted that both approaches are described for completeness, although the authors utilize the cervical technique due to its overall simplicity and excellent results.

Thoracoscopic Technique

Shaul et al. [8] were one of the first to describe the thoracoscopic approach, which is preferred over open thoracotomy. A patient older than 10 years should be prepared by establishing single-lung ventilation via a dual-lumen endotracheal tube. In a younger patient, it is sometimes possible to use a contralateral main stem intubation using a small cuffed endotracheal tube. The patient is then positioned on a bean bag so that the chest is almost full lateral while the hips are flatter, allowing for the abdomen to be in the semilateral position. Preoperative antibiotics are administered and surgical antiseptic techniques are utilized. The spare wire connecting the internal platinum electrode to the receiver is coiled upon itself and loosely held together with a nonabsorbable suture so that the appropriate length of wire unravels as the child grows. With the establishment of single contralateral ventilation, 0.5% bupivacaine is infiltrated into the subcutaneous tissue and a 5-mm trocar is introduced at the seventh intercostal space in the posterior axillary line. To inflate the chest and speed lung deflation, 5-mm Hg pressure is used. Two additional 5-mm trocars are inserted, one at the ninth intercostal space and the other at the fifth intercostal space, all in the posterior axillary line. A fourth trocar can be placed at the discretion of the surgeon if a lung retraction is required. The phrenic nerve is located and identified at the cephalad aspect of the pericardium. The nerve will overlie the mediastinal pleura. Two small incisions are made on either side of the phrenic nerve in a parallel trajectory to the nerve. Attention is then turned to implanting the device. A small subcostal incision is made, and a subcutaneous pocket is formed to house the radio receiver and excess wire. A 10-cm Penrose drain is placed over the male end of the connector and tied in place with a heavy suture. The opposite end of the Penrose drain is inserted through the ninth intercostal space trocar, and the drain, wire, and electrode are placed into the

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chest. A small tunnel is then created with a tonsil clamp, which is inserted into the chest through the anterolateral aspect of the diaphragm. The male end of the Penrose drain is brought through the chest into the subcutaneous pocket through the fifth intercostal space trocar. The phrenic nerve lead is then passed under the mediastinal pleura so that the nerve lies over the groove in the lead. This is sutured in place using a 4-0 silk suture. The lead is attached to the receiver, and the system is tested with the help of a representative. This step ensures the integrity of the circuit and adequate diaphragm contraction. The radio receiver and silastic coils are placed in the subcutaneous pocket and retested. Care must be taken to leave enough slack in the wiring so that the phrenic nerve is not under traction. A 20-Fr chest tube is place through the caudal-most incision where it will not interfere with the wire, and the lung is inflated under direct vision. Wounds are closed in the usual fashion, and occlusive dressings are applied. The patient then requires repositioning, and the procedure is repeated on the opposite side. It is customary to obtain a chest X-ray at the conclusion of the procedure. If there is no evidence of pneumothorax, the chest tubes may be removed while the patient is still under anesthesia. The patient is left intubated and placed in the intensive care unit. The total operative time is typically 3–4 h, and patients require aggressive pulmonary hygiene and physiotherapy to help prevent pneumonia. Patients are generally discharged 24–48 h later.

Cervical Technique

This technique was originally described by Glenn et al. [7] in 1976 and has undergone minor modifications to suit the modern-day needs of the implants. This is the preferred technique due to ease of patient positioning, implant placement, and shorter recovery time as compared with the thoracoscopic approach. The patient is placed supine on the operating table and intubated with a single-lumen endotracheal tube. A small roll is placed under the shoulders to accentuate the upper chest and lower neck. Gentle traction can be applied to the shoulders bilaterally via tape to maintain them caudally. Care is taken to ensure that the patient's head is not rotated to either the right or left side. Antibiotics are administered, and a sterile surgical field is prepared, including the entire neck down to the nipples bilaterally. The sternocleidomastoid (SCM) muscles are palpated bilaterally. Approximately 5 cm above the clavicle, a horizontal incision is marked. The area is infiltrated with 0.5% bupivacaine. A 2- to 3-cm horizontal incision is carried out over the lateral border of the SCM. The SCM is easily identified under the platysma muscle. Care is taken to mobilize the lateral border of the SCM, working both inferiorly and superiorly to the level of the incision. Once the SCM is freed, it is mobilized medially. It may be gently retracted medially by an assistant with a blunt handheld retractor. The body of the anterior scalene will be found on the posterior side of the SCM. The phrenic nerve will either be immediately identifiable or the surgeon may first need to mobilize the internal

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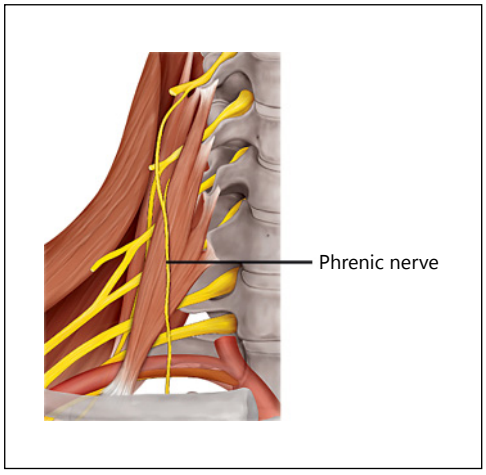

