Prevention of Muscle Atrophy With Exercise Countermeasures

Where we are and where we are going

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Goals of the Presentation

– Overview of Muscle Atrophy
– Models for Studying Atrophy
– Exercise Countermeasures
– How Does Strength Relate to Function?

Muscle Atrophy=Decreased Mass

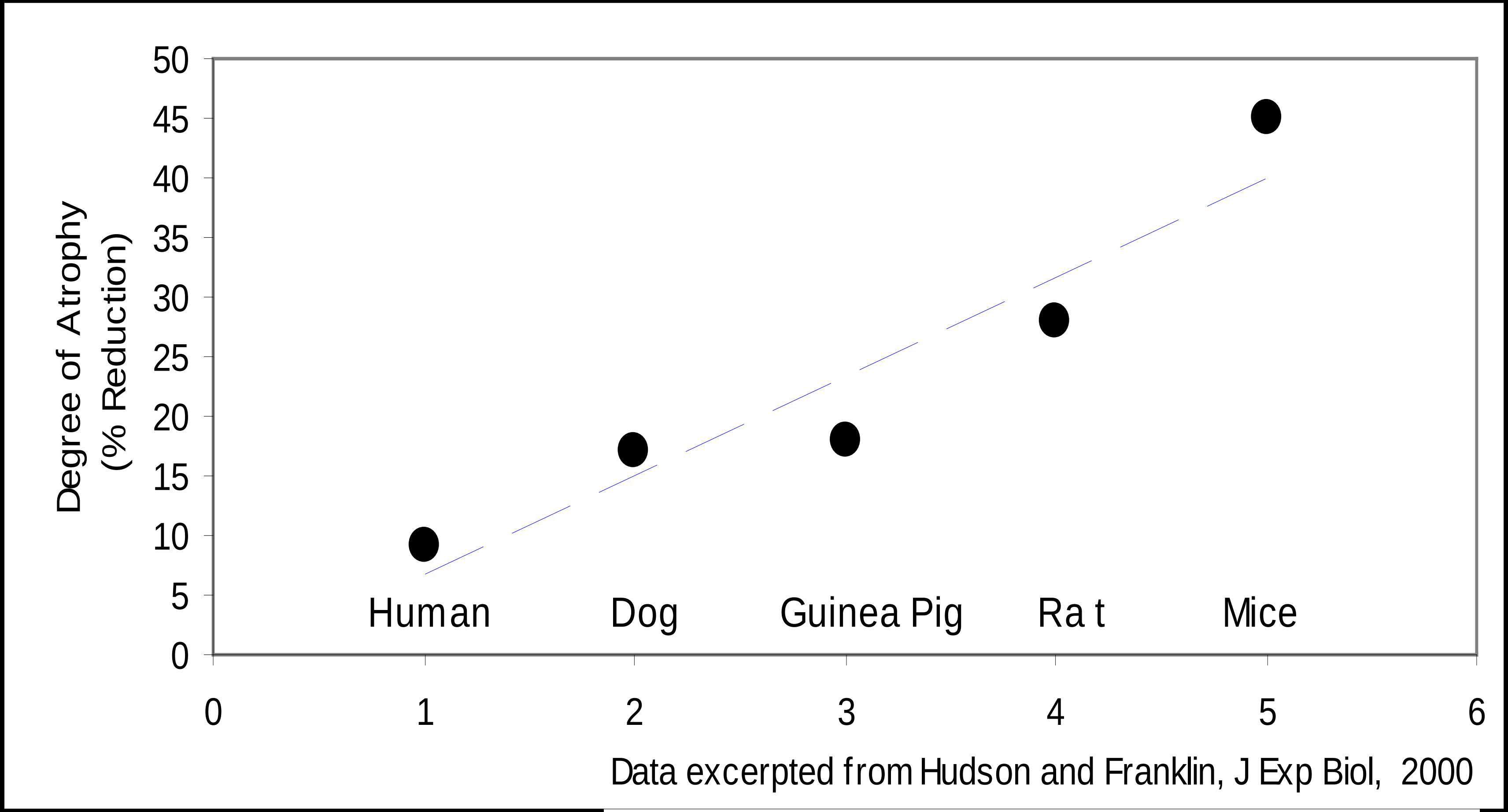
Disuse Models

- Outcomes are dependent on specifics of disuse model used (i.e. bedrest vs immobilization [shortened casting vs lengthened casting]).

