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RARE DISEASE WORKSHOP SERIES

Improving the Clinical Development Process

Electrical Impedance Myography as a Biomarker in Neuromuscular Disorders

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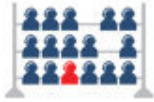
Convergence Medical Devices, Inc



Neuromuscular disorders: some common, many rare

- Common:
 - Carpal tunnel syndrome, sciatica, diabetic neuropathy, statin-induced myopathy
- Rare:
 - **Muscle diseases:** Pompe's disease, inclusion body myositis, Duchenne muscular dystrophy, Becker's muscular dystrophy, myotonic dystrophy, dermatomyositis
 - **Nerve diseases:** Charcot-Marie-Tooth neuropathy, chronic inflammatory polyradiculoneuropathy, amyotrophic lateral sclerosis, spinal muscular atrophy
 - **Neuromuscular junction diseases:** Myasthenia gravis, Lambert-Eaton Myasthenic syndrome, botulism





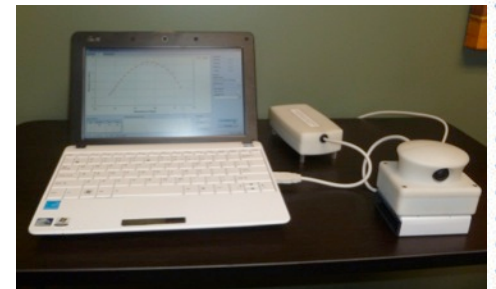
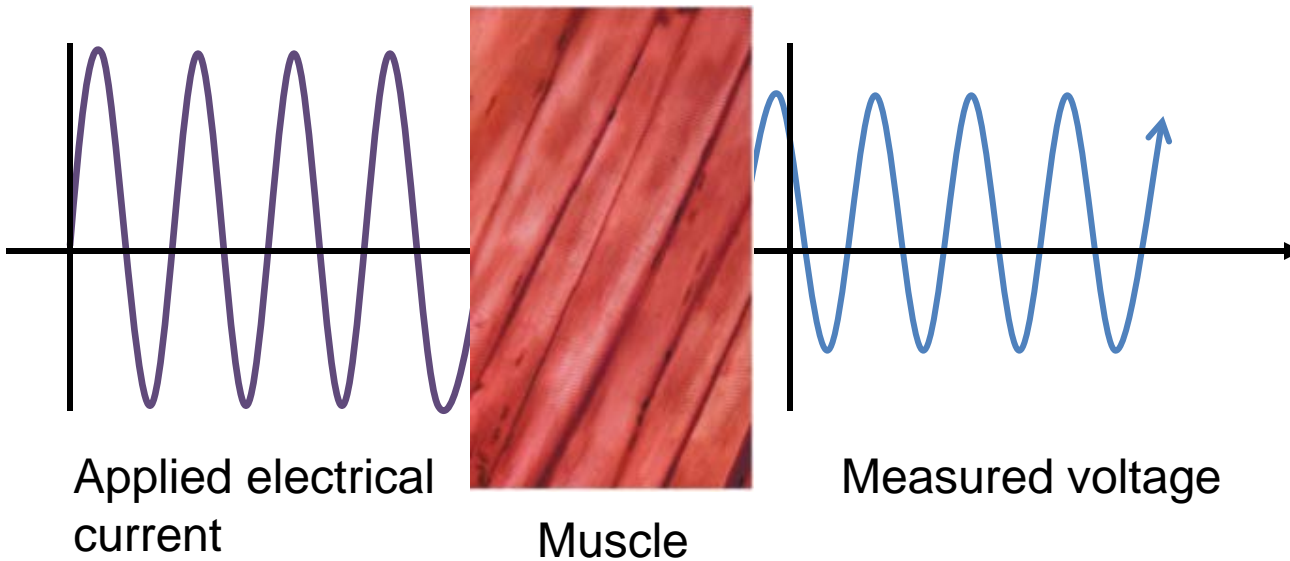
Limitations of current approaches

- Strength measurements
 - What apparatus to use? Variable depending on strength of examiner
 - Fatiguing
- Functional measurements
 - Generally not especially repeatable
 - Limited assessment of non-ambulatory cases, young children, or those who can't follow directions
 - Fatiguing
- Questionnaires
 - Influenced by mood, generally insensitive
- Imaging
 - Expensive and often inconvenient
 - Difficult to assess multiple body regions
- Serologic markers
 - Very few identified, especially to follow disease status and response to therapy



Electrical impedance myography (EIM)

