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Clinical Study

Phrenic nerve stimulation: The Australian experience

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ABSTRACT

Phrenic nerve stimulation is a technique whereby a nerve stimulator provides electrical stimulation of the phrenic nerve to cause diaphragmatic contraction. The most common indications for this procedure are central alveolar hypoventilation and high quadriplegia. This paper reviews the available data on the 19 patients treated with phrenic nerve stimulation in Australia to date. Of the 19 patients, 14 required pacing due to quadriplegia, one had congenital central hypoventilation syndrome and one had brainstem encephalitis. Information was unavailable for the remaining three patients. Currently, 11 of the pacers are known to be actively implanted, with the total pacing duration ranging from 1 to 21 years (mean 13 years). Eight of the 19 patients had revision surgeries. Four of these were to replace the original I-107 system (which had a 3–5-year life expectancy) with the current I-110 system, which is expected to perform electrically for the patient's lifetime. Three patients had revisions due to mechanical failure. The remaining patients' notes were incomplete. These data suggest that phrenic nerve stimulation can be used instead of mechanical ventilators for long-term ongoing respiratory support.

1. Introduction

Phrenic nerve stimulation is a technique whereby a nerve stimulator provides electrical stimulation of the phrenic nerve to cause diaphragmatic contraction. First described conceptually by Duchenne[1] in 1872 as the "best means of imitating natural respiration", the groundbreaking work came in the late 1960s by Glenn et al.[2–4] – subsequently, in conjunction with Avery Biomedical Devices (Commack, NY, USA), the first phrenic nerve stimulators were brought into commercial distribution. Phrenic nerve stimulation has been practiced for several decades in Australia, with the first being performed in 1977; however, it remains relatively uncommon.

The two main indications for phrenic nerve stimulation are central alveolar hypoventilation and high quadriplegia. Of the former, children suffering from congenital central hypoventilation syndrome (CCHS) form a unique group that often benefit drastically from this procedure. In the latter, patients typically with high cervical injuries (at or above C3) are the best candidates. The ultimate aim is to improve quality of life through temporary or permanent relief from the use of an artificial ventilation device.

Although phrenic nerve stimulation has now been described, and practiced, for several decades, it is still in its relative infancy, and there is still much work in innovation and advancement in this area. We describe the Australian experience of phrenic nerve stimulation in this series. To date, there have only been 19 patients who have undergone this procedure in Australia (Table 1).

2. Methods and device

The phrenic nerve stimulator consists of an electrode placed on the phrenic nerve and connected to a subcutaneous receiver via lead wires (Fig. 1). An external battery-operated transmitter sends radiofrequency energy to the receiver through an antenna, which is placed on the skin overlying the receiver. The receiver converts this energy into an electrical current that is directed to the phrenic nerve in order to stimulate the nerve, thereby causing contraction of the diaphragm.

The surgery can be performed via either a cervical or thoracic approach.

2.1. Cervical approach

A linear, horizontal skin incision is made and the sternocleidomastoid muscle is retracted medially. The phrenic nerve is identified over the anterior scalenus muscle and isolated, and an electrode is attached (Fig. 2). The lead is tunnelled into a pocket in the anterior chest wall, and the receiver placed in a subcutaneous pocket.

2.2. Thoracic approach

This procedure is performed either via open thoracotomy at the 2nd or 3rd intercostal space, or thorascopically using trochars at the 5th, 7th and 9th intercostal spaces along the posterior axillary line. The lungs are deflated one side at a time and the phrenic nerve is mobilised over cardiac structures. The electrode is positioned

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Table 1
Details of the 19 patients with phrenic nerve stimulators implanted in Australia