Animal Models	Human Models
Immobilization	Immobilization
Hindlimb Unweighting	Limb Suspension
Spinal Transection	Spinal Cord Injury
Pharmacological Blockade	Bedrest
Spaceflight	Spaceflight
Nerve Compression	Cancer Cachexia (Atrophy)
Hibernation	Kwashiorkor (Atrophy)

Comparative Animal Physiology

- Macroscopic Level:Rate of muscle wasting in different mammalian species following 12-days of disuse



Certain dormant species display no muscle atrophy, despite months of disuse

- *Cyclorana alboguttata*
  - No loss of muscle mass, in vitro force production or swimming performance following 9-months aestivation

- *Ursus americanus*
  - Minimal atrophy following 4-months disuse

- *Cynomys leucurus*
  - Maintenance of slow MHC isoforms

Hudson & Franklin, J Exp Biol, 2002

Hudson & Franklin, J Comp Physiol, 2002

Rourke et al, 2006

Between species differences is related to mass-specific metabolic rate

- Low metabolic rate (normalized to muscle mass) = Less Atrophy
  - $R^2 = 0.76$

- Hypotheses:
  - 1) Lower metabolic rate species are less active… thus disuse is a smaller stimulus
  - 2) Low-metabolic rate species would have lesser reactive oxygen species (ROS) insult

So what about that tiny frog???

- Pre-dormancy & Dormancy: Metabolic rate is drastically reduced
  - Thus, the demands placed on the muscular defense (antioxidants) and repair (*de novo* protein synthesis) systems are alleviated, and the rate of atrophy are reduced accordingly.

Skeletal Muscle Plasticity

- Highly plastic & responsive tissue
- Genotype & phenotype modulated by usage
- Growth (+ or -) depends upon the balance of protein synthesis or degradation

Molecular Biology of Muscle Atrophy

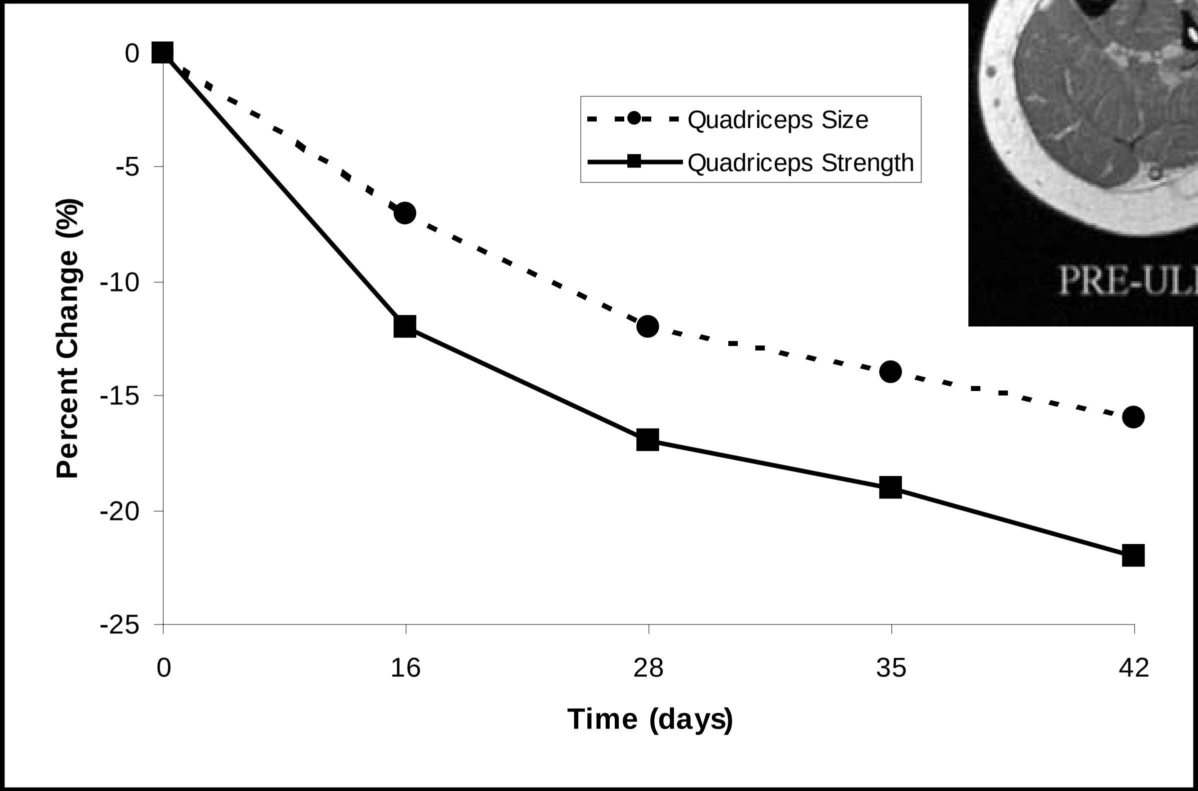
- Three known proteolytic systems involved in muscle protein breakdown:
  - Lysosomal
  - Cytosolic Calcium Dependent
  - ATP-dependent ubiquitin-proteasome pathway*
    - For pathway to occur myofibrillar disassembly is required.

