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Diaphragm Pacing: A Safety, Appropriateness, Financial Neutrality, and Efficacy Analysis of Treating Chronic Respiratory Insufficiency

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ABSTRACT

Objectives: This study aimed to evaluate the safety and applicability of treating chronic respiratory insufficiency with diaphragm pacing relative to mechanical ventilation.

Materials and Methods: A literature review and analysis were conducted using the safety, appropriateness, financial neutrality, and efficacy principles.

Results: Although mechanical ventilation is clearly indicated in acute respiratory failure, diaphragm pacing improves life expectancy, increases quality of life, and reduces complications in patients with chronic respiratory insufficiency.

Conclusion: Diaphragm pacing should be given more consideration in appropriately selected patients with chronic respiratory insufficiency.

Keywords: Diaphragm pacing, phrenic nerve pacing, phrenic nerve stimulation, respiratory insufficiency

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NEURAL ANATOMY OF THE RESPIRATORY SYSTEM

Respiration is a complex homeostatic process that requires synchronization of conscious and autonomic outputs with input from chemoreceptors and mechanoreceptors in the circulatory system and lungs. Central chemoreceptors reside in the medulla, whereas peripheral chemoreceptors transmit information from the aortic arch and carotid body through the vagus and glossopharyngeal nerves, respectively. Mechanoreceptors in the lungs measure stretch and coordinate cyclical breathing. Input from the hypothalamus coincides with emotional states, and autonomic regulation of breathing is predominantly controlled by corticobulbar nerves interacting with respiratory nuclei in the brainstem. Voluntary control of respiration comes from neural pathways originating in the cerebral motor cortex.

Efferent neural impulses arise from either the motor cortex or respiratory center, a collection of brainstem nuclei located in the pons and medulla. The dorsal respiratory group is within the nucleus tractus solitarius of the medulla. It controls inspiration and receives chemotactic input from peripheral chemoreceptors. The ventral respiratory group (VRG) is also in the medulla and has roles in both inspiration and expiration. Within the VRG, the pre-Botzinger complex functions as the central pattern generator to synthesize rhythmic breathing.[1]

The phrenic nucleus resides in the C3–C5 region of the spinal cord and is the origin of lower motor neurons controlling respiration. From the phrenic nucleus, impulses leave the central nervous system and travel to the diaphragm through motor fibers of the phrenic nerve. The left and right phrenic nerves can be subdivided into supraclavicular and thoracic portions. The supraclavicular portions are superior to the clavicle, running posterior to the sternocleidomastoid muscles. The thoracic portions are found below the clavicle and associate with large blood vessels and the mediastinal pleura.[2] Three terminal branches of the thoracic portion of each phrenic nerve innervate the diaphragm to stimulate contraction and induce inspiration. Any interruption to the phrenic pathway can potentially lead to diaphragmatic paralysis and the need for artificial respiration.

The diaphragm and external intercostal muscles, which are innervated by the ventral rami from the thoracic spinal nerves, are primarily responsible for inspiration. However, there are secondary muscles that contribute to inspiration during periods of exercise or increased exertion, such as the sternocleidomastoid, trapezius, scalenes, pectoralis major and minor, serratus anterior, and

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latissimus dorsi. Under normal conditions, expiration is a passive process. During exercise or cough, the internal intercostals, rectus abdominis, external and internal obliques, and transverse abdominis are recruited.[2]

DIAPHRAGM PACING: DEFINITION AND INTRODUCTION

Diaphragm pacing (DP) is the delivery of artificially generated electric impulses to the diaphragm as a means of stimulating respiration sufficient to support basic metabolic demands. It was first achieved in the 1960s by William Glenn as a long-term treatment for a patient with congenital central hypoventilation syndrome (CCHS).[3] Subsequent collaboration with Avery Biomedical Devices Inc (Commack, NY) produced the first implantable DP system with Food and Drug Administration (FDA) approval in the 1970s.

