DISCLOSURE

Dr. Gay has declared no conflicts of interest related to the content of his presentation.
Diaphragmatic Pacers

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Objectives

- Discuss important issues about SCI and ALS
- Summarize the possible role for phrenic nerve stimulation therapy or diaphragm pacer system (DPS)
- Be transparent about challenges and potential complications associated with diaphragm pacing system therapy.
Question 1

Which of the following is true?

A. Most spinal cord injury patients are females aged <30 years
B. 80% of high quadraplegics (C2-8) will be able to wean from the ventilator
C. ALS peaks between 30-50 years of age
D. ALS survival is better for younger patients with bulbar onset disease
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Background
SCI Fun Facts

- Majority of SCI involves males < 30 yrs age
- A 20 yo tetraplegic ventilator dependent pt has a life expectancy >14 years shorter than a tetraplegic pt who does not use a ventilator.
- The leading causes of death are pneumonia, pulmonary emboli and septicemia.
- As of February 2011, the National Spinal Cord Injury Database estimated that between 232-316,000 pts in USA are living with SCI
- ~12,000 new cases occur each year.
Of new cases, more than 2,700 tetraplegics will require extended ventilator support (2009 Annual Report for the Spinal Cord Injury Model Systems).

Ultimately, 2,000 will wean themselves from ventilators

500 high tetraplegic injuries will result in permanent mechanical ventilator dependency.
Incidence of Respiratory Complications Following SCI
Jackson and Groomes, 1994

- Prospective case series multi-center N= 261
  Frankel A, B, or C SCI
- 67% rate of respiratory complications.
- Atelectasis, Pneumonia, Ventilatory failure
- Respiratory complication
  - Rate–C1-4, 84%; C5-8, 60%.
ALS Facts

- Jean-Martin Charcot described ALS in 1869.
- ALS can occur at any age but peaks between age 40 and 70 years of age.
- Incidence/Prevalence:
  - More than 5,600 Americans are diagnosed with ALS each year.
  - 2 new ALS cases per 100,000 people.
  - ~35,000 people at any given time are living with ALS in the United States or 6-8 people per 100,000.

Data from the Les Turner ALS Foundation.
ALS Facts
ALS: Therapy

- Multidisciplinary teams should include a respiratory/sleep professional

Miller, RG Neurology® 2009;73:1218–1226
DPS Types

- May 1971 - First clinical use phrenic pacing
- All devices require functional phrenic nerves
- There are two types of devices:
  - Conventional Phrenic Nerve Pacing
    - Avery Laboratories (Commack, NY, USA)
  - Phrenic Nerve Pacing with intramuscular diaphragm electrodes
    - Synapse BioMedical (Oberlin, OH, USA)
  - Intercostal muscle pacing
    - Not clinically available in the US

How does it work?

- Transmitter generates a radio-frequency signal, which is inductively coupled to the implanted receiver using antenna wires.
- The radio-frequency signal is converted by the receiver, to an electrical signal, which is transmitted to the electrode.
Avery DPS

- **Cervical**
  - May get a smaller VT due to inability to get all roots
  - Neck movement may increase risk of nerve/electrode injury
  - May get shoulder or neck contraction
Synapse DPS: Intramuscular diaphragm electrodes

- Laparoscopic placement
- The phrenic nerve in diaphragm is mapped
- The Peterson Electrode needles into the muscle

Methods: Outpatient Laparoscopic Procedure
Synapse DPS: Intramuscular diaphragm electrodes

- Anterior and posterior branches of the phrenic are isolated and fitted with electrodes.
- 4 leads, ground wire are tunneled to a single point on the abdomen to attach electrical stimulator.

AJRCCM Vol 166. pp 1604–1606, 2002
CLEVELAND, Feb. 28, 2003: Nearly eight years after the accident that left Christopher Reeve paralyzed and dependent on a ventilator, the 50-year old actor and activist has hopes of breathing more normally, with the aid of a surgically implanted investigational device.
Phrenic Nerve Stimulation
Laparoscopic Approach

- Minimally invasive surgery - laparoscopic
  - Surgeon Raymond Onders, MD,
  - Program director Anthony DiMarco, MD Case Western Reserve University.
- Electrodes placed in Reeve’s diaphragm muscle and are attached through subcutaneous wires to a small receiver. The external battery pack connects to a surface transmitter which stimulates the diaphragm and phrenics.
- Half the cost and risk of open procedure
- “I can smell again”
Question 2

Which is the correct statement?

