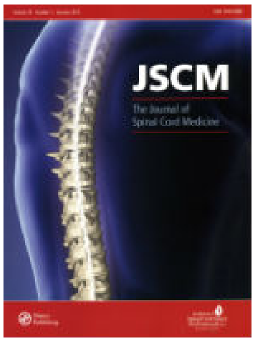

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Prospective analysis of a surgical algorithm to achieve ventilator weaning in cervical tetraplegia

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Research Article

Prospective analysis of a surgical algorithm to achieve ventilator weaning in cervical tetraplegia

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Objectives: Chronic ventilator dependency in cervical tetraplegia is associated with substantial morbidity. When non-invasive weaning methods have failed the primary surgical treatment is diaphragm pacing. Phrenic nerve integrity and diaphragm motor units are requirements for effective pacing but may need to be restored for successful weaning. A surgical algorithm that includes: 1. Diaphragm pacing, 2. Phrenic nerve reconstruction, and 3. Diaphragm muscle replacement, may provide the capability of reducing or reversing ventilator dependency in virtually all cervical tetraplegics.
Design: Prospective case series.
Setting: A university-based hospital from 2015 to 2019.
Participants: Ten patients with ventilator-dependent cervical tetraplegia.
Interventions: I. Pacemaker alone, II. Pacemaker + phrenic nerve reconstruction, or III. Pacemaker + diaphragm muscle replacement.
Outcome measures: Time from surgery to observed reduction in ventilator requirements (↓VR), ventilatory needs as of most recent follow-up [no change (NC), partial weaning (PW, 1–12 h/day), or complete weaning (CW, > 12 h/day)], and complications.
Results: Both patients in Group I achieved CW at 6-month follow-up. Two patients in Group II achieved CW, and in another two patients PW was achieved, at 1.5–2-year follow-up. The remaining two patients are NC at 6 and 8-month follow-up, respectively. In group III, both patients achieved PW at 2-year follow-up. Complications included mucous plugging ($n = 1$) and pacemaker malfunction requiring revision ($n = 3$).
Conclusion: Although more investigation is necessary, phrenic nerve reconstruction or diaphragm muscle replacement performed (when indicated) with pacemaker implantation may allow virtually all ventilator-dependent cervical tetraplegics to partially or completely wean.

Keywords: Diaphragmatic paralysis, Diaphragm pacemaker, Phrenic nerve reconstruction, Quadriplegia, Ventilator weaning

Introduction

Ventilator dependency associated with high spinal cord lesions and cervical tetraplegia is directly associated with increased morbidity and early mortality, as well as substantially greater health care costs compared to non-ventilator-dependent para- and tetraplegics.[1,2] Despite advances in non-invasive weaning protocols a large subset of patients will require surgical intervention for the potential to reduce or reverse ventilator requirements.

In properly selected patients diaphragm pacemakers have demonstrable efficacy at promoting ventilator

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weaning, implanted either around the phrenic nerves or at the nerve–muscle interface.[3] However, as many as 20% of patients with ventilator dependency due to high spinal cord injury will fail pacing attempts.[4] This is most often due to insufficiency in meeting the requirements for successful diaphragm pacing which include, most importantly, phrenic nerve integrity and preserved contractile function in the diaphragm. In multi-level cervical tetraplegia there will often be combined upper and lower motor neuron injuries rendering the phrenic nerves and diaphragm partially or completely dysfunctional. Furthermore, with longstanding, untreated spinal cord injury there is progressive neuromuscular degeneration leading to axonal loss in the phrenic nerves and irreversible denervation atrophy in the diaphragm.

Prior studies have retrospectively evaluated the application of phrenic nerve reconstruction simultaneous with pacemaker implantation for patients with combined upper and lower motor neuron dysfunction, and have demonstrated the feasibility of this approach for appropriately selected patients.[5–7]

The aim of the current study is to prospectively evaluate a surgical treatment algorithm that integrates pacemaker implantation with varying degrees of neuromuscular reconstruction, to provide the opportunity for virtually all ventilator-dependent cervical tetraplegics to reduce or reverse ventilator dependency.

Methods

Between 2015 and 2019 we prospectively evaluated ten patients with multi-level cervical tetraplegia and chronic, complete ventilator dependency. All ten patients had failed all prior attempts at non-invasive ventilation and weaning attempts. These patients have not been previously reported. Study approval was obtained by the institutional review board at Hackensack Meridian Jersey Shore University Medical Center, Neptune, NJ, and informed consent was obtained in accordance with study approval.

