Neuromuscular Adaptations to Reduced Use

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Disuse Models

- Outcomes are dependent on specifics of disuse model and species used.

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)

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.

Human Muscle Unloaded With ULLS

Sensitivity: 97.7%

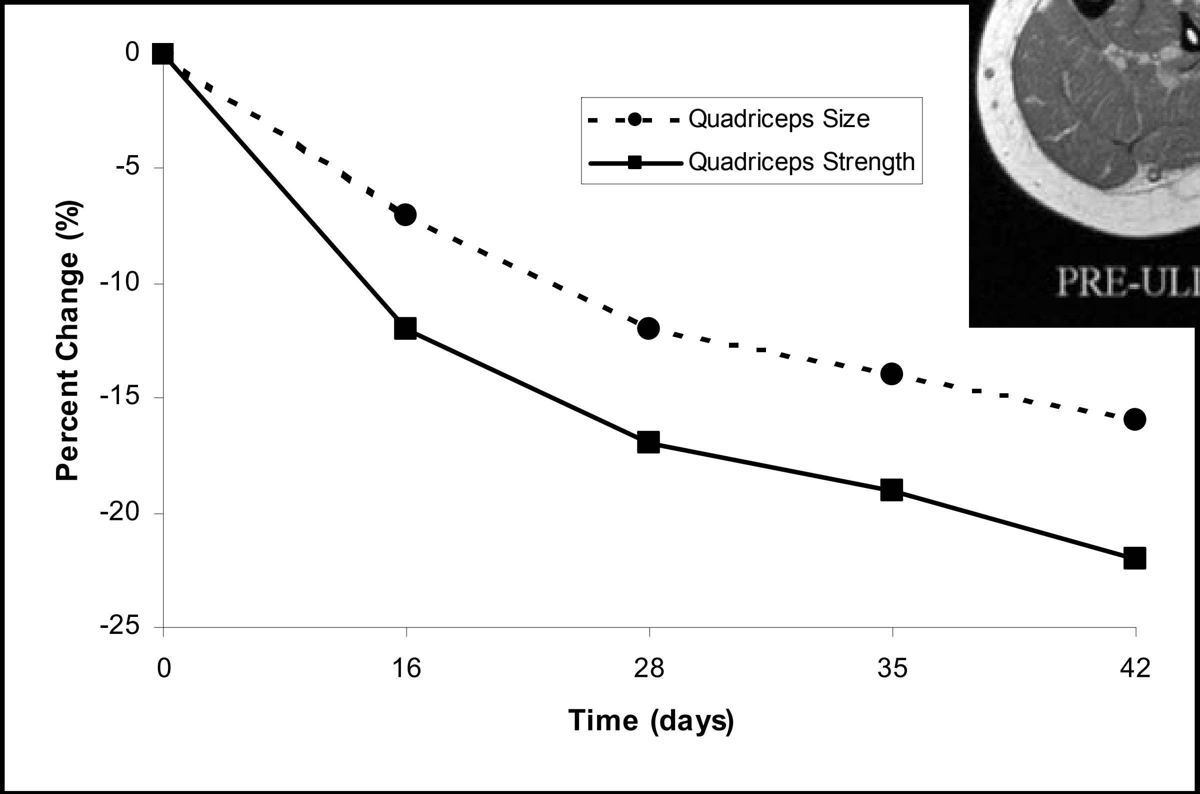
Specificity: 96.5%

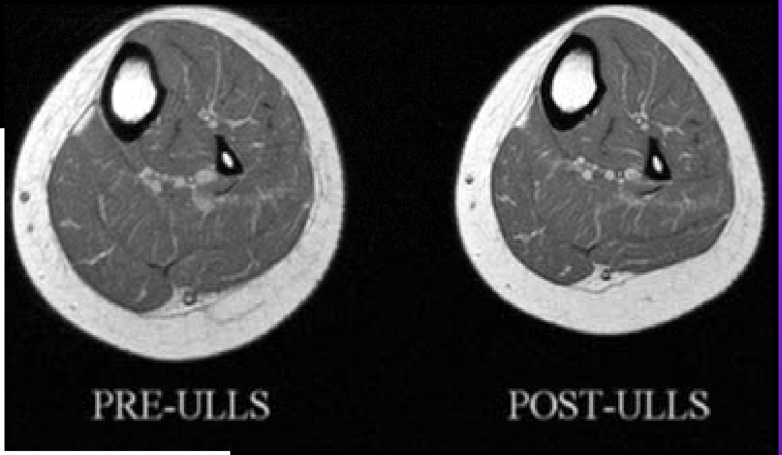
(Cook et al. *Aviat. Space Env Med* 2005)

3 sets of ULLS studies

- Early 1990's - more muscle required to lift same absolute load following 30 day ULLS
- 2005-06 - Neural vs. muscle morphologic changes with ULLS
- 2006-08 - Low load exercise countermeasure

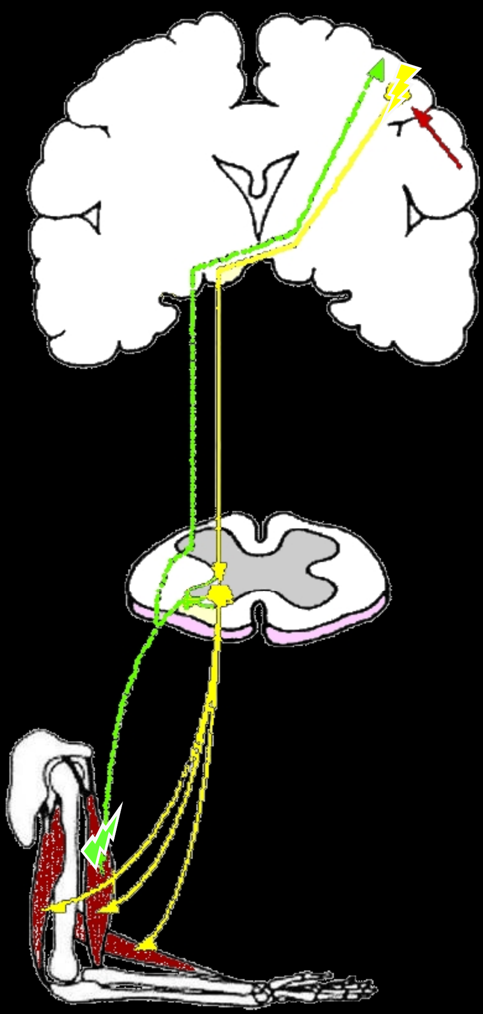
Muscle Strength Decreases More Than Mass

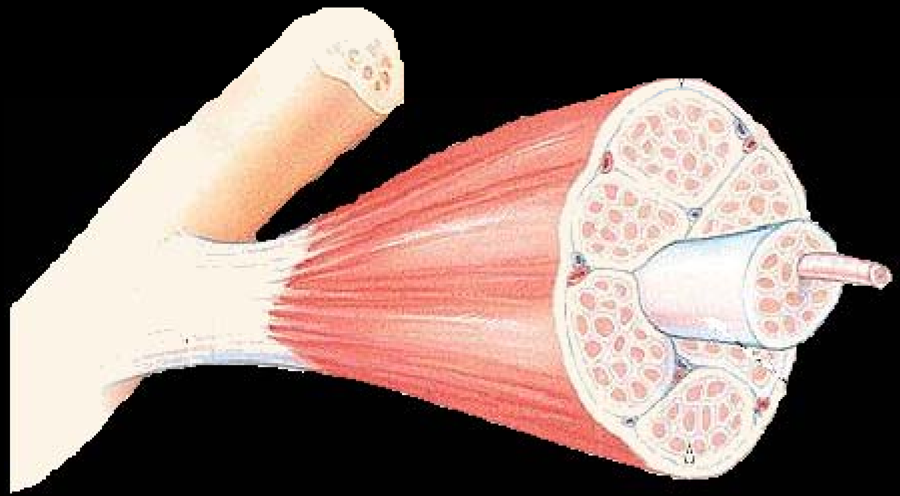




Combined data from: Adams et al., Berg et al., Hather et al., and Ploutz-Snyder et al.