A. Current FDA approved indications for DPS include SCI, ALS, and CCHS
B. The Synapse system advantage is that the direct diaphragm implantation does not require an intact phrenic nerve
C. Phrenic EMG studies have a high false positive and negative value
D. Most SCI pts say Passy Muir vent valve circuits gives good continuous speech
Question 2

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# Phrenic Pacing

## Indications

- Spinal Cord Injury*
- Amyotrophic Lateral Sclerosis*
- Central Congenital Hypoventilation Syndrome (CCHS)
- Newer possibilities:
  - Post operative phrenic injury
  - Idiopathic phrenic paralysis
    - Parsonage Turner
  - Prevent disuse atrophy of the diaphragm during prolonged mechanical ventilation

*FDA approved indications

## Requirements

- Intact Phrenic Nerve
- Good cognitive function
- Good family support
Phrenic Nerves Need to be Intact

- Dead meat don’t beat
- Phrenic EMG studies
  - High false positive and false negative test
- Combined ultrasound assessment
- Surgical evaluation is the final test

**PHRENIC NERVE CONDUCTION STUDIES IN SPINAL CORD INJURY: APPLICATIONS FOR DIAPHRAGMATIC PACING**

AMER ALSHEKHLEE, MD, MSc,1 RAYMOND P. ONDERS, MD,2 TANVIR U. SYED, MD, MPH,1 MARYJO ELMO, ACNP,2 and BASHAR KATIRJI, MD1
Diaphragm Movement and Contractility Evaluation by Thoracic Ultrasound: Ultrasonography Determination of Diaphragmatic Excursion

Bassel Ericsoussi, MD
Pulmonary and Critical Care Fellow
University of Illinois at Chicago

Diaphragm Movements and M-mode Ultrasonographic Measurements

- In inspiration the diaphragm descends, moving toward the ultrasound probe
  - Upward inspiration slope on M-mode
- The diaphragm inspiratory excursion: The amplitude between the foot of the inspiration slope and the apex of this slope
  - Always greater in men than in women
  - Always greater in the supine position than in the sitting or the standing positions
  - No significant correlation with age
  - Significant correlation with height and weight
### Table 2
Right Diaphragmatic Excursions and Limit Values in Men and Women

<table>
<thead>
<tr>
<th>Variables</th>
<th>Men, cm</th>
<th>Women, cm</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Quiet breathing</td>
<td>1.8 ± 0.3 (1.1-2.5)</td>
<td>1.6 ± 0.3 (1.2-2.2)</td>
<td>&lt; 0.001</td>
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<tr>
<td>Voluntary sniffing</td>
<td>2.9 ± 0.6 (1.8-4.4)</td>
<td>2.6 ± 0.5 (1.6-3.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Deep breathing</td>
<td>7 ± 1.1 (4.7-9.2)</td>
<td>5.7 ± 1 (3.6-7.7)</td>
<td>&lt; 0.001</td>
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### Table 3
Left Diaphragmatic Excursions and Limit Values in Men and Women

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<td>Quiet breathing</td>
<td>1.8 ± 0.4 (1-2.6)</td>
<td>1.6 ± 0.4 (0.9-2.4)</td>
<td>0.002</td>
</tr>
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<td>&lt; 0.001</td>
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<tr>
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<td>7.5 ± 0.9 (5.6-9.3)</td>
<td>6.4 ± 1 (4.3-8.4)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
Challenges

• During DB, the descending lung may obscure the diaphragm
  – The probe should be displaced caudally with an angle adjustment to maintain a perpendicular approach of the hemidiaphragmatic motion.

