Cardiopulmonary Dysfunction and Amyotrophic Lateral Sclerosis
Perspectives On Physical Therapy Evaluation and Intervention
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Objectives
• Understand the pathophysiology of ALS
• Measuring disease progression
• Physical Therapy “therapeutic exercise” interventions in ALS.

Amyotrophic Lateral Sclerosis
de la sclérose laterale amyotrophique

Amyotrophic: Atrophic muscular weakness
Lateral: Lateral columns of the spinal cord
Sclerosis: Scar “hardening” to palpation

Amyotrophic Lateral Sclerosis
Pathology due to loss of
Upper Motor neuron
• Motor cortex
  “Betz cells, precentral gyrus, and corticospinal tract”
Lower Motor neuron
• Motor nuclei in brain stem
  V, VII, IX, X, and XII
• Anterior horn cells in spinal cord

Spectrum of Motor Neuron Diseases

Amyotrophic Lateral Sclerosis
Demographics
— 10% Familial
— Incidence: 2.6 per 100,000 = MS and 5x > Huntington’s
— Prevalence; 3 -7 per 100,000 individuals
— Sex: Males 1.5 -2 times > females
— Race: white-to-nonwhite ratio is 1.6:1.
— Age: fourth to seventh decades of life.
**Amyotrophic Lateral Sclerosis**

**Phenotype**
- Phenotype based on site of onset
  - Limb: 65%
  - Bulbar: 30%
  - Respiratory: 5%
- Bulbar form more rapid deterioration and death

**Amyotrophic Lateral Sclerosis**

**Phenotype**
- Spread to neighboring motor neurons “anatomically progression”

**Amyotrophic Lateral Sclerosis**

**Rapidly progressive**
- Diffused generalized weakness
- Total dependant

**Amyotrophic Lateral Sclerosis**

**Fatal**
- Over 60% die within 3 years
- Up to 10% survive more than 8 years
- Few exceptions “Stephen Hawking”

**Mechanisms of Motor Neuron Injury**

**Not Known**
- Glutamate toxicity
- Oxidative stress
- Protein aggregation
- Mitochondrial dysfunction
- Neuroinflammation
- Current experimental trials are targeting these pathways
  - Riluzole, a glutamate antagonist
  - Neudexta for Emotional lability (Pseudobulbar affect) are the only FDA approved drug to treat ALS

**Diagnosis of ALS**

- Hard to diagnose: Mimics other common diseases
- Late to get to neurologist
- No definitive biomarker or electrophysiological test.
- The diagnosis is established by excluding other causes of progressive UMN and LMN dysfunctions
- Certainty of the diagnosis is based on clinical signs, symptoms, and progression according to the El Escorial criteria

*Brooks BR et al. Amyotrophic Lateral Scler Other Motor Neuron Disord.;1(5):293-9, 2000*
Management of ALS

Multidisciplinary ALS Clinic

Core Members
- Neurologist
- Nurse
- Speech pathologist
- Dietitian
- Respiratory therapist
- Physical therapist
- Occupational therapist
- Social worker
- Rehabilitation technologist
- Psychologist

Consultants
- Rehabilitation physician
- Pulmonologist
- Gastroenterologist

Associates
- Research scientists

Management of ALS

Clinical Features

- Upper motor neuron findings
  - Spasticity
  - Hyperreflexia
  - Babinski’s response
  - Hoffmann’s sign
  - Pseudo bulbar features
    "emotional lability"
  - Cognitive and Frontotemporal Lobe Dementia

Clinical Features

- Lower motor neuron findings
  - Dysphagia
  - Dysarthria
  - Dysphonia
  - Atrophy
  - Fasciculations
  - Weakness
  - Cramps
  - Extraocular, bladder, and anal sphincter muscles typically are spared

Clinical Features

- Mixed Upper and Lower motor neuron findings
  - Decline Force Production
    - Isokinetic faster than Isometric
    - Isometric faster than Manual
  - Increase Motor Fatigue
    - Central
    - Peripheral
  - Loss of Balance
  - Respiratory insufficiency

Emotional Lability

Crying

Laughing
Can Physical Therapy interventions influence the functional and clinical outcome in ALS

How would we know if we do not measure the rate of the disease progression

“Outcome measure”
Measuring disease progression

**General Classification of Endpoints**
- Clinically Relevant Endpoints
- Surrogate Endpoints
- Biomarkers
- Many other dimensions
  - Binary vs. continuous
  - Interval vs. not interval
  - Reliable, Sensitive to change