DP can target the phrenic nerve, sometimes called phrenic nerve pacing or phrenic nerve stimulation, or the neuromuscular junction where the phrenic nerve contacts the diaphragm. In this article, the approaches will be discussed together. The goal is not to promote one approach or device over another but to discuss the general principles and benefits of DP. However, if relevant differences exist between peripheral (along the phrenic nerve) and direct (along the diaphragm) electrode placement, they will be discussed in detail.

DIAPHRAGM PACING: INDICATIONS

The main indication for DP is respiratory insufficiency due to a neuromuscular insult. Respiratory insufficiency is not itself a disease but a consequence of conditions that inhibit the lungs from meeting the metabolic demands of the body. The most common indication for DP is high cervical spinal cord injury, at or above C3–C5, leading to respiratory insufficiency. These vertebral levels are involved in nearly 40% of spinal cord injuries.[4] In 2019, there were more than 17,000 patients living with cervical spinal cord injuries in the USA, among all ages and sexes. Within this group, 19.7% of patients required a ventilator upon admission to acute rehabilitation; 5.6% required a ventilator upon discharge from acute rehabilitation; and 3.5% required a ventilator at one year after injury.[5]

DP can be performed in patients with high cervical spinal cord injury through peripheral electrode placement along the phrenic nerve[6,7] or direct electrode placement at the diaphragm.[8–12] Other indications for DP include CCHS,[13–19] damage to the brainstem,[20] and certain neuromuscular diseases, such as glycogen storage disorders,[21] myelitis,[22,23] and others that may lead to nonspecific respiratory paralysis.[24] DP was approved to treat amyotrophic lateral sclerosis (ALS) in 2012 as a "humanitarian use device." However, subsequent trials revealed increased mortality and adverse events in this population.[25] The literature on DP in pediatric populations has shown success in treating respiratory insufficiency caused by high cervical spinal cord injuries[26–28] and CCHS.[15–17,28,29]

DIAPHRAGM PACING: PREOPERATIVE WORKUP

To be a candidate for a DP system, a patient must have a functional phrenic nerve (if placing the electrodes peripherally), a diaphragm without progressive atrophy, and a contractile environment for the diaphragm, including proper geometry, abdominal compliance, and rib cage compliance.[30] First, a patient must establish care with a pulmonologist to confirm appropriate indications for DP and schedule long-term pulmonary follow-up. A neurological assessment of the phrenic nerve using a nerve conduction study, or a more novel technique such as transcutaneous stimulation coupled with ultrasonography,[31] is used to confirm a functional nerve before the procedure. General medical clearance is also required. Contraindications to receiving a DP system include an irreversibly atrophied diaphragm, muscular dystrophies, severe primary lung disease, and any patient who is a poor surgical candidate for other medical reasons.

DIAPHRAGM PACING: MECHANISMS AND DEVICES

The mechanism for achieving diaphragmatic contraction has not changed since the 1970s, but technologic advancements have improved the performance and reliability of devices. The two types of DP systems are those that use a peripheral approach and those that use a direct approach (Fig. 1). The peripheral approach involves intrathoracic placement of electrodes along the phrenic nerve and requires four core components: a transmitter, two antennas, two receivers, and two electrodes. The radiofrequency transmitter is worn externally, generating and regulating the power of the system. One such model, made by Avery Biomedical Devices Inc, uses four AA batteries, and has an expected battery life of 400 hours when running 24 hours per day.[32] The antenna sends power to the implanted receiver through transcutaneous radiofrequency waves. The receiver converts incoming radiofrequency energy into an electrical impulse train. The electrode, composed of an insulated wire and a platinum nerve contact on its free end, delivers electrical impulses to the phrenic nerve, stimulating action potentials that cause diaphragmatic contraction. The direct approach involves