Treatment selection was based upon the extent of neuromuscular dysfunction [based on pre- and/or intra-operative electromyography (EMG)], prior failed attempts at pacemaker implantation, and duration of paralysis. The treatment protocol included: I. Pacemaker alone ($n = 2$), II. Pacemaker + phrenic nerve reconstruction ($n = 6$), or III. Pacemaker + diaphragm muscle replacement ($n = 2$).

Group I patients had no prior pacemaker implantation attempts and demonstrated the presence of bilateral phrenic nerve conduction on EMG assessment. Group II patients had prior unsuccessful pacemaker implantation attempts due to failure to stimulate, and/or exhibited uni- or bilateral loss of phrenic nerve conduction. Group III patients included those who failed to stimulate from prior pacemaker attempts, loss of bilateral phrenic nerve conduction, and/or greater than three years post-injury.

Pacemaker implantation was performed using one of three standard approaches: cervical, intra-thoracic, or laparoscopic, using one of the FDA approved devices (Synapse Biomedical, Oberlin, Ohio; Avery Biomedical, Commack, NY). The cervical approach was performed through bilateral supraclavicular incisions and exposure of the phrenic nerves along the anterior scalene muscles. The electrodes were secured around each phrenic nerve and connected to receivers that were implanted into subcutaneous pockets in the upper chest wall. Intra-thoracic implantation was performed through VATS or rib-sparing, limited bilateral antero-lateral thoracotomies. The phrenic nerve or nerve–muscle interface was exposed, permitting implantation of pacemaker electrodes and receivers as necessary. Laparoscopic pacemaker implantation was performed using standard technique for port access. Nerve mapping was performed in an attempt to identify areas of maximal contraction or through visual identification of the nerve–muscle interface. Electrodes were placed into each hemi-diaphragm and the wires were tunneled to a central location on the abdominal wall.

Phrenic nerve reconstruction was performed in the cervical or intra-thoracic regions using an available nerve donor, including: spinal accessory, intercostal, or thoraco-abdominal nerves. The phrenic nerve was exposed and dissected for several centimeters. An adjacent functional (or stimulatable) nerve donor was identified and confirmed using EMG assessment. The nerve donor was transected at its muscular insertion and transposed to the phrenic nerve. A microanastomosis was performed using standard methods. Sural nerve bridging grafts were harvested and coapted between the donor and phrenic nerves as needed when primary nerve transfer was not possible.

Diaphragm muscle replacement was performed using innervated, vascularized rectus muscles, and was based upon prior reports of abdominal muscle flaps to repair large congenital diaphragmatic hernias.[8,9] The rectus muscles were dissected while preserving the superior vascular pedicles. The segmental innervation to each muscle was identified and the integrity of the innervation was evaluated with EMG assessment. Intra-thoracic phrenic nerve and diaphragm exposure was performed and the rectus muscle was transposed onto the diaphragm and inset to approximate the geometric domain of the diaphragm. The proximal segmental innervation to the rectus muscle was preserved while distal nerve branches were divided to facilitate transfer and coapted to intercostal nerves adjacent to the diaphragm. The pacemakers were implanted around the proximal intact nerves to the rectus muscle (the neodiaphragm).

Parameters for assessment included: time from surgery to observed reduction in ventilator requirements (↓VR) (i.e. ability to tolerate > 1 h of CPAP), specific ventilatory needs as of most recent follow-up [no change (NC) (i.e. unable to disconnect from the ventilator), partial weaning (PW = 1–12 h/day without mechanical ventilation), or complete weaning (CW ≥ 12 h/day without mechanical ventilation)], and peri-operative complications.

Results

There were three females and seven males with an average age of 28 years (range = 16–47 yrs.) (Table 1). All patients had multi-level cervical tetraplegia classified as ASIA A. The average time from injury to treatment was 17 months (range = 1–48 months). In 7/10 (70%) patients there had been a prior aborted attempt at implantation of a diaphragm pacemaker due to failure to stimulate (5/6 in Group II and 2/2 in Group III).

A cervical approach was used for pacemaker implantation in both Group I patients and 1/6 Group II patients (simultaneous with a spinal accessory nerve transfer). In 5/6 patients in Group II, bilateral intra-thoracic access was performed for pacemaker implantation and thoraco-abdominal nerve transfers. Both patients in Group III required an intra-thoracic approach for rectus muscle flaps, pacemaker implantation, and intercostal nerve transfers (Table 2).

