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Original Research Article

Spinal cord injury level and Phrenic Nerve Conduction Studies do not predict diaphragm pacing success or failure- all patients should undergo diagnostic laparoscopy☆

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ABSTRACT

Background: Diaphragm Pacing(DP) demonstrates benefits over mechanical ventilation(MV) for spinal cord injured(SCI) patients. The hypothesis of this report is that phrenic nerve conduction study(PNCS) results cannot differentiate success or failure in selection of patients for DP. Direct surgical evaluation of the diaphragm should be performed.
Methods: Observational report of prospective databases of patients undergoing laparoscopic evaluation of their diaphragms to assess for ability to stimulate to cause contraction for ventilation.
Results: In 50 SCI patients who could not be weaned from MV, PNCS results showed latencies in stimulated patients ($n = 44$) and non-stimulated($n = 6$) overlapped (7.8 ± 2.5 ms vs 9.4 ± 2.8 ms) and the null hypothesis cannot be rejected (p-value>0.05). Amplitudes overlapped (0.4 ± 0.2 mV vs 0.2 ± 0.2 mV) and the null hypotheses cannot be rejected (P-value >0.05). In 125 non SCI patients with diaphragm paralysis, there were 78(62.4%) with false negative PNCS.
Conclusion: PNCS are inadequate pre-operative studies. Direct laparoscopic evaluation should be offered for all SCI patients to receive the benefit of DP.

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Background

Spinal cord injury (SCI) remains relatively rare with only 17,500 new cases per year in the United States but the outcomes are often catastrophic. High level injuries are associated with respiratory dysfunction including respiratory muscle weakness, decreased vital capacity, ineffective cough and airway clearance and requirement of mechanical ventilation (MV). The presence of MV in SCI significantly increases cost of care and decreases life expectancy. A 20-year old SCI patient on MV has a life expectancy of only 10.6 years.[1] That same 20 year old with the same level injury but not on MV has a life expectancy of 34 years.[1] Overall, life expectancy for mechanically ventilated SCI persons has declined over the last decade.[1] Pneumonia occurs in 61% of SCI patients during initial hospitalization and is the leading cause of death in SCI and in those on MV.[2] Not only does the presence of MV alter life expectancy, it is associated with a myriad of complications including compromising discharge to SCI rehabilitation and integration into society.

Diaphragm pacing (DP) was developed to replace or decrease mechanical ventilation in SCI patients who fail standard weaning protocols. DP drives respiration by replacing the lost upper motor neuron signal which activates the phrenic nerve. It also reverses disuse atrophy of the diaphragm. DP requires laparoscopic surgical placement of electrodes into the diaphragm muscle and the procedure has been well described.[3] Breathing with DP is more physiologic providing a negative pressure respiratory cycle with preferential posterior lobe ventilation.

There is an ever increasing body of recent data demonstrating the benefits of diaphragm pacing. In 2018, Kerwin et al. reported that SCI patients who develop pneumonia, mean ventilator days were significantly fewer for those patients who were implanted with DP. Mortality was 15% for the control group compared to 3% for the DP group ($p = 0.04$). Length of hospital stay was significantly shorter in the DP group (65 ± 61 vs 43 ± 24 days for the control and DP groups, respectively ($p = 0.03$).[4] This group subsequently

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reported in 2020, a significant improvement with DP in the median time to ventilator liberation after DP in SCI patients (10 days vs. 29 days; 95% CI 6.5–13.6 vs 23.1–35.3 days; $p < 0.001$).[5] Onders et al. also in 2018 reported on a group of 92 traumatic SCI patients on mechanical ventilation from 6 days to 25 years, 60.8% of patients overall became ventilator free with 88% achieving 4 consecutive hours of full time pacing. Early DP placement not only allows rapid ventilator wean time, it increases the possibility of spontaneous recovery.[6] DP is aggressive physical therapy and functional electrical stimulation of the diaphragm that can have neuroplastic effects.