**Outcome Measures to fit the staging of the Disease**

**Impairments**
- Muscle Strength
- Timed Functional Tests
  - STS
  - Stairs
  - 6MWT
  - 25FWT
  - TUG
- Fatigue
- Balance
- Pulmonary function

**Disability**
- ALSFRS-R

**Handicap**
- Survival
- Quality of life

**ALS = Motor Neuron Loss**
- Magnetic resonance spectroscopy
- Transcranial magnetic stimulation
- Motor unit number estimation
- Costly
- Time consuming
- Hard to interpret
- Sensitivity

**Motor Neuron Loss**
- Muscle strength
  - Manual muscle test
  - Hand held dynamometer
  - Computerized isometric
  - Computerized isokinetic
- Motor Fatigue
  - Fatigue scales
  - Computerized isometric
- Balance
  - Clinical balance scale
  - Computerized Posturography

**Manual Muscle test (MMT)**
- Fairly simple.
- Clinically useful
- Inexpensive; requires no equipment.
- Reliable (high intra, moderate inter-rater reliability) with well-trained evaluators.

- Ordinal: the steps between ranked grades can be grossly uneven
- Lack of sensitivity to change
- Poor correlation with absolute muscle strength, especially in strong muscles.
- MMT summary scores can be inaccurate and misleading
Manual Muscle test (MMT)

MMT vs. % Predicted Normal MVIC

Uneven Steps Between MRC Grades

Hand Held Dynamometer

- Portable
- Inexpensive
- Electronic units can be interfaced to computer.
- OK for weak muscle (up to 30 kg force)
- Sensitive to change within narrow range
- High intra-rater and moderate inter-rater reliability.
- Spring-based lose elasticity over time.
- Difficult to calibrate.
- No standard position for the point of force application or tester grasp
- Have high tester influence
- Subsequently, tendency to underestimate strong muscles and overestimate weak muscles.
**Computerized Isometric Muscle Strength**

**MVIC**

- MVIC correlates well with the number of firing motor units
- Accurate measurement in weak and strong muscles
- Correlate with ALSFRS-R, Timed function test
- High intra-rater and inter-rater reliability

Computer-based, fixed strain-gauge

- Muscle force analog signal is easily digitized, computed continuously.
- Produces documented results
  - for quality assurance monitoring.
- Requires extensive training, space, and equipment
- Does not correlate with survival or VC

**Computerized Isokinetic Muscle Strength**

- Sensitive to detect motor deficit in early stage
- ALS lose strength faster at higher angular velocity (Lose large Fast type II earlier)
- May be useful in basic clinical research
- Correlates well with functional task (e.g., walking).
- Expensive
  - Very fatiguing and
  - Lost to follow up in clinical trials

**ATLIS: Accurate Test of Limb Isometric Strength**


**KNEE FLEXION**

[Graph showing age vs. isometric strength]


Timed Functional Tests

- Objective result in ratio/interval
- More sensitive to change
- Complement strength tests to reflect UMN involvement.
- High reliability
- Influenced by external factors “assistive device and space”
- Each test measures only one function.

Motor Fatigue
Decline in MVIC and Shift in sEMG signal

- Decrease muscle conduction Velocity
- Preferential Loss of large type II
- Transformation from Type I to II “fatigable”
- Implication for therapeutic exercise!

Cytokinetiks
CK-2017357: a fast skeletal muscle troponin activator

Balance and Fall
– Increase Reliance on Vision/fixation
– Deconditioning of Vestibular function or
– Abnormality in Extrapyramidal/Cerebellum and its connections

Sanjak M, Neurology; 127, 2009

Balance and Fall

Inclusion criteria
– Early diagnosed
– Ambulatory without assistive devices
– No History of fall
– No Risk of fall by clinical balance scale
– Pass the mCTSIB


Table 1. Functional Evaluations.

<table>
<thead>
<tr>
<th>Test/Evaluation</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALSFRS-R</td>
<td>40.9 ± 4</td>
</tr>
<tr>
<td>VC %</td>
<td>90 ± 10</td>
</tr>
<tr>
<td>25FVT (sec)</td>
<td>4.4 ± 0.7</td>
</tr>
<tr>
<td>Up and down 4 steps (sec)</td>
<td>4.5 ± 0.8</td>
</tr>
</tbody>
</table>

Table 2. Balance Evaluation.