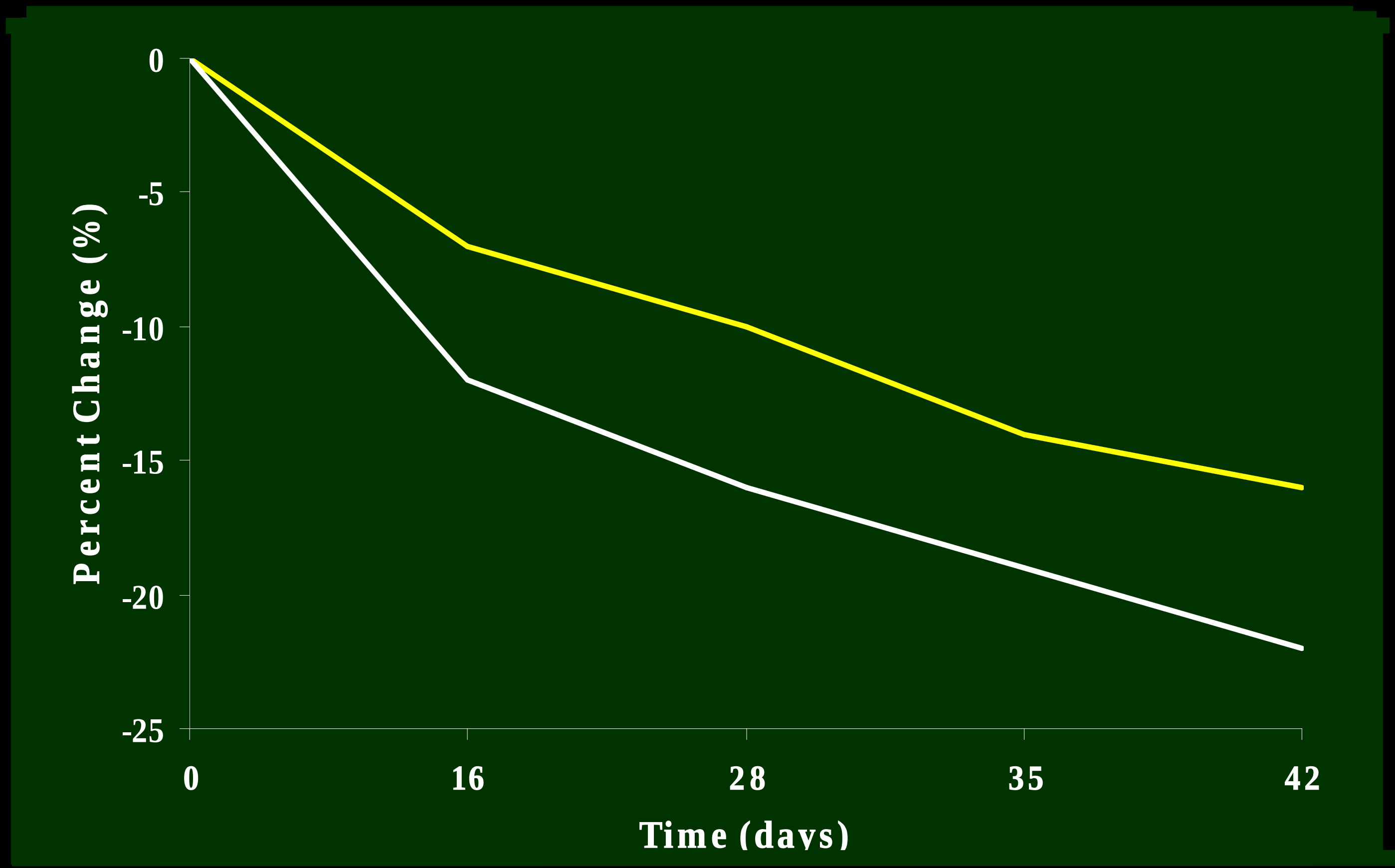
Neural & Contractile Control of Force



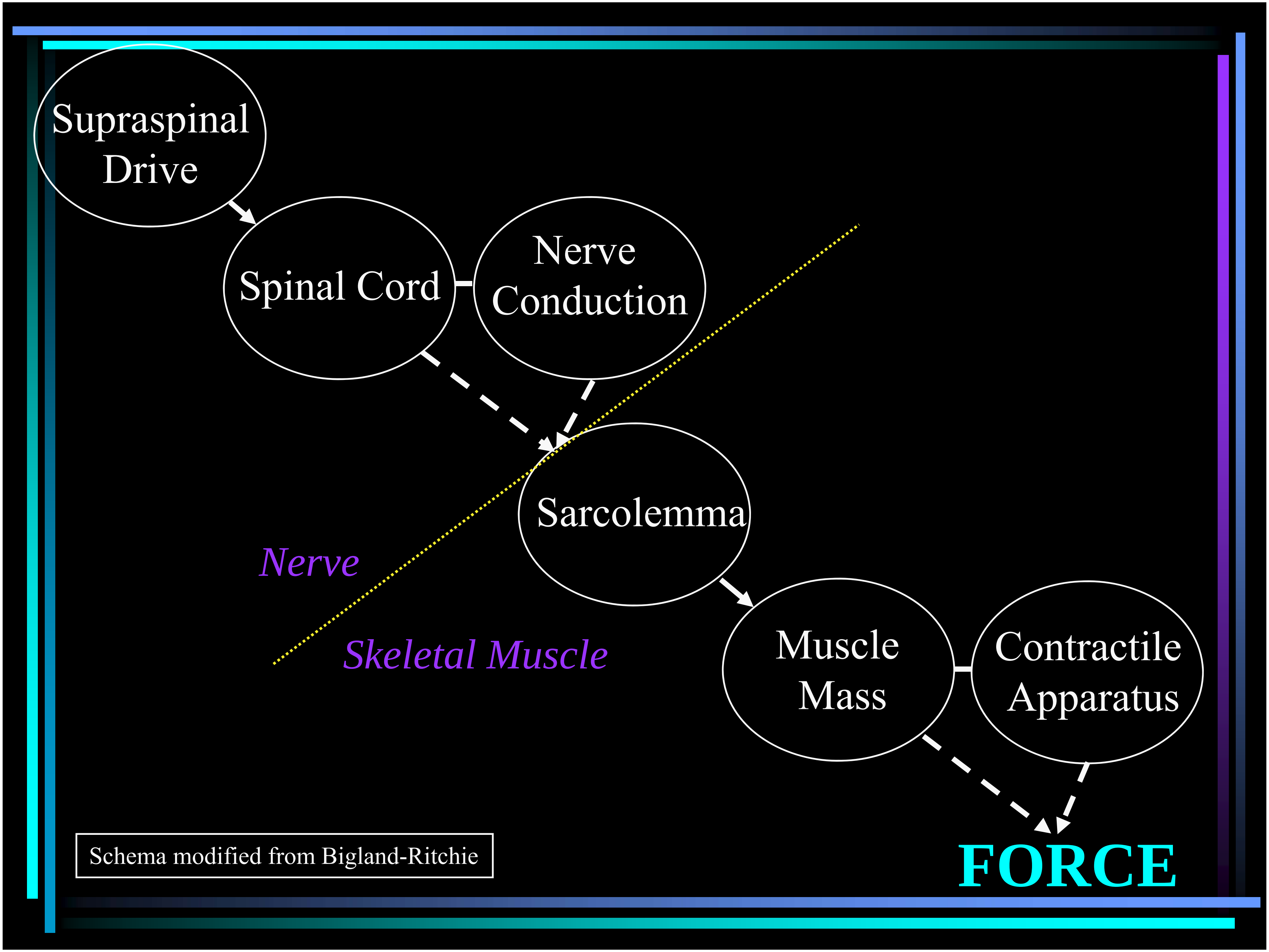


Adapted from Duchateau and Enoka,
Am J Phys Med Rehabil, 2002

Muscle Strength Decreases More Than Muscle Size



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


Supraspinal Drive
Spinal Cord
Nerve Conduction
Sarcolemma
Nerve
Skeletal Muscle
Muscle Mass
Contractile Apparatus
FORCE
Schema modified from Bigland-Ritchie

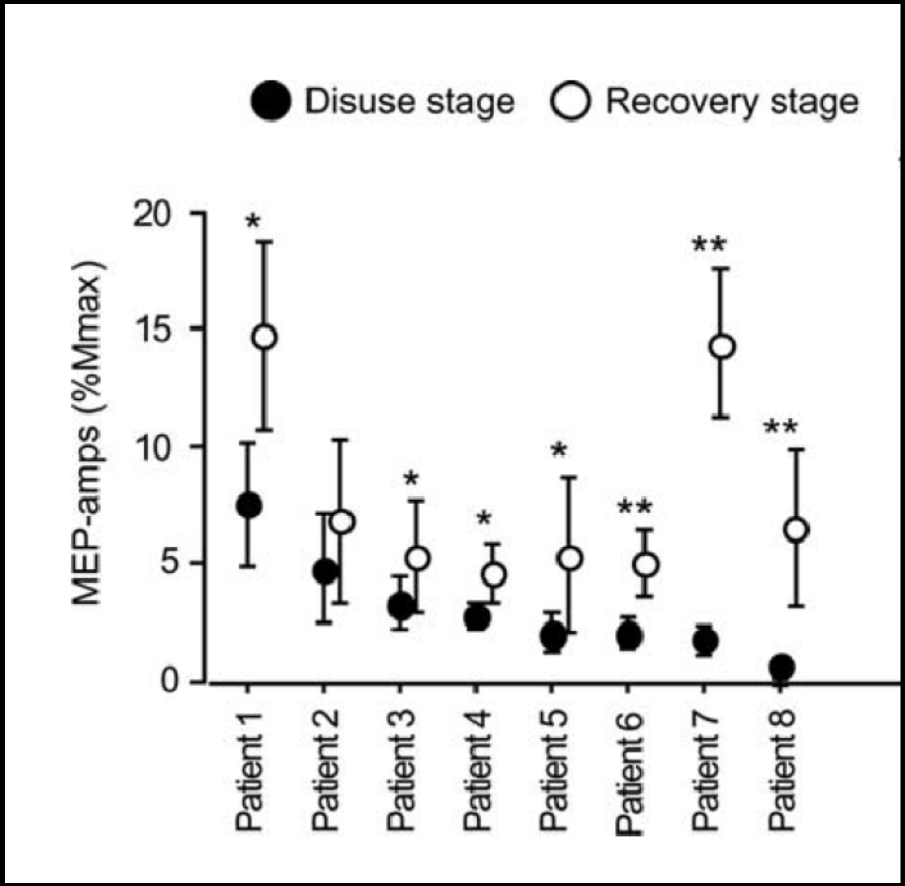
Neural vs. Morphologic Factors

- What neural factors are altered?
- What muscle factors are altered?
- What is the relative contribution of each?

Pertubations

- Neural
  - Mental imagery
- Muscular
  - Ischemia

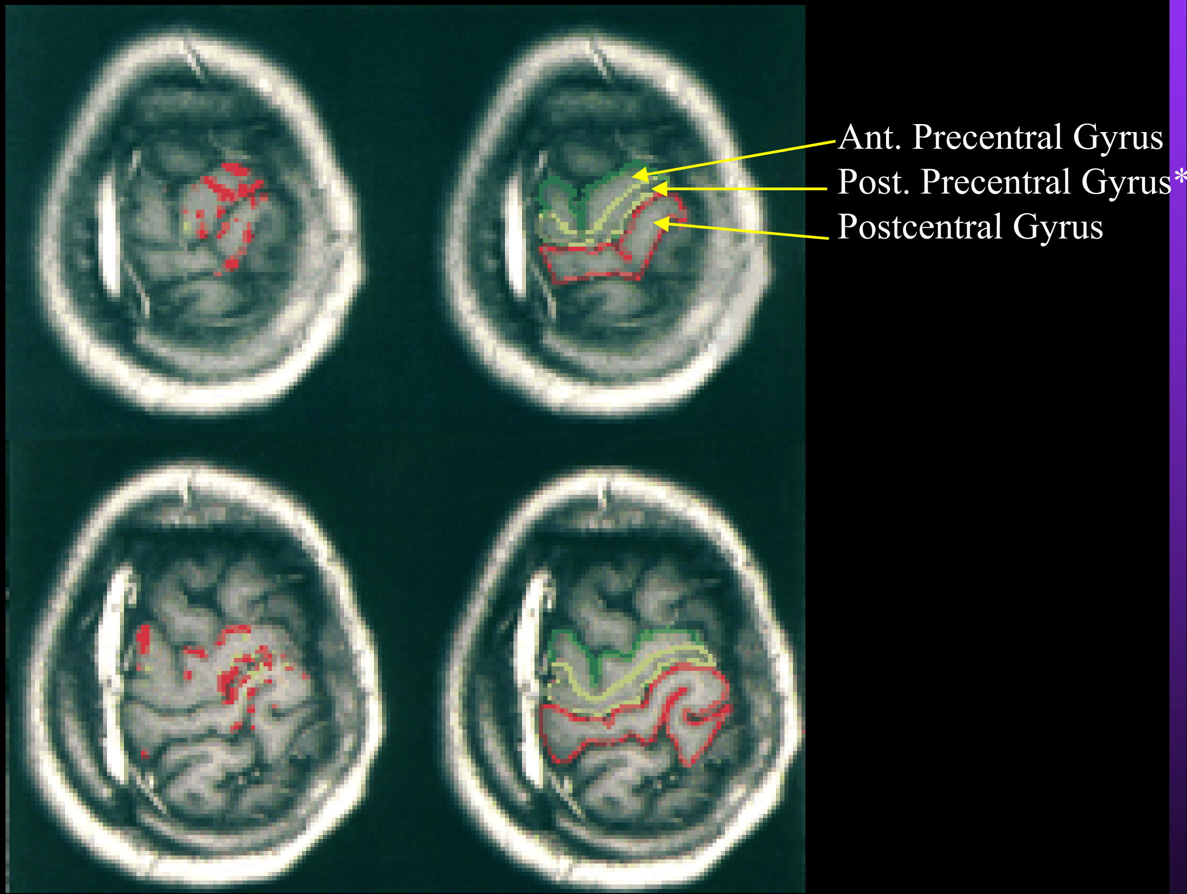
Immobilization Decreases Cortical Excitability