• Patients with respiratory disease and dyspnea
  – Increased respiratory effort can result in greater chest wall movement and cause the ribs and lung to obscure the images

• Visualization of the left hemidiaphragm is recognized as more difficult due to the smaller window of the spleen as compared with the liver window
Objectives of the DPS

- Provide Natural Negative Pressure Ventilation with the patient’s own diaphragm
- Provide it with limited trauma or risk
- Inexpensive
- Outpatient management
- Removable
DPS History

- Animal Models
  - Canine, swine, and rats

- Human - over 350 patients worldwide
  - 25 normal
  - >100 SCI patients
  - >120 ALS patients
  - Multiple other patients
DPS Theory

- **Conditioning the Diaphragm**
  - Diaphragm needs to regain strength
  - Conversion of fast twitch glycolytic (Type IIb) to slow twitch oxidative (Type I)
  - Increase length of sessions as tolerated
    - Typically increase length every 5-7 days
  - Using system continuously > 4 hrs then can use it at night
Not a diaphragm pacer. Need intact Phrenic nerves

Standard technique requires thoracotomy to place electrodes in direct contact with the phrenic nerves

Procedure carries substantial risk and requires a prolonged hospital stay

The early procedure typically costs more than $100,000 (device plus surgery, hospitalization and follow-up)
DPS Concessions

- Great advances in placement and management of diaphragm pacing systems (DPS) for pts with spinal cord injury (SCI)
- Pts may appreciate the ability to be freed from the ventilator dependence for part of the day
- Speculation that some patients can gradually condition and strengthen the diaphragm to allow more subsequent independent ventilation.
SCI Quality of Life “Stories”

- No need for continuous electricity
  - Hurricanes or Snowstorms concerns alleviated
- Silence of the pacer enabled sleeping
- Increased ability to attend school or church
- Transfer from ventilator nursing facility to home
- Increased ability for air travel
- One patient had not left her house for 7 yrs
  - First trip Disney World
DPS Replaces Mechanical Ventilation in Tetraplegics

- The DPS system is safe and effective
- In Ohio, save $13,000 dollars per patient per month
- No patients stopped pacing and all would recommend it
  – Adler et al Eur Resp J 2009
- Earlier use and temporary use in weaning could decrease pneumonias
DPS Contentions

- Procedure is not inexpensive and many patients may have substantial out of pocket expense
- Not without complication
- Very little long-term outcome data that justify the expense of the procedure and device
- Noninvasive ventilation, may be more appropriate until better supportive data available to support more widespread use of DPS esp in ALS
- Rapid extrapolation to other indications is being urged at patient expense without good studies
Pt Reported Down Side

- DPS strictly paced so can’t initiate breath
- SCI pts note that with 900cc breath and 12-14 br/min, a Passy Muir valve circuit allows almost continuous speech
- Elimination of the fear of disconnection from the mechanical ventilator is replaced by battery/pacer failure
- All SCI pacer users need backup so care plan requires 2 systems
Laparoscopic surgery has some associated risks

- Complications common to all surgical procedures
- Laparoscopy associated with the development of pneumothorax and subcutaneous emphysema
Pain associated with stimulation

- Another subject developed right shoulder pain during the maximum stimulation of a single electrode likely occurring as a consequence of the stimulation of phrenic nerve afferents.
- Symptoms may be alleviated by a modest reduction in stimulus current but may result in inadequate diaphragm function.
Side effects

DiMarco. CHEST 2005; 127:671–78

- Subject with rhino-sinusitis prior to his injury but not present when receiving mechanical ventilation. Restoration of nasal airflow during diaphragmatic pacing evidently resulted in the recurrence of symptoms.

- Another subject had intermittent food aspiration, which most likely was related to the large negative airway pressure generated during contraction of the diaphragm. Problem was eliminated by use of a Passy-Muir valve during meals.

- Potential long-term effects of prolonged pacing include electrode dislodgement and electrode breakage.
Question 3

Which of the following is correct?

A. DPS implant should be delayed at least a year to permit natural recovery time

B. Over 90% of selected SCI pts were able to replace the ventilator with a DPS

C. Cohort study shows similar survival advantages for DPS and early use NIV

D. A DPS should not be used simultaneously with NIV
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This report summarizes the complete worldwide multicenter experience with diaphragm pacing stimulation (DPS) to maintain and provide diaphragm function in ventilator-dependent spinal cord injury (SCI) patients and respiratory-compromised patients with ALS.
From March of 2000 to September of 2007, a total of 88 patients (50 SCI and 38 ALS) were implanted 29 with DPS at five sites.

