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

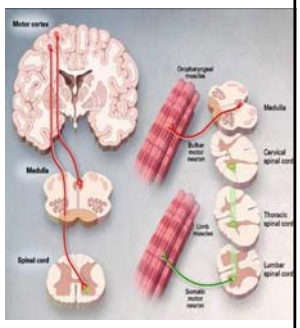
Pathology due to loss of

Upper Motor neuron

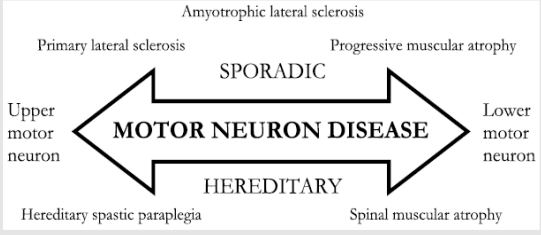
- Motor cortex
  - "Betz cells, precentral gyrus, and corticospinal tract"

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



Barohn RJ. Continuum Lifelong Learning Neurol 2009;15(1):111–131.

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
patterns of onset spread

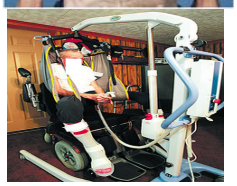
- Insidious
- Discrete
- Distal
- Focal
- Asymmetrical

- 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. Amyotroph Lateral Scler Other Motor Neuron Disord.;1(5):293-9, 2000

Management of ALS

European Journal of Neurology 2011 doi:10.1111/j.1468-1331.2011.03501.x

EFNS GUIDELINES

EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS) – revised report of an EFNS task force

The EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis: Peter M. Andersen[a], Sharon Abrahams[b], Gian D. Borasio[c], Mamede de Carvalho[d], Adriano Chio[e], Philip Van Damme[f], Orla Hardiman[g], Katja Kollewe[h], Karen E. Morrison[i], Susanne Petri[h], Pierre-Francois Pradat[j], Vincenzo Silani[k], Barbara Tomik[l], Maria Wasner[m] and Markus Weber[n]

Miller RG, Jackson CE, Ksarskis EJ, et al. Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009;73:1227-1233

Miller RG, Jackson CE, Ksarskis EJ, et al. Practice Parameter Update: The care of the patient with amyotrophic lateral sclerosis: Drug, nutritional, and respiratory therapies (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009; 73:1218-1226

Management of ALS

Multidisciplinary ALS Clinic

Core Members

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

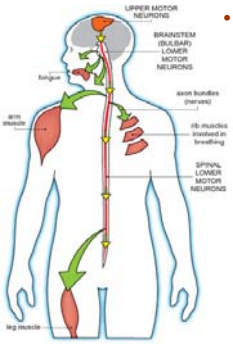
Consultants

- Rehabilitation physician
- Pulmonologist
- Gastroenterologist

Associates

- Research scientists

Clinical Features

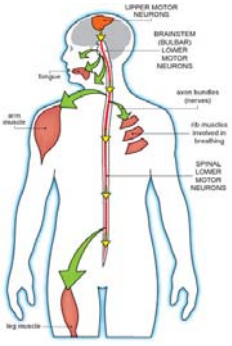


- **Upper motor neuron findings**
  - Spasticity
  - Hyperreflexia
  - Babinski's response
  - Hoffmann's sign
  - Pseudo bulbar features "emotional lability"
  - Cognitive and Frontotemporal Lobe Dementia

Emotional Lability

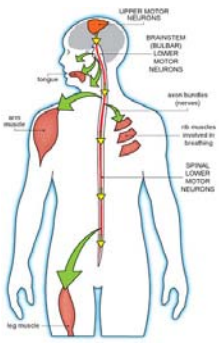
Crying	Laughing

Clinical Features



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

Clinical Features

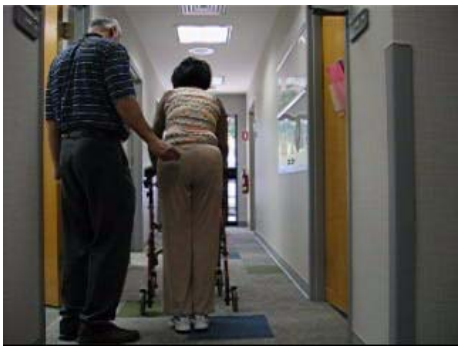


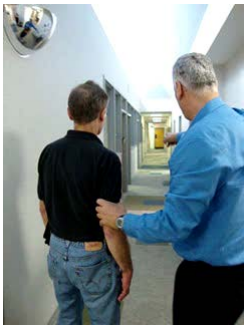
- **Mixed Upper and Lower motor neuron findings**
  - Decline Force Production
    - *Isokinetic faster the Isometric*
    - *Isometric faster than Manual*
  - Increase Motor Fatigue
    - Central
    - Peripheral
  - Loss of Balance
  - Respiratory insufficiency

