Helping Veterans Breathe: Diaphragm Pacing in Spinal Cord Injury, Amyotrophic Lateral Sclerosis and Diaphragm Dysfunction

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Disclosures

- Presenter(s) has the following interest to disclose:
  - Case Western Reserve University, University Hospitals and Raymond Onders MD- Intellectual Property and Founders of Synapse Biomedical

PESG and PVA staff have no interest to disclose.

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Learning Objectives

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

1. Describe evaluation for Diaphragm Pacing
2. Identify current DP uses
3. Describe benefits of DP
CE/CME Credit

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http://PVA.cds.pesgce.com
The Lung Association states “when you can’t breathe nothing else matters”

- Spinal Cord Injury
- Amyotrophic Lateral Sclerosis
- Diaphragm Dysfunction
  - All lead to respiratory compromise
  - Range is mild to severe requiring little to no therapy to the need for invasive mechanical ventilation or resultant respiratory failure death
Background
Over 20 years of work
ALS for 10 years

• Animal Models
  – Canine, swine, and rats
• Human - over 1500 patients worldwide
  – 25 normal
  – >300 SCI patients
  – >500 ALS patients
  – Multiple various other patients including acute

Summarizing multiple IDE trials and over ten IRB protocols at UHCMC
Diaphragm Pacing

- Goal of DP: move the diaphragm muscle for the patient who has lost central control of their diaphragm
  - An electrical charge is delivered
  - Stimulating the motor points of the phrenic nerve
  - Resulting in diaphragm contraction
  - Leading to respiration
The Key Point: Stimulating the Diaphragm

*The more it moves - the more you ventilate*

*Simple concept with broad applications*

Electrodes left diaphragm
Background: Diaphragm Pacing
Decrease - Delay - Replace Mechanical Ventilation

- First Human Implant – SCI January 2000
- FDA approved in SCI since 2008
- First ALS implant March 2005
- First pediatric SCI implant January 2009
- FDA approved in ALS September 2011
- Used to treat diaphragm dysfunction
- Over 1500 implants worldwide
Respiratory Complications in SCI

- Leading cause of death in SCI – 21% mortality rate
  - More common in cervical injuries
- 55% of injuries are cervical (US trend)
- 26% SCI patients discharged requiring ventilator support all with cervical injuries
- 80% of failed weans/extubations were due to pulmonary mechanical insufficiency
  - Higher incidence VAP
  - Longer hospital days
- Data same for both trach collar and ventilated patients.

Mechanical Ventilation

- Pneumonia
- Loud
- Short battery life
- Increase anxiety of both patient and caregiver
- Tethered to machine – decreasing mobility, freedom, independence
- Cuffed tracheostomy – Tracheal Malacia
Additional Problems with Mechanical Ventilation

• Non Compliance of Current Guidelines
  • Recommendation for evaluation for cuff deflation or cuffless tube
    • 47% with cuffed trach
    • 5% - told “not allowed to deflate cuff”
  • Large tidal volumes
  • Evaluation for Pacing
• Limited SCI rehab facilities take mechanical ventilation
• LTAC’s – do poor SCI rehab
PMV: Why is it a Problem?

- Poor functional outcomes
  - At 1-year, only 9% were able to perform activities of daily living (ADL) independently
  - 26% were moderately independent with ADL
  - 65% were completely dependent on help with ADL.

- Cost
  - 12-month medical cost, $306,000.00 (per pt.)
  - Population growing at rate of 5.5% annually (general hospital admission growth 1.1%)
  - By 2020, it is estimated 605,000 patients annually will require PMV at the cost of -
    - 64 Billion health care dollars annually

- VIDD
  - Ventilator Induced Diaphragm Dysfunction
PMV – Trauma Patients

- Three fold increase in mortality compared to general adult trauma population (Regional Trauma Center data)
- 12% patients required PMV
- 47% received tracheostomy

Study specifically comparing RTC to trauma centers – take away here – trauma patients have same problems with PMV as general population

- SCI – Substantial decrease in life expectancy for those dependent on mechanical ventilation

Rubano, 2015
Vol 78, N 2, 2015
SCI in the Military

- Incidence of spine trauma in modern warfare exceeds reported rates from earlier conflicts.
  - 11.1% combat casualties had one or more spinal trauma
  - SCI occurred at rate of 4 per every 100,000
- Average age 26.6 years
- 99% male
- 81% - Army
- 57.1% - enlisted
- 18% - cervical injuries

Schoenfeld et al
ALS (Lou Gehrig’s disease) Fatal Motor Neuron Degeneration

- Progressive muscular weakness
  - 1.8 to 3.5% per month
- Inspiratory muscle weakness leads to hypercarbic respiratory failure - death
- FVC < 50% up to 100% - 9 month mortality
- 5,000 new cases yearly (US)
- Symptoms to death is 3-5 years
- Limited therapies – NO CURE
- NIV – under-prescribed and poor compliance
- < 5% choose ventilator
UMN and LMN Control of Breathing and the Dysfunction in ALSMND