For DP to be effective in recruiting the diaphragm muscle to provide ventilatory support, the phrenic nerve must be able to provide conduction pathways through the muscle. Therefore, the lower motor neuron in the cervical spine must be intact to avoid muscle denervation and be able to stimulate the muscle at acceptable levels. The accepted clinical practice to determine the viability of the phrenic nerve lower motor neuron is the Phrenic Nerve Conduction Study (PNCS). Surface stimulation in the anterior cervical region recruits the phrenic nerve axons resulting in a compound muscle action potential (CMAP) recording using surface electrodes over the anterior diaphragm. CMAP amplitudes and latencies are then measured. Latencies assess the viability of the myelin to conduct down the axons and amplitudes evaluate the viability of the individual axons and diaphragm motor units.

Although the PNCS is a good indicator of phrenic nerve function, it has several limitations. First, anatomic variability between individuals may make it difficult to locate the phrenic nerve in the cervical region particularly in obese patients even with supramaximal stimulation; and second, discomfort of the stimulation doesn't allow for many attempts to stimulate the nerve. These limitations may lead to false negatives i.e., the phrenic nerve does not appear viable when it actually is. In contrast, misplacement of the EMG recording electrodes over the chest wall and inadvertent recruitment of the brachial plexus nerves produce responses that could be misinterpreted as phrenic CMAP which may also lead to false positives i.e., the phrenic nerve appears viable when it actually is not. PNCS is difficult to perform in the trauma intensive care unit with recent cervical spine surgery or tracheostomy and is contraindicated if there is a central line or cardiac pacemaker which are common occurrences in acute SCI patients.

This observational review is to report on PNCS compared to direct laparoscopic evaluation of the diaphragm. Given the significant morbidity of MV the goal is to identify all patients that could be weaned from MV with DP.

Method

This is an observational review of patients undergoing PNCS and direct laparoscopic stimulation of the diaphragm involved in 14 prospective protocols all which had institutional review board approval and included patients from 2000 to March 2020. Informed consent was obtained from all patients for the evaluation, implantation and post-operative care. Health Insurance Portability and Accountability Act of 1996 compliance was met. Data was assessed prospectively and analyzed retrospectively. Depending on patient diagnosis and IRB protocol different preimplantation exams would be performed and different levels of data was collected intra-operatively and post-operatively. The analyzed patients all had PNCS measuring CMAP amplitudes and latencies as we have describes previously.[7] All PNCS were performed and interpreted by one of us (BK), without the knowledge of the results of the subsequent direct intra-operative stimulation. Each patient then underwent diagnostic laparoscopy by one of us (RO) without paralytics and their diaphragms were directly assessed visually for the ability to contract to direct stimulation. A positive response would involve a diffuse contraction of the diaphragm visually along with a quantitative change in abdominal pressure that is measured with a sensor. A true negative (completely denervated and non-stimulatable) would be a diaphragm with no response to maximum stimulation parameters and decreased laparoscopic pressures.

Two separate groups of patients were analyzed. The first is SCI patients who were part the initial FDA IDE trial of DP and had PNCS performed as part of the screening process. This group was used to analyze PNCS in regard to false-positive results. A false positive would occur if phrenic nerve testing prior to implant indicated that a CMAP could be recorded successfully but the diaphragm did not show contraction with intra-operative direct stimulation. This could result in attempted implantation of the system only to have an unresponsive diaphragm. This would mean that the patient would undergo a laparoscopic procedure with the expectation of the nerve being intact for DP but in reality could not be implanted. During this time period if a patient had a negative pre-operative PNCS the patient would not go to surgery. For this group therefore we could not analyze false negative PNCS.