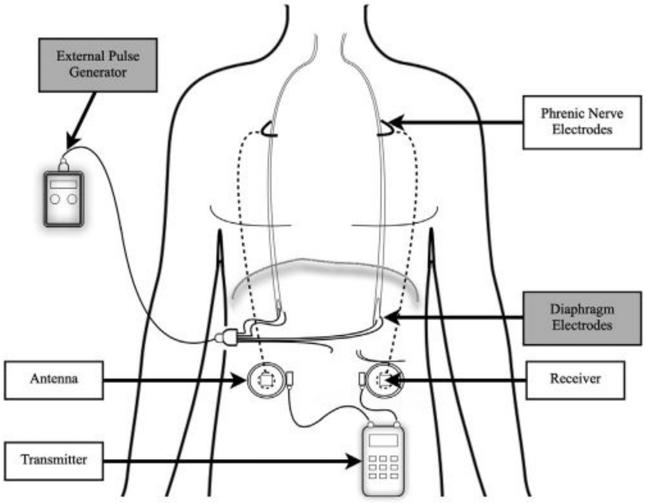

Figure 1. Differences in device components and electrode placement between direct (gray boxes) and peripheral (white boxes) diaphragm pacing systems. Shown are the exterior components (left side of the image), responsible for generating and regulating the system's power, and the interior components (right side of the image), responsible for converting and delivering the electrical impulse to the phrenic nerve.

intraabdominal placement of electrodes along the diaphragm and has two core components: an external pulse generator and five electrodes. The only FDA-approved model that uses direct DP is produced by Synapse Biomedical Inc (Oberlin, OH) and is powered by a single C battery with an expected battery life of approximately 96 hours.[33] The external pulse generator sends electrical impulses to four electrodes implanted within the diaphragm, two within each hemidiaphragm. The electrodes deliver the electrical impulses directly to the motor points, the most distal ends of the nerves, causing muscle contraction. The fifth electrode is implanted under the skin to ground the system and complete the circuit.

There are three DP systems on the market with full FDA approval in the USA: the Avery Diaphragm Pacemaker by Avery Biomedical Devices Inc, the NeuRx Diaphragm Pacing System by Synapse Biomedical Inc, and the remedē System by ZOLL Medical Corporation (Chelmsford, MA). A fourth DP system, the Atrostim Phrenic Nerve Stimulator by Atrotech (Tampere, Finland), is approved and available outside the USA. A fifth DP system, the AeroPace System by Lungpacer (Lungpacer Medical Inc, Vancouver, Canada), received emergency FDA approval to wean patients from positive pressure ventilation (PPV) owing to increased ventilator demand during the COVID-19 pandemic.[34] The Avery Diaphragm Pacemaker, remedē System, and Atrostim Phrenic Nerve Stimulator are peripheral systems with electrodes implanted along the phrenic nerve. The Avery Diaphragm Pacemaker has FDA approval for the treatment of respiratory insufficiency due to spinal cord injury, CCHS, and central sleep apnea.[32] The remedē System has FDA approval for respiratory insufficiency due to central sleep apnea.[35] The Atrostim Phrenic Nerve Stimulator is approved to treat respiratory insufficiency due to spinal cord injury and central sleep apnea.[36] The NeuRx Diaphragm Pacing System stimulates the diaphragm directly with electrodes implanted intramuscularly and has FDA approval for the treatment of respiratory insufficiency due to spinal cord injury and ALS.[33]

DIAPHRAGM PACING: OPERATIVE TECHNIQUE

During surgery, a tracheostomy is required for ventilation. There are differences in surgical approach depending on whether a direct or peripheral DP system will be used. In direct systems, the electrodes are placed intraabdominally along the diaphragm through a laparoscopic procedure.[37] In peripheral systems, the electrodes are placed along the cervical or thoracic portions of the peripheral nerve. For cervical placement, a small transverse incision is made above the clavicle just posterior to the sternocleidomastoid. For thoracic placement, a small thoracotomy is made for phrenic nerve dissection, and the electrode is placed through the fourth intercostal space at the anterior axillary line. Cervical electrode placement can be performed under local anesthesia and is typically associated with a shorter length of hospital stay.[38] After successful implantation of the electrodes, the DP system is connected and tested in vivo to confirm proper contraction of the diaphragm.