Kaneko, Murakami et al., *Clin Neurophys*, 2003

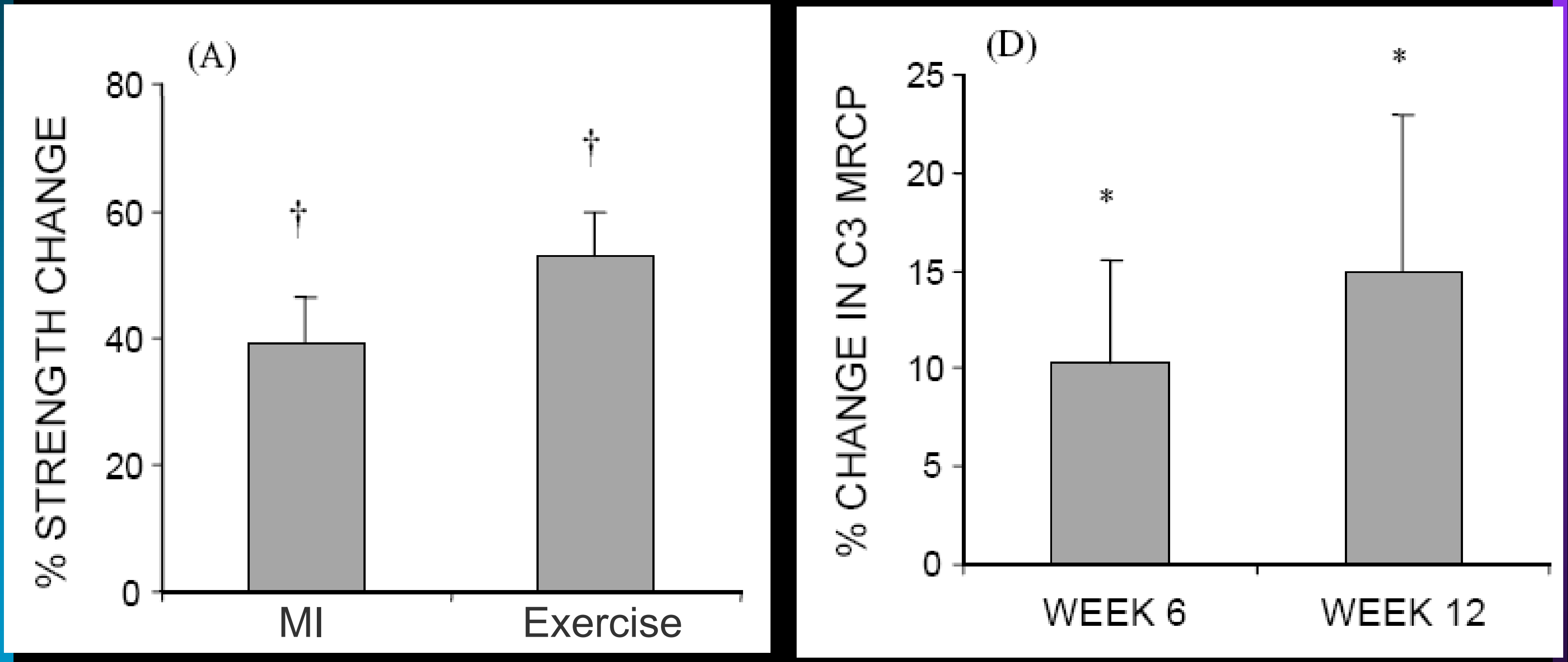
Motor Imagery Activates Same Neural Structures as Motor Performance

Red Pixels: Significant fMRI signal increases during both actual MP and MI



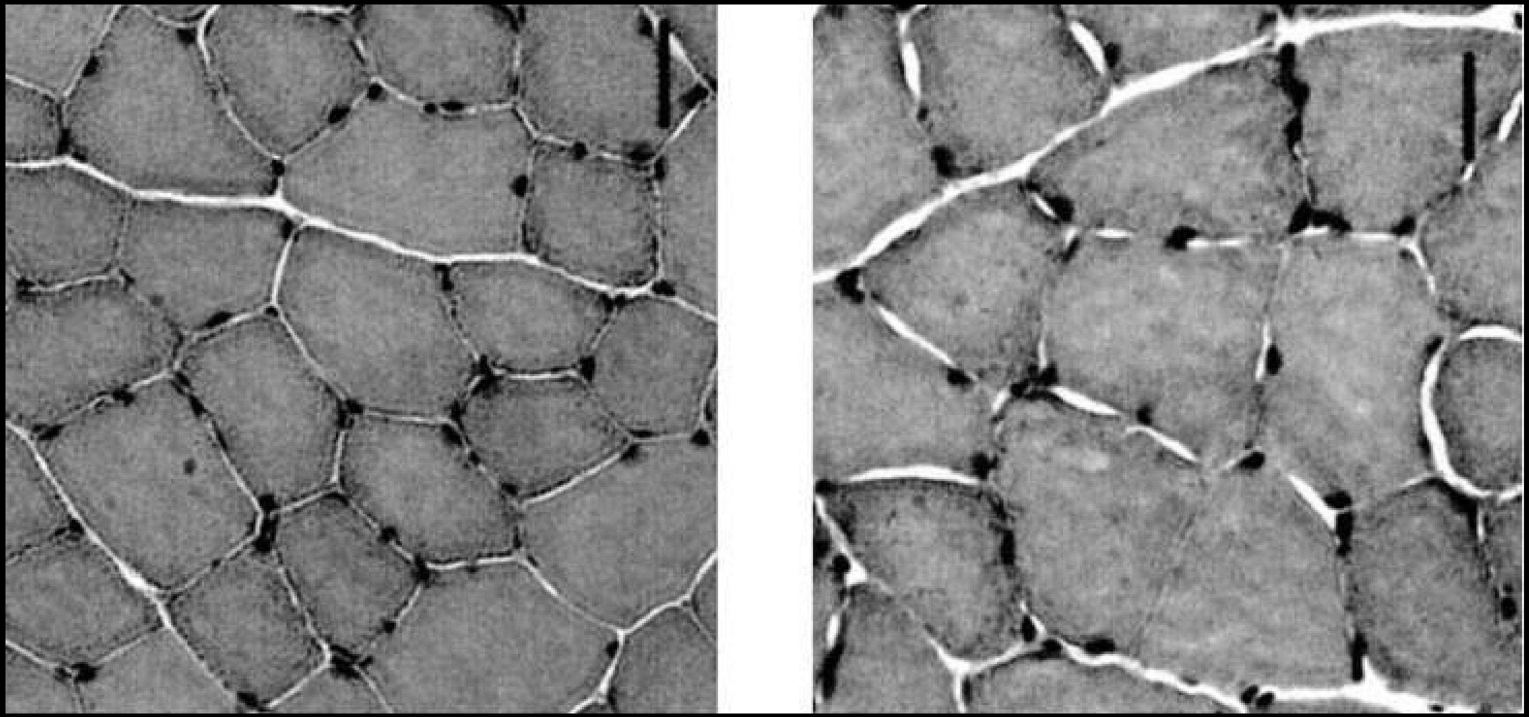
Porro, Francescato et al., *J. Neurosci*, 1996

Motor Imagery Training
↑ Strength & EEG Activity



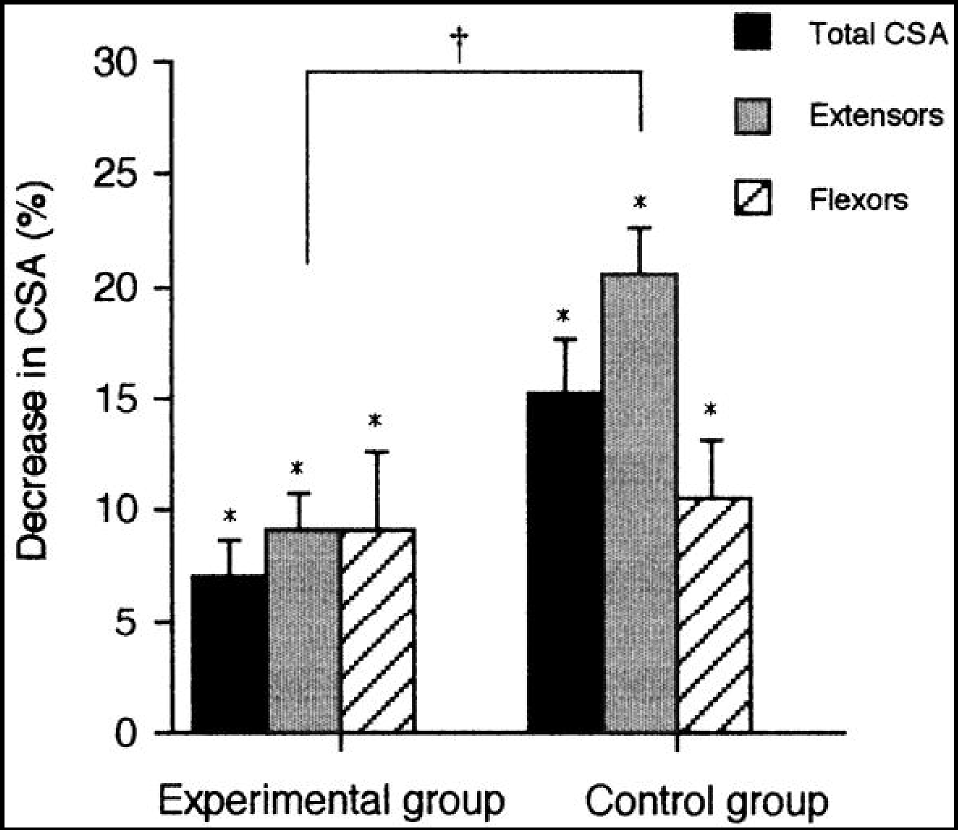
Ranganathan, Siemionow et al., *Neuropysch.*, 2004

Chronic Ischemia in Rats:
↑ HSP-72, ↓ Myostatin & ↑ Myofiber CSA



Kawada and Ishii, *Med Sci Sports Exerc*, 2005

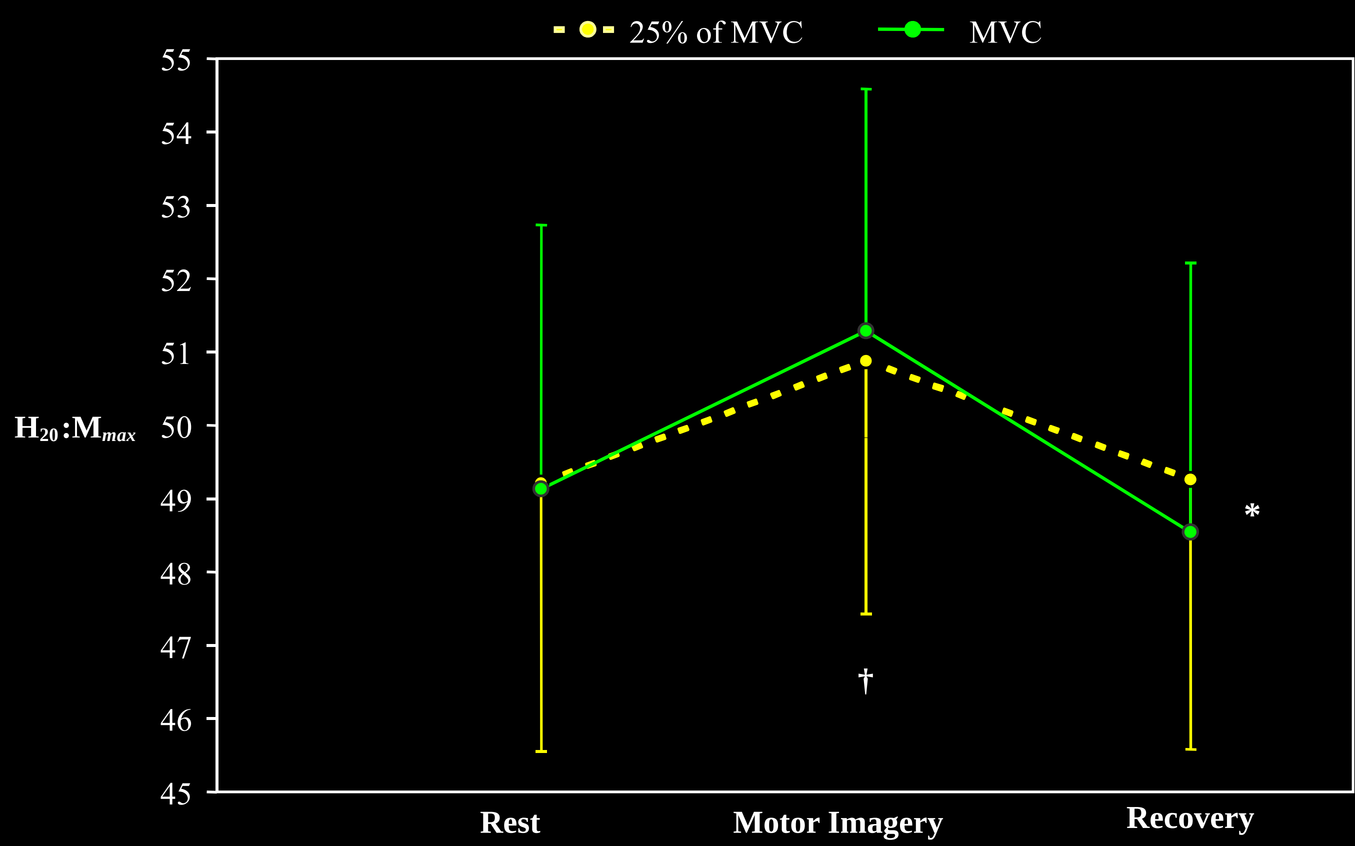
50% Atrophy Attenuation Following Surgically-Induced Bed Rest