- Patient age ranged from 18 to 74 years.
- Time from SCI to implantation ranged from 3 months to 27 years.
SCI Results IDE trial – 50 patients
Median Hospital stay < 24 hours

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>SCI Subjects (n=50)</th>
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<tbody>
<tr>
<td>Peri-operative Mortality</td>
<td>0</td>
</tr>
<tr>
<td>Device Related Mortality</td>
<td>0</td>
</tr>
<tr>
<td>Long Term Mortality</td>
<td>5(10%)</td>
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- 68% Decreased Secretions
- Less Suctioning
- Over 50% 24 hours a day
- Longest 10 years
In 87 patients the diaphragm motor point with successful implantation of electrodes with the only failure the 2d SCI patient who had a false-positive phrenic nerve study.
Complete worldwide operative experience in laparoscopic diaphragm pacing: results and differences in spinal cord injured patients and amyotrophic lateral sclerosis patients
Raymond P. Onders, Surg Endosc 2008

- In the SCI patients 96% were able to use DPS to provide ventilation replacing their mechanical ventilators and in the ALS studies patients have been able to delay the need for mechanical ventilation up to 24 months.
Complete worldwide operative experience in laparoscopic diaphragm pacing: results and differences in spinal cord injured patients and amyotrophic lateral sclerosis patients
Raymond P. Onders, Surg Endosc 2008

- There was no perioperative mortality even in ALS patients with forced vital capacity (FVC) below 50% predicted.
- There was no cardiac involvement from diaphragm pacing even in 10 patients who had pre-existing cardiac pacemakers.
- No infections occurred even with simultaneous gastrostomy tube placements for ALS patients.
Pacing in ALS

The Trial

- **Inclusion:**
  - FVC >50%
- **Design cross over**
  - Every pt serves as their own control
  - An FVC needed to stay >45% after 3 months to allow for implantation
- **Methods**
  - Pacer use 5 times a day for 30 mins
- **Assessment**
  - Lung function etc measured every 3 months

Why use pacing in ALS?

- Mortality is due to respiratory failure
- Electrical stimulation can help to overcome the deficits from UMN disease
- The greatest failure in NIV is from bulbar disease. Pacing avoids the upper airway

Prospective Studies of DPS in ALS

Initial FDA design began 2003
clinicaltrials.gov

- **20 Patient Pilot Study**
  - 2004-2007
  - 16 patients implanted / 4 patient fall-out

- **120 Patient Multicenter Pivotal Study**
  - Approved October 2006, patients implanted 2007-8
  - All patients have completed follow-up

**Devices do not have phases of trial – Pilot to Pivotal**
NIV in ALS

- **Design**
  - Pts assessed every 2 months and randomly assigned to NIV (n=22) or standard care (n=19) when they developed either orthopnea with MIP <60% predicted or symptomatic hypercapnia

Bourke, SC Lancet Neurol 2006; 5: 140-47
NIV in ALS: Benefits

- **Survival**
  - Best RCT
  - Median survival benefit of 205 days ($p=0.006$)
  - The use of NIV improves survival but is a challenge for those with bulbar disease.
  - The improvement in survival is greater than that seen with Riluzole

Bourke, SC Lancet Neurol 2006; 5: 140–47
Pacing in ALS

- The ALS diaphragm is much weaker
- Denervated areas can be seen as the pale radial bands

Pacing in ALS

Trial Results

- DPS can convert fast-twitch glycolytic (IIb) to functional slow-twitch oxidative muscle (I) fibers;
- DPS improves posterior lobe lung ventilation;
- DPS increases lung compliance, leading to decreased work of breathing;
- DPS to improve nighttime ventilation.
- Average rate of decline in FVC of 0.9% per month from the pre-implantation decline of 2.4% a month,
- Extrapolates to an additional 24 months of ventilator-free survival.

