Diaphragm Dysfunction and Treatment in Amyotrophic Lateral Sclerosis

Estelle S. Harris, MD
Associate Professor of Medicine
University of Utah
02/02/13
No Disclosers
Outline of Talk

- Case report VB
- Introduction to ALS
- Brief history of the diaphragm
- Respiratory support and ALS
- History of pacing
- DPS in ALS
- Summary
CASE of VB I

• 58 y/o F with PMH of MS (dx ‘98) with initial c/o difficulty with speech in Oct. of 2005

• March 2006 EMG showed denervation in multiple muscles including:
  – left arm, first dorsal interosseus on the right, thoracic paraspinal muscles and her tongue

• FVC in 2008 was already <40%
Case of VB II

- January 2008 traveled to San Francisco, for possible enrollment into the ALS diaphragmatic pacing study
- She did not qualify due to FVC (needed 50% at enrollment at >45% at implantation)
- Returned, continued on BIPAP (12/5) at night and then later during most of the days
Case VB III

- April 2009- Presented with pneumonia and pCO2 of 94
- Underwent elective tracheostomy
- Postoperative complication of ileus w/ progression to non-viable colon requiring emergent total colectomy
- D/C for 2 weeks to rehab May 2009
- Remains on ventilator at home at present (almost 4 years)
ALS

- ALS is a progressive neurodegenerative disease affecting nerve cells in brain & spinal cord
- Average life span of three years after onset
- Progressive damage to motor neurons
  - most patients lose 1-3% of their breathing ability each month
- Most ALS patients die from respiratory failure
- < 5 percent of ALS patients choose tracheostomy and mechanical ventilation
University of Utah
Motorneuron Disease Clinic

- MDA/ALS certified multispecialty clinic
- Launched in 1995
- 115 patients followed as of December 2012 (50 new patients/year)
- Intermountain Region-6 states
  - Neurology, Pulmonary, RT, PT, OT, MA, Nursing, Pharm D, Nutrition, Speech, MDA/ALS Representatives and Venders (adaptive technology, DME and hospice)
Respiratory Abnormalities in ALS

- Abnormal respiratory center
- Intracranial signal disruption
- Interruption of signaling to muscles
- Inability of diaphragm to contract
History of the Diaphragm

• Homer-(700 BC) thought that the “life spirit” was seated in the diaphragm
• Plato- (400 BC) believed the immortal soul lived in the head and the mortal soul in the body
  – The tranquil part lived in the chest
  – The appetitive part in the abdomen
  – The “phrenes” separated the nobler from the less noble parts
History of the Diaphragm II

• Hippocrates- (300 BC) “the diaphragm has obtained its name (phrenes) from accident and usage and not from reality or nature… I know of no power which it possesses… except that when man is affected with unexpected joy or sorrow, it throbs and produces palpitations, owing to its thinness”…

• Galen- (200 BC) showed anatomic evidence of diaphragm control by the phrenic nerve – yet the metaphysical languished for centuries
The Thoracic Diaphragm

- A sheet of muscle that extends across the bottom of the rib cage
- Separates the thoracic cavity from the abdominal cavity
- All mammals have a diaphragm
Causes of Diaphragm Dysfunction

Neuropathic Causes
- Abnormal brain
- Spinal cord injury
- MS, ALS, poliomyelitis
- Guillain-Barre syndrome
- Cervical spondylosis
- Brachial plexus neuritis
- Phrenic nerve dysfunction
  - Compression (tumor)
  - Surgery (cold or other)
  - Trauma (manipulation)
  - Postviral or XRT
  - Idiopathic

Myopathic Causes
- Dystrophes
- Thyroid disease
- Acid maltase deficiency
- Amyloidosis
- Inflammatory myopathies
  - Polymyositis, SLE
  - Dermatopolymyositis
  - Inclusion body myositis
  - Large artery vasculitis
  - MCTD
- Idiopathic
Anatomy

- **Sternal portion** - the back of the xiphoid process
- **Costal portion** - interdigitates with the transversus abdominis and connects the inner surfaces of the cartilages and adjacent ribs (7-12)
- **Lumber portion** - lumbocostal arches
- **Crural portion**
- **Central Tendon**
Normal Respiration

- Spontaneous breathing has orderly recruitment of diaphragm motor units
- Smaller motoneurons (slow fibers) with lower membrane surface area and higher input resistance
  - More excitable, fatigue-resistant, slow twitch
- Progressive recruitment of fast fibers with large force generated (cough, extra force)
- Usually does not need additional groups
  - “Accessory muscles”
Known Methods to Support Respiratory Failure in ALS

