From Surviving to Thriving: Phrenic Nerve Graft Surgery and Rehab.

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Objectives

• 1. Demonstrate awareness of appropriate candidates and the options for surgical re-innervation of the diaphragm muscle.
• 2. Identify and prioritize the multiple body systems requiring assessment and treatment post surgery.
• 3. Discuss appropriate and effective treatment strategies and sequencing.
• 4. Discuss the case of a 14-year-old athlete, surviving treatment for lymphoma, who underwent a sural to phrenic nerve graft and postsurgical rehabilitation, to re-innervate and reeducate her left hemi diaphragm after a tumor and subsequent ablation, crushed the phrenic nerve.

Background

– Introduction to pediatric phrenic nerve graft case

Roles of the diaphragm
– 3 systems
– Multi-system function

Phrenic Nerve Graft Surgery
– Technical aspects
– Algorithm for patient selection

Post-operative PT examination
– Participation
– Function
– System strengths/impairments

Patient case
– Surgical stand point
– PT treatment

Chemo drugs:
– IV daunorubicin, IV doxorubicin, IV cyclophosphamide, IV cytarabine and IV vincristine.
– High dose methotrexate infusion followed by a leucovorin "rescue" to save the liver and kidneys.
– Intrathecal cytarabine and methotrexate.
– SQ injections of cytarabine (at home)
– IM Peg-Asparaginase.
– oral mercaptopurine for twenty-eight days during one phase and forty-two during another, and daily during the last eighteen months of treatment.
– oral thioguanine for fourteen days during one phase.
– oral methotrexate once weekly during the last eighteen months of treatment.

Back Story

• 8 year old female
  – C/O SOB
    • Dx: “asthma exacerbation”
    • Tx: Steroids & antibiotics

  – Progressive SOB for 10 additional days
    • Seen in ER
      – Oral steroids
      – X-ray: Total left lung collapse
      – CT Scan: 10 cm tumor on Thymus gland, also crushing L Phrenic N.

• Surgical excision of the tumor, and 2 years of chemo

Conflict of Interest

Neither Dr. Matthew Kaufman, nor Patricia West-Low have any conflict of interest in regard to this presentation
Back Story

• “Ancillary Drugs”
  – High doses of oral prednisone for 35 continuous days.
  – High doses of oral dexamethasone twenty-eight straight days.
  – For the last eighteen months of treatment, high doses of prednisone for five days each month.
  – Multiple courses of antibiotics for upper respiratory infections

Pediatric Cancer Survivorship

• Physical Function/Activity Level
  – Childhood Cancer Survivors (CCS) scored lower on tests of LE strength, the TUG and the 6MWT (Hoffman et al 2013)
  – CCS nearly 2x more likely to report performance limitations (Ness et al 2009)
  – CCS 1.4 x more likely to be inactive (Rueegg et al 2013)
  – Only 42% CCS reach healthy activity levels (Rueegg et al 2013)
  – High PA in CCS correlated with improved cardiovascular profile (Slater et al 2014)
  – Factors predictive of decline in PA include female gender, BMI >30 kg/m, not completing high school and chronic musculoskeletal conditions (Wilson et al 2014)

Pediatric Cancer Survivorship

• Quality of Life Level
  – Female survivors reports lower HRQOL in Physical and Emotional QOL subscales than males
  – Female survivors ≥ 16 years of age scored lower on school QOL subscales than males

Complications of Left Hemidiaphragm Inactivity

• Dyspnea
  – Decreases breathing capacity by >1/3 (Elefteriades et al 2008)
• Reflux
  – Decreased competence of the LES-Left crus can result in GERD (Eherer et al 2012)
  – Reduced diaphragm function is a predictor of GERD (Pandolfino et al 2007)
  – Micro-inhalation of reflux secretions is associated with pneumonia (Gaillet et al 2015)

Cardio-toxicity of Chemo Drugs

• Cyclophosphamide as well as cytarabine & asparaginase have been associated with cardio-toxicity (Simbre et al 2005; Pai & Nahata, 2000)
• Cardio-toxicity may occur in 20% of patients treated with Doxorubicin and Daunorubcin (Pai & Nahata 2000)
• Effects include asymptomatic ECG abnormalities, blood pressure changes, arrhythmias, myocarditis, pericarditis, Acute MI, Cardiac failure, cardiac shock and long term cardiomyopathy (Simbre et al 2005)

Complications of Left Hemidiaphragm Inactivity

• Scoliosis
  – Chest wall deformity and scoliosis are common among children with repaired diaphragmatic defects (Peetsold et al 2009)
  – Muscle asymmetry is part of the pathogenesis of late onset idiopathic scoliosis (Grivas et al. 2002)
  – Increase risk of scoliosis after chest wall resection (Glotzbecker et al 2013)
Complications of Left Hemidiaphragm Inactivity

- Decreased balance and postural control
  - The diaphragm has a feed forward role in postural stability (Gandevia et al. 2002)
  - Phrenic motor neurons contribute to both respiration and postural during challenges to posture (Hodges and Gandevia 2000)

Roles of the Diaphragm

- Ventilation
- GI function (Pandolfino 2007; Feinsilver, 1944)
- Musculoskeletal structure/function (Grivas et al. 2002; Russell et al. 2014)
- Venous return (Willeput 1984)
- Postural control (Hodges & Gandevia, 2000; Smith 2006; Hudson 2010; Hamaoui, 2010; Jansens, 2013)

Summative Roles of the Diaphragm

The diaphragm is a respiratory muscle
The diaphragm assists the LES in inhibiting reflux
The diaphragm assists in elimination
The diaphragm impacts musculoskeletal alignment
The diaphragm assists in venous return
The diaphragm is a postural muscle

The diaphragm is a pressure regulator!!

