Diaphragm Muscle Replacement with Implanted Pacemaker to Reverse Ventilator Dependency in Cervical Tetraplegia

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Diaphragm Anatomy

• Diaphragm
  – Primary respiratory muscle
  – Separates abdominal & thoracic cavities
  – Contracts and flattens with inspiration
The Muscles of Respiration

• Principal Respiratory Muscles
  – Diaphragm
  – External intercostal
  – Internal intercostal

• Accessory Respiratory Muscles
  – Sternocleidomastoid
  – Scalenes
  – Other: trapezius, serratus, latissimus, pectoralis
Diaphragm Innervation

• **Phrenic Nerve**
  – Originates from C3-C5
  – Motor innervation to diaphragm
  – Sensory fibers
    • Pleura
    • Pericardium
    • Abdominal components
Ventilator Dependency Impact On the Diaphragm

- Compared 14 brain dead donors on PPV to 8 controls
- 18 hours of PPV causes marked atrophy
- 57% decrease Type 1 slow twitch
- Active muscles atrophy faster
- Inactivity leads to oxidative stress & proteolysis
Diaphragmatic Paralysis

Site of Lesion

- Upper Motor Neuron
  - Brain
  - Spinal Cord

- Lower Motor Neuron
  - Cervical Root
  - Phrenic nerve
    - Neck
    - Chest

- Intra-Muscular
Diaphragmatic Paralysis

- Treatment Options
  - Mechanical ventilation
  - CPAP/BiPAP
  - Non-invasive weaning/Diaphragm re-training
  - Plication of the diaphragm
  - Diaphragm Pacemaker
  - Phrenic Nerve Surgery
  - Diaphragm Muscle Replacement Surgery
Diaphragm Pacemaker

History

- High freq phrenic stim  Glenn 1976
- Low freq phrenic stim  Glenn 1984, Elefteriades 2002
- Increased survival  Carter 1993
- Pacemaker + Nerve transfer  Krieger 2000
- Long term successful pacing  Elefteriades 2002
- Diaphragm stim  Onders 2004, DiMarco 2005
- Prospective comparison  Hirschfeld 2008
Diaphragm Pacemakers

Avery Biolabs

Synapse Biomedical
Diaphragm Pacemaker
Cervical Implantation
Diaphragm Pacemaker
Laparoscopic Implantation
Diaphragm Pacemaker
Laparoscopic Implantation
Diaphragm Pacemaker
Demonstrable Benefits

- Quality of life
- Morbidity & mortality
- Healthcare costs

Romero-Ganuza et al. Med Intensiva 2011
Diaphragm Pacemaker
When to Refer?

• As early as possible when non-invasive methods have failed or stalled (< 1 year)

• Especially when:
  – C1-3 or multilevel cervical tetraplegia
  – EMG demonstrates uni- or bi-lateral phrenic neuropathy

• Even consider in certain less severe cases to “bridge to independent respiration”
  – Onders et al. *J Trauma Acute Care Surg* 2014
Diaphragm Pacemakers

• Up to 20% of attempted pacemaker implantation cases are aborted due to failure to stimulate
  – Q: Why?
  – A: Loss of phrenic nerve integrity
    • Wallerian degeneration along the phrenic nerve(s)
    • Progressive diaphragm muscle atrophy
• Nerve reconstruction + diaphragm pacemakers for ventilator dependent SCI
Diaphragmatic Re-Innervation in Ventilator Dependent Patients with Cervical Spinal Cord Injury and Concomitant Phrenic Nerve Lesions using Simultaneous Nerve Transfers and Implantable Neurostimulators
Kaufman et al. J Reconstr Microsurg, June 2015

- **Purpose**
  - A surgical treatment to reverse ventilator dependency in pacemaker failures or absent phrenic nerve integrity

- **Demographics (N=14)**
  - Mean age=33 yrs. (range 10-66 yrs.)
  - Injury level
    - C1 (2), C2 (2), C3 (1), C4 (2), Multilevel (7)
    - ASIA A(13), ASIA B(1)
  - 57% failed prior pacemaker attempt
  - Time from injury to surgery: **34 months** (range 6-90 months)
Methods

Inclusion Criteria

- Ventilator dependent cervical tetraplegia (>6mos.)
- EMG/Nerve Conduction Studies
  - Absent phrenic nerve conduction
  - Poor/Absent voluntary motor units detected in diaphragm
  - Available donor nerve(s)
- No active respiratory infection
- Good cognitive function
- Adequate family support & nursing care
Methods

Parameters for assessment

- Age, Sex
- Level of injury, ASIA classification
- Time from injury to treatment (mos.)
- Time from treatment to re-innervation (mos.)
  - Trans-telephonic monitoring (TTM)* biphasic activity
- Average time pacing (hrs.)