Table 1 Demographic data of patients undergoing surgical treatment for ventilator dependency.

Patient	Age	Sex	Level	ASIA	I-S (month)	Prior PA
1	22	F	C1-C5	A	12	Y
2	30	M	C2-C4	A	8	Y
3	47	M	C3-C4	A	8	Y
4	27	M	C4-C5	A	1	N
5	19	M	C3-C4	A	16	Y
6	42	F	C2-C4	A	10	N
7	25	M	C3-C4	A	17	Y
8	16	M	C2-C3	A	21	Y
9	28	F	C1-C2	A	28	N
10	33	M	C1-C4	A	48	Y
Mean	28	3F,7M			17	

Abbreviations: I-S, time (month) from onset of injury to surgical treatment; Prior PA, prior pacemaker placement attempted (failed or aborted).

Both patients in Group I (2/2) and one patient in Group II (1/6) demonstrated ↓VR at 1 month and achieved CW at 6-month follow-up. One Group II (1/6) patient exhibited ↓VR at 3 months post-operatively and achieved CW at 2 years. In two Group II (2/6) patients ↓VR was observed at 6 months and PW was achieved at 1.5–2 years. The remaining two patients in Group II (2/6) have demonstrated ↓VR but are designated NC at 6 and 8-month follow-up, respectively. In group III, one patient exhibited ↓VR at 3 months post-operatively, whereas ↓VR began at one year in the other patient. At 2-year follow-up both patients in Group III had achieved PW (Table 2).

PW (4/10) or CW (4/10) was achieved in 8/10 patients (80%) whereas the remaining two patients (Group II) have demonstrated ↓VR without weaning (NC) as of the most recent follow-up (<1 year). The mean duration from surgery to observed ↓VR was 4 months, and the overall mean follow-up was 23 months (range = 6–58 months).

Complications consisted of one patient who developed post-operative mucous plugging managed conservatively, and three patients who required pacemaker lead or receiver replacement due to malposition or malfunction.

Discussion

High spinal cord injuries are associated with dysfunction in numerous bodily systems, and despite advances in rehabilitation and biotechnology the potential for functional recovery is extremely limited. Achieving partial or complete restoration of respiratory activity is especially important given the poor outcomes associated

Table 2 Treatment details and patient results.

Patient	Treatment group	Surgical approach	↓VR (month)	Weaning status
1	III	Intra-thoracic	3	PW
2	II	Intra-thoracic	3	CW
3	II	Intra-thoracic	6	PW
4	II	Cervical	1	CW
5	II	Intra-thoracic	6	PW
6	I	Cervical	1	CW
7	II	Intra-thoracic	8	NC
8	II	Intra-thoracic	6	NC
9	I	Cervical	1	CW
10	III	Intra-thoracic	12	PW
Mean			4	

↓VR = time (month) from surgery to reduction in ventilator requirements.
NC = no change (unable to disconnect from the ventilator).
PW = partial weaning, 1–12 h/day without mechanical ventilation.
CW = complete weaning, >12 h/day without mechanical ventilation.

with long term ventilator dependency.[1,2] Fortunately there are surgical treatment options for respiratory recovery, contrasting with the absence of restorative surgical procedures for other systems, such as bowel control, sexual function, or locomotion.

Diaphragm pacemakers have been used effectively since the 1970s in ventilator dependency associated with high spinal cord injury, achieving 80% or greater rates of weaning.[10,11] A recent report supports diaphragm pacing in the acute setting after spinal cord injury to promote weaning in patients with a poor prognosis, as well as to shorten the time to weaning even in those that would otherwise achieve this over a longer time period.[12] Requirements for successful application of a diaphragm pacemaker include: phrenic nerve integrity, diaphragm contractility, motivated patient and caregiver, preserved patient cognition, and absence of active respiratory infection.[13] The benefits of successful weaning to a diaphragm pacemaker have been clearly elucidated in prior reports.[3,5–7,14,15] Patients exhibit reductions in respiratory morbidity, improved quality of life, ease of speaking and eating, and are able to reduce their health care costs.