Patient	Age (yrs), sex	Diagnosis	Pacer status (no. yrs)	Location	Reason for reoperation
1	U, M	Not on file	? Active: Implanted	Not on file	N/A
2	U, F	Not on file	Deceased: Unknown	C unilateral (R)	N/A
3*	35, F	Quadriplegia	Deceased: Implanted	T bilateral	Upgrade 5 yrs after initial surgery§
4	47, M	Complete tetraplegia: C4–5 fracture with ascending paralysis to C2–3 level	Deceased: Implanted	C unilateral (L)	N/A
5*	30, F	Quadriplegia	Active: Implanted (21)	C bilateral	Upgrade 5 yrs after initial surgery§
6*	28, M	Quadriplegia	Active: Implanted (21)	T bilateral	Upgrade 5 yrs after initial surgery§
7*	38, F	Quaplegia: C3–4 incomplete quadriplegia	Deceased: Unknown	Not on file	Upgrade 5 yrs after initial surgery§
8	63, F	Quadriplegia: C1–2 fracture, complete C2 quadriplegia	Deceased: Unknown	C bilateral	N/A
9*	38, M	Quadriplegia	Active: Implanted (17)	C bilateral	Malfunction in pacer 4 yrs after initial surgery, upgraded§
10**	19, F	Quadriplegia: High cervical quadriplegia, disrupted spinal cord at C1–2 level	Active: Implanted (15)	T bilateral	Failure of both right and left receivers due to breast development; receivers replaced in a more inferior and superficial position
11	66, F	Not on file	Deceased: Unknown	T bilateral	N/A
12*	15, M	CCHS	Deceased: Unknown	T bilateral	Not on file
13	36, F	Quadriplegia	Active: Implanted (12)	C bilateral	N/A
14*	15, M	Brainstem encephalitis	Active: Implanted (12)	C bilateral	R lead replacement due to mechanical failure
15	16, M	Quadriplegia	Active: Implanted (12)	C bilateral	N/A
16	33, F	Quadriplegia	Active: Implanted (11)	C bilateral	N/A
17	28, M	Quadriplegia	Active: Implanted (10)	T bilateral	N/A
18	7, F	Quadriplegia: Pneumococcal mastoiditis complicated by cervicomedullary infarct	Active: Implanted (3)	C bilateral	N/A
19	24, M	Quadriplegia	Active: Implanted (1)	C bilateral	N/A

C = cervical, CCHS = congenital central hypoventilation syndrome, F = female, L = left, M = male, N/A = not available, R = right, T = thoracic, U = age unknown, yrs = years.
* = reoperation.
** = reoperation twice.
§ = upgrade from I-107 to I-110 system.

below the nerve and sutured into place. The leads are brought through the thoracic cavity and tunnelled into a subcutaneous pocket inferior to the 12th rib, and the receiver is placed into this pocket.

Generally, pacing is initiated four to six weeks post-operatively, and gradually increased over several weeks.

2.3. Methods of analysis

We reviewed the available data on patients who have had phrenic nerve stimulators implanted in Australia. These data were obtained from Avery Biomedical Devices, who have been, and are currently, the sole distributor of this device to Australia. The available medical records were then obtained from the relevant hospitals and any additional useful information was retrieved from these, including infections, failure of device, lead migration and longevity of stimulation.

3. Results

A total of 19 patients have had phrenic nerve simulators implanted in Australia. The first of these was performed in 1977; however, this patient has been lost to follow-up. Seven of the 19 patients have since died. Unfortunately the information regarding cause of death was unavailable in all but one patient, who died from pneumonia.

Eleven patients are still actively implanted, with total pacing duration ranging from 1 year to 21 years. The average pacing duration for actively pacing patients in whom records were available is 13 years. Several of the patients were either lost to follow-up or the records were unobtainable.

In the 16 patients on whom information was available regarding the original condition that required the use of phrenic nerve stimulators, 14 were listed as having quadriplegia (most were traumatic, although one was related to a cervicomedullary infarct following pneumococcal mastoiditis), one patient suffered from absent respiratory drive as a result of brainstem encephalitis, and one patient had CCHS.

Eleven patients underwent cervical approaches, of which two were unilateral and nine were bilateral. Six patients had thoracic approaches, all of which were bilateral. There were two undocumented approaches.

Eight patients had repeat operations for replacement/reimplantation of hardware. The original I-107 receiver design was known to have a 3-year to 5-year life expectancy, and four patients have had re-implantations for this reason. The current I-110 receiver design is expected to perform electrically for the patient's lifetime.

Of the reasons for the other replacement/reimplantations, one patient's notes were not on file, and the other three were all related to mechanical failure.

One patient experienced malfunction of the diaphragmatic pacemaker 4 years after initial surgery, requiring ventilation at home. Eventually, a I-110 pacer was used to replace the older I-107 device. One patient required lead replacement on the right side due to mechanical failure of implanted components – in the interim, he required full ventilation during sleep for 1 month.

Another patient experienced failure of both left-sided and then right-sided receivers due to breast development. The receivers were replaced in a more inferior and superficial position (with ventilation via tracheostomy used in the interim). In a recent follow-up of this patient 15 years after the initial surgery, she was using the pacing during the day and mechanical ventilation at night. The left pacer was also noted to be less efficient – this was due to difficulty in locating the antenna over the receiver due to weight gain, and increasing the amplitude of the stimulating current of the transmitter provided some improvement to this problem.