Surgical Management of the Paralyzed Diaphragm: A Peripheral Nerve Approach

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- Regional, national, & international referral center
- Conditions treated
  - Peripheral nerve disorders (i.e. trauma, neuropathy)
  - Sequelae of stroke & spinal cord injury
- Diaphragmatic paralysis experience (Since 2007)
  - More than 200 patients treated
  - Well over 400 patients evaluated
  - 4-5 new inquiries per week
- Official Synapse Pacemaker Treatment Center (2014)
Peripheral Nerve Disorders

- Occipital Neuralgia/Migraine
- Facial Paralysis
- Cranial Nerve Injury
- Brachial Plexus Injury
- Diaphragm Paralysis
- Upper/Lower Extremity Paralysis
- Hand Injury
- Perineodynia (Pudendal Neuralgia)
- Lower Extremity Neuropathy
- Footdrop

CNS Disorders

- Spinal Cord Injury
  - Ventilator Dependency
  - Pressure Sores
  - Upper Extremity
- Stroke
  - Dysphagia
  - Hemiparesis
  - Facial paralysis
- ALS
- Central Sleep Apnea
- CNS tumor

Diaphragm Anatomy

- **Diaphragm**
  - Primary respiratory muscle
  - Separates abdominal & thoracic cavities
  - Contracts and flattens with inspiration

The Muscles of Respiration

- **Principal Respiratory Muscles**
  - Increase thoracic dimensions
    - Diaphragm
    - External intercostal
    - Internal intercostal
- **Accessory Respiratory Muscles**
  - Activate during exercise, stress response, diaphragm paralysis
    - 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

Etiology
- Peripheral
  - Iatrogenic
  - Surgery
  - Anesthetic Blocks
  - Chiropractic
- Trauma
  - Blunt
  - Penetrating
- Neuropathy / Neuromuscular
- Viral / Idiopathic
- Central
  - Spinal Cord Injury
  - Cervical Radiculopathy
  - Central Hypoventilation Syndrome
  - Tumors
  - Neurodegenerative conditions

Diaphragmatic Paralysis

Treatment Options
- Pulmonary rehabilitation
- Diaphragm retraining therapy
- CPAP/BiPAP
- Mechanical ventilation
- Plication of the diaphragm
- Diaphragm Pacemaker
- Phrenic Nerve Surgery
- Diaphragm Muscle Replacement Surgery

Diaphragm Pacemakers

- Indications
  - Ventilator dependency
    - Cervical tetraplegia
    - ALS
    - Stroke
    - Cord compression
    - CNS tumor
    - Central sleep apnea
  - Off label use
    - Unilateral diaphragm paralysis
    - Intractable hiccups
    - Diaphragm flutter/myoclonus

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 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 Pacemaker
Which Device?

<table>
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<tr>
<th>Synapse</th>
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<tr>
<td>Laparoscopic or VATS</td>
<td>Cervical approach or VATS</td>
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<td>Wires emerging (FDA application for implantable)</td>
<td>All implantable</td>
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<td>Direct muscle stimulation</td>
<td>Transmission through applied antennae</td>
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<td>Requires IRB for humanitarian use</td>
<td>Fully FDA approved</td>
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<td>Good Customer service</td>
<td>Mediocre Customer service (Improving)</td>
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<td>Not MRI compatible</td>
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<td>Outdated technology</td>
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<td>Demonstrable efficacy</td>
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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

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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)

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Diaphragmatic Reinnervation...using Simultaneous Nerve Transfers and Implantable Neurostimulators
Kaufman et al. J Reconstr Microsurg, June 2015

- **Methods**
  - **Inclusion Criteria**
    - Cervical Tetraplegia
    - Ventilator Dependency (>6 mos.)
    - EMG/Nerve Conduction Studies
      - Absent phrenic nerve conduction
      - No voluntary motor units detected in diaphragm
      - Available donor nerve(s) (i.e. spinal accessory, thoracodorsal, intercostal)
    - No active respiratory infection
    - Good cognitive function
    - Adequate family support & nursing care

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Diaphragmatic Reinnervation...using Simultaneous Nerve Transfers and Implantable Neurostimulators
Kaufman et al. J Reconstr Microsurg, June 2015

- **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)
    - Mean= 10 hrs. (range >1-24 hrs.)
  - Two patients recovered spontaneous respiratory activity (no pacemaker, no vent)
  - Treatment resulted in a 20% (p<0.05) reduction in vent. dependency
Diaphragmatic Reinnervation...using Simultaneous Nerve Transfers and Implantable Neurostimulators
Kaufman et al. J Reconstr Microsurg, June 2015

• Outcomes
  – No intra-operative complications
  – One patient developed bilateral effusions post-op requiring drainage
  – Mean f/u=16 mos. (Range= 6-40 mos.)