Takarada, Takazawa et al., *Med Sci Sports Exerc*, 2000

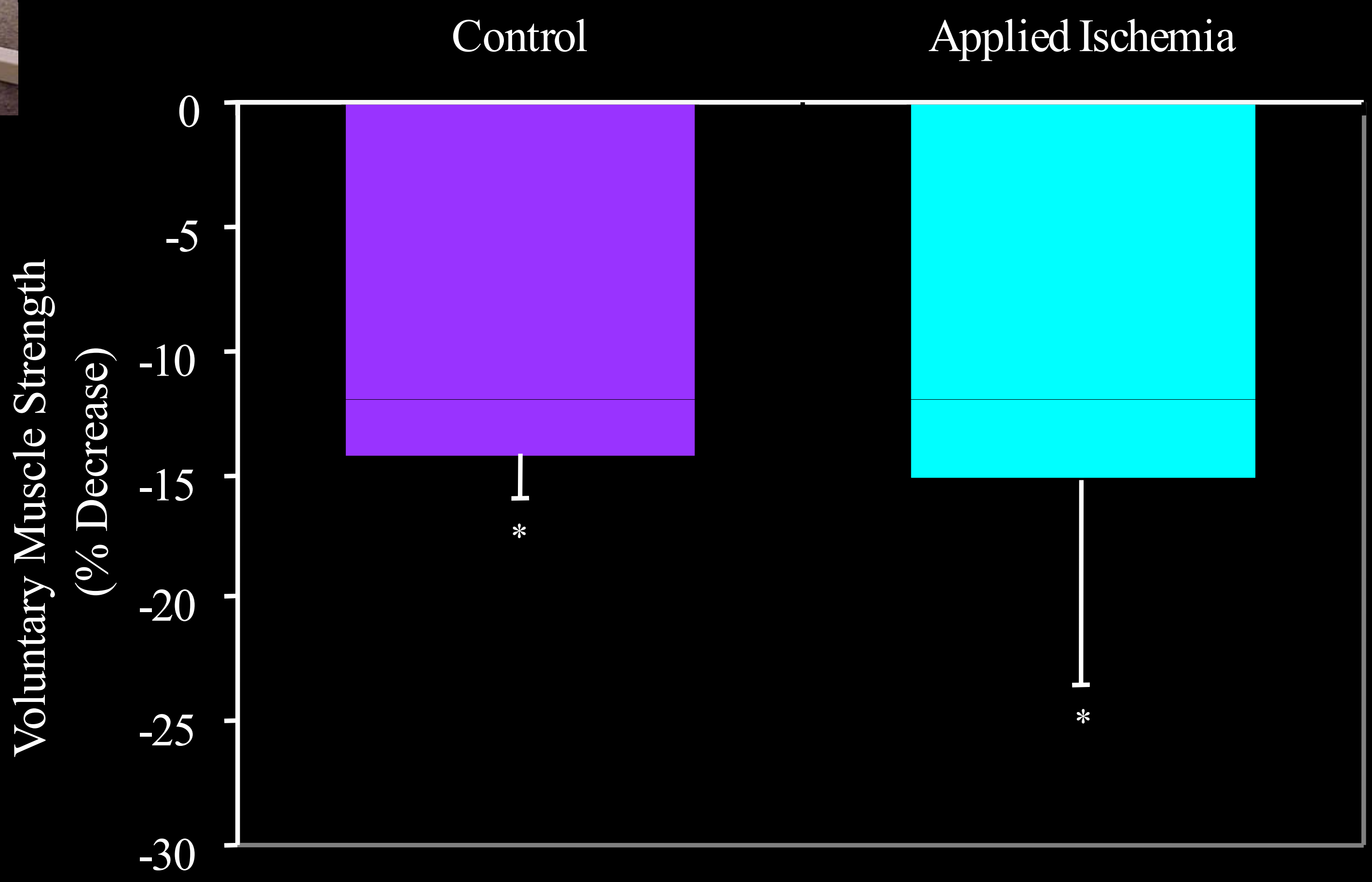
- 18 subjects
  - 6 men & 12 women
  - 18-29 years
    - ULLS + No Intervention (n=6)
    - ULLS + Ischemia (n=6)
      - 3x/wk
    - ULLS + Motor Imagery (n=6)
      - 4x/wk

Spinal Excitability ↑ w/ Motor Imagery



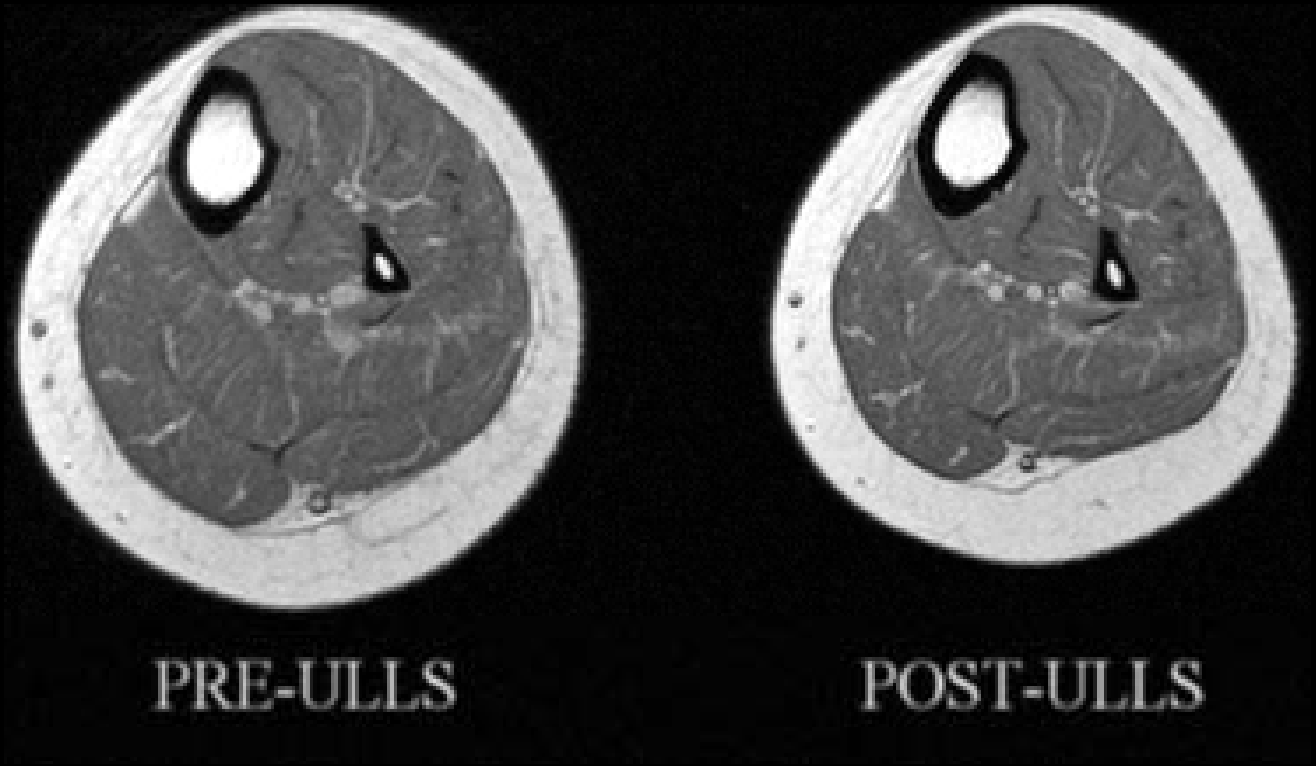
Cowley, et al., *Med Sci Sports Exerc*, Abstract, 2006

Muscle Strength



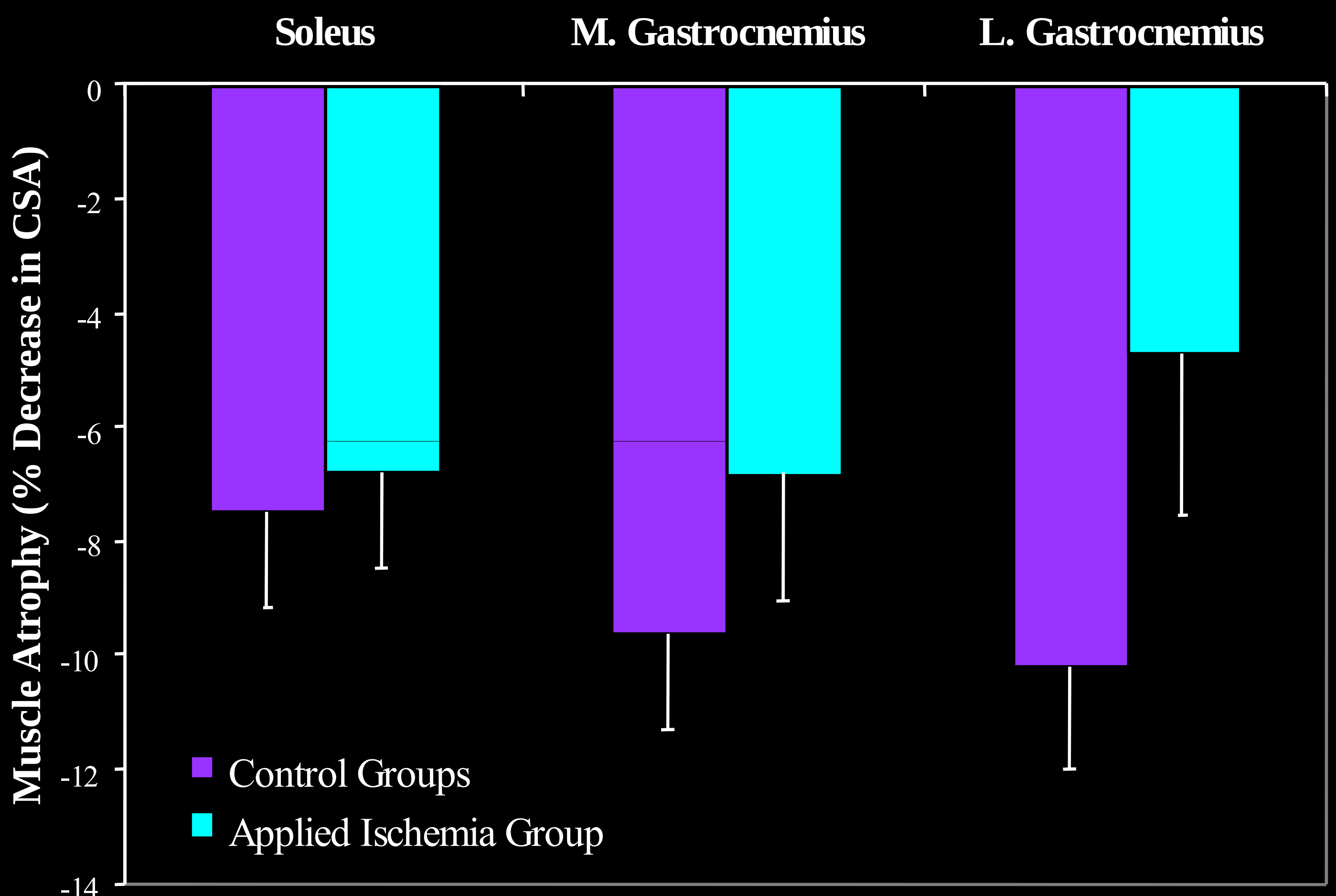
Clark, Fernhall et al., Part I. *J Appl Physiol*, 2006.