DIAPHRAGM PACING: POSTOPERATIVE REGIMEN

After implantation of a DP system, most patients are discharged on the first postoperative day. DP can be initiated as early as two weeks postoperatively.[39] Because of diaphragmatic atrophy, the treating team establishes a pacing regimen to recondition the weakened muscle. The length of rehabilitation depends on the patient's age and time spent on ventilation but is typically between one and four weeks.[40,41] However, it may take longer if substantial diaphragmatic hypotrophy has occurred. Once conditioned, DP can be used 24 hours per day.[41] The earlier DP is initiated after the onset of respiratory insufficiency, the greater the chance a patient has of achieving continuous pacing.[42]

SAFETY, APPROPRIATENESS, FISCAL NEUTRALITY, AND EFFICACY ANALYSIS: POSITIVE PRESSURE VENTILATION AND DIAPHRAGM PACING

Medical algorithms differ from mathematical algorithms in their need for adjustment, flexibility, and improvement that accompanies the circumstances of an individual patient and treating physician. Traditional algorithms tend to judge treatments on the basis of invasiveness and cost-effectiveness, placing implantable technologies at the bottom of the list. Although these are important factors to consider, there is more to the picture. Specifically, a balance must be struck between cost, efficacy, and the overall impact on a patient's quality of life. Only then will an optimal solution for physicians, patients, and payers be obtained.

The safety, appropriateness, fiscal neutrality, and efficacy (SAFE) principles were introduced by Krames et al[43,44] as an alternative method for evaluating care. These principles are similar to the population, intervention, comparison, and outcomes and setting, perspective, intervention, comparison, and evaluation models for analyzing clinical questions. The four SAFE principles can be applied to existing treatments as a means of determining the best method of care based on the available literature.

Safety

An assessment of safety regarding treating respiratory insufficiency must include procedural risks, rates of infection, and tissue damage. Chronic PPV through tracheostomy and DP systems both require a surgical procedure. Surgery comes with risk of complications, infections, and scarring. However, PPV has unique postoperative complications, such as ventilator-associated pneumonia (VAP),[45–48] diaphragmatic atrophy,[49,50] and a reduced quality of life.[51,52]

Chronic PPV is associated with frequent lung infections. Rates of VAP range from five to ten days per 1000 ventilator days.[46,48] Disorders of the respiratory system are the leading cause of death in patients with spinal cord injury, representing approximately 21% of all-cause mortality.[5] A prospective study of 64 patients conducted over 20 years found that patients who were ventilator dependent had an average of 2.07 respiratory infections per 100 days while admitted to inpatient facilities. After discharge, patients dependent on ventilators had an average of 0.14 respiratory infections per 100 days whereas patients using only DP systems did not acquire a single respiratory infection.[53]

Ventilator-induced diaphragmatic dysfunction (VIDD) is hypotrophic damage to the diaphragm that occurs while on a ventilator. VIDD has a multifactorial mechanism involving increased levels of reactive oxygen species and decreased nutrient availability, leading to high lactate concentrations and proteolysis within muscle tissue.[54,55] Together, these changes are responsible for the observed loss of type I and type II muscle fibers after periods of prolonged

PPV.[40] A Canadian study involving 428 patients found that tissue damage can occur in as little as 18 hours of PPV and is substantial after 72 hours.[49] The severity of damage correlates directly with the length of time spent on a ventilator and can be effectively measured as the decrease in diaphragm muscle thickness over time.[49,50,56–58] DP systems stimulate contraction of diaphragmatic muscle, maintaining functional muscle fibers and inducing myogenin expression.[59] In fact, DP causes little tissue damage of any kind. Electron microscopic evaluation of 34 phrenic nerves that received four to 374 days of electrical stimulation revealed no morphologic changes that could be attributed to the electrical stimulation.[60]