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

How would we know if 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**

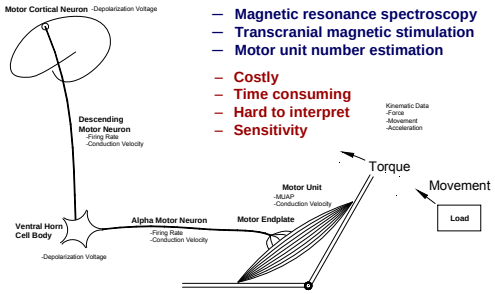
Disability

- **ALSFRS-R**

Handicap

- **Survival**
- **Quality of life**

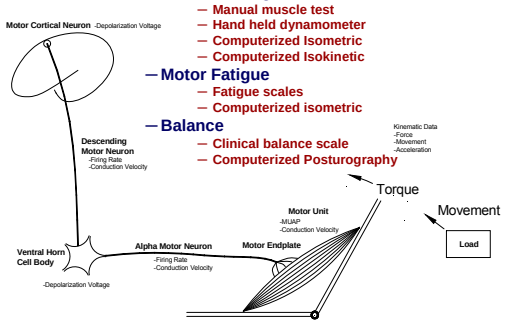
ALS = Motor Neuron Loss



- **Magnetic resonance spectroscopy**
- **Transcranial magnetic stimulation**
- **Motor unit number estimation**

- **Costly**
- **Time consuming**
- **Hard to interpret**
- **Sensitivity**

Motor Neuron Loss



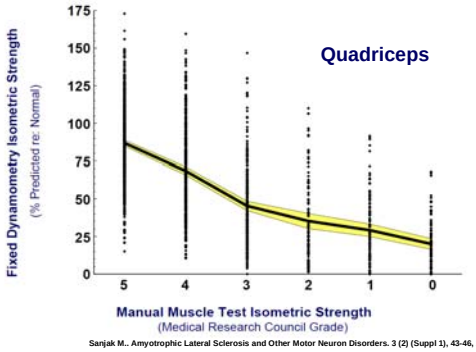
- **Muscle strength**
  - **Manual muscle test**
  - **Hand held dynamometer**
  - **Computerized Isometric**
  - **Computerized Isokinetic**
- **Motor Fatigue**
  - **Fatigue scales**
  - **Computerized isometric**
- **Balance**
  - **Clinical balance scale**
  - **Computerized Posturography**

Manual Muscle test (MMT)

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

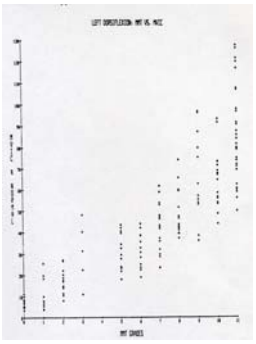
- **Ordinal: the steps between ranked grades can be grossly uneven**
- **Lack of sensitivity to change**
- **Poor correlation with absolute muscle strength, especially in strong muscles.**
- **MMT summary scores can be inaccurate and misleading**

Manual Muscle test (MMT)



Sanjak M.. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders. 3 (2) (Suppl 1), 43-46, 2002.

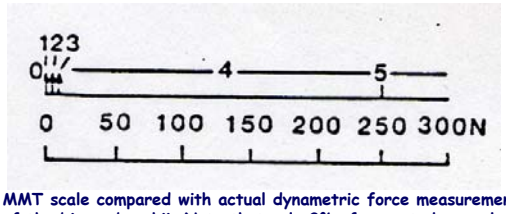
MMT vs. % Predicted Normal MVIC



Dorsiflexion

Andres PL et al. J Neurol Sciences: 1996

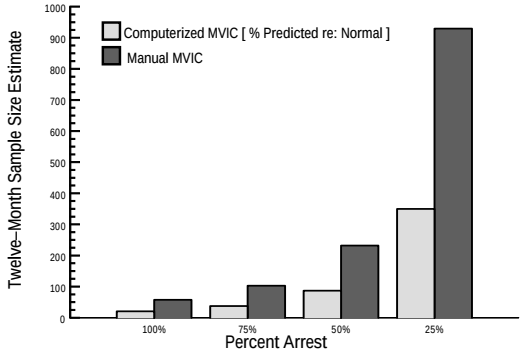
Uneven Steps Between MRC Grades



MMT scale compared with actual dynametric force measurement of the biceps brachii. Note that only 3% of expected normal force corresponds to a MMT grade of 3 (Fair).

van der Ploeg: J Neurol, 1984

High Variability in MMT will compromise statistical power



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.