Fig. 5. Anatomic depiction of the phrenic nerve. The phrenic nerve lies directly anterior to the anterior scalene muscle as it courses inferiorly and slightly medially between the levels of the midbody of C5 and the midbody of C7. Approaching the nerve at this location is advantageous because vascular structures remain inferior to the surgical field and the nerve has received all of its contributions from the C3–C5 nerve roots.

jugular vein medially. Typically, this is not necessary if the incision is 5 cm above the clavicle. The phrenic nerve will be approximately 0.5 cm in diameter at this location, directly overlying the anterior scalene muscle (fig. 5). Occasionally, an accessory phrenic nerve may be observed, but its caliber is smaller. If there is any question about its location, the accessory phrenic nerve can be traced superiorly to the lateral border of the anterior scalene muscle where it clearly emerges from the anterior ramus of C5. It also lies laterally to the phrenic nerve. This nerve does not need to be incorporated into the pacing lead. Attention is then turned toward fashioning the subcutaneous pocket. Halfway between the clavicle and the nipple, 0.5% bupivacaine is injected and an approximately 3-cm incision is made. A small subcutaneous pocket is created, and a tonsil clamp is used to tunnel from the pocket to the cervical incision site, superficial to the clavicle. The male end of the wire is gently grasped on the silastic tubing, and the tonsil clamp is brought back through to the subcutaneous pocket. The male end is then connected to the radio receiver, and heavy suture is used to tie the two together. The phrenic nerve is then laid over the groove in the platinum lead, and a 4-0 nonabsorbable suture is used to secure the lead in place around the nerve (fig. 6). The lead should be anchored to the nearby anterior scalene muscle or SCM, such that the lead does not cause a kink in the nerve when laid flat without tension. The system is tested with the help of a representative, and the diaphragm will contract with good force at low impedance if the circuit is intact. The radio receiver and extra wire are then placed in the subcutaneous pocket and retested to ensure functionality prior to closing the incisions in layers (fig. 7). The procedure is then repeated on the opposite side of the patient without need to re-prep the skin or reposition (fig. 8). The total surgical time is approximately 1 h. At the authors' institution, most of the patients do not live in the immediate vicinity and are typically discharged from the hospital the next morning. There is no medical contraindication to discharge on the same day as the procedure.

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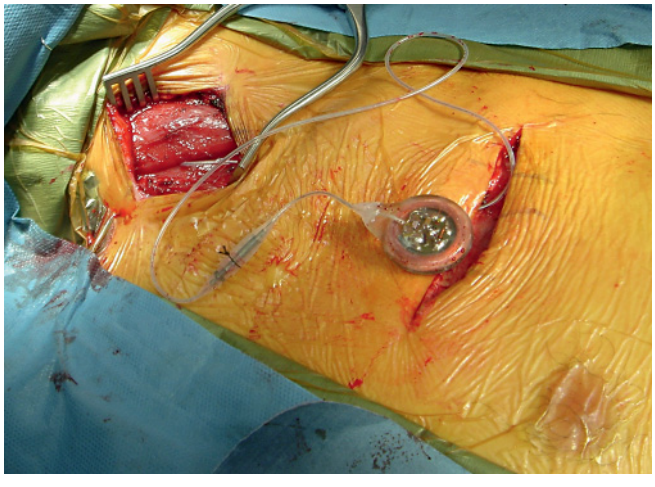
Fig. 6. Leads attached to the phrenic nerve via the cervical approach. The SCM seen at the top of the picture is gently displaced medially by a cerebellar retractor. The twin-lead version of the Avery Mark IV Breathing Pacemaker System™ is being implanted. The superior lead has been attached to the phrenic nerve and is held closed by a Weck clip. The phrenic nerve is seen distally before the second lead is secured to the nerve. The anterior scalene, which lies deep to the phrenic nerve, is not shown.



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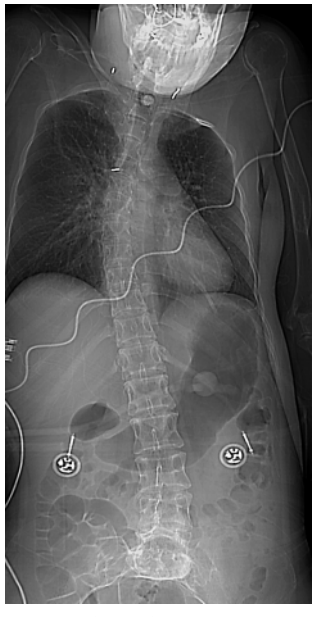

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Follow-Up Care

Return to clinic appointments are typically 2 weeks from the date of surgery when the wound is assessed for integrity. While some surgeons prefer to delay pacing for 6 weeks to allow fibrotic scar formation around the lead when placed thoracoscopically, this is not necessary after using the cervical approach.