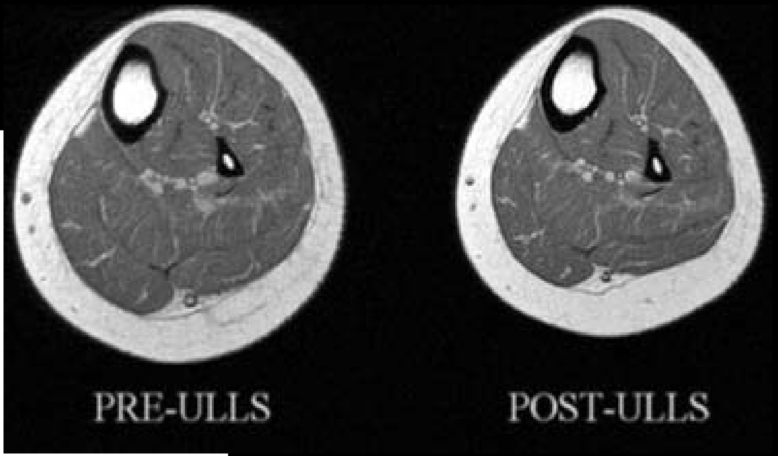
Atrophy Time Line

- Fast
  - Rats: decreased protein synthesis within 6-hours of hindlimb suspension
  - Humans: Increased urinary nitrogen excretion after 5-days of bed rest
  - Decreased synthesis, followed by increased degradation
- Humans:
  - Linear through about 4-months, then slows slightly.
  - Paralysis: 50% reduction after 1-year, appears to be plateau.
  - *Antigravity skeletal muscles most affected*