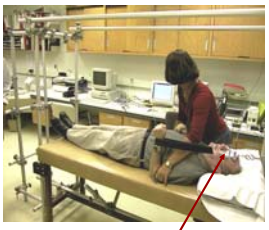
Microfet

Hand Held Dynamometer

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

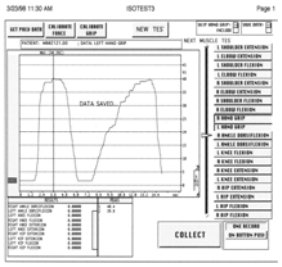


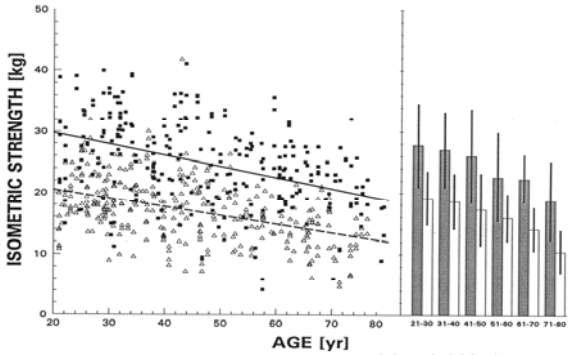
Computer-based, fixed strain-gauge

Computerized Isometric Muscle Strength

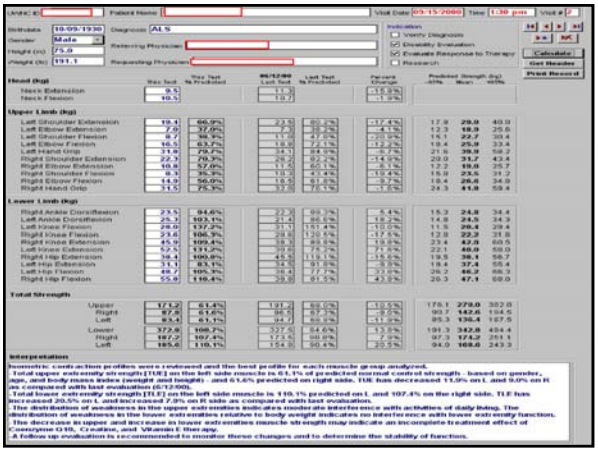
MVIC

- 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





Arch Phys Med Rehab (1996). 77:1251–1255.



Computerized Isometric Muscle Strength

MVIC

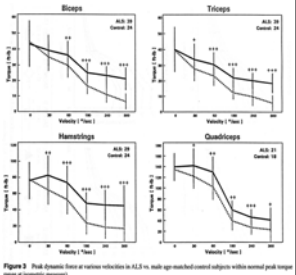
- Portable
- Computerized
- Wireless

ATLIS: Accurate Test of Limb Isometric Strength

Andres P et al. Muscle & Nerve, 45 (1): 81-85, 2011

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



Sanjak M et al. Neurology, 42: 454, 1992

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.

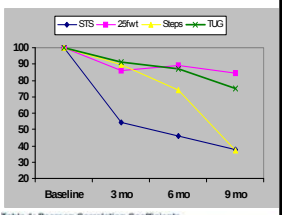


Table 1: Pearson Correlation Coefficients

Outcome measures	STS	25 FWT	Steps	FVC	TUG
ALSFRS-R	0.14	-0.51*	-0.47*	0.37	-0.45*
STS		0.46*	0.09	-0.23	0.09
25 FWT			0.46*	-0.36	0.32
Steps				-0.15	0.40
FVC					-0.07

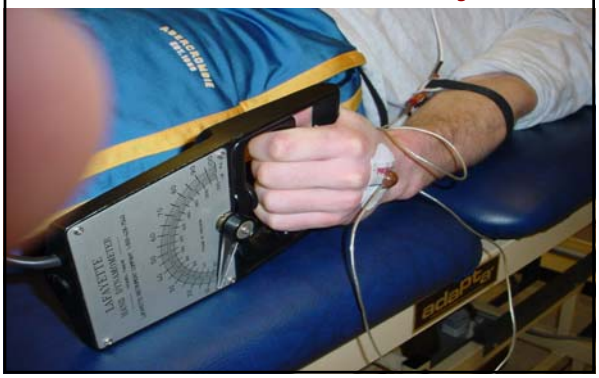
*P ≤ 0.05

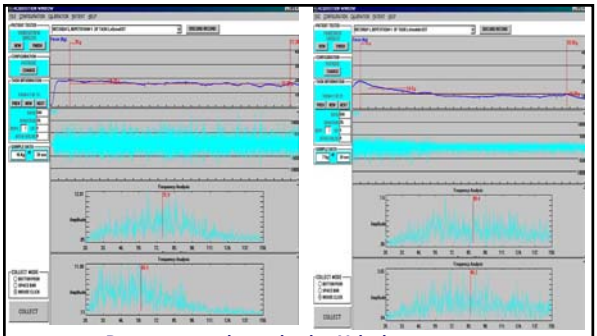
Motor Fatigue

Decline in MVIC and Shift in sEMG signal

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

Vol. 28 • No. 1 • 2004 Journal of Neurological Physical Therapy 12

Interrater and Intrarater Reliability of the Tinetti Balance Test for Individuals with Amyotrophic Lateral Sclerosis

Anne D. Kloos, PhD, PT, NCS,[1] Vanina Dal Bello-Haas, PhD, PT,[2] Rachel Thome, MS, PT,[2] Jan Gassidy, PT,[2] Lisa Lewis, PT,[3] Tricia Cusma, PT,[3] Hiroshi Mitsumoto, MD, DSc[3]

Amyotrophic Lateral Sclerosis. 2007; 8: 292–295

informa

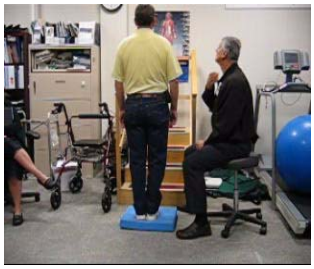
ORIGINAL ARTICLE

The Timed Up and Go test: Predicting falls in ALS

JACQUELINE MONTES[1], BIN CHENG[2], BEVERLY DIAMOND[3], CAROLYN DOORISH[1], HIROSHI MITSUMOTO[1] & PAUL H. GORDON[1]

[1]Department of Neurology, College of Physicians and Surgeons, The Eleanor and Lou Gehrig MDA/ALS Research Center, [2]Department of Biostatistics, Mailman School of Public Health, and [3]General Clinical Research Center, Columbia University, New York, NY, USA

modified Clinical Test of Sensory Integration and Balance (mCTSIB)



- Increase Reliance on Vision/fixation — Sanjak M, Neurology; 127, 2009
- Deconditioning of Vestibular function or
- Abnormality in Extrapyramidal/Cerebellum and its connections

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

Sanjak M et al. Neurology 74 (Suppl 2), 207, 2010.