When diaphragm pacing and conditioning is initiated, patients are admitted to a rehabilitation unit or hospital for 2–3 days. The amplitude, rate, and time of phrenic nerve stimulation are adjusted to achieve the desired tidal volume and ventilation determined by noninvasive measures such as pulse oximetry and end-tidal PCO_2. Initially, most patients are able to tolerate 1–2 h of pacing per day. This is somewhat dependent on the physiology of the patients and their medical condition. The phase of endurance training will then take place on an outpatient basis. Pacing is increased 1 h each week until the pacing goal is reached. Pacing is replaced with mechanical ventilation at the first sign of fatigue because patients can decompensate quickly. The initiation of pacing and conditioning/endurance training is typically managed by a pulmonary care, physical medicine and rehabilitation, or neurorehabilitation physician.

Complications

Typical complications of anesthesia, infection, and bleeding are possible. Procedure-specific complications include possible injury to the phrenic nerve and surrounding vascular structures. The battery life of the radio receiver can be 5 years or more with the current state of technology. Patients can expect to need a revision at that time. Shaul et al. [8] presented a total of 9 patients, including one who had pneumonia and one who had a liver laceration. Glenn et al. [9] retrospectively collected a multicenter complication profile that essentially represented a meta-analysis of several centers; therefore, the statistical data are limited. Despite this, they found a 4.5% rate of infection and a 5–15% rate of pacing failure that was attributed to iatrogenic nerve injury.

Fig. 7. Cervical implant placement. This is a right-sided intraoperative image after the lead has been placed and the distal wiring has been tunneled and connected to the radio receiver. Note that the wire emerges from the lateral aspect of the SCM and is tunneled superficially to the clavicle where the male end of the connector is secured to the radio receiver with a silk tie. Excess wiring is then coiled in the subcutaneous pocket behind the radio receiver, and the wounds are closed in layers.

Fig. 8. X-ray showing placement of bilateral phrenic nerve stimulation system. This scout image from a computed tomography scan shows leads from both a right thoracoscopic and bilateral cervical approach in a patient that had phrenic nerve stimulation performed over 20 years ago. The radio receivers were placed over the abdomen at that time, and the pacers were verified as functional 20 years after placement.

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Outcomes

In well-selected patients, phrenic nerve pacing provides an opportunity for partial or complete freedom from mechanical ventilation. Current outcome data are difficult to amalgamate because the number of patients that fit current indications for phrenic nerve stimulation is small. Data are scattered across multiple centers and are typically collected in a retrospective manner without matched controls. Nevertheless, the multicenter study conducted by Glenn et al. [9] from 1966 through 1988 showed that 84% of patients had gained significant respiratory support from their stimulator. The majority of these patients were able to pace for at least 12 h a day. A total of 16% experienced failure. Over 45% of the patients in the study were able to pace for 24 h per day. More recent data from 1998 indicate that 18 of 22 patients were able to pace continuously for 24 h. The remaining 4 patients paced during sleep [10].

An analysis of unpublished data conducted by the authors addresses quality of life outcomes in patients who have received the Avery Mark IV Breathing Pacemaker System™. These data contain 127 patients worldwide, the vast majority of whom had their implant placed for congenital central hypoventilation syndrome or SCI. Only 25–30% of these patients were able to pace for 24 h per day as compared to the preceding numbers. In contrast, over 90% of patients were using their pacers, which is a higher rate than reported elsewhere. Moreover, 96% of all patients stated that their pacer improved their quality of life, and 84% of patients said their pacemaker had a positive impact on their school/work and social life. Over 50% of quadriplegic patients also believed that their phrenic nerve pacers improved their ability to swallow, speak, and smell compared to mechanical and other means of positive pressure ventilation. When surgical indications are less stringently applied, these outcomes are not as favorable. The outcomes data show that phrenic nerve stimulation is safe, effective, and can positively impact numerous metrics in properly selected patients.

Future Directions

The field of neuromodulation is rapidly evolving as technology improves and physicians and industry partners learn more about the physiologic properties of peripheral nerves and derangements that occur because of injury, infection, metabolic insults, and other pathologies. Surgeons are continuously applying new neuromodulation techniques. A major limitation is the clinical indication for SCI patients at C3 and above. The most common location for SCI is at C4–C6. Krieger et al. [11] and Krieger and Krieger [12] have reported reanimation of the diaphragm after intercostal to phrenic nerve anastomosis for patients with SCI below C3 [11, 12]. More recently, a technique modification leading to direct diaphragmatic muscular pacing has been ap-

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plied to patients with amyotrophic lateral sclerosis and poliomyelitis. Patients with amyotrophic lateral sclerosis are able to delay ventilator dependency for an average of 2 years if pacing is utilized [13, 14]. These techniques, if proved fruitful, will provide new indications for the procedure and may allow more patients to live independently of mechanical ventilation.

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