Of the patients on whom follow-up information was readily obtained, several complications were noted in most. These were not

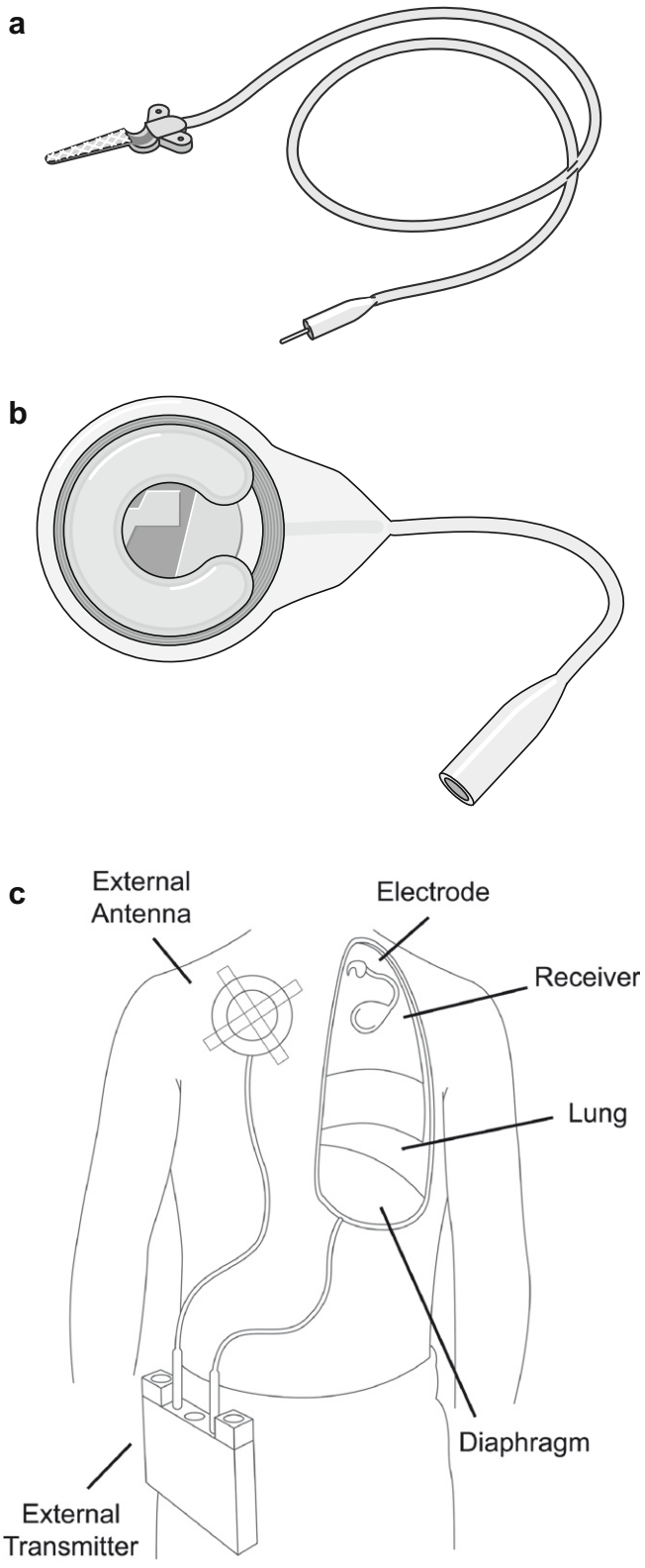

Fig. 1. The phrenic nerve stimulator system showing (a) a monopolar electrode, (b) a I-110 receiver (Avery Biomedical Devices; Commack, NY, USA) and (c) location of the system components.

unexpected, and typical of patients with quadriplegia. They included recurrent respiratory tract infections, urinary tract infections, pressure sores, kyphoscoliosis, neurogenic bladder and muscle spasms.

