Diaphragm Rehabilitation through Diaphragm Pacing – Not just for Ventilator Dependent Traumatic Tetraplegics

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Disclosures

• The Presenter has the following interest to disclose:
  • Grant /research from (Synapse Biomedical)
  • The presenter, Case Western Reserve University and University Hospitals of Cleveland all have intellectual property rights and founders shares in Synapse Biomedical
  • The Presenter is also Chief Medical Officer for Synapse Biomedical

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Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. Review the history of diaphragm pacing for upper motor neuron based respiratory failure
2. Describe surgical implantation procedure
3. Identify how diaphragm pacing can be used to wean off mechanical ventilation, replace non-invasive ventilation, and aid in recovery via neuroplastic effects of electrical stimulation.
CE/CME Credit

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Background: Diaphragm Pacing

Decrease - Delay - Replace Mechanical Ventilation

• Over 20 years of research
• Animal Models- Canine, Swine, Rats
• Summarizing 14 IRB Protocols; IDE protocols
• Over 60 million dollars spent on this project
• Over 2000 patients implanted worldwide
  – 27 countries
  – Over 600 patients in my hospital
• Over 30 peer reviewed articles; numerous book chapters and published abstracts with presentations
The Diaphragm

- Diaphragm is KEY muscle of respiration – responsible for 70-90% of resting tidal volume and is the ONLY muscle during REM sleep
- Innervated at C3-5 levels
- Composed of both type 1 and type 2 muscle fibers
  - Type 1: slow twitch fatigue-resistant
  - Type 2: Fast fatigueable
Neural Control of Ventilation

• Breathing rhythmicity originates in the Brainstem
• Pre-Botzinger complex is a network of neurons believed to control respiratory rhythm
• Respiratory centers in the medulla receive input
• Signals are integrated into a combined output to respiratory muscles to modulate breathing frequency, inspiratory time, and expiratory time.
Impact of Diaphragm Pacing on Respiratory Abnormalities

- **UMN- Cerebral Cortex, Brainstem**
  - SCI and ALS
  - Central Sleep Apnea

- **LMN- Spinal Cord C3-5**
  - SCI and ALS

- **Phrenic Nerves**
  - Trauma or Neuropathy

- **Diaphragm Motor Units**
  - Disuse Atrophy
  - Conversion from Slow twitch Type I to Fast Twitch Type IIb
Respiratory Complications in SCI

• Remains the most common cause of morbidity and mortality – 36-83%
• Significant economic burden
• All levels of SCI have some degree of compromise
• Small increases in resistance cause muscle fatigue and precipitate hypoventilation (occurs at much lower resistance compared to general population)
• Decreased hypoxic and hypercapnic respiratory drives which increase over time and with age
• Hypoventilation is more common during sleep
  – 10% ≥ 15 CSA events/hours
  – Microatelectasis, secretions, mucous plugs, lung consolidation all increase risk for pneumonia, respiratory failure
Sleep Disordered Breathing

• 27% - 62% of SDB in chronic SCI
• *Journal of Clinical Sleep Medicine, Vol. 10, No. 1, 2014*
  – 77% had symptomatic SDB
  – 60% cervical injuries had Central Sleep Apnea
  – Cervical injuries had larger decrease in ventilation during sleep - (21% drop) compared to thoracic injuries (11% drop)

• Clinical Implication Identified:
  – Therapeutic methods that target hypoventilation during sleep in cervical SCI may play important role in the treatment of SDB.
DP Started for UMN Loss
Spinal Cord Injury
First Implant 2000

- 100% success in meeting tidal volumes for successfully implanted patients
- Longest 13 years
- 100% had improved speech and more normal breathing
- 100% increased sense of independence
- 100% of patients prefer DP over ventilators

Christopher Reeve “Superman”
Second patient implanted

Over 125 SCI implants at UHCMC
Ages 1-74
Multicenter report describing DP early after injury and replacing ventilators

- 82% implanted completely weaned from ventilator
- 36% had complete recovery of diaphragm respiration and DP wires were removed
- Using the electrodes to monitor for recovery
  - dEMG (diaphragm EMG)
Early Implantation and Neuroplasticity in SCI patients

- Patients have gone from Mechanical Ventilators to DP to volitional breathing
  - Has allowed tracheostomy removal
- DP electrodes function as EMG to assess recovery
- Functional Electrical Stimulation can lead to recovery