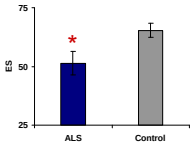
Table 1. Functional Evaluations.

Test/Evaluation	Mean ± SD
ALSFRS-R	40.9 ± 4
VC %	90 ± 19
25FWT (sec)	4.4 ± 0.7
Up and down 4 steps (sec)	4.5 ± 0.8

Table 2. Balance Evaluation.

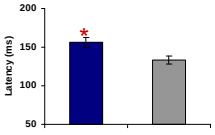
Balance Scale	Mean ± SD	Range Min-Max	Risk of fall score
DGI	22.7 ± 1.1	21-24	17-19/24 = ↑ Risk of falls
BBS	55.6 ± 0.8	54-56	41-56 = independent < 41 = ↑ Risk for falls
TUG	6.5 ± 1.1	5.1-9.0	> 14 sec= Risk for falls

Balance and Fall



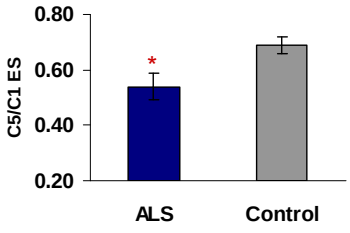
Condition 5

Fig. 2. Sensory Organization Test



Large backward Translation

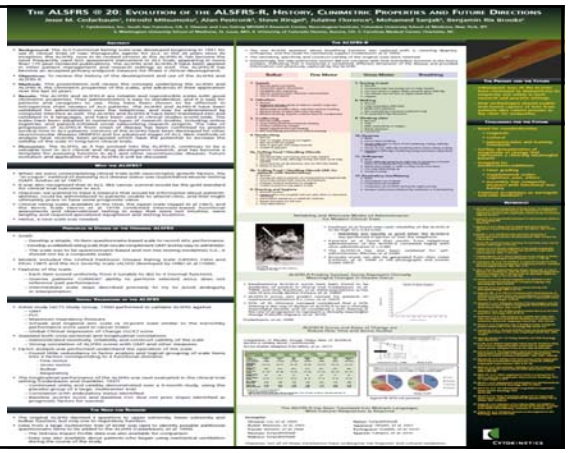
Fig. 3. Motor Control Test



Ability to use Vestibular

Disability

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



ALSFRS-R

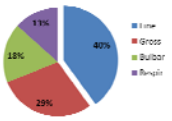
Characteristics

- 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:
  - Turning in bed and adjusting bed clothes
  - Walking
  - Climbing stairs
- Respiratory Domain:
  - Dyspnea
  - Orthopnea
  - Respiratory insufficiency

- Changes in sub-domain scores validated across two studies conducted a decade apart in time

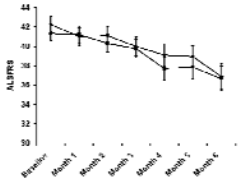


From: Cedarbaum et al, 1999

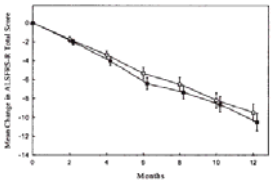
Decline in ALSFRS-R Score is linear

0.95 pint per month on the average

Creatine

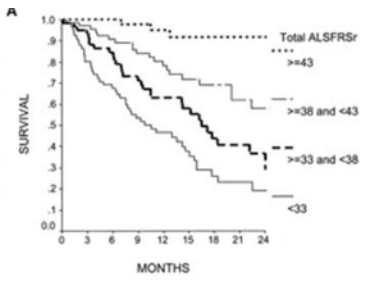


Celecoxib (Celebrex)



From: Cudkowicz et al., 2006, Shefner 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



Kaufmann P et al. Neurology 2005;64:38-43

AMERICAN ACADEMY OF NEUROLOGY

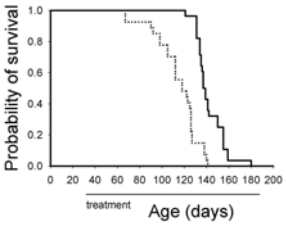
Limitations to ALSFRS-R

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

Survival
Time to Death or Tracheostomy

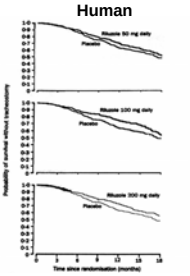
clinically relevant, derivative of a binary endpoint

MICE



Drachman et al., 2000

Human



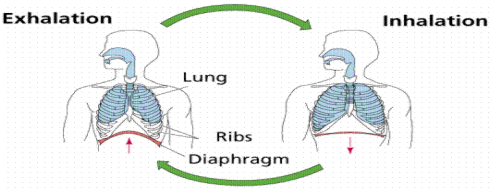
Lacomblez et al., 1996

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

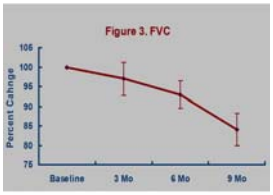


Not a pulmonary disease but a ventilation pump disease

- Loss of innervations of muscles of inhalation and exhalation
- CO2 retention and oxygen desaturation due to hypoventilation
- Rapid/shallow breathing and increased caloric 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