- Respiratory dysfunction is more than weakness of breathing muscles
- UMN
  - *Leads to Apnea*
    - Cerebral Cortex- volitional
      - *Loose the ability to take in deep breath*
    - Carotid Body
      - O2 saturation
    - Brainstem- Special somatic nuclei
      - CO2 levels
        - *Loss of central drive breath – retention of CO2*
- LMN
  - C3-5
  - Small, medium and large neurons with different resistance levels
- Diaphragm Motor Units
  - Slow twitch Type I
  - Fast Twitch Type IIb
    - *Fast Twitch die off faster in ALS patient than Slow Twitch*
ALS and the Military

• Several studies now confirm there is a higher incidence of ALS in the military compared to civilian populations (Weisskopf et al., 2005, Weisskopf et al., 2015, Seals et al., 2016, Bergman et al., 2015).

• More common in 4 main branches (Army, Air Force, Marines, Navy) – less in Coast Guard, Reserves

• More prevalent in enlisted personnel

• Trend with overall deployment time
  – Substantial conflicting data on which VETS are most at risk – but now accepted all VETS are at greater risk
Diaphragm Dysfunction

• Any disease processes affecting the brain, nerves, or the muscle may result in diaphragmatic dysfunction.

• Phrenic nerve damage due to injury during surgery, trauma, compression caused by bronchogenic or mediastinal tumors, illnesses including Guillain–Barre syndrome, spinal cord injuries, myasthenia gravis, botulinum toxin, metabolic abnormalities such as hypophosphatemia, hypomagnesemia, hypokalemia, hypocalcemia and Idiopathic

• May effect one or both hemi diaphragms
DP Evaluation

• Diagnosis determines scope of pre-operative testing
• Pre-Operative evaluations may include
  – H&P, Pulmonary Function Testing including FVC, MIP and Arterial Blood Gas, Chest X-ray both on inspiration and expiration, fluoroscopy of the diaphragm, sleep studies, and Phrenic Nerve Conduction Study
• Operatively: visualization of direct stimulation of the diaphragm
• Regardless of pre-operative test results, only stimulable diaphragms at surgery were implanted.
Methods: Implantation

Laparoscopic Surgery

Implanting 2 electrodes in each Diaphragm

Mapping to Identify Optimal Location for Wire Implantations

Conditioning the Diaphragm with external system

Clinical Station to Program Unit To condition diaphragm with no pain
Implanting Electrodes and Stimulating the Diaphragm
Results

- Data collected from 9 separate IRB and/or FDA trials from 2000-2016 (single site)
- 408 patients were implanted with DP
- 25 of this group were Veterans
  - 15 ALS
  - 5 SCI
  - 5 DD
- No Peri-Operative Mortality
- No internal wire malfunction/breakages
Result SCI: 2000-2016

- 125 Implanted
- Age range 2 to 74 years old
- Time spent on mechanical ventilation 11 days to 29 years
- No peri-operative complications
- No pneumonia deaths
- Clinical trial - 100% success of >4 hours ventilator free breathing
- Maintained 82% > 4 hours of vent free breathing daily since completion of clinical trial with 50% replacing ventilator full time
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)
Additional Benefits of Early Implantation

• Sub analysis of the 18 full time DP patients
  – Weaned in average of 5.7 days
  – Average implantation occurred 11 days post injury
  – 67% did not go to LTAC
  – 36% had complete recovery of respiration
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
Decreasing pneumonia with DP by improving posterior lobe ventilation*

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

Day before implantation
Incomplete SCI C3
Three previous pneumonias

One Day of Pacing

5 Months Later Recovered Diaphragm Control and no longer elevated

*Onders, Elmo et al, Chest 2007
Other Benefits

- Improved sense of smell
- Increased Independence
- Decrease in secretions
- Decrease in suctioning
- Better socialization
Replacing the Ventilator - Changes the life of a SCI patient

Can delaying a ventilator do the same in ALS?

Cannot skydive with a ventilator
Delaying Ventilators in ALS
Initial concept after 2\textsuperscript{nd} SCI patient

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

\textit{DP Augments Respiration}
DP ALS Results- UHCMC

- 30-day morbidity 0.4% or 3 patients
  - 2 deaths
  - 1 tracheostomy
- Not all patients were implanted
  - 20% screen failures
  - 10% non stimulable diaphragms at surgery
- Median survival 21.8 months (95% CI 18.1, 26.0 months) post implantation
- Ages ranged from 22 years to 82 years
- Average FVC was 56%, age 56, MIP 40
- Initial DP Post Approval Study data presented at the ALSMND meeting in December 2015 mirrored the above and the US FDA clinical trial survival data.
Identifying Appropriate Patient in ALS is KEY

- Comprehensive pre-implant work up is imperative in ALS patients
- All but 2 patients had inspiratory/expiratory chest x-rays
- 219 had phrenic nerve studies
- 81% had fluoroscopic evaluations of their diaphragms
Anesthesia Protocol