Prior to DP: No EMG Activity

After DP Conditioning: Recovery of Natural Function
Large burst activity
Conclusion: Traumatic cervical spine injury and failure to wean

Early Laparoscopic Diaphragm Mapping

Not Stimulatable (24%)

Stimulatable (76%)

Laparoscopic Diaphragm Pacing

No pacing; No ventilator weaning

Peripheral Nerve Transfer + Pacing (93% success)

Weaned (72%)

Delayed Wean (9%)

Partial Wean (9%)

Preference (5%)

Withdrawn Care (5%)

Electrode removal (36%)

RECOVERY OF RESPIRATION

81% Weaned
Early Implantation Without Tracheostomy - High School Wrestler

Recovery of Strong Volitional Breathing
Rapid ventilator weaning in incomplete injury accelerates rehabilitation
Decreasing pneumonia with DP by improving posterior lobe ventilation*

Day before implantation
Incomplete SCI C3
Three previous pneumonias

*Oonders, Elmo et al, Chest 2007

From 2 pulmonary infections per year to 0 after pacing in SCI

One Day of Pacing

5 Months Later Recovered Diaphragm Control and no longer elevated
Pediatric DP Implantations In SCI- Now Worldwide

- 11 SCI children
- Age at injury range 1-17 (average 13)
- Injury to DPS average 9 years (range 1-19)
- All Successful

First reported experience with intramuscular diaphragm pacing in replacing positive pressure mechanical ventilators in children

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<table>
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<th>Age at Implant</th>
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<th>Pacing Achieved (hours)</th>
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Delaying Ventilators in ALS
Initial concept after 2nd SCI patient

- ALS is UMN and LMN
- DP overcomes UMN loss of control
- DP conditions the diaphragm before failure

Diaphragm Pacing Augments Respiration


Midwest Surgical Association: Presidential Address

The diaphragm: how it affected my career and my life. The search for stability when the problem is instability
452 implant months
- 2260 months of wire exposure- one infection
Median survival 19.7 months
- Respiratory cause of death only 31%
- LONGEST PATIENT 6 YEARS THEN TERMINAL WEAN OF DP

Improvement in rate of decline of FVC
Decrease in rate of Hypercarbia
50% used with sleep
Identification of Unexpected Respiratory Abnormalities in Patients with Amyotrophic Lateral Sclerosis through Electromyographic Analysis Using Intramuscular Electrodes Implanted for Therapeutic Diaphragmatic Pacing

- In ALS unilateral diaphragm abnormalities occur from brainstem bulbar control issues
- Surgery and dEMG identified the abnormality and allowed therapy
- DP can prevent elongated diaphragm muscle with permanent sarcomere damage
Extended use of diaphragm pacing in patients with unilateral or bilateral diaphragm dysfunction: A new therapeutic option

Raymond P. Onders, MD, MaryJo Elmo, ACNP, Cindy Kaplan, MSN, Bashar Katirji, MD, and Robert Schilz, DO, PhD, Cleveland, OH

- 86% of implanted patients showed improvement
- 4 tracheostomy ventilator dependent patients weaned
- DP can have a positive role in diaphragm dysfunction
- Results are similar to Parsonage Turner syndrome with Physical Therapy
dEMG Showing Recovery in Idiopathic patient

- **Subject 19**
  - Bilateral DD
  - Tracheostomy Mechanical Ventilation (MV)

On MV no dEMG Day 1
Complete Suppression

First Day off of MV
minimal dEMG Day 1

Complete Recovery, Tracheostomy Removed, Wires pulled after overnight study
Diaphragm Recovery From a Phrenic Nerve Injury with DP

Prior to DP conditioning

After DP conditioning

Right

Left
Methods/Design-For Present Report

• Retrospective review of prospective databases of all patients at a single site evaluated for diaphragm dysfunction.
• Under 13 separate IRB and/or FDA trials.
• Included patients with non-acute respiratory failure and non-traumatic damage of the brainstem/spinal column.
• All patients had complete diaphragm neurophysiologic testing.
  – Radiographs, PFT, sniff fluoroscopy, ABGs and Phrenic Nerve Conduction Studies
Diaphragm Dysfunction Evaluation

• CXR
  – Not sensitive to bilateral paralysis
  – 90% specificity for unilateral dysfunction

• Fluoroscopy of the Diaphragm (sniff)
  – Evaluates paralysis, paradoxical
  – 6% of patients without diaphragmatic paralysis have false positive.
  – False negative results can occur with abrupt contraction/relaxation of abdominal muscles resulting in caudal motion of diaphragm which is often misinterpreted as diaphragm motion.