• Benefits of ventilator weaning are dramatic
• Current practice standards seem to under-utilize surgical options for weaning failures, or delay initiation
• Estimated 20-25% of potential pacemaker candidates will never be treated or will undergo failed procedures likely due to “double lesions”
• Consideration of a treatment algorithm that includes the option of phrenic nerve surgery when necessary
• Timing appears to be very critical for pacing success with nerve surgery
  – 12 months or less is optimal

Evaluation Of Current And Future Surgical Treatment Options For Diaphragmatic Paralysis And Ventilator Dependency In High Cervical Tetraplegia
Kaufman et al. (ISCoS/ASIA 2015)

• How do we define progressive diaphragm atrophy?
  – Electrodiagnostics: Absent voluntary motor units
  – Ultrasound measurements: <2-3mm 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

Limitations

- Rapid and progressive diaphragm muscle atrophy = limited clinical success (incomplete weaning)
- Electrical recovery without clinical recovery
Ventilator Weaning in SCI
Current & Future Directions

- Peripheral Nerve Stimulation
- Preventing irreversible muscle atrophy
  - J Neurophysiol, 2015

Diaphragm Muscle Replacement Surgery

- Transferring innervated, vascularized muscle (rectus abdominis/latissimus dorsi) into the atrophic diaphragm
- Implanting a pacemaker into the transferred nerve-muscle unit

First Diaphragm Replacement using Innervated Rectus with Pacemaker for SCI
5/8/2015

MVA
Complete ventilator dependency
Failed attempt at Synapse pacemaker

ICF Model

(disorder or disease)

Body Functions & Structure → Activity → Participation

Environmental Factors | Personal Factors

Starting From the “End Game”

Participation → Function → Impairment
“Physical therapy is a health profession whose primary purpose is the promotion of optimal health and function. This purpose is accomplished through the application of evidence-based principles to the processes of examination, evaluation, diagnosis, prognosis, and intervention to prevent or remediate impairments in body structures and function, activity limitations, participation restrictions or environmental barriers as related to movement and health.”

APTA House of Delegates, 2012

Post-op Examination

• Integument
  — Mobility of all scars in all directions
    • How does CT mobility affect symmetry?
    • Is scar tissue limiting chest wall expansion?
  — Pain can have an impact on internal scar tethering “(Esposito et al 2013)
  — Scars can tether in remote areas (Massery and Vicari 2015)

Post-op Examination

• Musculoskeletal
  — Rib mobility
    • Ribs 8-10 may be limited due to diaphragm pull
    • Ribs 4-7 may be limited due to intercostal coupling
  — Spinal symmetry
    • Asymmetrical diaphragm pull
  — Upper quarter screen
    • Effect of pre-surgical breathing pattern
    • Effects of rib mobility limitations
  — Lower quarter screen
    • Effects of graft site sensory impairments (strength, power, agility)

Post-op Examination

• Neuromotor
  — Diaphragm activation
    • Look and feel
    • Supported and unsupported positions
    • Diaphragm excursion
  — Diaphragm intercostal coupling
    • Watch for intercostal retraction
    • Lateral chest wall excursion
  — Diaphragm/Intercostal muscular endurance
    • How long can they continue to use the involved side diaphragm before it fatigues?

Post-op Examination

• Cardiopulmonary
  — Pre-surgical hx
  — Meds
  — Breathing pattern, sequence and rate
    • At rest
    • With aerobic challenge
  — O2 sats. during Cardio-pulm. challenges
  — Get as close as possible to the activity they hope to return to

Post-op Examination

• GI System
  — Reflux
    • Frequency
  — Constipation
    • Frequency and ease of BM
  — GI Meds?
    • Anti reflux
    • Laxatives
Post-op Examination

• Postural stability
  – Can the patient use their diaphragm to breathe while performing activities that challenge their postural stability?
  – Timed Unilateral Stance, Pediatric Berg, TUG, Timed floor to stand, Timed shuttle run

• Sensory
  – Proprioceptive awareness in the graft side Lower Chain
  – Reactive postural control
  – Unilateral stance eyes open versus eyes closed

• Diagnosis
  – Medical Dx:
    • S/P phrenic Nerve graft
    • S/P Lymphoma tx
  – PT DX:
    • Impaired muscle performance Impaired ventilation
    • Impaired aerobic capacity, impaired joint mobility,
    • Muscle weakness
    • Impaired sensory integrity

• Treatment
  • Prioritize and treat impairments as they relate to function
  • Treat multiple impairments simultaneously
  • Track the results of your treatments objectively

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**Take Home Messages**

- The diaphragm impacts multiple systems and functions; treat them all
- Watch and prevent for secondary impairments
- EBM has 3 parts, don’t ignore patient/family values
- Keep learning. Let your curiosity keep pulling you forward. BE A TRAILBLAZER!


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