Although DP mitigates many harmful sequalae of PPV, it has a unique set of risks. As previously mentioned, all surgical procedures carry an inherent operative risk to local structures. However, over the last decade, the rate of irreversible injury during surgery has fallen to near zero.[61–63] There is some evidence that DP can lead to passive collapse of the vocal cords, but there are only two documented case reports of such an event.[64,65] Additional risks include the potential for migration of the device or leads into adjacent tissue and device infection. According to an analysis of available data from Avery Biomedical Devices Inc, electrode migration requiring surgical revision occurred in 9.7% of patients with a peripheral DP system using cervical electrodes and in 21.8% of patients with a peripheral DP system using thoracic electrodes.[38] The same study found that 5% of all patients required surgical revision due to device infection. Perhaps the most significant risk associated with DP systems is that of device malfunction. Patients using a battery-powered device for respiration risk hypoventilation if the device fails. For this reason, some physicians recommend that patients always carry their ventilator with them. However, there are multiple redundancies built into DP systems. For example, the Spirit transmitter, by Avery Biomedical Devices Inc, has two separate circuits, both of which will continue to work if the other fails. The Spirit transmitter is also equipped with alarms for disconnected antennas, low battery, and internal errors.[66] The other DP systems have similar alarms and redundancies to prevent patient death from malfunction.

Appropriateness

In the words of Sir William Osler, “It is much more important to know what sort of patient has a disease than what sort of disease a patient has.” Disorders causing respiratory insufficiency are debilitating regardless of etiology. Both DP and PPV are appropriate ways to treat respiratory insufficiency. If the anticipated time on a ventilator is relatively short, PPV is likely a more appropriate option. However, treating chronic respiratory insufficiency requires more nuance. To determine which is more appropriate, one must consider the impact it will have on the quality of life for this subset of patients.

PPV and DP are both invasive means of achieving artificial inspiration. It is important to note that both methods require a mechanism for assisted cough and expiration, such as manually assisted cough or mechanical insufflator-exsufflator.[67] Ventilation through endotracheal tube is generally only considered safe for a maximum of three weeks. Chronic PPV is achieved through tracheostomy and insertion of ventilator tubing through the tracheal stoma; it has been described by patients as uncomfortable, even painful, and often impedes the ability to swallow. Continuous positive airway pressure (CPAP) is more comfortable and less invasive than PPV, but CPAP is not a viable option for many patients with severe respiratory insufficiency. Even those who can use CPAP are subjected to an uncomfortable, cumbersome, and unreliable lifestyle. Although DP requires a more invasive procedure, it offers improvements in mobility, external appearance, and quality of speech.[53,68] Furthermore, olfaction, a sense strongly associated with respiration, is often impaired during ventilation. When patients’ olfactory sensitivity was measured before and after implantation of a DP system, the average sensitivity increased by more than 100%.[69]

Although it is difficult to quantify, most agree that a measurement of life quality must include how one views oneself, the ability to do things that one finds enjoyable, and physical comfort. Patients with respiratory insufficiency typically have a low self-perceived quality of life owing to feelings of uselessness.[51] Another quality-of-life measurement is the ability to perform activities one considers important. Researchers using the 36-Item Short Form Health Survey (SF-36), a scored set of questions designed to evaluate health-related quality of life, found patients with DP systems scored significantly higher than did patients on a ventilator.[68] The largest improvements were related to fewer social constraints and improvements in mobility and quality of speech. The third, and possibly most important, quality-of-life measurement is physical comfort. PPV requires a loud external ventilator and is frequently associated with patient pain events. On the Behavioral Pain Scale, a scored system ranging from 3 to 12 developed for assessing pain in intensive care unit (ICU) patients on the basis of facial expression, limb activity, and ventilator compliance, 20% of patients using PPV scored > 5.[52] Using a multivariable cox regression analysis, researchers found scores > 5 to correlate with increased mortality. Most importantly, patients seem to report a strong preference for DP systems over PPV. When 32 patients were interviewed after switching from PPV to DP, all expressed their preference for DP, and scores on the Spinal Cord Independence Measure increased from 3 of 100 to 11 of 100.[53] A separate survey was given to 28 patients with respiratory insufficiency requiring PPV after implantation of DP systems. All patients preferred DP and would recommend it to others in the same situation.[70]

There are situations in which DP is relatively contraindicated. For example, patients with large amounts of adipose tissue who use peripheral systems risk disruption of the signal from the antenna to the receiver, increasing variability and the likelihood of device migration.[15] It was also believed that DP could be used to delay the need for PPV in patients with ALS by preserving diaphragmatic function.[63,70–72] However, subsequent studies indicated no reduction in the functional decrease of the diaphragm,[73,74] increased mortality, and increased incidence of serious adverse events.[25] Given this conflicting data, it is pertinent that larger clinical trials are performed before concrete recommendations can be made about the appropriateness of DP in patients with ALS.