Muscle Atrophy



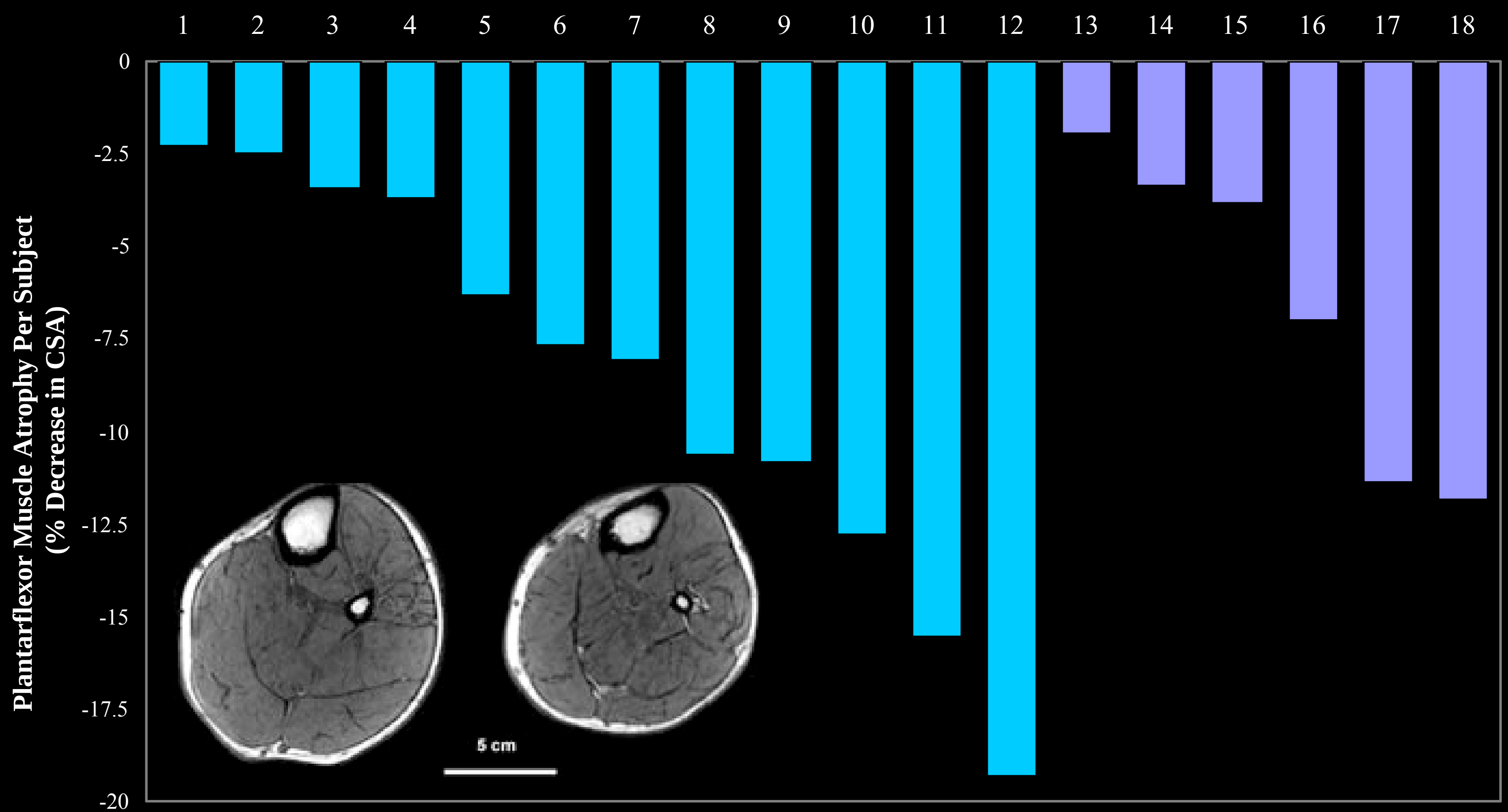
Magnetic Resonance Imaging

Muscle Atrophy



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

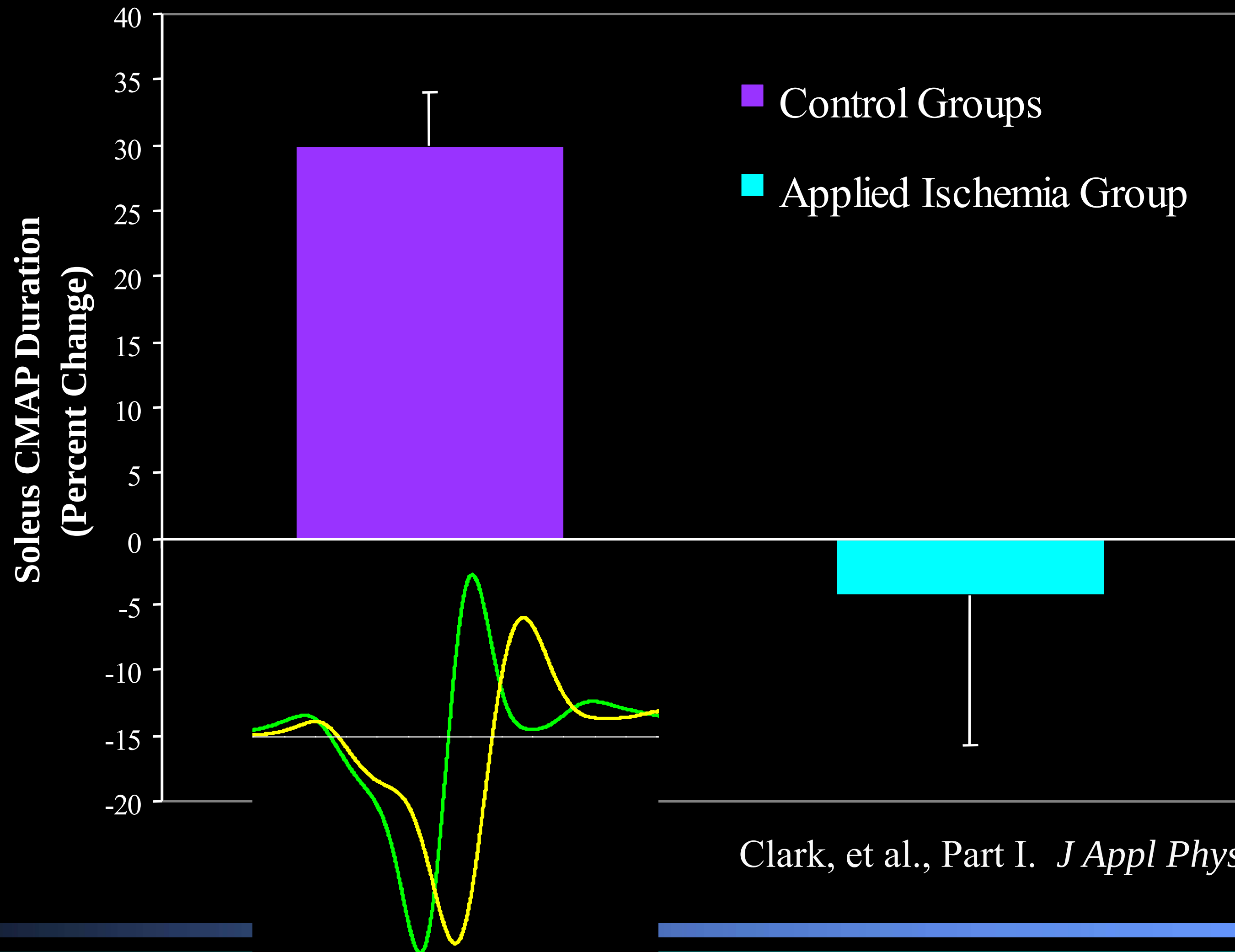
Large Variability In Atrophy With Unloading



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

Muscle Action Potential Duration

Slowed Muscle Fiber Conduction Velocity (Keenan, Farina et al., *Exp Brain Research*, 2006)

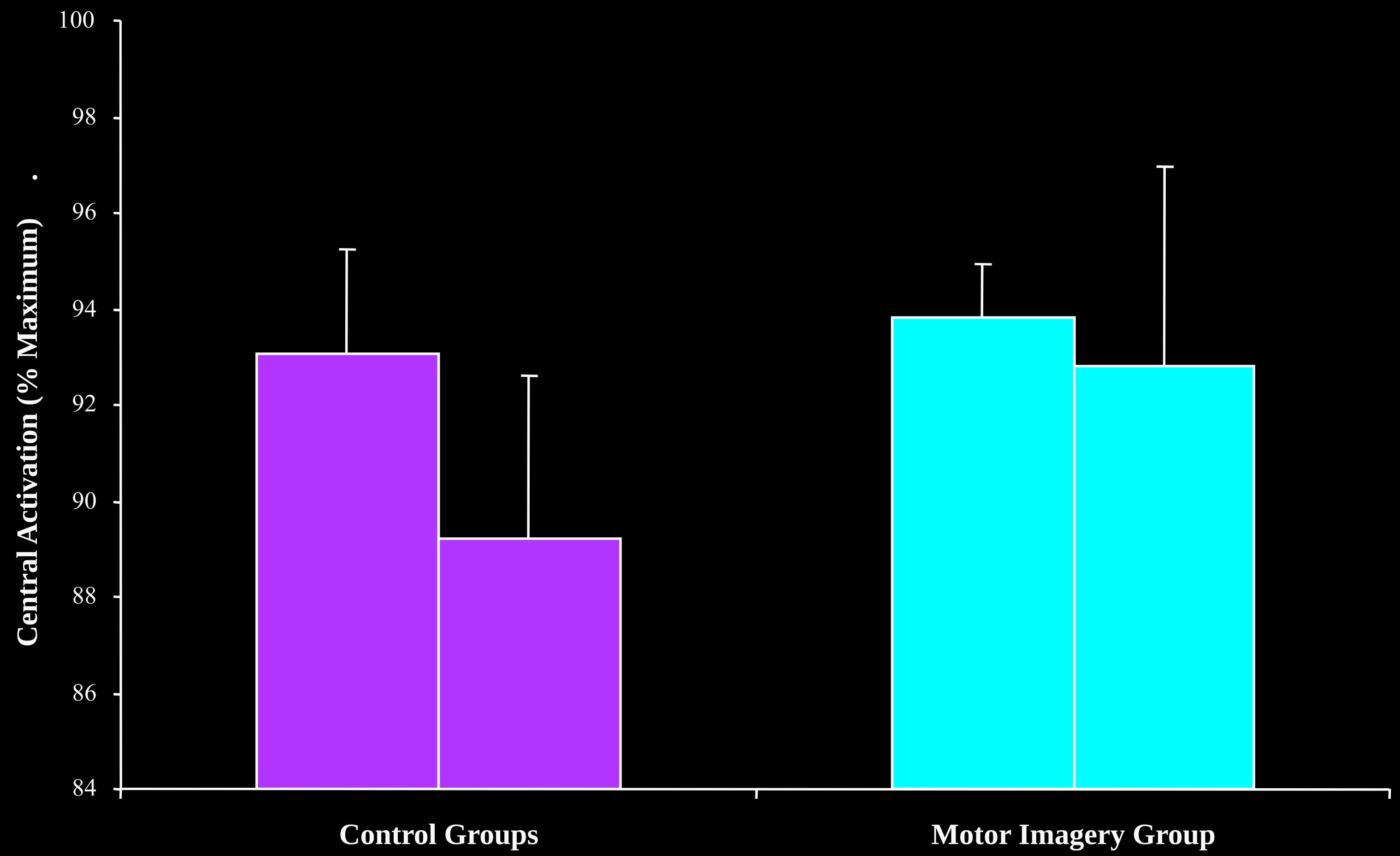


Clark, et al., Part I. *J Appl Physiol*, 2006.