<table>
<thead>
<tr>
<th>Balance Scale</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>Risk of fall score</th>
</tr>
</thead>
<tbody>
<tr>
<td>DGI</td>
<td>22.7 ± 1.1</td>
<td>21-24</td>
<td>17/19/24 = ↑ Risk of falls</td>
</tr>
<tr>
<td>BBS</td>
<td>55.8 ± 0.8</td>
<td>54-56</td>
<td>41-56 = Independent</td>
</tr>
<tr>
<td>TUG</td>
<td>6.5 ± 1.1</td>
<td>5.1-9.0</td>
<td>&gt; 14 sec = Risk for falls</td>
</tr>
</tbody>
</table>

Balance and Fall

Fig. 3. Sensory Organizations Test

Fig. 3. Motor-Control Test

Disability

Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R)

Ability to use Vestibular
**ALSFRS-R**

**Characteristics**
- Clinically relevant, non-interval
- Validated in ALS patients in large clinical trials
- Test-retest reliability >0.88 for all items
- Can be conducted over phone
- Correlate with
  - Survival
  - Quality of life
  - Muscle strength
  - Timed function
  - But Not with VC

**ALSFRS-R Domains**

- **Bulbar Domain:**
  - Speech
  - Salivation
  - Swallowing

- **Fine Motor Domain:**
  - Handwriting
  - Cutting food, handling utensils
  - Dressing and Hygiene

- **Gross Motor Domain:**
  - Getting in bed and adjusting bed clothes
  - Walking
  - Climbing stairs

- **Respiratory Domain:**
  - Dyspnea
  - Orthopnea
  - Respiratory insufficiency

From: Cedarbaum et al, 1999

**Limitations to ALSFRS-R**

- No strong relationship to pathophysiology of disease
- Not clearly sensitive to disease modifying treatment
- What is a meaningful change in rate of decline?

**Decline in ALSFRS-R Score is linear**

0.95 pint per month on the average

Creatine

Celecoxib (Celebrex)

From: Cudkowicz et al., 2006, Shiffrin et al., 2004

**Figure.** Kaplan-Meier survival plots (endpoint: death or tracheostomy) in an amyotrophic lateral sclerosis clinic population (n = 267), according to quartiles of the total Amyotrophic Lateral Sclerosis Functional Rating Scale–revised

**Quality of life**

**Quality of life questionnaires**

- **ALS Assessment Questionnaire**: the ALSAQ-40.
- **ALSAQ-5**: health related QOL
- **McGill QoL Questionnaire (MQOL)**
- **Sickness Impact Profile**

**Respiratory Impairments in ALS**

Not a pulmonary disease but a ventilation pump disease

- Loss of innervations of muscles of inhalation and exhalation
- CO2 retention and oxygen desaturation due to hypoventilation
- Rapid/shallow breathing and increased catoric expenditure
- Lack of ventilatory reserves
- Risk of acute and chronic respiratory insufficiency
- Respiratory insufficiency may lead to reduced physical activity

**Vital Capacity**

- **Surrogate, continuous**
- Independent measure ALS Progression, does not correlate with
  - ALSFRS-R
  - Timed function
  - 6 minute walk test
  - Muscle strength
  - Decline 2 - 3% per month

**ALS Respiratory Impairment**

- Non-invasive ventilation
- Assisted Coughing
- Diaphragm stimulation
- Invasive ventilation
- Nutritional support

**ALS Respiratory Management**

**Non-invasive ventilation**

The best treatment for Respiratory insufficiency

- Relief respiratory distress
- Improve mental awareness
- Improves quality of life
- Extends Survival
- Reduce progression of respiratory muscle function

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Drachman et al., 2000, Lacomblez et al., 1996

MICE Human Survival Time to Death or Tracheostomy clinically relevant, derivative of a binary endpoint


ALS Respiratory Management

- Non-invasive ventilation
  - Pressure Support Ventilation
  - Volume Support Ventilation

ALS Respiratory Management

Key Points to Remember
- CPAP is NOT for ALS, it is for sleep apnea
- Volume Support Ventilation
- No direct O2 supply to ALS patients
- Keep it in the back of your mind when managing exercising the patient
  - SOB
  - Borg perceived exertion
  - Monitor O2 saturation and heart rate

Can exercise improve clinical and functional outcome in ALS

Physical Therapy for ALS

- Patient education on energy conservation and compensation
- Mild stretching and ROM
- Recommendation for assistive devices

SESSION 9B EXERCISE, METABOLISM AND NUTRITION

Q2. IS EXERCISE A PREDISPOSING FACTOR IN ALS? THE CASE FOR

Cardiac Pts
Parkinson
MS
Cancer
etc

50/50 split

Q3. IS EXERCISE A PREDISPOSING FACTOR FOR ALS? THE CASE AGAINST

Wijck, J. Veldink, J. van den Berg, I.
Department of Neurology, University Medical Centre, Utrecht, Netherlands

Asymptotic Lateral Science. 2009 (Suppl.), 10-7-03
Risk / Benefit of therapeutic exercise in ALS

Therapeutic Exercise for ALS

Can ALS patients Exercise?