There are also absolute contraindications to receiving a DP system. First and foremost, the patient must have a functional phrenic nerve to use a peripheral system. Patients with nerve trauma, neurogenic tumors, and neuropathies cannot achieve DP owing to a nonfunctional phrenic nerve. However, nerve repair may be an option for a subset of these patients. Other contraindications include an irreversibly atrophied diaphragm, presence of muscular dystrophies or severe primary lung disease, and the use of diathermy.[32] Patients with persistent exposure to powerful transmitters, such as those used in maritime or aerospace industries, or previous implantation of other stimulating medical equipment, are considered poor candidates for a DP system owing to potential interference. Similarly, some DP systems are not compatible with magnetic resonance imaging (MRI) and thus are not appropriate for patients with anticipated needs for future MRI, such as those diagnosed with multiple sclerosis or brain tumors.[32]

Temporary DP is a relatively novel application of the technology. There are circumstances in which patients may be expected to recover respiratory function but have experienced VIDD owing to prolonged periods on a ventilator. In these situations, DP can be used to restore diaphragmatic function after injury to the muscle.[75,76] Studies have shown the earlier DP is initiated, the greater chance of recovering to the point of self-sustained respiration.[12,42]

There are also less invasive means of stimulating the phrenic nerve. Transcutaneous electrical diaphragm stimulation is similar in concept to neuromuscular electrical stimulation used in physical therapy to increase muscle strength. It has shown efficacy in reducing the time required to wean patients off PPV.[77] Transvenous phrenic nerve pacing (TPNP) accesses the venous system through guidewires to place electrode leads within the right brachiocephalic or left pericardiophrenic veins.[78] These veins run adjacent to the right and left phrenic nerves. TPNP effectively reduced nocturnal events and improved daytime somnolence in 151 patients with central sleep apnea.[79] Long-term follow-up five years after implantation revealed few adverse events and zero mortality.[80]

Financial Neutrality

Treatments with a steady cost over time are typically preferred over interventional procedures with a large upfront cost. This model of financial analysis is typical for many neuromodulation techniques.[81–83] When calculating the time to financial neutrality for PPV and DP systems, both initial and maintenance costs must be considered. These include, but are not limited to, nursing wages, hospital charges, and treatment of associated infections.

The greatest discrepancy between the two treatments is the initial cost. Avery Biomedical Devices Inc estimates the initial cost of their DP system to be $65,000.[84] After the initial procedure, maintenance costs include scheduled replacement of batteries and other short-lived components of the system.[32,33] In contrast, the average annual cost of health care and living expenses for patients with tetraplegia and ventilator dependency is $170,000.[5] Patients dependent on ventilators in the ICU can accrue bills upwards of $1500 per day.[85,86] When patients with acute spinal cord injury who received DP systems were compared with those who did not, hospital charges adjusted for year, severity of injury, sex, ethnicity, and age were significantly lower.[87] Even after discharge from an inpatient facility, renting a ventilator and nursing wages cost approximately $2000 per month.[53] Other analytical studies have concluded that DP systems save patients $18,000 to $30,000 per year, relative to PPV, and the price difference is offset one to four years after the procedure.[53,85] Based on this information, the expected time spent on ventilation should be an important factor in determining which method of respiration is best for each patient financially.