Physiologic Interpretation

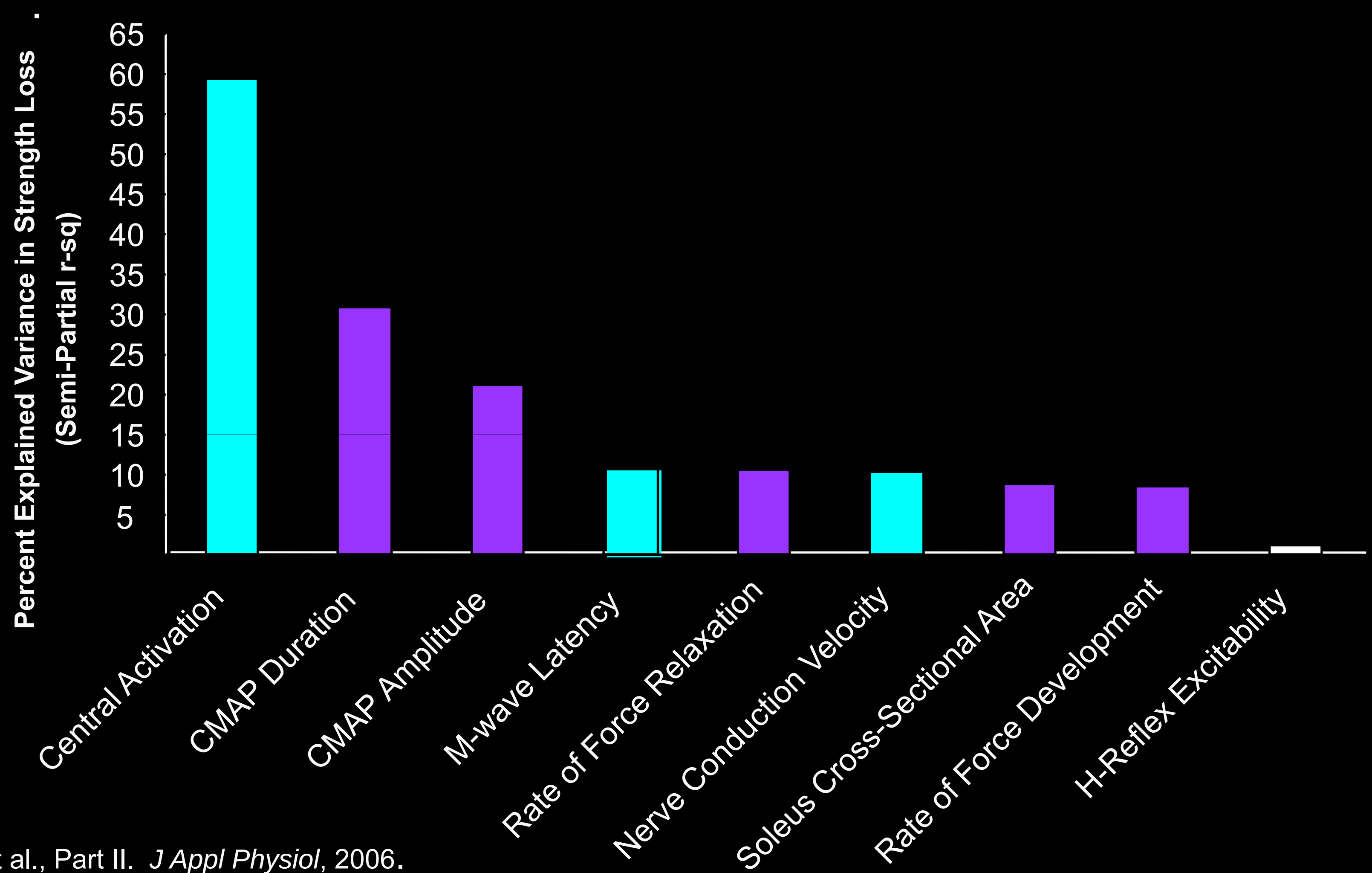
- Maintenance of potentiated force, despite ↓ doublet force
  - Common Interpretation: Phosphorylation of Myosin Light Chains increasing Ca^{2+} sensitivity? (MacIntosh, *News Physiol Sci*, 2003).
  - Shift towards Type II muscle fiber type composition? (Sweeney, Bowman et al. *Am J Physiol*, 1993)

Central Activation



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

Neural vs Muscle Changes



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

Limitations

- Sample Size
  - 2nd largest to date, but still relatively small
- Unaccounted for variables
  - Skeletal Muscle Pennation Angle
  - Skeletal Muscle Fiber Type
  - Cortical Excitability
  - Motor Unit Discharge Rate

Exercise Countermeasure

- Ischemia alone maintained only CMAP duration
- Ischemia + low load exercise
- Japanese kaatsu
- Potential for rehab or situations where heavy loading is undesirable.

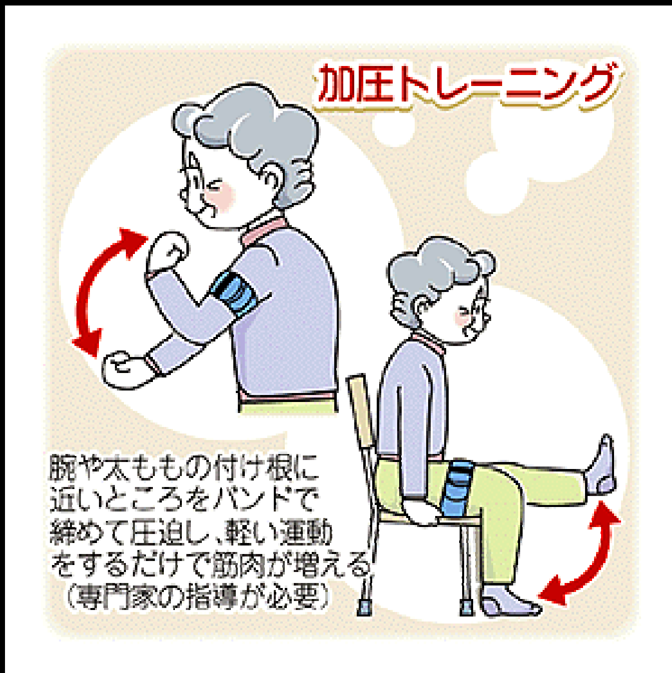
Countermeasures to unloading

- High-load resistance training has maintained muscle mass and strength during unloading.
  (Ferrando et al. 1997, Akima et al. 2000, Schackelford et al. 2004, Schulze et al. 2002)

- Low-load resistance training with a blood flow restriction (LL_{BFR}) has been shown to increase muscle mass and strength.
  (Shinohara et al. 1998, Takarada et al. 2000, Burgomaster et al. 2003)

Recent Interest in Tourniquet Training

- Kaatsu - Japanese
  - Japan Kaatsu Training Society
  - *International Journal of Kaatsu Training* - their own journal, unclear review process.
  - Inventor/Owner=Yoshiaki Sato, Department of Ischemic Circulatory Physiology
  - Body building websites
    - Testosterone Nation
    - Giant
    - Cutting Edge Muscle


加圧トレーニング
腕や太ももの付け根に
近いところをバンドで
締めて圧迫し、軽い運動
をするだけで筋肉が増える
（専門家の指導が必要）

Unbelievable or Amazing?

Author	Year	Main Finding
Moritani	1992	Increase motor unit spike amplitude and frequency
Yoshida	1997	Limited ATP synthesis
Shinohara	1998	26% increase in KE strength after 4 weeks
Takarada	2000	GH increased 290x
Takarada	2000	20% increase in CSA and 18% increase in strength in 16 weeks
Takarada	2002	14% increase in CSA, 15% increase in strength in 8 weeks
Takarada	2004	16% increase in CSA and 9% increase in strength in 8 weeks
Abe*	2005	9% increase in CSA in 2 weeks
Takano*	2005	GH increase 80x
Abe*	2005	5% increase in CSA and 10% increase in strength in 8 days
Ishii*	2005	3% increase in CSA after 8 weeks of circuit training
Sato*	2005	GH increase 25x
Tanimoto*	2005	GH increase 17x
Yasuda*	2005	8% increase in CSA and 14% increase in strength in 2 weeks
Abe*	2005	3% increase in CSA and 17% increase in strength in 7 days
Abe*	2005	8% increase in CSA and 6% increase in strength in 3 weeks

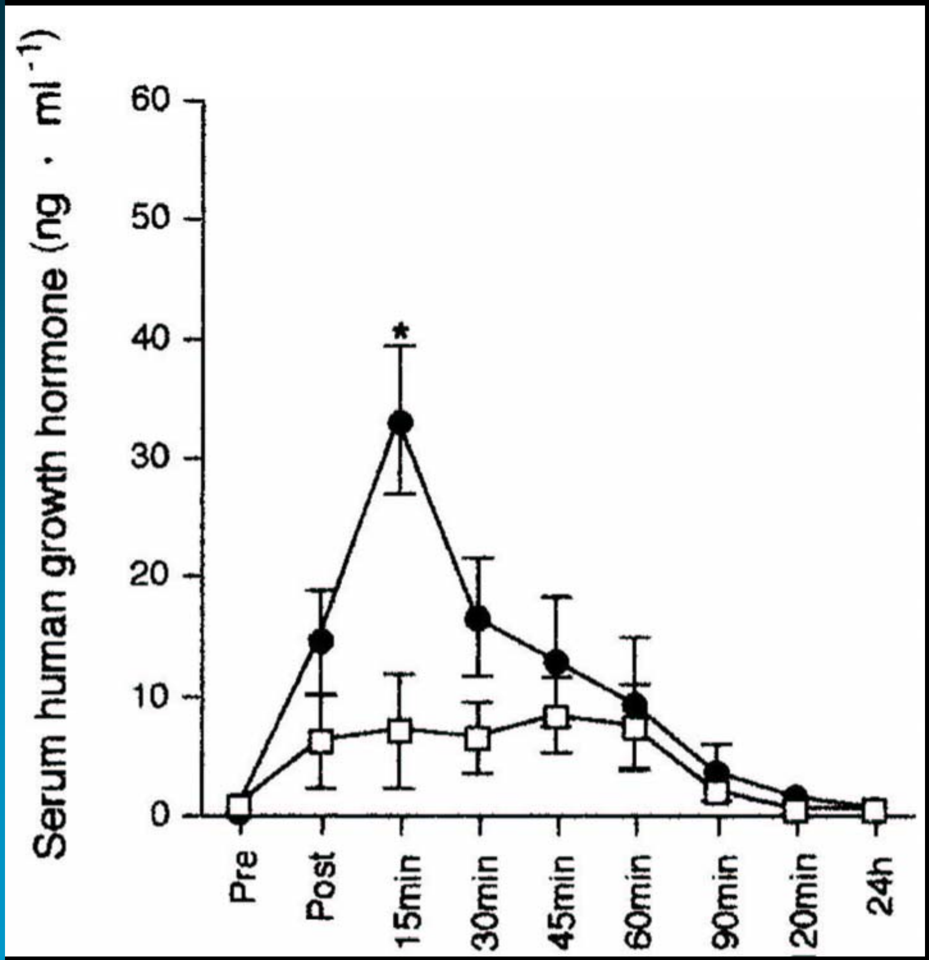
Tissue Blood Flow at Rest and During Dynamic Exercise