First study to evaluate work capacity in ALS

- Intermittent
- Discontinuous Workload
- We were able to obtain VO2 Max in large # of pts
- Reduction in VO2 Max correlate to clinical impairment

No increase in work of breathing or cardiac work

Figure 2: Intermittent workload (A) and continuous workload (B) in relation to ALS Functional Score: [●] = control subjects; [△] = patients with ALS matched to control subjects. [●] = ALS patients.
Can ALS patients engage in prolonged exercise?

**Metabolic Demands**

1. The cardiopulmonary response to exercise in ALS is normal.
2. Reduction in VO2 max correlates to clinical impairment (Lower VO2 max = lower ALS score).
3. ALS patients could exercise up to 90 min at 50% of their VO2 max with no adverse effect.
4. Similar lactate levels in ALS patients and controls suggest no hypoxia in the muscles.
5. Increased oxygen cost and decreased mechanical efficiency may require attention to O2 desaturation and supply O2 if necessary.

**Conclusion**

1. The cardiopulmonary response to exercise in ALS is normal.
2. Reduction in VO2 max correlates to clinical impairment (Lower VO2 max = lower ALS score).
3. ALS patients could exercise up to 90 min at 50% of their VO2 max with no adverse effect.
4. Similar lactate levels in ALS patients and controls suggest no hypoxia in the muscles.
5. Increased oxygen cost and decreased mechanical efficiency may require attention to O2 desaturation and supply O2 if necessary.

6. ALS patients who could not exercise on a treadmill due to respiratory insufficiency were able to exercise on the treadmill with BiPAP up to their anaerobic threshold up to 12 months.

**Regular exercise training in ALS**

**Case Study**

46-year-old man, Norris ALS score = 93/100. ALS duration approximately 1 year, upper motor neuron signs in the upper extremities (UE), and mixed dysfunction in the lower extremities (LE) (Weaker).

**Home Exercise Regiment**

- combined arm and leg training using an Air-Dyne bicycle ergometer
- At 50% of predetermined VO2 max
- 4 days per week, 6 weeks.
- 30 minutes per day (5 minutes work and 5 minutes rest).
Regular exercise training in ALS

Results: Pre to post exercise training
1. Increase VO₂ max , W max, and VE max
2. Increase maximal HR
3. Decrease resting HR, indicating a cardiovascular training effect
4. No change in muscle strength


– RCT (n=25), early diagnosed ALS patients
– Moderate range of motion training designed to improve muscle endurance (n=14) or regular daily activities (n=11)
– 15-minutes, twice-daily for 6 months
– At 3 mo: significantly less decline in ALSFRS and Ashworth Scale scores with no effect on muscle strength
– At 6 mo, no significant difference between groups, but a strong trend was shown towards a protective effect in the treatment group
– At 9 and 12 months, there were too few patients in each group for statistical evaluation


• RCT in 27 ALS patients.
• Daily resistance exercise and stretching (n=13) vs. Stretching alone (n=14)
• 3X a week
• After 6 months
  – Quality of life was better
  – Less ALS functional rating score decline


What is Lacking? The Parameters

➢ Type (Aerobic, Resistant)
➢ Mode (Treadmill, Bicycle, Swimming)
➢ Dosing
  ✓ Duration
  ✓ Frequency
  ✓ Intensity
  ✓ Repetition
  ✓ Progression

High Intensity Decrease motor performance

– Low to moderate treadmill running speed (3.4 to 16 m/min) improved survival, and delayed the onset of motor deficit
– Intense treadmill running speed (> 22 m/min) decreased survival and hastened motor function


Lessons from Animals using transgenic mice Model of ALS
**Voluntary Intermittent Running or Walking Exercise Promote Survival & Function**


**Swimming “body weight supported” but not running delay disease onset and death and improve function in ALS mice**


**Only the swimming-based training significantly protects lumbar motoneurons in ALS mice**

Deforges S et al. J Physiol 2008;587:3561-3572

**Inclusions Criteria**

- Definite ALS.
- Stand and ambulate independently with AD.
- Complete the 25FWT < 1 minute.
- VC ≥ 65%
- Use of NIV is OK