Sanjak M. Amyotrophic Lateral Scler; 2010; 11(4):383-388,2010

ALS Respiratory Impairment

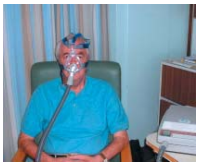
- Non-invasive ventilation
- Assisted Coughing
- Diaphragm stimulation
- Invasive ventilation
- Nutritional support

ALS Respiratory Management

- **Non-invasive ventilation**

The best treatment for Respiratory insufficiency

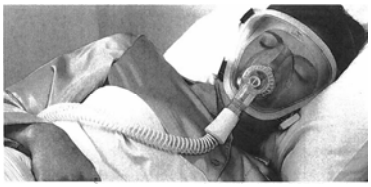
- Relief respiratory distress
- Improve mental awareness
- Improves quality of life
- Extends Survival
- Reduce progression of respiratory muscle function



Mustfa N, Walsh E, Bryant V, et al. The effect of noninvasive ventilation on ALS patients and their caregivers. Neurology 2006; 66: 1211–1217.

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

"I know nothing about the subject, but I'm happy to give you my expert opinion."

52 *Exercise, Metabolism and Nutrition* *20th International Symposium on ALS/MND*

SESSION 9B EXERCISE, METABOLISM AND NUTRITION

C82 IS EXERCISE A PREDISPOSING FACTOR IN ALS? THE CASE FOR

CHIÒ A

Department of Neuroscience, Torino, Italy

50/50 split

Cardiac Pts
Parkinson
MS
Cancer
etc>>>>>

C83 IS EXERCISE A PREDISPOSING FACTOR FOR ALS? THE CASE AGAINST

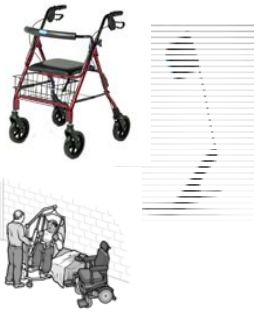
WOKKE J, VELDINK J, VAN DEN BERG L

Department of Neurology, University Medical Centre, Utrecht, Netherlands

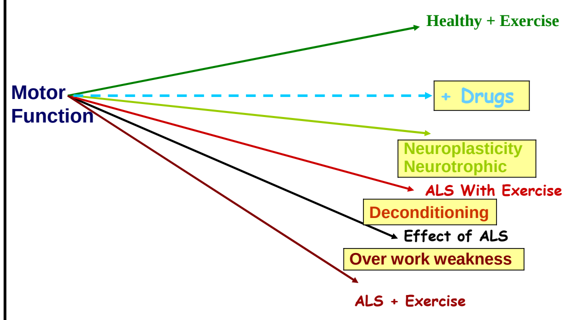
Amyotrophic Lateral Sclerosis. 2009 (Suppl. 1); 10: 7 63

Physical Therapy for ALS

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



Risk / Benefit of therapeutic exercise in ALS



Therapeutic Exercise for ALS

Can ALS patients Exercise ?

Physiologic and metabolic response to progressive and prolonged exercise in amyotrophic lateral sclerosis

Article abstract—Physical work capacity in 35 ALS patients and 6 untrained controls was evaluated during progressive bicycle ergometry. In the ALS patients, maximum oxygen consumption (VO_2max) and work capacity (Wmax) drop in relation to the decrease in ALS functional score. However, the oxygen cost (ml O_2/kpm) of submaximal exercise was significantly increased. Prolonged submaximal exercise tests in six ALS patients and six matched untrained controls indicated that the exercise-induced increase in plasma free fatty acids, beta-hydroxybutyrate, esterified carnitine, and muscle esterified carnitine was significantly retarded in ALS patients.

NEUROLOGY 1987;37:1217-1220

M. Sanjak, PhD; D. Paulson, PhD; R. Sufit, MD; W. Reddan, PhD; D. Beaulieu, RN, BSN; L. Erickson, MS; A. Shug, PhD; and B.R. Brooks, MD

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

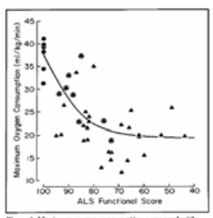
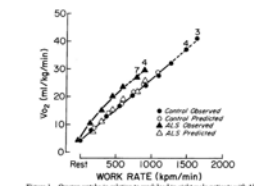
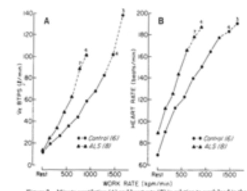


Figure 1. Maximum oxygen consumption compared with ALS functional score. (●) = control subjects; (●) = ALS patients matched by age, sex, and weight to control subjects; (▲) = ALS patients.