Before surgical treatment is considered for chronic ventilator dependency all attempts at non-invasive ventilation and weaning methods should be exhausted during the acute and sub-acute phases after injury. Unfortunately, there are a large subset of patients who fail to wean using conservative measures, and also fail attempts at diaphragm pacing. Two major reasons for pacing failures are the isolated or combined impact of level(s) of spinal cord injury and delay of intervention. Cervical spinal cord injuries involving C3–5 often result in Wallerian degeneration along the cervical roots and phrenic nerves leading to loss of phrenic nerve integrity. Without intervention, this progressive neural degeneration results in loss of the motor units in the diaphragm and irreversible denervation atrophy. In an earlier report analyzing the parameters associated with successful pacing after phrenic nerve reconstruction, we identified a higher rate of weaning failure (despite reinnervation) when surgical treatment was performed more than three years post-injury.[5] The ability for nerve regeneration persists as demonstrated on follow-up EMG testing, however the diaphragm loses contractile ability due to severe atrophy that eventually becomes irreversible.

Utilizing advanced peripheral nerve microsurgery methods and vascularized muscle flaps it is possible to replace components (or all) of the respiratory system's neuromuscular apparatus in order to facilitate successful pacing and achieve ventilator weaning. Nerve transfers for diaphragmatic reinnervation in high spinal cord injury were first reported in a series by Krieger and Krieger.[7] Additional reports have supported the safety and feasibility of this surgical technique, however success is likely limited by the time from injury to intervention.[16–18] Nerve regeneration may occur without the ability for functional muscle activity in longstanding injuries. In the current series, there were six patients who underwent phrenic nerve reconstruction (nerve transfers) simultaneous with pacemaker implantation. The two patients in this group who achieved CW were treated at 1 and 8 months post-injury, respectively, and surgery was performed 8 and 16 months post-injury in the two patients who achieved PW, respectively. All four of these patients began weaning within the first year post-operatively. The two patients designated as NC have begun converting from assist control to spontaneous ventilation (CPAP) for several hours per day, however they have not yet tolerated being completely disconnected from mechanical ventilation. There was a longer interval from injury to treatment in these patients, each undergoing surgery at 17 and 21 months post-injury, respectively.

For the most severe cases of neuromuscular degeneration, muscle replacement may be considered for the potential to wean to a pacemaker. Diaphragm replacement using vascularized muscle flaps is based on the work of Barnhart *et al.*[19] and others, who reported the successful use of abdominal muscle flaps to repair large congenital diaphragmatic hernias.[8,9] In the current study both of the patients receiving this treatment had failed prior pacemaker attempts. One of these patients had a pre-operative EMG with evidence of severe neuromuscular degeneration, and the second patient was 48 months post-injury. Both have achieved PW at 2-year follow-up. The application of diaphragm muscle replacement in this patient population is novel and further investigation is necessary to validate these early results.

The ultimate goal in chronic ventilator-dependent spinal cord injury is to achieve both ventilator weaning and decannulation. Non-invasive ventilation with decannulation is under-utilized yet has demonstrated significant efficacy with the ability to support respiratory function, maintain clearance of secretions, and allow for decannulation.[20] Patients implanted with pacemakers may also benefit from these methods especially if they exhibit nocturnal apneas. In our patient population, most of whom required neuromuscular reconstruction simultaneous with pacemaker implantation, there may be a benefit of post-operative non-invasive respiratory management to enhance results. Future studies may explore multi-modality therapy in these complex patients.

In this prospective analysis we have demonstrated that the application of a comprehensive surgical treatment algorithm provides ventilator-dependent cervical tetraplegics the opportunity for reduction or reversal of mechanical ventilation requirements, regardless of the severity of neuromuscular degeneration. In eight of ten (80%) patients PW or CW was achieved, and the remaining two patients have reduced ventilator requirements, but have yet to be fully evaluated. Of the seven patients who had initially failed pacemaker implantation and were told they would never be able to wean, five have achieved the ability to pace the diaphragm without mechanical ventilation following phrenic nerve reconstruction or diaphragm muscle replacement (four PW, one CW). The limitations of this study are the small number of patients and the specialty nature of the surgery making the widespread application more difficult.

Conclusion

Although more investigation is necessary, phrenic nerve reconstruction or diaphragm muscle replacement performed (when indicated) with pacemaker implantation may allow virtually all ventilator-dependent cervical tetraplegics to wean partially or completely.