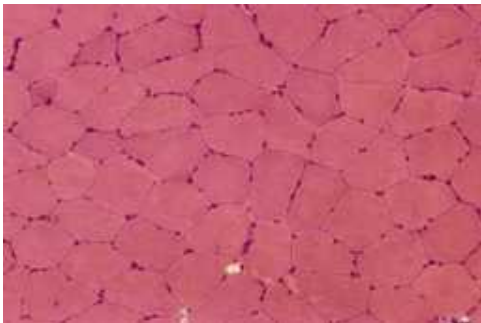
- Technique based on application of low-intensity, high frequency electrical current to localized areas of tissue and measurement of resulting voltages



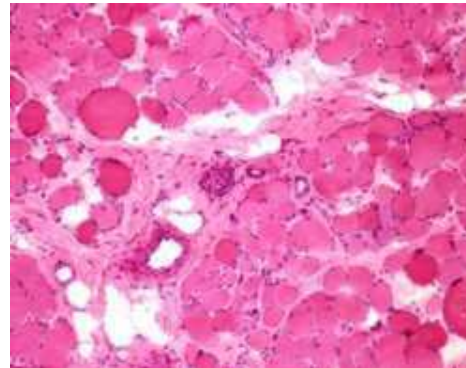


Basic concept underlying EIM

Changes in composition and structure of muscle with disease impact the impedance of muscle in unique and reproducible ways.



Normal Muscle



Myopathy/Dystrophy

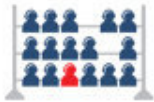


Neurogenic Atrophy

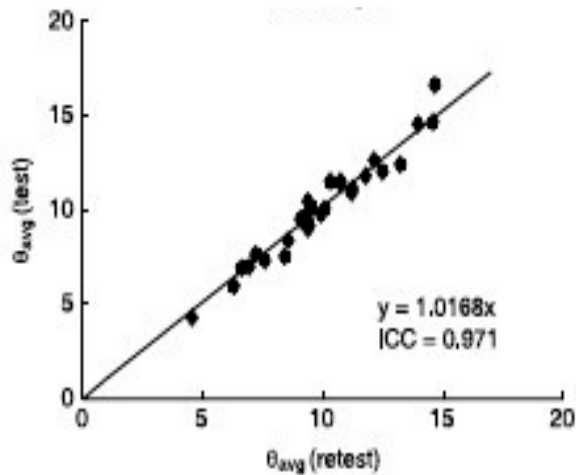


Advantages of EIM

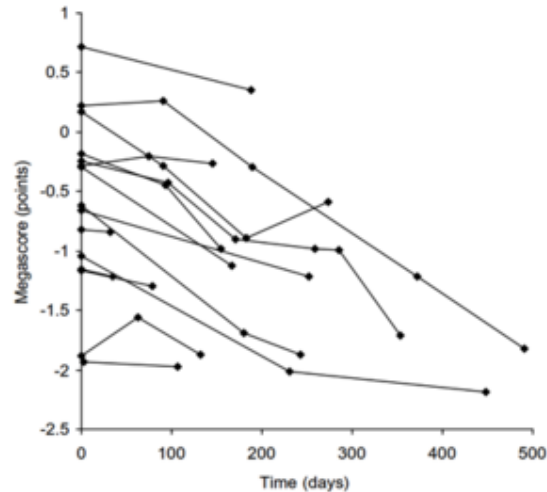
- Looks at the relevant compartment (ie, the muscle itself)
- Fast and easy to apply
 - At the bedside
 - Requires minimal patient cooperation
- Can use in all age groups
 - From children to the elderly
- Can focus on area of disease activity
 - Proximal or distal muscles for example
- Requires relatively little training
 - Measurements could even be done at home by a caregiver
- Painless and non-invasive



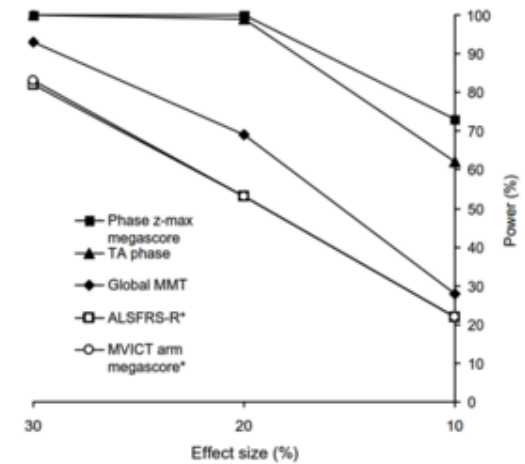
EIM is repeatable and sensitive to change: ALS as an example