	REST		MAX EXERCISE	
Tissue	Blood flow (ml/min^{-1})	Flow rate ($ml/100g^{-1}/min^{-1}$)	Blood flow (ml/min^{-1})	Flow rate ($ml/100g^{-1}/min^{-1}$)
CNS	825	55	1125	75
Heart	260	87	900	300
Muscle	**1200**	**25**	**18000**	**60-100**
Viscera	2400	65	500	14
Skin	500	24	500	24

Brooks, Fahey and Baldwin 2005

Low Load With Blood Flow Restriction LL_{BFR}

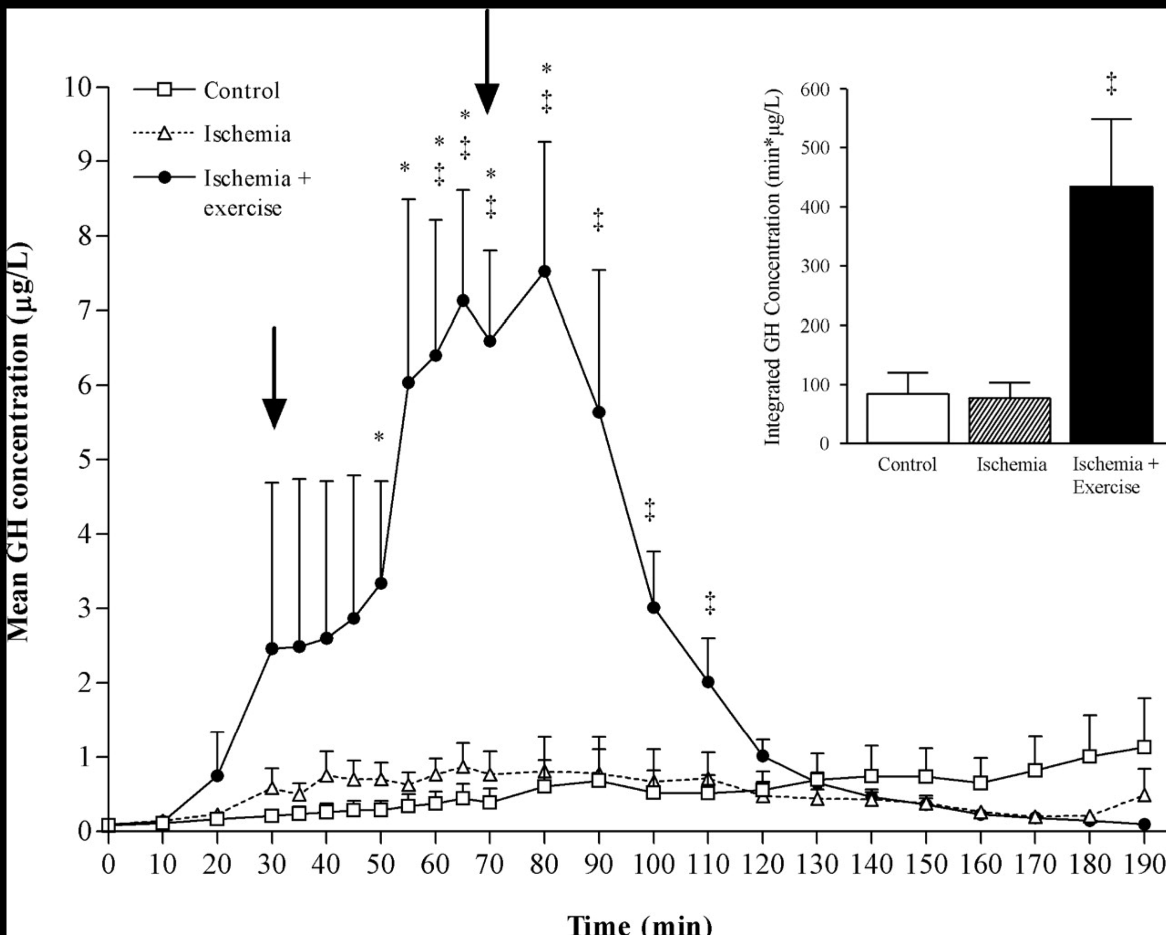
Growth Hormone Response to Acute LL_{BFR} Exercise



GH increased
290 times baseline!!

Takarada et al. *J Appl Physiol*, 2000

Growth Hormone Response to Acute LL_{BFR} Exercise



~8-fold increase but not 290!

Pierce et al. *J. Appl. Physiol.* 2006

Possible mechanisms of hypertrophy via LL_{BFR}

- Greater reliance on anaerobic metabolism (Shinohara et al. *Eur J Appl Physiol,* 1998)
- Increased angiogenesis during hypoxia (Suzuki et al. *Eur J Appl Physiol,* 2000)
- Altered motor unit recruitment patterns (Shinohara et al. *Eur J Appl Physiol,* 1998, Pierce et al. *J Appl Physiol*. 2006)
- Increased levels of growth hormone (Takarada et al. *J Appl Physiol*, 2000, Pierce et al. *J Appl Physiol,* 2006)
- Mechanical signaling of muscle cell

Methods

16 subjects aged 18-50 yrs

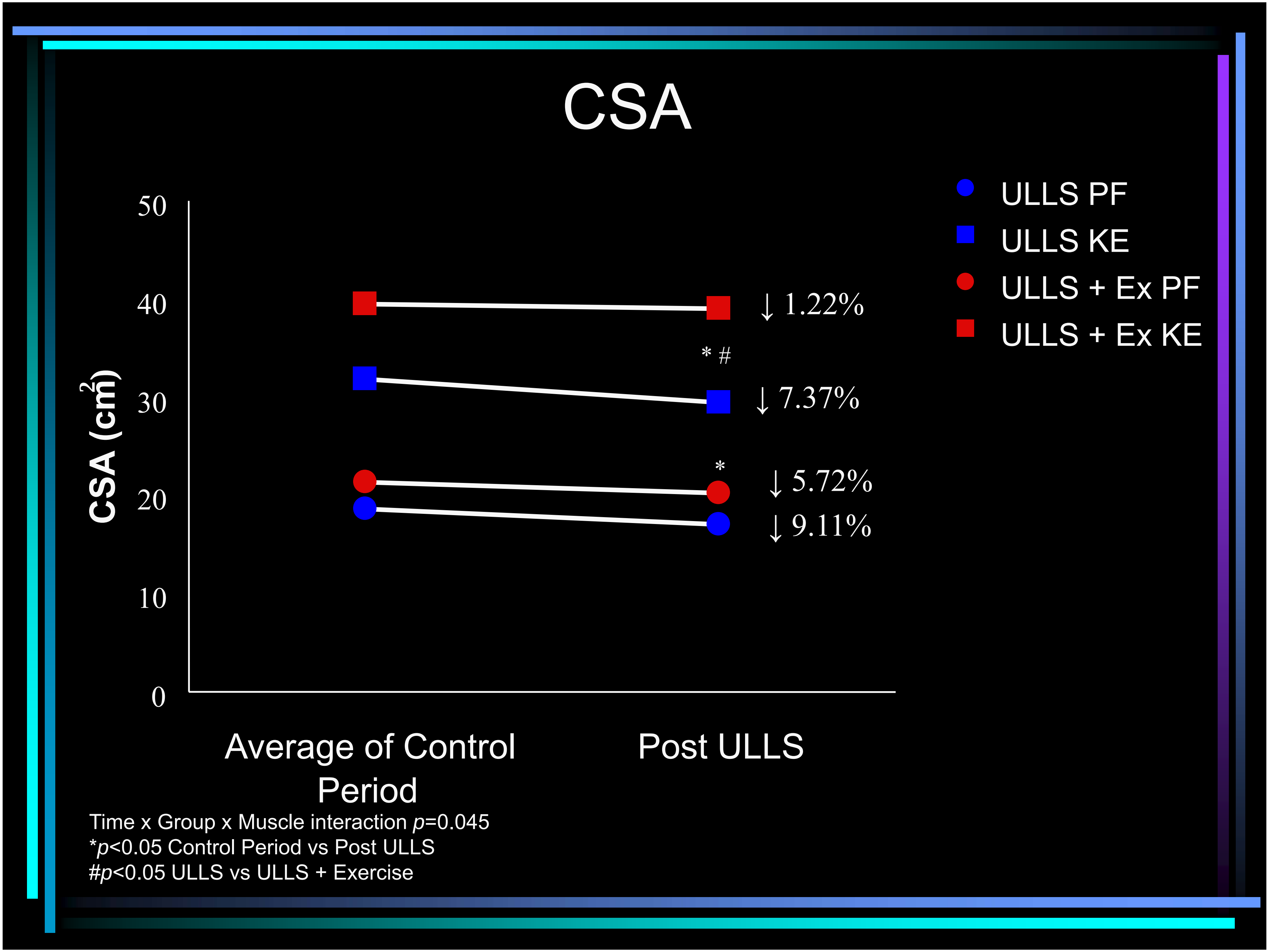
8 subjects performed unilateral lower limb suspension (ULLS)

8 subjects performed ULLS and LL_{BFR} exercise on the KE 3 times per week (ULLS + Exercise)