Skeletal Muscle Atrophy

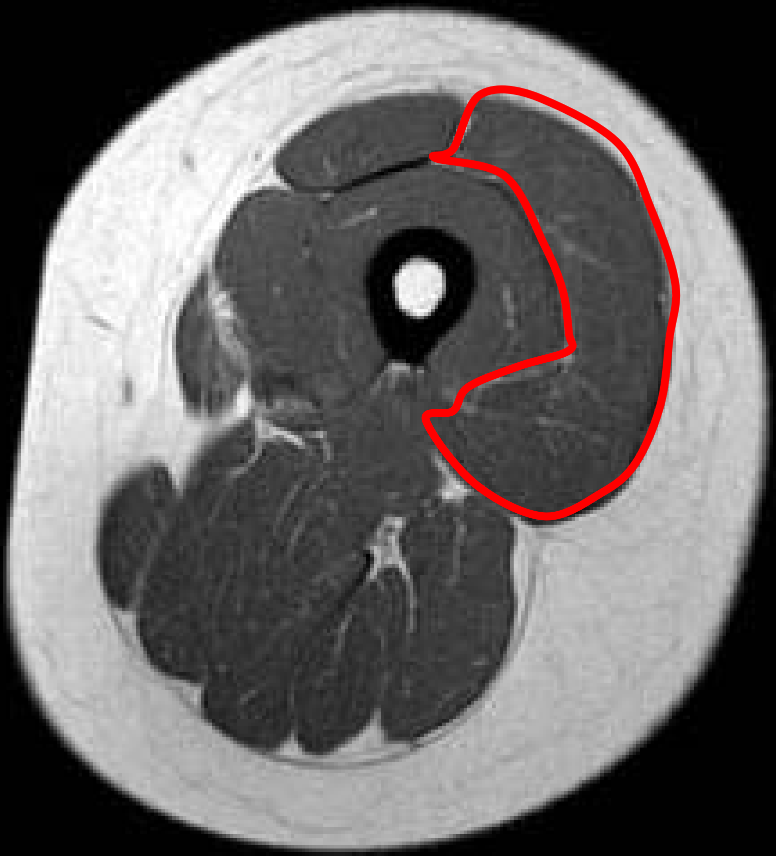
- Humans: ~ 0.4%/day

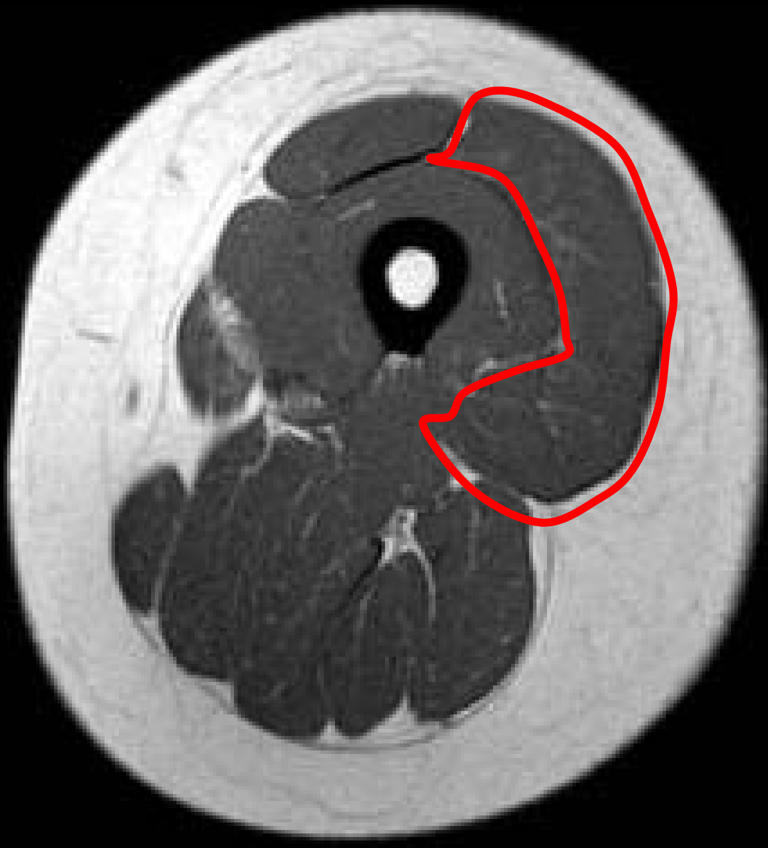




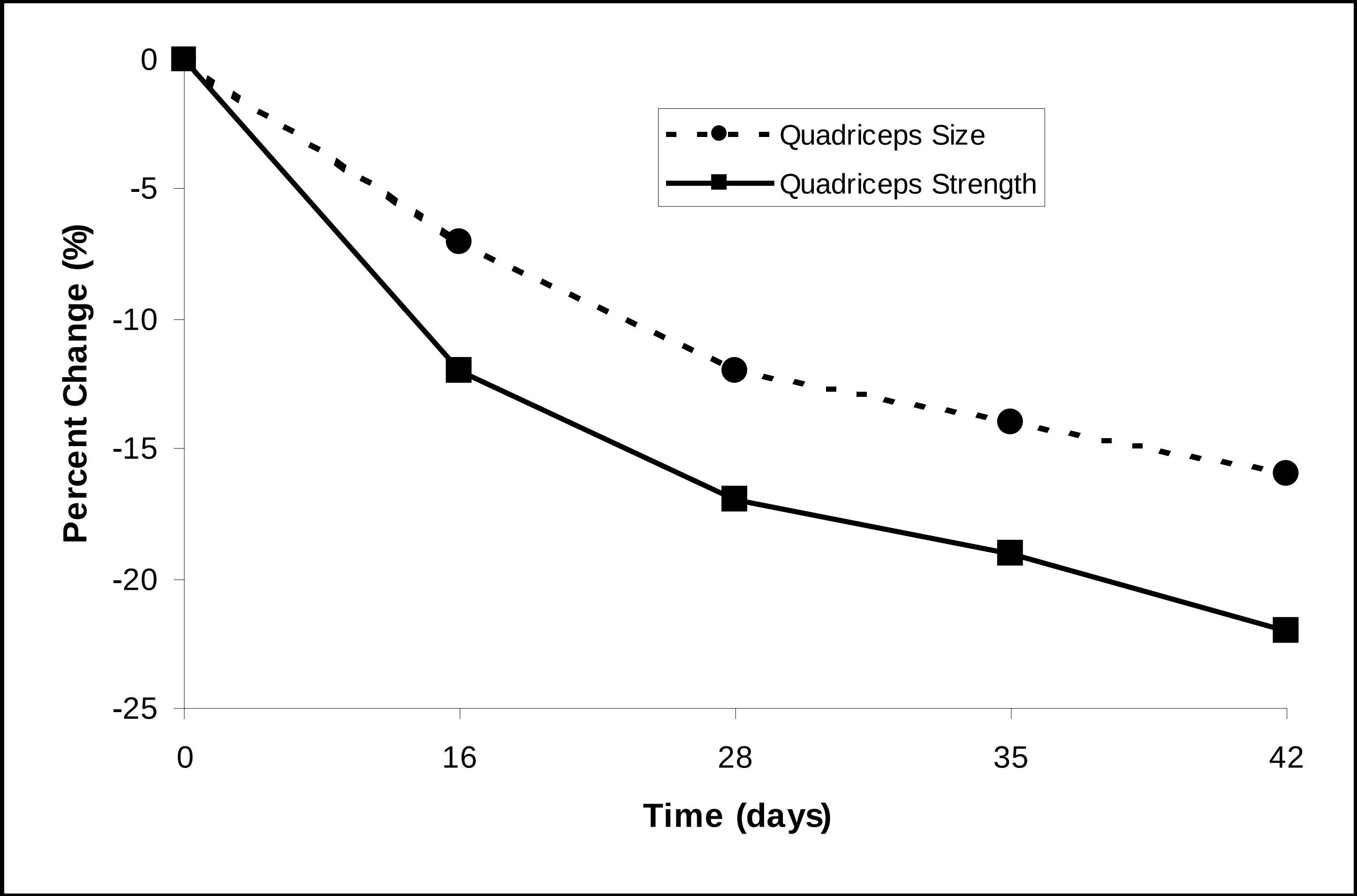
Combined data from: Adams et al., Berg et al., Hather et al., and Ploutz-Snyder et al.

7% decrease in KE CSA





Muscle strength decreases (~0.6-.7%/day)