Long Term Results

- One internal electrode failure
- One patient superficial wire infection stopped pacing temporarily
- Causes of Death (10)- No Device Related deaths
  - 3 Urosepsis
  - 3 Cardiac (Elderly and long term injured)
    - 1 Endocarditis
  - 2 Complications from Decubiti
    - 1 Systemic Mastocytosis
  - 1 Aspiration- Sepsis
  - 1 recurrence of tumor and sepsis
Evidence of Survival Benefit

- **Comparison to Lechtzin 2007**
  - DPS Demographics between early and late NIV use populations

- **DPS Survival**
  - 100% 30 day survival
  - 86% 6 month survival
  - 74% 12 month survival

- 64 month median survival from diagnosis
- Approaching 24 month median survival from implant

Conclusions for DP in ALS

- Safe and tolerated
- Positively affects diaphragm physiology
- Positively affects survival
  - Especially with PEG
  - 74% 12 month survival
NIV + DPS in ALS: Benefits

- Adding NIV to nocturnal Pacing increases survival in ALS pts from:
  - NIV alone vs NIV + DPS (months) 21 ± 5 VS. 12 ± 2; p < 0.001

Ounders, RP. Amyotrophic Lateral Sclerosis 2010;11:137
NIV + DPS in ALS: How to’s

- **How to make it work**
  - Set the NIV as a slave to the pacer
    - Use a standard ST device
    - Set the rate 1-2 less than the back up rate of the pacer (12 BPM)
    - Set the Ti time equal to the pacer (1.1 sec)

- **How to monitor**
  - The download software from the NIV will allow for adequate monitoring
  - Augment Tidal volume with increases in IPAP
  - Augment rate by turning up the rate of the pacer
  - Occasional additional overnight oximetry may be helpful

Oonders, RP. Amyotrophic Lateral Sclerosis 2010;11:137
Leaps of Faith

- **Disuse Atrophy**
  - 14 brain dead donors on PPV vs 8 controls
  - 18 hrs of CMV causes marked atrophy
  - 57% decrease Type 1 slow twitch fibers
  - Inactivity leads to oxidative stress
  - Increased proteolysis

Sanford Levine et al

Rapid Disuse Atrophy of Diaphragm Fibers in Mechanically Ventilated Humans
Can DPS decrease Mechanical Ventilation in the ICU?

- 33-50% of ICU pts require mechanical ventilation
- 20% on ventilator > 7 days
- 40% time spent on weaning
- Over 100,000 tracheostomies performed yearly for failure to wean
- ICU costs $4000 per day
PPV Stops Diaphragm Activity

Sleep studies looking at diaphragm EMG shows no activity when on PPV - Making Diaphragm Weaker??

Diaphragm EMG with and without CMV
Decreasing Pneumonias

Historically average 2 per year

- No deaths from pneumonias
- 5 hospitalizations for pneumonias
- Pts and Caregivers report 60% less secretions with DP
Improving Ventilation - Preventing Pneumonia with DPS
N = 1!!!!

Day before implantation
Incomplete SCI C3
Three previous pneumonias

*Onders, Elmo et al, Chest 2007

One Day of Pacing

5 Months Later Recovered Diaphragm Control
Specific reasons for the underperformance of LVRS have been suggested

- Restricting LVRS performance to NETT, lung transplant, or JCAHO approved centers limits patient access
- LVRS assessment is perceived as overly complicated
- Many physicians still remain unaware of the benefits of LVRS and what constitutes an appropriate patient candidate
- LVRS is perceived by many in the medical community as too costly
Specific reasons for the underperformance of LVRS have been suggested

- Beneficial outcomes that occur after LVRS are not uniform and even in the group of high benefit the variability of changes in physiological and functional parameters after LVRS are great.

As a result, nonsurgical approaches to lung volume reduction have been pursued to achieve the benefits of LVRS, but with less patient morbidity and mortality
What Do You Believe?

“You are completely free to carry out whatever research you want, so long as you come to these conclusions.”
Question 4

Describe DPS practice at your site:

A. I have no experience with a DPS
B. I have small (<5) experience with a DPS
C. I have experience (>5) with a DPS
D. I do not believe DPS is ready for primetime
Conclusions

- DPS technique has improved immensely and holds clear promise in certain subsets of patients with diaphragm dysfunction
- Indications for DPS need better clarification especially for ALS patients
- Need to be more transparent about the long term outcomes- Role for a patient registry?
- Future research should clearly proceed in several areas but not with patient financing