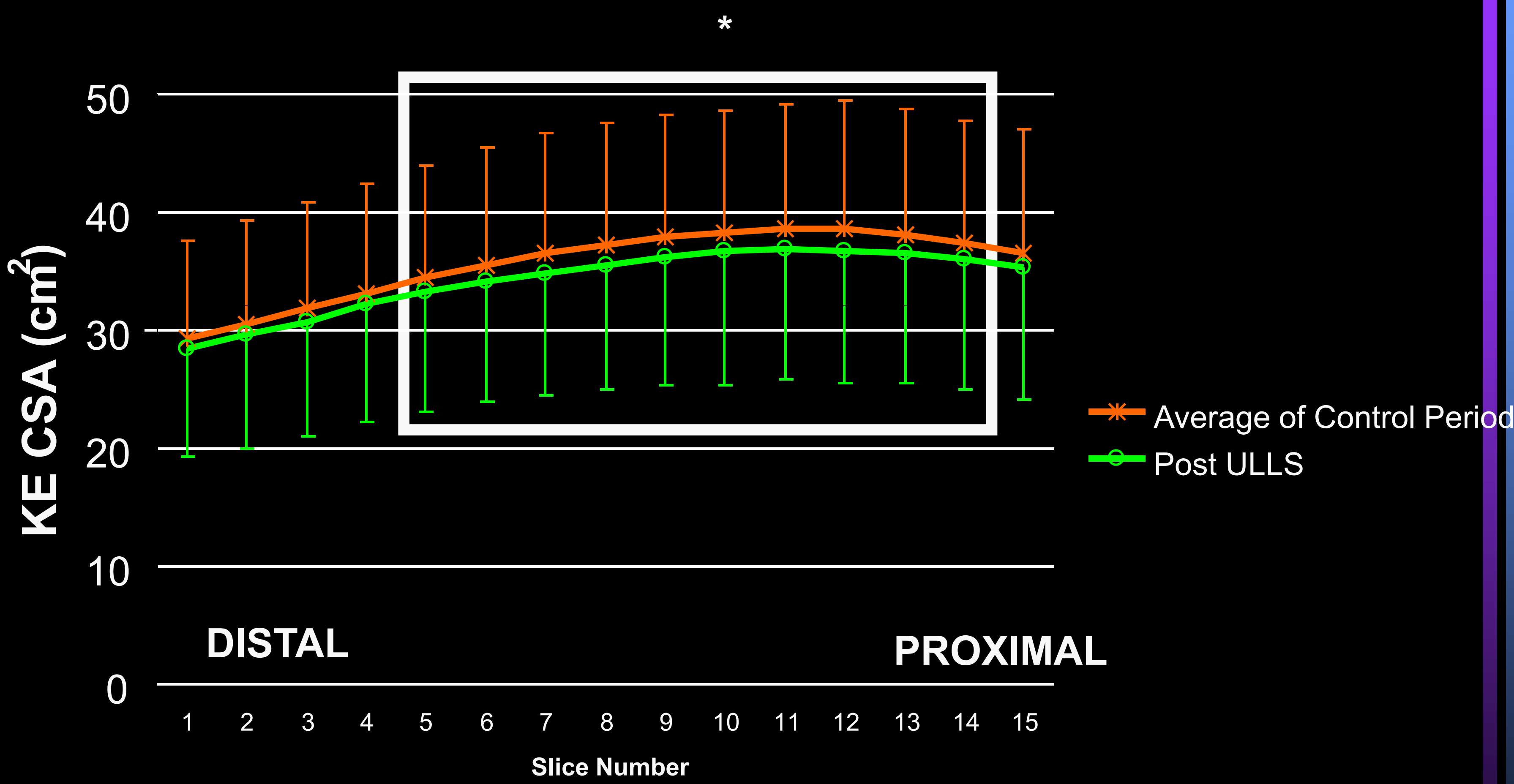
LL_{BFR} Exercise

- Performed 3x per week
- 3 sets of KE to volitional failure
  - 20% MVC
  - 2-sec con, 2-sec ecc
  - 90 sec rest between sets

- 6 x 83 cm tourniquet cuff around proximal thigh
  - Inflated to 1.3 x SBP for the duration of exercise session
- 100% subject compliance

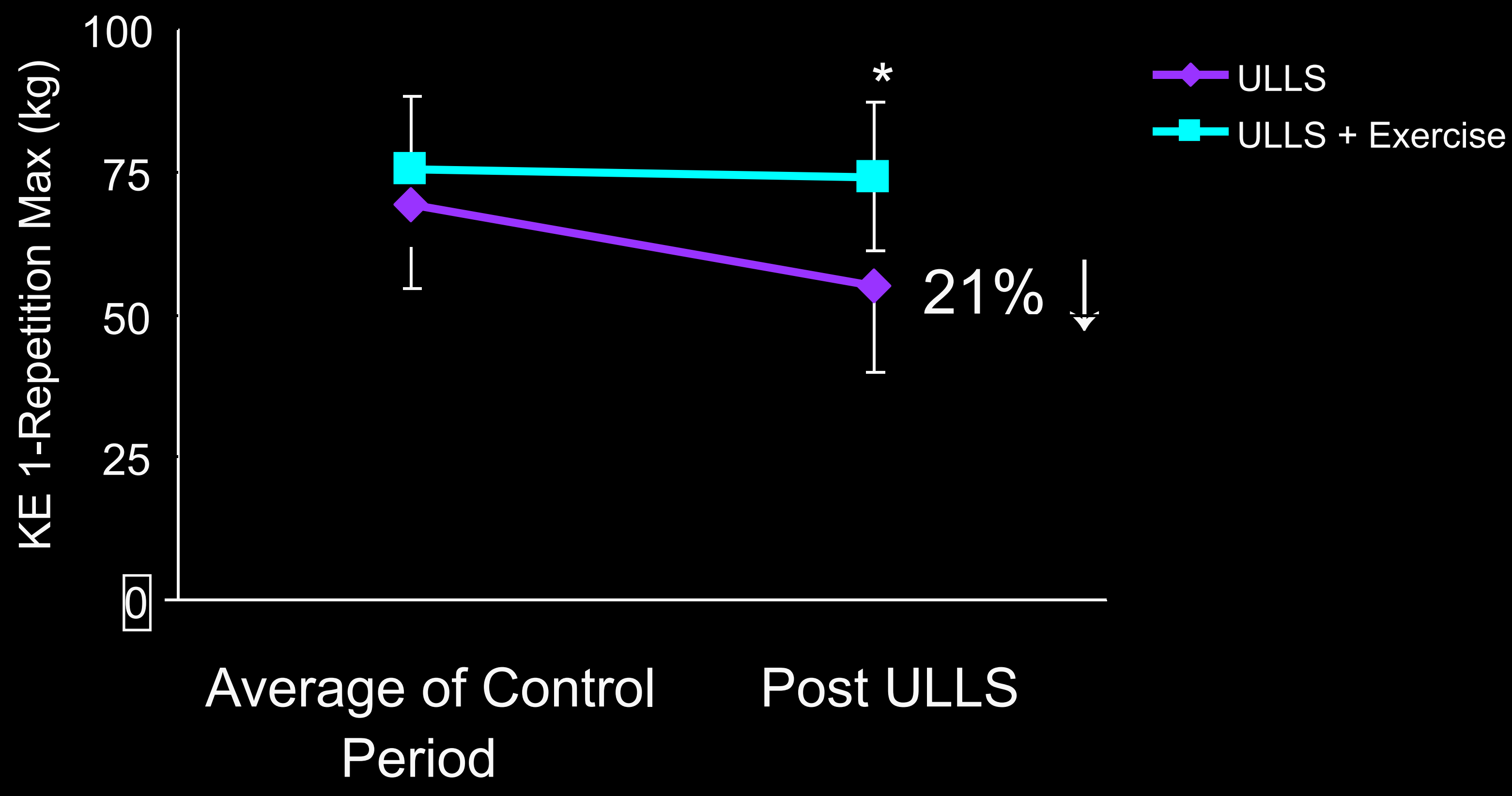

CSA
50
40
30
20
10
0
CSA (cm2)
↓ 1.22%
* #
↓ 7.37%
*
↓ 5.72%
↓ 9.11%
Average of Control Period
Post ULLS
ULLS PF
ULLS KE
ULLS + Ex PF
ULLS + Ex KE
Time x Group x Muscle interaction p=0.045
*p<0.05 Control Period vs Post ULLS
#p<0.05 ULLS vs ULLS + Exercise

CSA along the KE



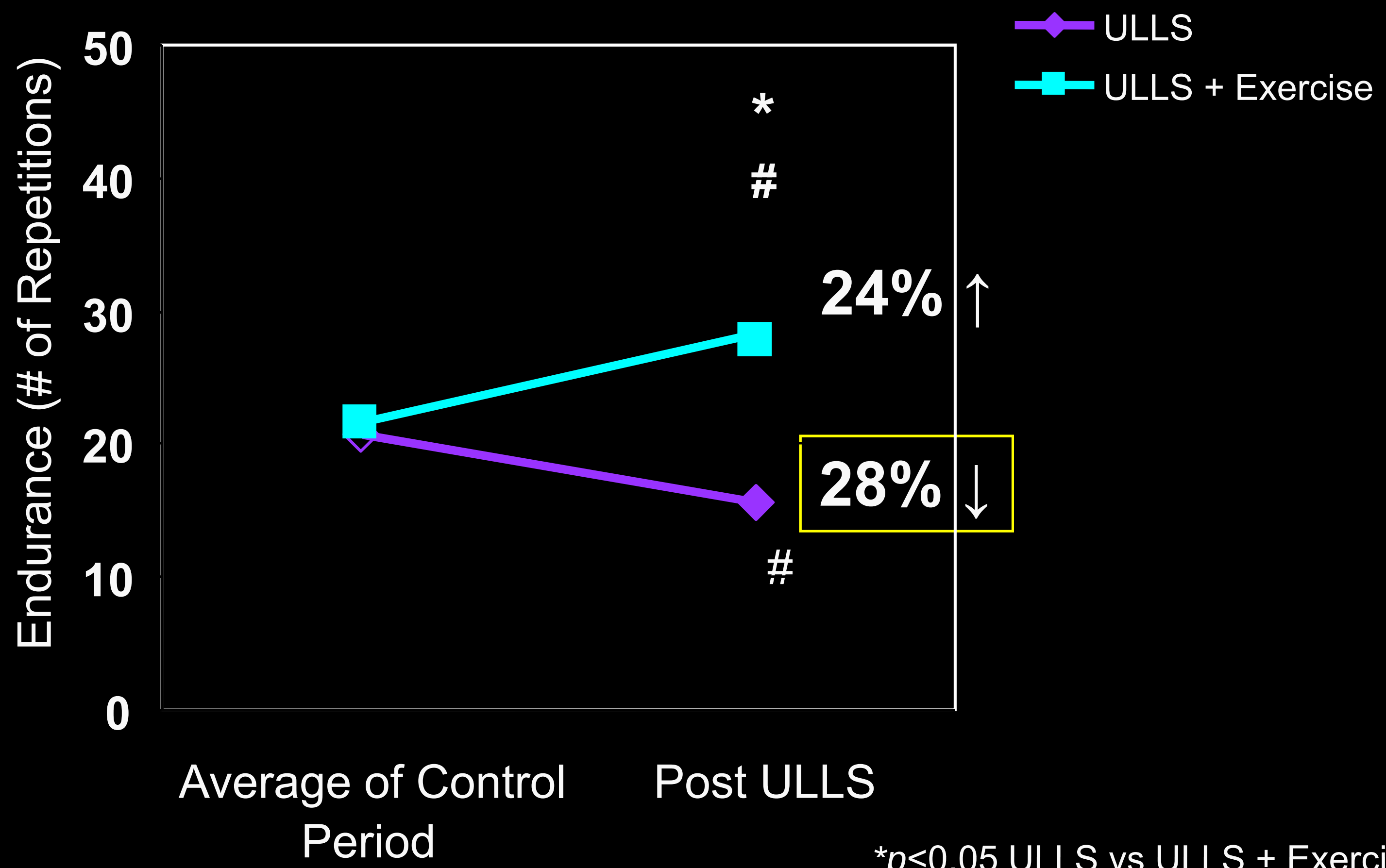
* Time x Slice Interaction *p*=.018

RESULTS: KE 1-RM



*p=.002 ULLS vs ULLS + Exercise

RESULTS: KE Endurance



**p*<0.05 ULLS vs ULLS + Exercise

# *p*<0.05 Control period vs Post ULLS

Conclusion

- Performing LL_{BFR} KE exercise during 30d of unloading can maintain muscle size and strength of the KE and even improve muscular endurance.