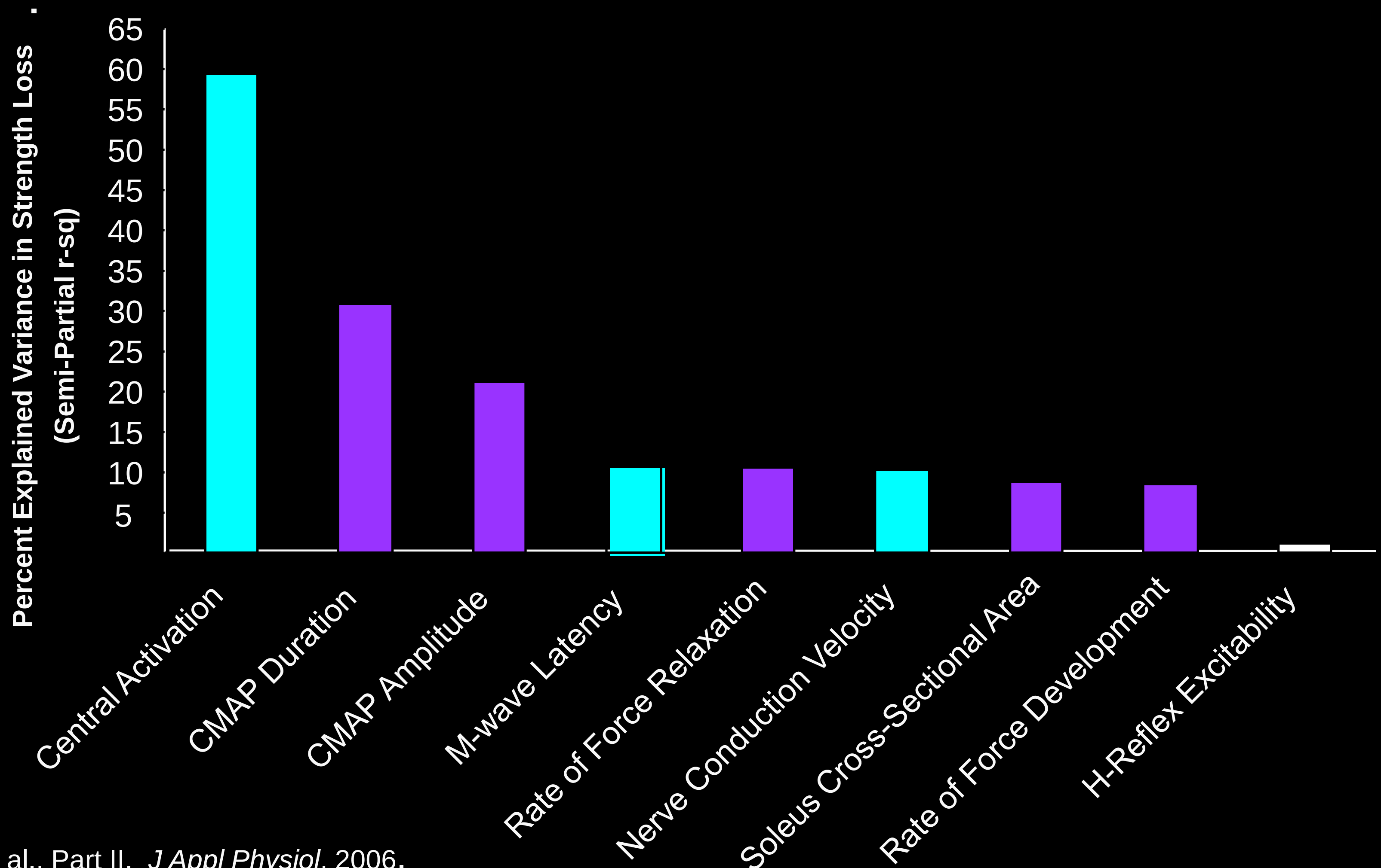


Combined data from: Adams et al., Berg et al., Hather et al., and Ploutz-Snyder et al.