The second group included patients who did not have SCI but had significant diaphragm dysfunction. These patients had non-functioning diaphragms as noted by fluoroscopy with the most common causes included idiopathic or injured phrenic nerves. This involved looking at PNCS in these patients to quantify false negatives which occur if the PNCS showed absent CMAP but the diaphragm at laparoscopy is viable and contracts with intra-operative stimulation. A false negative would mean that someone who could benefit from DP would not receive the device. We had previously reported on a group of 21 DP implanted patients in which 10 had an absent CMAP on PNCS but had an intact diaphragm with intra-operative stimulation categorized as false-negative studies.[8] In this study we are expanding at a much larger database to assess for the rate of false negative PNCS.

Results

In the SCI FDA IDE database, a total of 50 patients underwent both PNCS and laparoscopic evaluation of the diaphragm. 44 patients could be stimulated at surgery and 6 patients could not be stimulated. The results of PNCS testing indicate that the PNCS data (latencies and amplitude) alone are not sufficient to determine candidacy for the DP. For diaphragms that showed contraction during intra-operative stimulation ($n = 44$), latencies averaged 7.8 ± 2.5 ms. For diaphragms that did not contract to direct laparoscopic stimulations ($n = 6$), latencies measured 9.4 ± 2.8 ms. As shown in Fig. 1a, the latency between the two populations overlap and the null hypothesis (that the means are equal) cannot be rejected (P-value > 0.05).

The range of CMAP amplitudes also overlapped (Fig. 1b) in patient groups with 0.4 ± 0.2 mV for those with diaphragms that could be stimulated and 0.2 ± 0.2 mV for those that could not be stimulated. As shown in Fig. 1b, the amplitude between the two groups overlap and the null hypothesis (that the means are equal) cannot be rejected (P-value > 0.05). The 6 patients who could not be stimulated were not implanted with diaphragm pacing. These patients therefore had false-positive PNCS in that they were expected to be able to be implanted at surgery but failed at the final intra-operative testing.

There were another 125 non-SCI patients who had diaphragm dysfunction and underwent both preoperative PNCS and laparoscopic diaphragm evaluation. There were 78 (62.4%) false negative studies in regard to PNCS These patient did not have CMAP by PNCS yet at laparoscopic surgery with direct stimulation there was