• Phrenic Nerve Conduction Study
  – Can be false negative/false positive

• Ultrasound of diaphragm
Methods

- Low risk minimally invasive
- 4 port laparoscopic approach
- Less than 1 hour surgical time
- General anesthesia
  - No paralytics

- Clinical Station-delivers stimulus intra-operatively and programs pacer for conditioning

Surgical Instrument

Pacer box
Stimulating the Diaphragm and Implanting the Electrodes at the Motor Point

Direct visualization of diaphragm contraction

Electrodes-2 in each diaphragm

Electrode implantation
The pacers are programmed to the unique needs of the patient with no pain.

Each individual electrode can be programmed with different amplitude and pulse width settings.

Other parameters programmed include breaths per minute rate, inspiratory time, hertz (Hz, electrical cycles per second), and pulse modulation.

Maximum settings are amplitudes of 25, pulse width of 200 and 20 Hz.
Conditioning

- Patient specific conditioning guideline is developed.
- The pacer is turned on and used with the current mode of ventilator support or the patient is removed from the ventilator.
- The patient is monitored for shortness of breath, distress, or decreases in pulse oximetry.
- Initial time breathing with the pacer depends on diaphragm strength.
- The length of time needed to condition or strengthen their diaphragm muscle so that it can sustain ventilation depends on the length of time spent on MV-invasive or non-invasive.
Results

From September 2008 – February 2017

• **21** out of 470 patients were included with chronic hypoventilation/diaphragm paralysis unrelated to traumatic high spinal cord injury

• **9** had a cervical or thoracic injury who developed central sleep apnea or recurrent pneumonias (6mo-44yrs. post injury)

**Other 12**

• 3 brain tumors; 1 meningitis; 1 Myasthenia Gravis; 2 post-polio; 2 Spinal Muscle Atrophy; 1 Pompe Disease; and 2 spinal cord abcess/infections
Patient Characteristics

• Average age 45 years (20 years old to 66 years old)
• 10 patients dependent on Invasive Ventilation
• 3 patients used Non-Invasive Ventilation
• 2 patients were intolerant of NIV
• 4 patients were hypercarbic
• 3 patients used oxygen

• Time of respiratory dysfunction to implant ranged from 1 month to 134 months with average time 26.3 months
Cervical/Thoracic Injury Patient Characteristics (9 patients)

- 2 - developed pneumonia – trach/vent – failure to wean
- 1 – tracheostomy – recurrent pneumonias/secretions
- 1 – trach/vent – apnea/hypercarbia
- 1 – recurrent pneumonia (4 hospitalizations)
- 2 – apnea/hypercarbia – NIV
- 2 – diaphragm paralysis - oxygen
- 7 of the patients developed respiratory problems 8 to 44 years post initial injury
The Other 12

- 7 tracheostomy ventilation
- 3 full time non-invasive ventilation
  - 2 post polio and 1 Pompe
- 2 patients hypercarbic and intolerant to NIV
  - 1 SMA and 1 Brain Tumor
Outcomes

- 2 Patients with spinal abscess had recurrence of infection and no benefit with pacing
- Pompe’s Patient – decreased NIV support
- 1 SCI patient with recurrent pneumonia has had no pneumonia since implant – 2.5 years
- 6 patients weaned off mechanical ventilation – 2 trach patients were decannulated

Myasthenia Gravis Patient Decanullated Tracheostomy after DP
Outcomes

- 2 post polio patients had improvements
  - 1 decreased full time NIV use by 8 hours
  - 1 went from 5 hospitalization for pneumonia in year prior to DP to 0 pneumonias in year post DP
- Hypercarbia was corrected 2 and halted in 1
- Oxygen was weaned completely from 2 patients and decreased in 1 patient
- 1 SMA patient intolerant NIV - went from significant central apneas to normal sleep study
- 8 patients had serial diaphragm EMGs – all 8 had improvement in burst activity with both volitional and automatic breathing
Diaphragm Pacing as a Rehabilitative Tool for Patients With Pompe Disease Who Are Ventilator-Dependent: Case Series