Increase oxygen cost of submaximal exercise

Increase VE of submaximal exercise

Increase HR of submaximal exercise

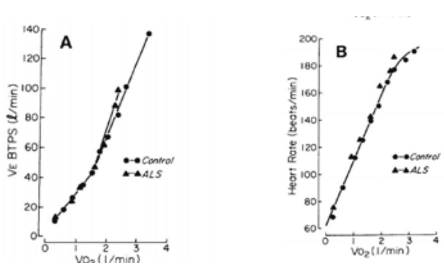


Figure 3. Rate of increase in minute ventilation (A) and heart rate (B) in relation to oxygen consumption in patients and control subjects.

No increase in work of breathing or cardiac work

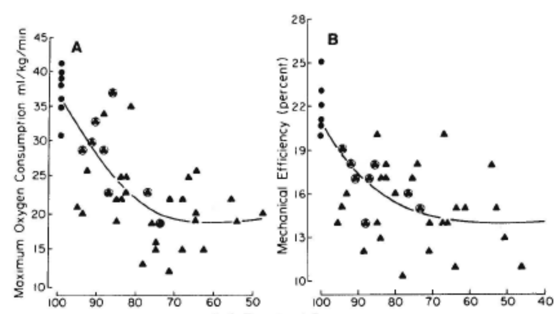


Figure 4. Maximal oxygen consumption (A) and mechanical efficiency (B) in relation to ALS Functional Score. [●] = control subjects; ([▲] = patients with ALS matched to control subjects [▲] = ALS patients.

Can ALS patients engage in prolong exercise

Metabolic Demands

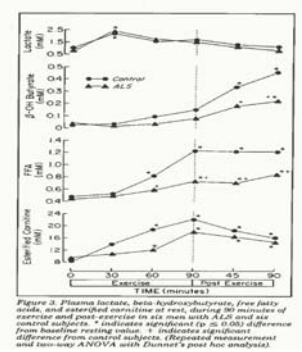


*Figure 3. Plasma lactate, beta hydroxybutyrate, free fatty acids, and esterified carnitine at rest, during 90 minutes of exercise and post-exercise in six men with ALS and six normal subjects. * indicates significant ($p \leq 0.05$) difference from baseline resting value. ‡ indicates significant difference from control subjects. (Repeated measurement and two-way ANOVA with Dunnet's post hoc analysis).*

Can ALS patients engage in prolong exercise

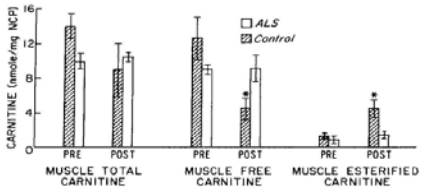


Figure 5. Muscle carnitine in pre- and postexercise muscle samples obtained from six patients with ALS and six untrained control subjects. * indicates significant difference from pre-exercise ($p < 0.05$).

Conclusion

1. **The cardiopulmonary response to exercise in ALS is normal ±**
2. **Reduce in $V0_2$ max correlate 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 that there was no hypoxia in the muscles**
5. **Increase oxygen cost and decrease mechanical efficiency may requires attention O2 desaturation and to supply O2 if necessary.**

± Mezzani A et al. *Amyotrophic Lateral Sclerosis*, 1–8, 2011

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.**

Pinto AC et al. J Neurol Sci; 169:69–75, 1999

Can ALS patients response to exercise training?

Few studies

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% 0f predetermined Vo2
- 4 days per week, 6 weeks.
- 30 minutes per day *(5 minutes work and 5 minutes rest)*,

Sanjak Met al. Neurol Clin, 1987; 5:251–268.

Regular exercise training in ALS

Results: Pre to post exercise training

1. Increase $V0_2$ 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

Sanjak M et al. Neurol Clin, 1987; 5:251–268.

Regular exercise training in ALS

- 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

Drory VE et al . J Neurol Sci; 191:133–137 , 2003

Regular exercise training in ALS

- 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

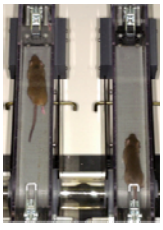
V. Dal Bello-Hass et al Neurology 2007 88:2003-2007

What is Lacking ? The Parameters

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

Lessons from Animals using transgenic mice Model of ALS

High Intensity Decrease motor performance



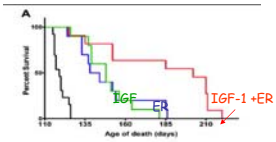
- low to moderate treadmill running speed (3.4 to 16 m/min) improved survival, and delayed the onset of motor deficit
- intense treadmill running speed (> 22 m/min) decreased survival and hastened motor function

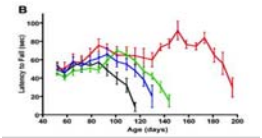
Carreras I et al. Moderate exercise delays the motor performance decline in a transgenic model of ALS. Brain Res, 2010; 1313:192-201.