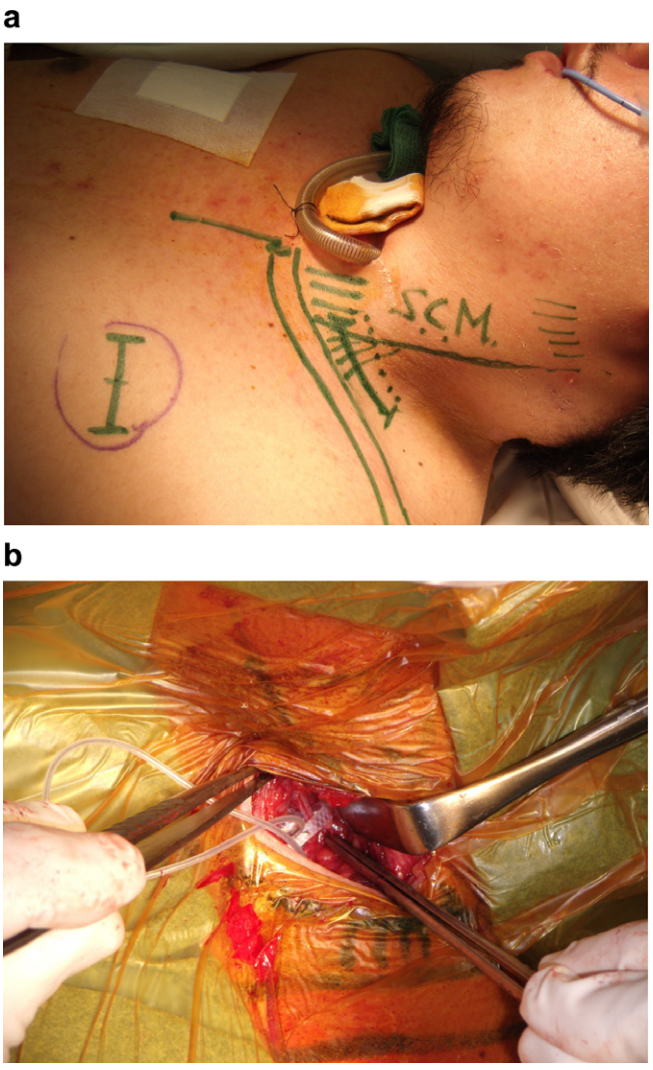

Fig. 2. (a) Surface marks on a patient indicating position of the incision (dotted line) in relation to the clavicle, sternocleidomastoid (S.C.M.), and the position of the subcutaneous receiver (broken circle). (b) Intraoperative photograph showing attachment of the electrode to the phrenic nerve via the cervical approach. This figure is available in colour at www.sciencedirect.com.

4. Discussion

Phrenic nerve stimulators can be implanted via two routes – a cervical approach, or a thoracic approach. Initially, the thoracic approach involved a thoracotomy, but more recently a less-invasive thorascopic approach[5] has been used successfully. Intramuscular diaphragm stimulation is another technique described that aims to cause less potential injury to the phrenic nerve through direct stimulation of the diaphragm – however, electrode wires that exit the skin carry a small but significant infection risk.[6]

Multiple complications may be associated with the implantation of phrenic nerve stimulators. Complications involving the hardware include mechanical failure, electrode failure or dislodgement, and broken or disconnected wires – this can often result in the replacement of the stimulator or reversion back to ventilatory support. Lung complications including atelectasis, pneumonia and pneumothorax are all possible with the thoracic approach.[5] Infection is also a potentially serious complication which may require removal of the affected device. Damage to the phrenic nerve may occur acutely during surgery and render a phrenic nerve stimulator ineffective – there are also questions as to whether chronic, long-

term stimulation itself may damage the nerve over time or even cause diaphragmatic failure, athough results thus far have been positive and there is no evidence to support this.

Weese-Mayer et al.[7] published a review of the international experience with quadruple diaphragm pacer systems, which included 35 children and 29 adults. They noted that 2.9% of patients experienced infection, and 3.8% experienced mechanical trauma. Presumed electrode and receiver failure occurred in 3.1% and 5.9% of patients with tetraplegia and CCHS respectively. Overall, the figures were overwhelmingly positive, with 94% of paediatric patients pacing successfully, 60% of these complication free, and 86% of adult patients pacing successfully, 52% of these complication free.

Garrido-Garcia et al.[8] published a series in 1998 on 22 patients treated with diaphragmatic stimulators: 18 patients achieved permanent pacing, and the remaining four required pacing only during sleep. One patient had phrenic nerve entrapment by scar tissue and four experienced infections, all of whom required operative reimplantation. Pacemaker complications included antenna fractures and receiver failure. Five patients died during follow-up. Although the mean duration of follow-up was only 3 to 4 months, one patient was followed up for 11 years and four for 10 years, indicating that it may be possible for diaphragmatic pacing to achieve complete stable long-term ventilation.

Shaul et al.[5] successfully implanted phrenic nerve stimulators through a thoracoscopic approach. Nine patients, all children, were described. Over a mean follow-up period of 30 months, eight patients reached their long-term pacing goals. Four patients experienced post-operative complications (pneumonia, atelectasis, bradycardia and pneumothorax), with the recognition that aggressive post-operative pulmonary hygiene was required.