**Figure 1. Study Procedures**

- Screened for Eligibility (n = 13)
- Enrolled (n = 9)
  - Not meeting inclusion criteria (n = 4)
  - Unable to tolerate or participate (n = 2)
  - Lost to follow-up (n = 1)
  - Death of participant (n = 1)
- Discontinued (n = 3)
  - Participant lost to follow-up (n = 1)
  - Participant withdrew consent (n = 1)
  - Discontinuation of chronic back pain (n = 1)
- Completed the Intervention (n = 6)

Outcome measures:
- F-MS (modifiedWhats the strength here?
- F-MS (modifiedWhats the strength here?)
5 min Walk 5 min Rest

**Supported Treadmill Ambulation Training**

- **Body Weight Supported**: 30 - 40%
- **Type**: RRE - STAT
- **Frequency**: 3x/wk
- **Duration**: 30 minutes (build up endurance to 30 min as tolerated)
- **Intensity**: Walk as tolerated (comfortable cadence) RPE ≤ 12-13 (mild to moderate)
- **Progression**: Speed and distance as tolerated.

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**Table 1. Patients Demographics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (Yrs)</th>
<th>Ht (in)</th>
<th>Weight (lb)</th>
<th>BMI (m²)</th>
<th>Assistive Device Used</th>
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</thead>
<tbody>
<tr>
<td>001</td>
<td>F</td>
<td>23</td>
<td>53</td>
<td>64</td>
<td>111</td>
<td>19 L AFOs, 4 WW, PWC</td>
</tr>
<tr>
<td>002</td>
<td>F</td>
<td>53</td>
<td>41</td>
<td>68</td>
<td>150</td>
<td>23 L AFO</td>
</tr>
<tr>
<td>003</td>
<td>F</td>
<td>61</td>
<td>61</td>
<td>61</td>
<td>139</td>
<td>27 Bi AFOs, 4 WW, PWC</td>
</tr>
<tr>
<td>004</td>
<td>M</td>
<td>49</td>
<td>74</td>
<td>74</td>
<td>203</td>
<td>26 Bi AFOs</td>
</tr>
<tr>
<td>005</td>
<td>M</td>
<td>72</td>
<td>73</td>
<td>183</td>
<td>26</td>
<td>4 WW, BiPAP</td>
</tr>
<tr>
<td>006</td>
<td>M</td>
<td>77</td>
<td>70</td>
<td>150</td>
<td>22</td>
<td>4 WW, BiPAP</td>
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<tr>
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<td>F</td>
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<td>148</td>
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<td>4 WW</td>
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<td>009</td>
<td>F</td>
<td>77</td>
<td>85</td>
<td>124</td>
<td>19</td>
<td>Bi AFOs, BiPAP</td>
</tr>
</tbody>
</table>

*AFO = bilateral ankle foot orthosis, WW = four wheeled walker, PWC = power wheelchair, L = Left, BiPAP = Bilevel Positive Airway Pressure.*

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**Figure 4.** Total walking distance (miles) performed during each shift (Mean ± SE).
Table 3. Safety Outcome Measures

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline</th>
<th>4 wks</th>
<th>8 wks</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALSFRS-R</td>
<td>34 ± 5</td>
<td>38 ± 6</td>
<td>37 ± 6</td>
<td>0.022†</td>
</tr>
<tr>
<td>VC (%)</td>
<td>88 ± 16</td>
<td>92 ± 17</td>
<td>93 ± 19</td>
<td>0.433</td>
</tr>
<tr>
<td>TLM MT</td>
<td>62 ± 12</td>
<td>65 ± 13</td>
<td>67 ± 13</td>
<td>0.096</td>
</tr>
</tbody>
</table>

ALSFRS-R = Amyotrophic Lateral Sclerosis functional rating scale-Revised; VC = Vital capacity

TLM MT = Total lower extremities manual muscle test (Mean ± SD)

†indicates statistically significant difference from baseline.
Fig. 10. Percent change in total upper extremities (TUE) and total lower extremities (TLE) MVIC (Mean ± SE).

Future direction

1. RCT of resistant vs. endurance training is underway in 4 centers.
   - CMC/Charlotte
   - John Hopkins
   - Wash Univ. St Louis
   - Mass General

2. Trial of combined RRT-STAT and NIV in early stage ALS Patients
   - CMC/Charlotte

RRT-STAT
- Feasible
- Safe
- Well Tolerated
- Have a positive Treatment size affect due to its characteristics
  - Functional "Gait"
  - Low to moderate intensity
  - Active assistive
  - Discontinues "interval" non fatiguing

Richard K. Olney, MD
Founding Director ALS Treatment and Research Center at UCSF
The New York Times 02/21/2005

This pts is an expert on Benefit of Exercise