Prevention of Muscle Atrophy With Exercise Countermeasures
Where we are and where we are going

Lori Ploutz-Snyder, Ph.D
Project Scientist
Exercise Physiology and Countermeasures Project
Lyndon B Johnson Space Center
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]).

<table>
<thead>
<tr>
<th>Animal Models</th>
<th>Human Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immobilization</td>
<td>Immobilization</td>
</tr>
<tr>
<td>Hindlimb Unweighting</td>
<td>Limb Suspension</td>
</tr>
<tr>
<td>Spinal Transection</td>
<td>Spinal Cord Injury</td>
</tr>
<tr>
<td>Pharmacological Blockade</td>
<td>Bedrest</td>
</tr>
<tr>
<td>Spaceflight</td>
<td>Spaceflight</td>
</tr>
<tr>
<td>Nerve Compression</td>
<td>Cancer Cachexia (Atrophy)</td>
</tr>
<tr>
<td>Hibernation</td>
<td>Kwashiorkor (Atrophy)</td>
</tr>
</tbody>
</table>
Comparative Animal Physiology

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

Data excerpted from Hudson and Franklin, J Exp Biol, 2000
Certain dormant species display no muscle atrophy, despite months of disuse

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

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

- **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

Large Variability In Atrophy With Unloading

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