Elefteriades et al.[9] published long-term pacing results on 12 patients with quadriplegia: six of 12 patients continued full-time pacing with a mean of 14.8 years. Patients who stopped full-time pacing did so due to social/financial reasons or medical comorbidities rather than complications directly related to the phrenic nerve stimulators themselves. They also pointed out that there was no evidence to suggest long-term nerve injury could result from chronic pacing, with no apparent clinical deterioration in pacing parameters or respiratory measurements from continuous pacing for over 10 to 15 years.

B. M. Soni, in his article "Use of phrenic nerve stimulator in high ventilator dependent spinal cord injury" (P. Khong, pers. comm.. 2009) reviewed 20 ventilator-dependent patients with high cervical spinal cord injuries who had undergone phrenic nerve stimulator implantation. One paediatric patient failed to produce adequate tidal volumes with stimulation; one patient developed a cable fracture requiring conversion of the system to an intrathoracic stimulator, and 18 of the 20 patients reported significant benefit in mobility, access and overall improvement in quality of life.

More recently, Hirschfeld et al.[10] conducted a prospective study comparing the outcomes of 64 spinal cord-injured patients who were respiratory device-dependent. Half had functioning phrenic nerves and diaphragm muscles and were treated with phrenic nerve stimulators, and the other half with destroyed phrenic nerves were mechanically ventilated. They found that those treated with phrenic nerve stimulators had a reduced frequency of respiratory tract infections and improved quality of speech – these results were statistically significant. Subjectively, they felt that those with stimulators had improved quality of life.

In our case series, we found a total of 19 patients in whom phrenic nerve stimulators have been implanted in Australia: 11 patients had undergone cervical approaches and six had thoracic approaches – this largely reflected surgeon preference, and to date there are no conclusive data to show whether one approach is better than another. Of interest, eight patients had to undergo reimplantations – four were expected due to the 3-year to 5-year life expectancy of the original I-107 receiver design, three were due to mechanical failure (one patient's notes were not available).

5. Conclusion

To the time of writing, 19 patients have had phrenic nerve stimulators implanted in Australia. Although the devices have been available for several decades, their use is still regarded as specialised and uncommon, especially in Australia. We acknowledge that complications can arise attributable to mechanical failure, as well as the expected complications inherent in patients with quadriplegia. Of the patients known to be actively pacing, the average duration of ongoing pacing is 13 years – this suggests that phrenic nerve stimulators can be used in the long term instead of mechanical ventilators for ongoing respiratory support. Follow-up studies will be valuable in determining whether phrenic nerve stimulators can be a permanent solution to the respiratory issues related to central alveolar hypoventilation and high quadriplegia.

References

1. Duchenne GB. *De l'electrisation localisee et de son application a la pathologie et la therapeutique par courants induits at par courants galavaniques interrompus et conius*. 3rd ed. Paris: J.B. Bailliere et Fils; 1872. pp 907–18.
2. Judson JP, Glenn WWL. Radio-requency electrophrenic respiration. Long-term application to a patient with primary hypoventilation. *JAMA* 1968;**203**:1033–7.
3. Glenn WWL, Phelps ML, Elefteriades JA, et al. Twenty years of experience in phrenic nerve stimulation to pace the diaphragm. *Pacing Clin Electrophysiol* 1986;**9**:780–4.
4. Glenn W, Brouillett R, Dentz B, et al. Fundamental considerations in pacing of the diaphragm for chronic ventilatory insufficiency; a multicentre study. *Pacing Clin Electrophysiol* 1988;**11**:2121–7.
5. Shaul DB, Danielson PD, McComb JG, et al. Thoracoscopic placement of phrenic nerve electrodes for diaphragmatic pacing in children. *J Pedriatr Surg* 2002;**37**:974–8.
6. DiMarco AF, Onders RP, Ignagni A, et al. Phrenic nerve pacing via intramuscular diaphragm electodes in tetraplegic subjects. *Chest* 2005;**127**:671–8.
7. 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.
8. Garrido-Garcia H, Alvarcz JM, Escribano PM, et al. Treatment of chronic ventilatory failure using a diaphragmatic pacemaker. *Spinal Cord* 1998;**36**: 310–4.
9. Elefteriades JA, Quin JA, Hogan JF, et al. Long-term follow-up of pacing of the conditioned diaphragm in quadriplegia. *Pacing Clin Electrophysiol* 2002;**25**: 897–906.
10. Hirschfeld S, Exner G, Luukkaala T, et al. Mechanical ventilation or phrenic nerve stimulation for treatment of spinal cord injury-induced respiratory insufficiency. *Spinal Cord* 2008;**46**:738–42.