Muscle Mass vs. Strength

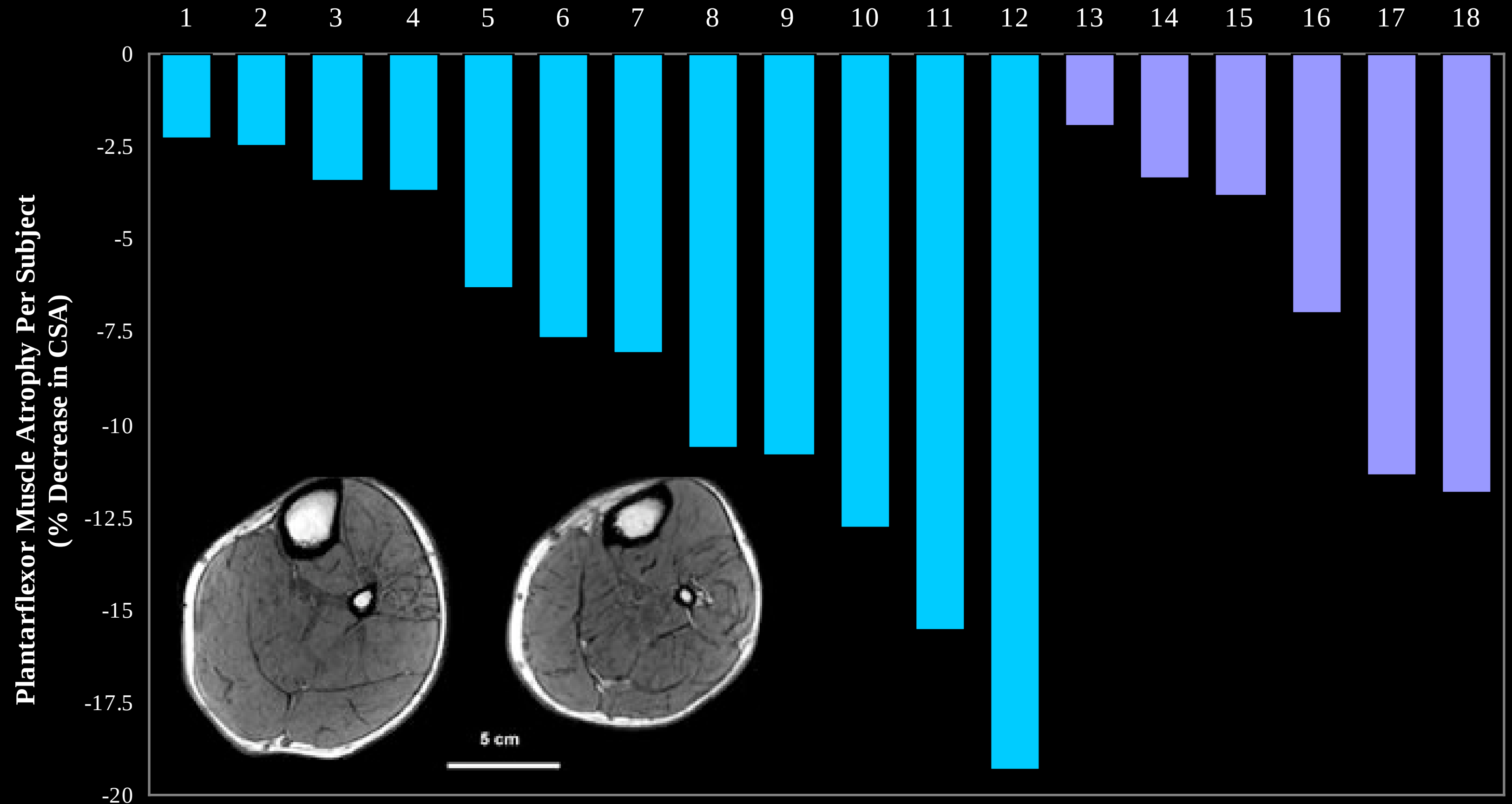
- Muscle mass correlated with strength
  - ~0.7 biceps brachii (MacDougall et al, 1984; Reed et al., 1991)
  - ~0.3 quadriceps femoris (Clark et al., 2006;Reed et al., 1991)
- Need to understand more about how atrophy affects strength & function

Neural vs Muscle Changes



Clark, et al., Part II. *J Appl Physiol*, 2006.

Large Variability In Atrophy With Unloading



Clark,et al., Part I. *J Appl Physiol*, 2006.

Exercise Countermeasures

- >25 bedrest and ULLS studies evaluating exercise as a countermeasure
- Variety of exercises used
  - LBNP treadmill
  - Flywheel
  - Traditional weights

Atrophy Models

- ULLS
- Bedrest
- Spinal cord injury
- Casting
- Spaceflight

ULLS

Sensitivity: 97.7%
Specificity: 96.5%

(Cook et al. *Aviat. Space Env Med* 2005)

Examples of Effective Countermeasures

- Traditional weights
  - 21 day ULLS KE and PF
  - 10 reps at 40%, 2 MVIC, 10 reps at 80%, a final set of as many reps as possible of isotonic exercise at 80%.
  - Every 3 days
  - Total exercise time (including rest) was 6.5 min

Schulze et al., 2002

Countermeasures

- Traditional weights
  - 14 Days Bedrest
  - 5 sets of leg press every other day at 8 RM
  - 1RM & CSA maintained, MVIC not

Bamman et al., 1998

Countermeasures

- Inertial flywheel
- 60 Day Bedrest exercise for squat & calf press every 3 days beginning on day 2
- LBNP treadmill
- Effective to maintain VL size and strength but not SOL (28% vs 8% loss)

(Trappe et al., 2007, 2007, 2008)

Common To Effective Countermeasures

- Use of maximal or nearly maximal contractions!