• Outcomes

– 13/14 (93%) successful diaphragm re-innervation

– Time from surgery to re-innervation: 7 mos. (range= 3-18 mos.)

– 8/13 (62%) achieved sustainable pacing (>1 hr. day)

– Two patients recovered spontaneous respiratory activity (no pacemaker, no vent)

– Treatment resulted in a 20% reduction in vent. dependency (p<0.05)
23 y.o. male
C1-4, ASIA A

9 months post-op

24 months post-op

36 months post-op
Limitations

- Rapid and progressive diaphragm muscle atrophy = limited clinical success (incomplete weaning)
- Electrical recovery without clinical recovery
How do we define progressive diaphragm atrophy?

- Electrodiagnostics: Absent voluntary motor units
- Ultrasound measurements: <1-2mm maximal thickness
Ventilator Weaning in SCI
Dealing with Progressive Diaphragm Atrophy
Current & Future Directions

• Prevention
  – Early electrical stimulation to prevent or delay irreversible muscle atrophy

• Treatment
  – Diaphragm muscle replacement surgery when irreversible degeneration
Diaphragm Muscle Replacement Surgery

- Transferring innervated, vascularized muscle into the atrophic diaphragm
- Implanting a pacemaker into the transferred nerve-muscle unit
Diaphragm Replacement Surgery

• Review of literature
  – Congenital diaphragmatic hernia
    • Animal and human studies
• Cadaveric feasibility study
• Our Experience (2015-current)
  – Cervical tetraplegia (2)
  – Bilateral diaphragmatic paralysis/paresis (2)
Diaphragm Replacement Surgery

• Replacing all components of neuromuscular system
  – Brain & Spinal Cord
  – Phrenic Nerve(s)
  – Diaphragm muscle

  Pacemaker
  Nerves to rectus
  Intercostal nerves
  Rectus muscle
Diaphragm Replacement Surgery
Diaphragm Replacement Surgery

- Innervated, vascularized rectus abdominis muscle flap(s)
Diaphragm Replacement Surgery

- Intercostal nerve transfers to distal rectus nerves
Patient 1

Diaphragm Replacement using Innervated Rectus with Pacemaker for SCI

22 year-old female, C2-5, ASIA A (May 2014, MVA)
Complete ventilator dependency
Failed attempt at laparoscopic pacemaker implantation
Right thoracotomy with harvested 9th intercostal nerve pedicle graft
Intra-thoracic view of left non-functional phrenic nerve and hemi-diaphragm
Intra-thoracic view of non-functional left phrenic nerve and hemi-diaphragm with harvested 9th intercostal nerve pedicle graft.
Rectus abdominis harvested for diaphragm replacement
Rectus muscle harvested with preservation of segmental innervation
Rectus abdominis with segmental innervation for diaphragm replacement
Rectus muscle transposed into thoracic cavity with preservation of proximal innervation
Close-up of transposed rectus with intact innervation
Rectus muscle transposed to diaphragm and pacemaker implanted
Rectus muscle inset to diaphragm
Preparation of nerve transfer between intercostal nerve and distal segmental innervation of rectus muscle
Diaphragm Replacement Surgery
Patient 2

Diaphragm Replacement using Innervated Rectus with Pacemaker for SCI (@UCLA Med. Ctr.)

29 year-old male, C1-3, ASIA A (Sept. 2011, MVA)
Complete ventilator dependency
Failed attempt at laparoscopic pacemaker implantation
Three weeks post-op at initiation of pacing trials
Diaphragm Replacement Surgery

- SCI Patient Outcomes to date
  - **Patient 1**
    - No peri-/post-op complications
    - 10 months post-op
    - Tolerating 5-6 hours/day on pressure support alone
    - Anticipate continued progress with transition to full vent. weaning
  - **Patient 2**
    - No peri-/post-op complications
    - 2 months post-op
    - Pacing trials initiated and visible contractions observed in office
Diaphragm Replacement Surgery

• May be performed safely
• Intra-operative demonstration of muscular contraction (2/2)
• Post-operative reduction in ventilatory requirements (1/2) thus far
• Long term follow up and complete weaning pending
• Additional recruitment underway
Ventilator Dependent Cervical Tetraplegia

- Diaphragm pacemakers
- Diaphragm pacemakers + nerve transfers
- Diaphragm pacemakers + muscle replacement

Could it soon be that all ventilator dependent SCI patients, regardless of neuromuscular dysfunction, have a potential therapeutic option to wean from ventilator?