Mahoney DJ et al. Effects of high-intensity endurance exercise training in the G93A mouse model of amyotrophic lateral sclerosis. Muscle Nerve. 2004 May;29(5):656-62

Voluntary Intermittent Running or Walking Exercise Promote Survival & Function

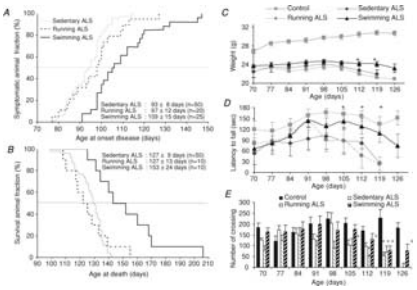
Mouse Rota Rod Treadmill





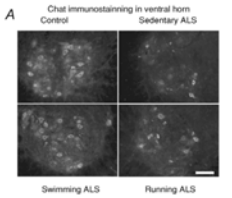
Kaspar BK, et al. Ann of Neurol 2005

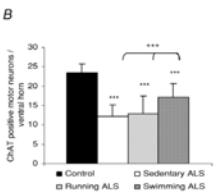
Swimming "body weight supported" but not running delay disease onset and death and improve function in ALS mice



Deforges S et al. J Physiol 2009;587:3561-3572

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





Deforges S et al. J Physiol 2009;587:3561-3572

Arch Phys Med Rehabil Vol xx, Month 2010

ORIGINAL ARTICLE

Supported Treadmill Ambulation for Amyotrophic Lateral Sclerosis: A Pilot Study

Mohammed Sanjak, PhD, PT, Elena Bravver, MD, William L. Bockenek, Jim Norton, PhD, MD, Benjamin R. Brooks, MD

From the Carolinas Neuromuscular/ALS-MDA Center, Department of Neurology, Neuroscience and Spine Institute, Carolinas Medical Center, Charlotte (Sanjak, Bravver, Brooks); Department of Kinesiology, College of Health and Human Service, University of North Carolina, Charlotte (Sanjak); Department of Physical Medicine and Rehabilitation, Carolinas Rehabilitation/Carolinas Medical Center, Charlotte (Bockenek); and Department of Biostatistics, Carolinas Medical Center (Norton), Charlotte, NC.

Presented in part to the International Symposium on Amyotrophic Lateral Sclerosis and Motor Neuron Disease, December 8–10, 2009, Berlin, Germany, and the American Academy of Neurology, Toronto, ON, Canada, April 10–17, 2010.

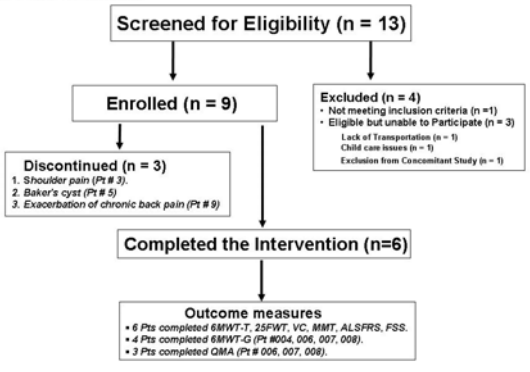
Supported by Harrison Foundation Fund grant # 1299; Pinstripes Fund grant # 200082, Carolinas ALS Research Fund grant # 201771, Carolinas Healthcare Foundation grant # 346100, and Muscular Dystrophy Association ALS/Division grant # 203253.

Reprint requests to Mohammed Sanjak, PhD, PT, Carolinas Neuromuscular/ALSMDA Center, Dept of Neurology, Neuroscience and Spine Institute, Carolinas Medical Center, 1010 Edgehill Rd N, Charlotte, NC 28207-1885, e-mail: *mohammed.sanjak@carolinashealthcare.org.*

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



6MWT-T =Treadmill six minutes walk test, **25FWT** = 25 foot walk test, **VC** =Vital Capacity, **MMT** = Manual Muscle Test, **ALSFRS-R** = Amyotrophic lateral Sclerosis functional rating scale-Respiratory, **FSS** = Fatigue Severity Scale, **6MWT-G** = Ground six minutes walk test, **QMA** = Quantitative Muscle Strength test.-

Table 1. Patients Demographics

Patient #	Sex	Age (Yrs)	Ht (in)	Weight (lb)	BMI (m^2)	Assistive Device Used
001	F	58	64	111	19	Bi AFOs, 4 WW, PWC
002	F	41	68	150	23	L AFO
003	F	61	61	139	27	Bi AFOs, 4 WW, PWC
004	M	39	74	203	26	Bi AFOs
005	M	72	73	183	26	4 WW, BiPAP
006	M	77	70	150	22	Bi AFOs, 4 WW
007	F	68	67	148	23	4 WW
008	M	65	66	155	25	Bi AFOs
009	F	77	65	124	19	Bi AFOs, BiPAP

Bi AFO = bilateral ankle foot orthosis, **4WW** = four wheeled walker, **PWC** = power wheelchair, **L** = Left, **BiPAP** = Bi-level Positive Airway Pressure,

Supported Treadmill Ambulation Training

Body Weight Supported = 30 – 40%

5 min Walk

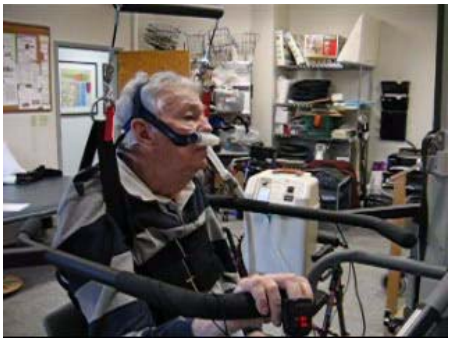
5 min Rest

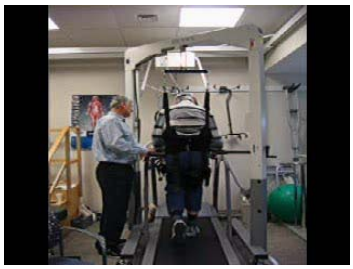
Type = **RRE – STAT**

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 distant as tolerated.