Countermeasures

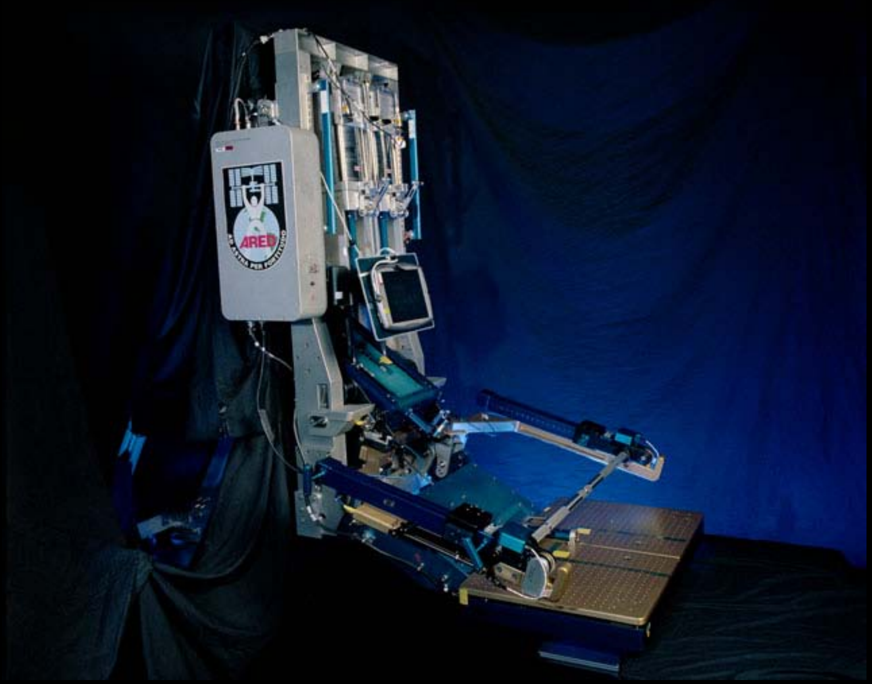
- So…how do you design exercise programs for spaceflight?
- If it works in bedrest does it work with spaceflight?

Spaceflight

- NASA/MIR – elastic expanders
  - 16 crew, ~140 days, 10%, 13% loss in muscle mass in QF and calf
- ISS – IRED
  - 18 crew, ~180 days 11%, 18% loss QF, calf strength

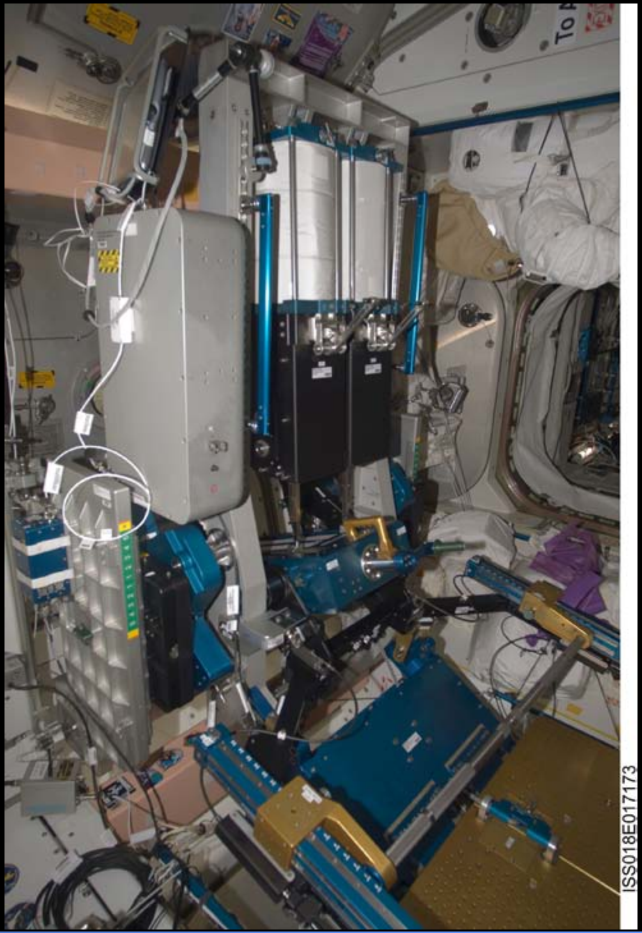
Exercise Equipment on ISS

- Advanced Resistance Exercise Device (ARED)



ARED

- Greater loads – 600 lbs
- 29 different exercises
- Inertial constant load
- Instrumented



ISS Exercise Equipment

- TEVIS
- CEVIS

Conclusions

- Loss of muscle mass is not fully predictive of strength loss
- Despite 2.5 hr/day devoted to exercise, muscle atrophy apparent after long duration spaceflight
- Variety of successful ground based exercise countermeasures exist
- New ISS exercise equipment will allow for greater loading