SINGLE MUSCLE repeatability in 30 normal subjects over a mean of about 2 weeks



15 ALS patients followed over time (average of muscles)



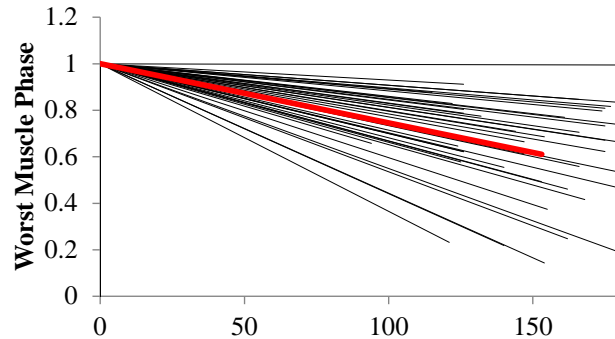
Summary of power analyses

From Rutkove et al, 2005

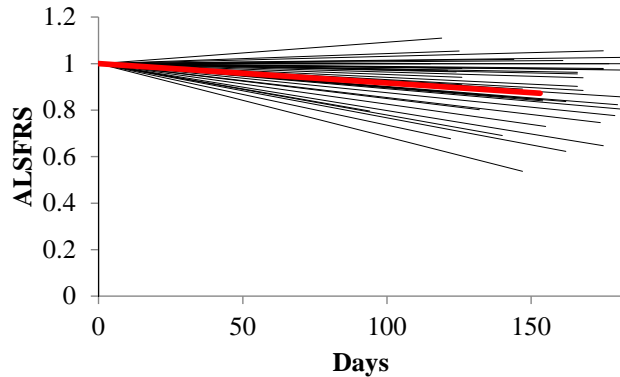
From Rutkove et al, 2007



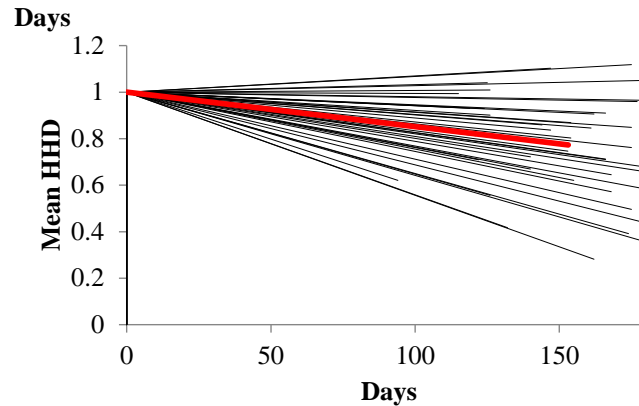
Data in 50 subjects over 6 months in just completed ALS Association funded study



Coefficient of variation
in rate of decline = 0.55



Coefficient of variation
in rate of decline = 0.84



Coefficient of variation
in rate of decline = 0.93



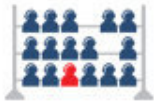
Numbers needed for clinical trial based on 6 month data

Number of patients needed per arm for a placebo-controlled trial*

Outcome measure	Patients needed per study arm
EIM	95
HHD	266
ALSFRS-R	220

*Assuming a 6 month, placebo-controlled study, aiming to identify a 20% treatment effect with 80% power, one-tailed, $p < 0.05$

And EIM correlates to survival...with hazard ratio of 1.40, $p = 0.035$
Also correlates to rate of decline in HHD ($r = 0.41$) and ALSFRS ($r = 0.43$) over 1 year, $p < 0.001$ for both



One challenge: how to get the best data



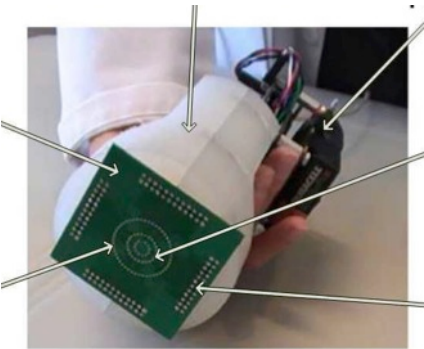
Circa 2001



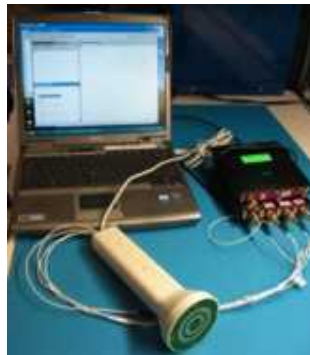
Circa 2004



Based on off-the-shelf technology



MIT collaboration (2006-09)