- Oxygen
- Non invasive ventilation
  - Sip puff
- Breath stacking approaches
- Cough Assist Machine
- Invasive ventilation-Tracheostomy and mechanical ventilation
Sip and Puff System
First study to show survival benefit w/ NIV in ALS

Cleveland Clinic March 1993- Feb. 1996

Initiated NIV when pCO2 >45 mmHg and patient refused tracheostomy (MV)

Prior to ‘94 volume ventilation via vent w/ mask and after ‘94 could choose a Respironics BIPAP machine

Tolerant Patients (18/39):
  - Less bulbar (30%)
  - Higher MIP
Medicare Dx Hypoventilation

- Necessary to qualify for BIPAP (1999)
- Nocturnal oximetry
  - <88% SaO2 for over 5 min during sleep
- ABGs
  - PCO2 >45 mmHg
- PFTs (only neuromuscular patients)
  - FVC <50% predicted
  - MIP <60 cm H2O
Non Invasive Ventilation in Diaphragm Dysfunction

• Nocturnal rest allows improved daytime function
• Bilevel support- an inspiratory pressure gradient above the expiratory pressure
• Good mask fit and ability to tolerate the NIV is critical
122 patients at Hahnemann University (retrospective 1993-1997)
Evaluated if use of NIV mattered and if > 4 hours a day use was important

Groups
1- Bipap $>4$ h (n=38),
2- Bipap $<4$ h (n=32)
3- no Bipap (n=52)

Similar at baseline characteristics including: bulbar, % FVC at study entry and BIPAP introduction and PEG

Survival rates after Bipap

12 months:
- 50% at 1 month
- 19% at 2 months
- 8% at 3 months

18 months:
- 21% at 1 month
- 5% at 2 months
- 2% at 3 months

Survival rates in the three patient groups (1–3) at 12 and 18
Survival and Decline of FVC

[Graph showing survival rates over months for different groups]

[FVC before and after BIPAP graph]
Comparison of Medicare Criteria

- 161 patients from Western ALS study natural history database at study enrollment
- Patients met MIP criteria 4 to 6.5 months earlier

Mendoza et al. ALS 2007; 8: 106-111
Comparison of MIP and FVC Over Time

Mendoza et al.  ALS 2007; 8: 106-111
History of Pacing I

1777 Cavallo-electricity as means of artificial respiration

1818 Ure- phrenic nerve stimulation of criminal hung w/ contractions of the diaphragm

1872 Duchenne- phrenic nerve stimulation was the “best means of imitating natural respiration”

1873 Christoph Hufeland- proposed using electrical stimulation of the phrenic nerve to treat asphyxia

1948 Sarnoff- 52 hours of phrenic nerve stimulation as the only means of artificial respiration in a 5 year-old boy w/ respiratory paralysis s/p a cerebral aneurysm
History of Pacing II

• 1968-William W.L. Glenn published “Radio-frequency electrophrenic respiration. Long-term application to a patient with primary hypoventilation” in JAMA.

• Glenn’s prototypes were brought into commercial distribution by Avery Laboratories, Inc. 1st available in 1973

• Avery pre-market FDA approval in 1986

• In 2002- Elefteriades presented a long-term, analysis 12 quadriplegic patients implanted with PNP devices between 1981 to 1987

• Over 2,000 placed in 20 countries to date
Phrenic Nerve Pacing (PNP)

- Placed on phrenic nerve via cervical site or thoracotomy (now by VATS)
- Implantable electrode, RF receiver, external RF stimulator, and an antenna
- Low frequency @ 7-10 Hz
- 2 main indications are SCI and alveolar hypoventilation
- No randomized control trials
PNP in Patient with NMD

- 2000-10 year old boy from Dhaka w/ polio vent dependent and in ICU for months
- Phrenic nerve testing of neck was negative and FVC = 0.35 L
- OR-phrenic nerves were viable and system was implanted
- 1 year post implantation the patient was able to breath on his own for 4 hours a day
Use of PNP in ALS Patients

- FDA approved for upper motor neuron respiratory muscle paralysis…
- Recommend 4 weeks healing before use
- Older electrodes surrounded nerve with increased rate of injury
- Runs on standard batteries
- Cost is closer to 40,000 dollars US

Example of Cervical Approach
PNP for ALS Patients

- 3 Patients underwent placement of PNP
- 2/3 benefit within 48 hours of starting pacing
- After one month
  - QOL increased
  - FVC stabilized
  - Use of BIPAP decreased