Given the high rates of infection associated with PPV, the time to financial neutrality could potentially be much shorter. VAP is acquired by approximately one-third of patients on PPV for more than 48 hours.[45,47] Treating just one of these infections can accrue a cost more than six times greater than patients in control groups on positive pressure ventilation[88]; on average, hospital bills are approximately $40,000 higher for patients with VAP than for those on PPV without infection.[89]

Efficacy

Ideally, an effective treatment for respiratory insufficiency would restore a patient's ability to breathe, or mimic physiology as closely as possible, while maintaining high procedural success rates and maximizing life expectancy. DP systems have shown efficacy in treating high cervical spinal cord injuries,[6–9] central sleep apnea,[13–18] and certain neuromuscular disorders.[21,22] DP mimics physiology by stimulating contraction of the diaphragm. When patients with quadriplegia who were using a DP system were switched to CPAP, a subsequent decrease in PaO_2 was observed.[90,91]

Historically, PPV had higher procedural success rates than did DP systems, but this is no longer true. The rates of complications during implantation of a DP system have been rapidly decreasing over the past two decades,[54,61] and procedural success rates are now universally approximately 100%.[62] When outcomes for patients with cervical spinal injuries were compared, those who received DP systems had significantly lower mortality and length of hospital stay than did patients receiving only PPV.[92]

The final measure is postoperative life expectancy. It has been proven time and again that patients using DP systems have a longer life expectancy than those who are ventilator dependent. One such study analyzed patients with high level spinal cord injury, controlling for age, sex, race, the level, cause, and completeness of injury, sponsor of care, and hospital, and it found that patients who were ventilator dependent were 39.5 times more likely to die in the first year after injury, and 2.61 times more likely to die each year thereafter, than were patients with high level spinal cord injury who did not require ventilatory support.[93] A follow-up study was performed to control for additional variables, including health status, community integration, and economic status. Again, they found that patients with high level spinal cord injury requiring PPV are 3.53 times more likely to die in any given year than are patients who do not require a ventilator.[94] A separate long-term study followed 126 patients, 38 of whom had a DP system and 88 of whom were ventilator dependent. The average life expectancy after injury was 8.69 years for patients who were ventilator dependent and 21.78 years for patients using a DP system.[69]

Although the procedural and longitudinal efficacy of DP systems continues to improve, they do have shortcomings. As previously mentioned, there is documented risk of passive vocal cord collapse and procedural error.[64,65] Video assistance and improved surgical technique have reduced the rate of irreversible injury during implantation to near zero, but the rate of reoperation due to device failure or migration can be as high as 40%.[61]

CONCLUSIONS AND IMPLICATIONS

It is often difficult to determine the best treatment for a patient. Although straightforward in concept, the reality is often complex. The purpose of this analysis was to determine whether clinicians should more readily consider DP as a viable alternative to PPV in patients with chronic respiratory insufficiency. A separate evaluation of the available literature concluded that although DP is a safe and effective option for decreasing ventilator dependence, the overall quality of literature is lacking.[95] Despite these limitations, we can still draw important conclusions. PPV and DP are both relatively safe procedures, each with a unique risk profile. Both are an appropriate and effective means of treating respiratory insufficiency. One has a larger initial cost and the other substantial maintenance expenses. However, the use of DP potentially reduces complications, increases quality of life, and improves life expectancy in patients with chronic respiratory insufficiency. These outcomes suggest that DP may be a beneficial option for patients who are appropriately selected.

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Authorship Statements

Curren E. Giberson, Lawrence R. Poree, Samuel H. Cheshier, and Michael F. Saulino designed the literature review, including the necessary components and selected analytic tools. The literature review and manuscript were drafted by Curren E. Giberson with significant intellectual input from all four authors. All four authors have approved the final manuscript.

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COMMENTS

This is a very well-written review that clearly summarizes alternative treatment options for chronic respiratory insufficiency in patients with specific diagnoses. The authors' very well chosen SAFE analysis allows the reader to comprehensively evaluate this therapy option, from the basic safety aspect for the patient, through the appropriateness of the indication, the precisely analyzed potential financial impact, to the efficacy of the therapy itself. I particularly appreciate the case-by-case consideration of the various indications for phrenic nerve pacing, focusing not only on the simple extension of the patient's life expectancy, but especially on his or her quality of life.

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