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Dedicated EIM devices

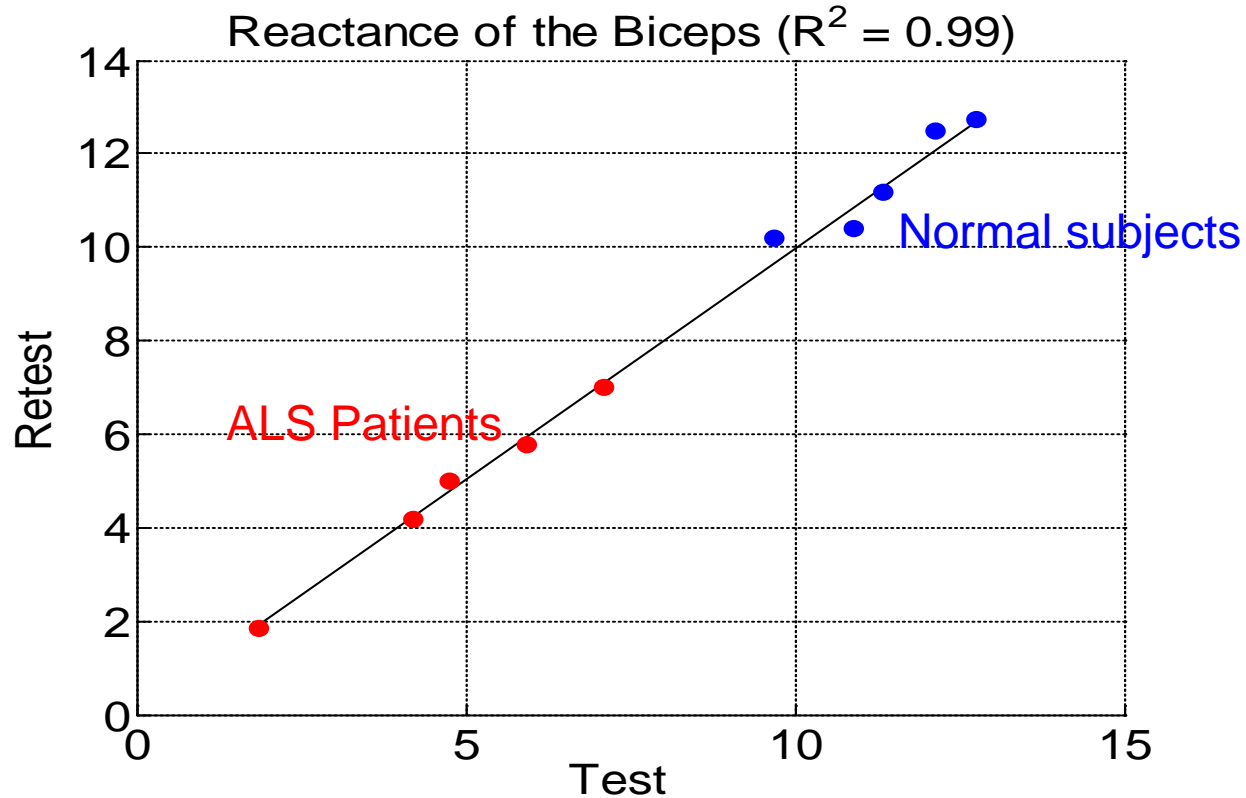


Collecting data with our newest device





ALS data using latest device





Limitations

- Not directly measuring molecular mechanisms
 - “Blunt tool”
- Discriminating primary muscle from primary nerve disease remains a challenge
- Exact significance of changes uncertain
 - Fat, connective tissue imposition? Loss of normal structure?
 - Animal research program underway to help sort that out
- Superimposed conditions could impact certain aspects of data
 - Obesity, congestive heart failure, kidney failure
- Still relatively new and unfamiliar to most investigators



Future directions/application

- Multiple studies in neuromuscular disease being planned
 - Studies in amyotrophic lateral sclerosis, spinal muscular atrophy, Duchenne muscular dystrophy, hereditary inclusion body myositis, facioscapulohumeral muscular dystrophy now ongoing or planned.
- Identification of best EIM indices
- Establishment of relationship between EIM data and other functional and meaningful outcomes
 - An example: correlation to survival in ALS
- Getting the technology in many people's hands to increase familiarity and get feedback
- Continually improve and refine the technology



Collaborators and Funding

- **Neurologists and colleagues around the US**
 - Jeremy Shefner, Merit Cudkowicz, William David, Nick Maragakis, Ted Burns, Jim Caress, Michael Benatar, Khema Sharma, Jonathan Glass, Eva Feldman
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