Phrenic Nerve Pacing to Improve Respiratory Function in Patients with ALS

Rosenfeld et al. ALS 2006;7(3)supplement C91
NeuRx DPS

- Stimulates the phrenic nerve at motor point(s) in the diaphragm
- Collaboration of industry and academia (physicians and engineers)
- Developed at Case Western Reserve University and University Hospitals Case Medical Center w/ funding from the VA
- FDA approved (HUD and HDE) for spinal cord injury in June 2008 and ALS in September 2011
NeuRx DPS

- 4 electrodes implanted at phrenic nerve motor points
- A fifth electrode to complete the electrical circuit
- A connector holder
- Small, external, battery-powered pulse generator and two batteries (rechargeable battery and disposable lithium battery @ 500 hours)
The DPS System
2003 Christopher Reeve Had the DPS System Placed

- Multiple centers now doing this procedure
- Most are covered by insurance, Medicare or Medicaid
- Total Cost cost is about $21,000 (excluding hospital, OR etc.)
Phrenic Nerve Motor Points (viewed from abdomen)

Isolating Motor Point and Placing Electrode

Clinical Objectives w/ DPS

- Can adjust stimulus amplitude, stimulus duration, frequency, inspiratory rate and RR
  - Example: 24mA, 0.150ms, 50-Hz, 1.1 seconds and 12 bpm
- Treat any component of central apnea
- Better nocturnal rest
- Less atelectasis
- Decrease respiratory decline/maintains diaphragm strength
- Delay or augmentation of NIV
- Delay death and/or tracheostomy
DPS Complications

- Anesthesia or surgical complications
  - Hypotension or capnothorax
- Infection, skin irritation or pain at exit site
- Discomfort on stimulation (shoulder pain)
- Need to adjust settings
- Wire or connector damage
  - Higher in ALS vs. SCI (increased mobility)
- Dysfunction of unit (2 provided)
- Broken cables
- 4 cardiac events sent to FDA since 2009
ALS Pilot Study

- 51 patients had DPS systems implanted (2005 and 2008)
- Ages 42-73
- FVC range 20-87% (>45% at surg.)
  - 2 patients w/ low FVCs by compassionate use
- All patients extubated postop without complications
  - Used at the end of case to decrease atelectasis and to assist with extubation

Onders et al, American J of Surgery, 2009;197:386
Summary ALS Pilot Study

- Pre-DPS rate of FVC decline was 2.4% per month
- Post-DPS rate of FVC decline was 0.9% per month
- Extrapolated to a 24 month improvement in respiratory functions
- In patient jargon “may delay respiratory failure by two years”

Onders et al, American J of Surgery, 2009;197:386
ALS Multicenter Trial

- Multicenter trial 11@sites closed 10/09 (N = 106)
- Patients served as their own controls (pre and post testing)
- Survey scores
  - SF36
  - ALS functional rating scale-revised (ALSFR)
- Diaphragm thickness (by US) and Sniff
- Serial pulmonary function tests, ABGs and phrenic nerve CMAPs
- Still awaiting published results
## Data Used For FDA as Median

144 enrolled, 106 implanted, but N=86

### Table 1

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<thead>
<tr>
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<th>N = 86</th>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>58.8 (49.1, 65.4)</td>
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<tr>
<td><strong>Gender (% female)</strong></td>
<td>33%</td>
</tr>
<tr>
<td><strong>Onset Type (% bulbar)</strong></td>
<td>34%</td>
</tr>
<tr>
<td><strong>Onset to Diagnosis (months)</strong></td>
<td>11.7 (6.0, 21.4)</td>
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<tr>
<td><strong>Onset to DPS (months)</strong></td>
<td>32.9 (23.5, 49.5)</td>
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### Table 2

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<tr>
<td><strong>Riluzole Use (% yes)</strong></td>
<td>79%</td>
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<tr>
<td><strong>NIV Use</strong></td>
<td></td>
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<tr>
<td>Before DPS</td>
<td>59%</td>
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<tr>
<td>After DPS</td>
<td>15%</td>
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<tr>
<td>None</td>
<td>26%</td>
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<tr>
<td><strong>NIV to DPS (months)</strong></td>
<td>5.3 (1.1, 8.3) N=64</td>
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<td><strong>PEG with DPS (%) at DPS implant</strong></td>
<td>29%</td>
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### Additional Data