- No paralytics
- Short acting anesthetic agents: remifentanil, sevoflorane, propofal
  DP utilized for subsequent operations

Complete worldwide operative experience in laparoscopic diaphragm pacing: results and differences in spinal cord injured patients and amyotrophic lateral sclerosis patients

Raymond P. Onders · MaryJo Elmo · Sacid Khansarinia · Brock Bowman · John Yee · Jeremy Road · Barbara Bass · Brian Dunkin · PalI E. Ingvarsson · Margréét Oddsdóttir

Received: 16 April 2008 / Accepted: 17 October 2008
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Final analysis of the pilot trial of diaphragm pacing in amyotrophic lateral sclerosis with long-term follow-up: diaphragm pacing positively affects diaphragm respiration


- 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

2014
Evidence of UMN Effect of DP and Augmenting Respiration: Pilot Study

DP Increases Muscle Thickness/Mass:

*DPS converts Type IIb (fast twitch) to Type 1 (slow twitch) muscle fibers*

<table>
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<tr>
<th>Test location (hemidiaphragm/position)</th>
<th>Thickness (mm)</th>
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<th>Postimplant</th>
<th>P value</th>
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<td>4.7 ± 1.1</td>
<td>.01</td>
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</tr>
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</table>
Evidence of DP Augmenting Respiration and Overcoming Loss of LMN Control: DP Improved Movement of Diaphragm Under Fluoroscopy

- Increase in diaphragm contraction with stimulation compared to volitional movement
- Allows visualization of upper motor neuron involvement
- Confirms surgical findings
Augmenting Respiration: Treating Hypercarbia

Pt 01-11- DPS decreased pCO2 from 54 to 40 Patient became more alert

- Multi-center Trial
- Paired Sample
- Post DP pCO2- Total (n=74)
  - Decreased 2.0 mmHg
  - P<0.001
- Elevated pCO2 greater than 45 pre-implant (n=18)
  - Decreased 2.6 mm Hg
  - P< 0.03
Augmenting Respiration: Overcome Central Sleep Apnea & NIV Impact on Diaphragm Activity
Sleep studies show diaphragm EMG suppression when on NIV

Augmenting Respiration: Improvements in Sleep with DP

Diaphragm pacing improves sleep in patients with amyotrophic lateral sclerosis

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Why ALS patients should get Chest X-Ray:

70% had significant unilateral abnormalities

Healthy Chest X-Ray
- Diaphragms equal
- Left HD - bottom heart border

Onders et al ALS 2013

Significantly Elevated Right Hemi-diaphragm
Pt. with FVC 85%

Significantly Elevated Left Hemi-diaphragm
• Onders et al, Am J Surgery 2015
• 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
Case Example 1: Radiographic Analysis of Upper Motor Neuron Disease of Diaphragm

No discernible diaphragm movement with sniff test or inspiratory-expiratory CXR

Case Example 1: Operative Analysis of Upper Motor Neuron Involvement

Diaphragms Pre-stimulation

Substantial contraction with stimulation

Stimulation Generated - Tidal Volumes of 700cc

*DP WILL SIGNIFICANTLY HELP THIS SUBJECT*
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
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
DP: DD Results

- 57 total patients
- Mechanisms of Diaphragm Paralysis falls into 4 major categories

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<th>Category</th>
<th>Subjects</th>
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<td>Shoulder Surgery/Trauma</td>
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<td>Chest Surgery</td>
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<tr>
<td>Other (diseases such as CMT, BVVL, SMA)</td>
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</table>
Ventilator Induced Diaphragm Dysfunction: VIDD

• Positive pressure causes muscle inactivity
  – Leading to diaphragm muscle atrophy and weakness

• 18 hours Controlled Mechanical Ventilation (CMV) causes diaphragm atrophy

• Pressure Support Ventilation (PSV) – also causes diaphragm atrophy
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

*Oonders et al Chest 2007
<table>
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<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Time on PMV -Days</th>
<th>(#Days to DeCann)</th>
<th>Days to Wean</th>
<th>Survival (Months)</th>
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DP Electrodes to Monitor dEMG
Assess Recovery

Failure to Wean - Tracheostomy Mechanical Ventilation (MV)

On MV no dEMG Day 1
Complete Suppression

First Day off of MV
minimal dEMG Day 1

Complete Recovery
Diaphragm Recovery From a Phrenic Nerve Injury with DP

Prior to DP conditioning

After DP conditioning

Right

Left
Conclusions

• Published data showing benefits of early implantation in SCI
  – DP can have neuroplastic effects of the diaphragm and aid in spontaneous respiration recovery, decrease MV/ICU time,
• Patients prefer DP to MV
• DP surgery in ALS is safe
• DP had a positive effect in overcoming UMN involvement that can be difficult to predict pre-operatively
• In ALS, current DP data in U.S, continues to mirror FDA clinical trial data
• In PMV population, DP had significant improvement of overall survival and quality of life compared to similar groups of patients
• Shorter wean time
Nobody Chooses to go Back to Ventilators
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