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References

1 van den Berg ME, Castellote JM, de Pedro-Cuesta J, Mahillo-Fernandez I. Survival after spinal cord injury: a systematic review. J Neurotrauma 2010;27(8):1517–28.
2 Shavelle RM, DeVivo MJ, Strauss DJ, Paculdo DR, Lammertse DP, Day SM. Long-term survival of persons ventilator dependent after spinal cord injury. J Spinal Cord Med 2006;29(5):511–19.
3 Tedde ML, Vasconcelos Filho P, Hajjar LA, de Almeida JP, Flora GF, Okumura EM, *et al.* Diaphragmatic pacing stimulation in spinal cord injury: anesthetic and perioperative management. Clinics (Sao Paulo) 2012;67(11):1265–69.
4 Marvisi M, Balzarini L, Mancini C, Confortini M, Betri E. A rare case of dyspnoea the Parsonage-Turner syndrome. J Med Cases 2012;3:169–71.
5 Kaufman MR, Elkwood AI, Aboharb F, Cece J, Brown D, Rezzadeh K, Jarrahy R. Diaphragmatic reinnervation in ventilator-dependent patients with cervical spinal cord injury and concomitant phrenic nerve lesions using simultaneous nerve transfers and implantable neurostimulators. J Reconst Microsurg 2015;31:391–5.
6 Nandra KS, Harari M, Price TP, Greaney PJ, Weinstein MS. Successful reinnervation of the diaphragm after intercostal to phrenic nerve neurotization in patients With high spinal cord injury. Ann Plast Surg 2017;79(2):180–2.
7 Krieger LM, Krieger AJ. The intercostal to phrenic nerve transfer: an effective means of reanimating the diaphragm in patients with high cervical spine injury. Plast Reconstr Surg 2000;105(4):1255–61.
8 Horta R, Henriques-Coelho T, Costa J, Estevão-Costa J, Monteiro D, Dias M, Braga J, *et al.* Fascicular phrenic nerve neurotization for restoring physiological motion in a congenital diaphragmatic hernia reconstruction with a reverse innervated latissimus dorsi muscle flap. Ann Plast Surg 2015;75:193–6.
9 Hyvärinena A, Sankilampic U, Tyrväinend E, Vanamo K. Abdominal muscle flap for repair of large congenital diaphragmatic hernia: ultrasound evidence for retained motor muscle function. J Pediatr Surg Case Reports 2019;45:101199.
10 Stuban RS. The latest facts about the diaphragm pacing stimulation (DPS) system. Vent-Assist Living 2006;20(3):2–3.
11 Le Pimpec-Barthes F, Legras A, Arame A, Pricopi C, Boucherie JC, Badia A, Panzini CM. Diaphragm pacing: the state of the art. J Thorac Dis 2016;8(Suppl 4):S376–86.
12 Posluszny JA, Onders R, Kerwin AJ, Weinstein MS, Stein DM, Knight J, *et al.* Multicenter review of diaphragm pacing in spinal cord injury: successful not only in weaning from ventilators but also in bridging to independent respiration. J Trauma Acute Care Surg 2014;76(2):303–9; discussion 309–10.
13 Kaufman MR, Bauer TL, Brown DP. Surgical treatment of phrenic nerve injury. In: Collins KA, Friedberg JS, (eds.) UpToDate. Waltham, MA; 2019. https://www.uptodate.com/contents/surgical-treatment-of-phrenic-nerve-injury
14 Hirschfeld S, Exner G, Luukkaala T, Baer GA. Mechanical ventilation or phrenic nerve stimulation for treatment of spinal cord injury-induced respiratory insufficiency. Spinal Cord 2008;46:738–42.
15 Fodstad H, Blom S, Linderholm H. Artificial respiration by phrenic nerve stimulation (diaphragm pacing) in patients with cervical cord and brain stem lesions. Scand J Rehabil Med 1983;15(4):173–81.
16 Tung TH, Mackinnon SE. Nerve transfers: indications, techniques, and outcomes. J Hand Surg Am 2010;35(2):332–41.
17 Terzis JK, Vekris MD, Soucacos PN. Outcomes of brachial plexus reconstruction in 204 patients with devastating paralysis. Plast Reconstr Surg 1999;104(5):1221–40.
18 Wiertz-Hoessels EL, Krediet P. Degeneration of the motor endplates after neurectomy in the rat and the rabbit. Acta Morphol Neerl Scand 1965;6:179–93.
19 Barnhart DC, Jacques E, Scaife ER, Yoder BA, Meyers RL, Harman A, *et al.* Split abdominal wall muscle flap repair vs patch repair of large congenital diaphragmatic hernias. J Pediatr Surg 2012;47(1):81–6.
20 Bach JR. Noninvasive respiratory management and diaphragm and electrophrenic pacing in neuromuscular disease and spinal cord injury. Muscle Nerve 2013;47(2):297–305.