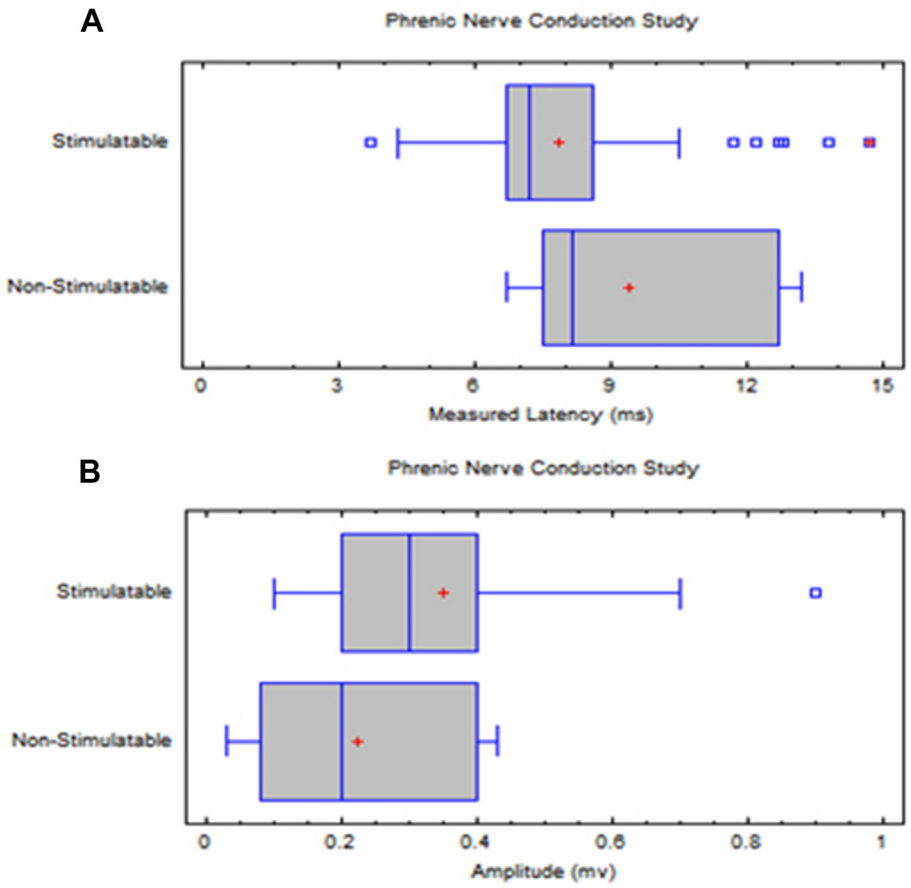

Fig. 1. Comparison of Phrenic Nerve Conduction Studies in spinal cord injured patients with diaphragms that could contract with intra-operative direct stimulation labeled as stimulatable (n = 44) compared to diaphragms that did not contract to direct intra-operative stimulation labeled as non-stimulatable (n = 6).

diaphragm muscle contraction. In these patients the PNCS was a false negative.

Discussion

The hypothesis of this observational report that PNCS are inadequate pre-operative predictors of surgical success or failure was met. In SCI patients even though there were patients who were predicted to have stimulatable diaphragms at surgical evaluation this was not the case. In non-SCI patients, we were able to identify patients in whom the diaphragm could be stimulated at surgery yet the pre-operative PNCS did not predict this. In our own practice after the FDA trial and experience with diaphragm dysfunction from our other reports we no longer perform PNCS on SCI patients prior to considering them for diaphragm pacing. The risks for diagnostic laparoscopy in a SCI patients on MV are minimal considering the complication of long term MV.[6]

Using cervical level as a factor in determining DP appropriateness also does not correlate to DP success. There has always been concern that SCI below C3 would damage the phrenic motor neurons and therefore patients would not benefit from DP. There is significant variability in the cervical variation of phrenic nerves with 8 different variations of cervical roots to make up the phrenic nerve. The classic description of one third of nerve roots coming from each of C3, C4 and C5 only occurs 22% of the time. Three recent publications show pacing success in patients with lower cervical injuries.[4,6,9] In a 2014 report of 29 SCI patients, 18 had injury involvement at C3-5 with 11 (61%) having successful diaphragm stimulation.[9] Kerwin (2018) reported success of DP with 65% having injuries below C4.[4] Onders also reported successful DP in weaning from MV in 29 patients with C3 or lower level injury.[6] These studies demonstrate that level of injury had no bearing on DP success indicating that all SCI patients on MV should be offered diagnostic laparoscopy.

Utilizing PNCS or cervical injury level as a criterion to undergo DP surgery could significantly eliminate patients who would benefit from DP placement. The only dependable and reliable method to verify the integrity of the phrenic nerve lower motor neuron and determine if the diaphragm responds to the electrical charge is by direct stimulation with the mapping techniques as part of DP implantation or as a stand-alone diagnostic laparoscopy. A move toward direct visualization in the OR would preclude the exclusion of patients based on testing that has poor predictive value. Additionally, this allows for the maximal amount of patients to be eligible for the benefits of DP which would decrease the need for tracheostomy mechanical ventilation and its associated morbidity and mortality. In conclusion given the benefits of DP, all SCI patients who cannot wean from MV should undergo diagnostic laparoscopy for direct evaluation of the diaphragm.

Conflict of interest disclosure

Dr. Raymond Onders, University Hospitals of Cleveland and Case Western Reserve University School of Medicine have intellectual property rights involved with the diaphragm pacing system and equity in Synapse Biomedical who manufactures the device.

No other authors have a conflict of interest disclosure.

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