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<tr>
<td>ALSFRS-r</td>
<td>29.0 (22.0, 34.0) N=85</td>
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<tr>
<td>FVC (% predicted)</td>
<td>59.0 (51.0, 68.0)</td>
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<tr>
<td>MIP (cm H₂O)</td>
<td>42.0 (30.5, 52.0) N=76</td>
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<tr>
<td>PCO₂ (mm Hg)</td>
<td>39.0 (36.0, 43.3) N=82</td>
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*Data expressed as median (interquartile range)*

- 84% of patients reported orthopnea / dyspnea on ALSFRS-r subscore
- 93% of patients met criteria through MIP
- 31% of patients met criteria through PCO₂
- 20% of patients met criteria through FVC (limited by the inclusion criteria)
Overall Survival

- Kaplan-Meier Analysis
  - N=84

- Median 19.7 ± 2.6 month
  - 20 months with NIV
  - 16 months without NIV

- PEG Patients
  - N=24, simultaneous with DPS
  - 30 day = 100%
  - 6 month = 79%
  - 12 month = 54%
Selected 43 pts w/ Historical Controls

- DPS implantation surgery was uncomplicated and well tolerated.
- Survival w/ Diaphragm Pacing & NIV improved $\infty \times$; 
  - +16 months from diagnose (21.4 mths vs. 37.5 mths)

Lechtzin et al. ALS 2007;8:185-188
DPS and Sleep

Current Concerns About DPs

• Data submitted to FDA was not obtained in any type of randomized or controlled trial

• Dr. Miller (Johns Hopkins Univ.) with 7 patients in DPS study
  – “did not observe any dramatic impact”
  – Characterizes DPS as “adjunct therapy”
  – “too much hype before the facts are in”
DPS Better Or Do We Need NIV Initiated Earlier?

- Used FVC <75% for NIV initiation
- 72 consecutive patients in Italy between July 2003 and January 2008
  - Group 1: 44 controls (>75%)
  - Group 2: 16 FVC <75 and used NPPV
  - Group 3: 12 FVC <75 intolerant or refused NPPV
- No difference in baseline between groups 2 and 3
  - Age, BMI, bulbar onset, PaCO2, FVC, FEV1, ALSFRS-R and sleep parameters

- Carratue et al. Orphanet Journal of Rare Diseases 2009; 4:10
Earlier NIV Suggests Better Survival

Carratue et al. Orphanet Journal of Rare Diseases 2009; 4:10
Earlier NIV May Preserve FVC Over Time

Slope of FVC% in 1 year between survivors of the groups 2 and 3. Blue line: Group 2 (12) (NPPV); Red line: Group 3.
Current DPS/ALS Studies
USA

- HDE Post-Approval
- PI-Miller at Forbes Norris Center
  - 07/2012-09/2017
  - 60 patients
  - All pts ≥ 2 years
- Primary endpoint- type and frequency of adverse events
- Secondary endpoints are the relationship of DPS with survival times and use of NIV, riluzole or PEG

- NEALS
- PIs Gruis and Katz
- Phase II trial
- 20 sites
- 180 total patients with 2/3 randomized to DPS
- Primary endpoint- survival at 18 months
- Secondary endpoints are diaphragm function, QOL and dyspnea
Current DPS/ALS Studies

Europe

DiPALS
- Protocol for diaphragm pacing in patients with respiratory weakness due to motor neurone disease
- McDermott, Sheffield Institute for Translational Neuroscience
- Randomized and controlled
  - 10 sites, N=108
  - 34% enrolled
  - Study closes 8/30/13
  - Standard (NIV) vs DPS + NIV
  - Survival 12 mo (2,3,6,9,12)
  - Safety and QOL

RespiStimALS
- Early stage ALS phrenic stimulation
- PI Gonzalez-Bermejo, Assistance Publique-Hopitaux de Paris
  - 09/2012-09/2014
- Patients with FVC 60-85% get DPS
- Sham or stimulation (N =37 each)
- NIV and stimulation for sham started per Standard of care
- # months between DPS and NIV
  - Survival @ 2 years
  - Effects on sleep
  - QOL and daily activities
U of U ALS DPS Program

- Drs. Rosenbluth, Nirula, Bromberg, Gibson, Harris and Sundar
  - Dana Hughes-hospital support
- IRB Submitted
- Medicare approval obtained
- Participating in the HDE Post-Approval Study
In Summary

• Diaphragm pacing is likely “mostly safe” in ALS, but is it better than NIV?
  • This is currently being studied

• Much remains unknown about the mechanisms of diaphragm dysfunction in ALS
  • Study opportunities w/ ALS Clinic, Pulmonary and Sleep Wake Center Partnership
Thank You

Questions?