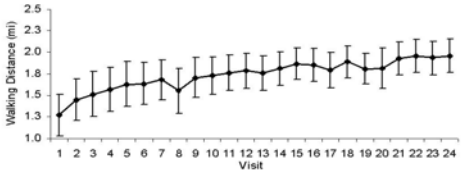


Figure 4. Total walking distance (miles) performed during each visit (Mean ± SE).

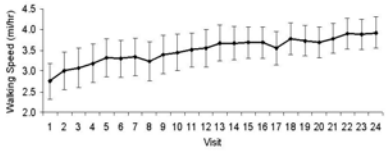


Figure 5. Average walking speed (miles/hours) achieved in each visit (Mean ± SE).

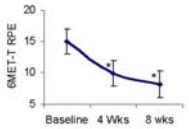


Figure 2. Change in rate of perceived exertion score (RPE) (Mean ± SE).
† Indicates significant different at 4 Wks ($p \leq 0.05$, and 8 Wks ($p \leq 0.008$) compared with baseline.

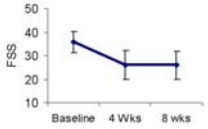


Figure 3. Change in fatigue severity scale (FSS) (Mean ± SE).

Table 3. Safety Outcome Measures

Outcome	Baseline	4 wks	8 wks	P value
ALSFRS-R	34 ± 5	38 ± 6	37 ± 6	0.022†
VC (%)	88 ± 16	92 ± 17	93 ± 19	0.433
TLMMT	62 ± 12	65 ± 13	67 ± 13	0.096

ALSFRS-R=Amyotrophic Lateral Sclerosis functional rating scale-Revised, **VC**=Vital capacity, **TLMMT**=Total lower extremities manual muscle test (Mean ± SD).
† indicates statistically significant difference from baseline.

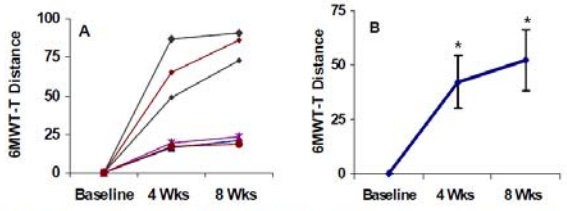


Fig 5. Percent change in 6MWT-T distance (A) individuals (B) (Mean ±SE).
*Indicates significant difference at 4 and 8 Wks ($p \leq 0.05$) compared with baseline.

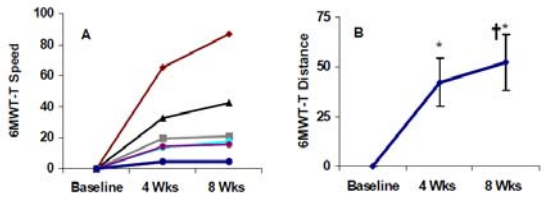


Fig 6. Percent change in 6MWT-T Average walking speed (A) individuals (B) (Mean ± SE). * Indicates significant difference at 4 Wks.
†* Indicates significant difference at 8 Wks ($p \leq 0.05$) compared with baseline

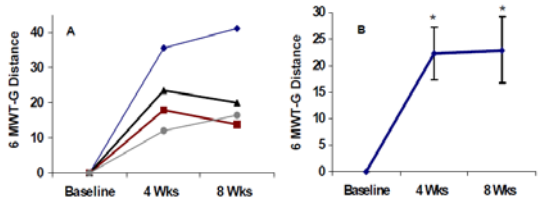


Fig 8. Percent change in 6MWT-G distance (A) individuals and (B) Mean ± SE. *Indicates significant difference at 4 Wks and 8 Wks ($p \leq 0.05$) compared with baseline.

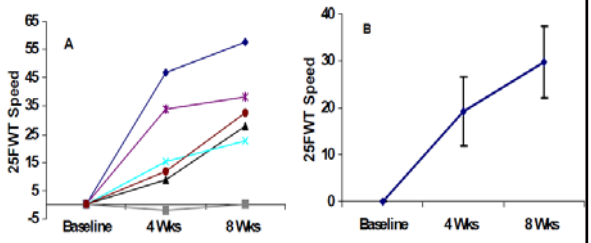


Fig 9. Percent change in 25FWT walking speed (A) individuals and (B) (Mean ± SE).

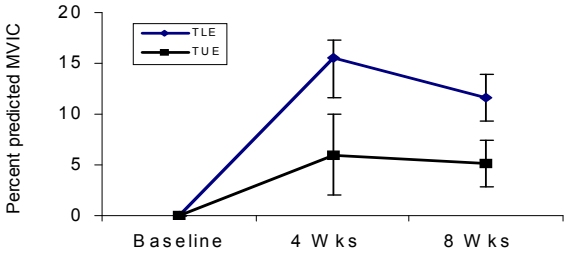


Fig. 10. Percent change in total upper extremities (TUE) and total lower extremities (TLE) MVIC (Mean ± SE).

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

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

This pts is an expert on Benefit of Exercise

Richard K. Olney, MD
Founding Director ALS Treatment and Research Center at UCSF

The New York Times /2005/02/21/