Barbara K. Smith, David D. Fuller, A. Daniel Martin, Lawrence Lottenberg, Saleem Islam, Lee Ann Lawson, Raymond P. Onders, Barry J. Byrne

- Diaphragm Pacing allowed removal of mechanical ventilation
- Identified UMN involvement of respiratory control
- dEMG data showed a respiratory neuroplasticity effect to improve respiratory control
• Two Patients implanted with success
• Clear identification of central component of respiratory failure
  – Lack of bilateral dEMG is evidence of absence of diaphragm contraction which leads to respiratory instability causing respiratory failure
Why Temporary Diaphragm Pacing?
Disuse causes diaphragm atrophy which translates to longer stays and higher cost

Since the 2008, over 20 studies have corroborated disuse atrophy, with reports of:
- 35% reduction in diaphragm force following 2 hours surgery on mechanical ventilation
- Diaphragm pressure rapidly decreasing over the first 5 – 7 days of MV
- Diaphragm thickness decrease of 6% within 1 week of MV
- 32% reduction in twitch airway pressure over a course of 1 week of MV support

- Most patients wean quickly from mechanical ventilation, although ~25% experience difficulty.
- In the U.S., that translates to ~400,000 patients per year, growing at 5.5% per year (ICD9 96.72 M.V. for 96+ hours)
- Annual cost of prolonged (>96 hours) mechanical ventilation predicted to be $64 billion
- Post-operative pulmonary complications (PPC’s) are a major cause of morbidity & mortality and require longer lengths of stay
Growing Trend of Annual Incidence of Prolonged Mechanical Ventilation in U.S.

Patient Source
- Surgical
- Medical
- Trauma / Emergency

ICU Care

Ventilation Outcomes
- Tracheostomy with Positive Pressure Mechanical Ventilation: ICD9 31.1 = 96,515 discharges (temporary tracheotomy)
- Prolonged Positive Pressure Mechanical Ventilation: ICD9 96.72 = 395,950 discharges (mechanical ventilation 96+ Hrs)
- Short-Term Positive Pressure Mechanical Ventilation: ICD9 96.71 = 742,510 discharges (mechanical ventilation < 96 Hrs)
- Non-Invasive Ventilation: ICD9 93.90 = 664,765 discharges (non-invasive ventilation)

CCS 216 = 1,752,250 discharges (mechanical ventilation and respiratory intubation)

Weighted national estimates from HCUP National Inpatient Sample (NIS), 2014, Agency for Healthcare Research and Quality (AHRQ)

(note: patients overlap between some of the above categories)
• A retrospective review of compassionate off label use of an FDA approved device under IRB approved(#02-10-18) of Failure to Wean (FTW)
• Normal weaning options reviewed and/or already failed
Conclusion

• DP had a significant positive effect in weaning patients from positive pressure ventilation
• No device related morbidity
• DP – can be temporary – when full recovery, electrodes easily removed
• DP can monitor recovery with dEMG
• DP can be used to overcome disuse atrophy as therapeutic powered muscle stimulator
• Early application of DP through temporary wires can prevent atrophy before ventilator induced diaphragm dysfunction even occurs
Changing the Paradigm in the ICU
Early Diaphragm Pacing - Overcome VIDD and Therapy for Respiratory Insufficiency, Arrest and Failure (RIAF)

- Implantation at the time of high risk operations could
  - Decrease tracheostomy rate
  - Decrease pneumonia rate
  - Decrease cost

- Central Sleep Dysfunction in critical care
  - Congestive heart failure

- Diaphragm Pacing
  - Reduction in atelectasis
  - Improve respiratory compliance*
    - 20% improvement
  - Converts muscle to Type I
  - Increase diaphragm strength
  - Reduce barotrauma
  - Improves cardiac output
Final Conclusions

• DP can help rehabilitate the diaphragm in more than SCI patients
• In SCI earlier implantation should be standard
• In ALS, in a subgroup, DP overcomes loss of Upper Motor Neuron Control and improves ventilation
• In phrenic nerve injury DP facilitates recovery
• DP overcomes diaphragm atrophy in the intensive care unit patient and can shorten ventilator times
The Key Point: Stimulating the Diaphragm

*The more it moves - the more you ventilate*

*Simple concept with broad applications*

Electrodes left diaphragm
Nobody Chooses to go Back to Ventilators
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