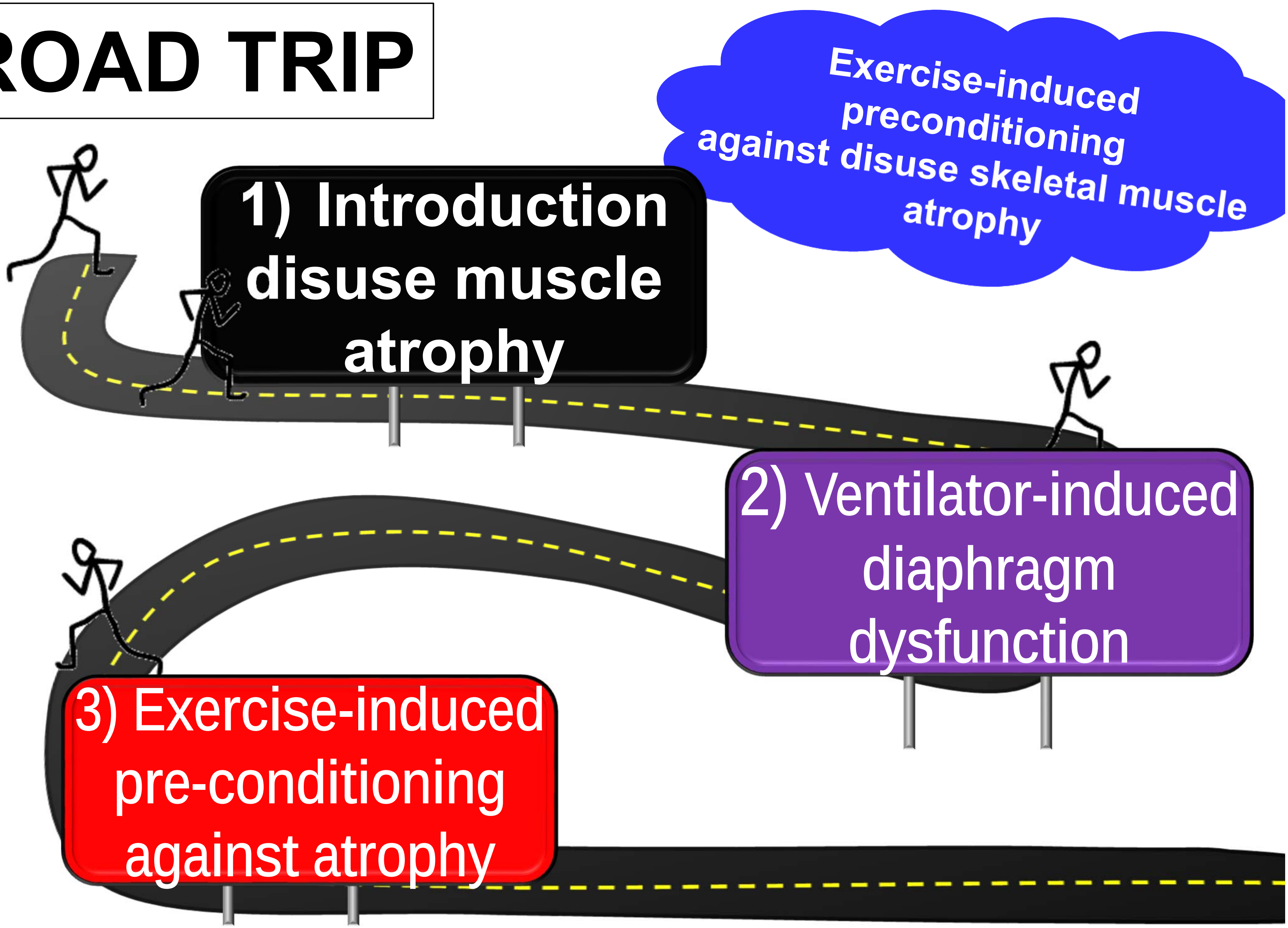
Exercise-induced preconditioning in skeletal muscles

Scott K. Powers
Department of Applied Physiology and Kinesiology

UF UNIVERSITY of FLORIDA
The Foundation for The Gator Nation

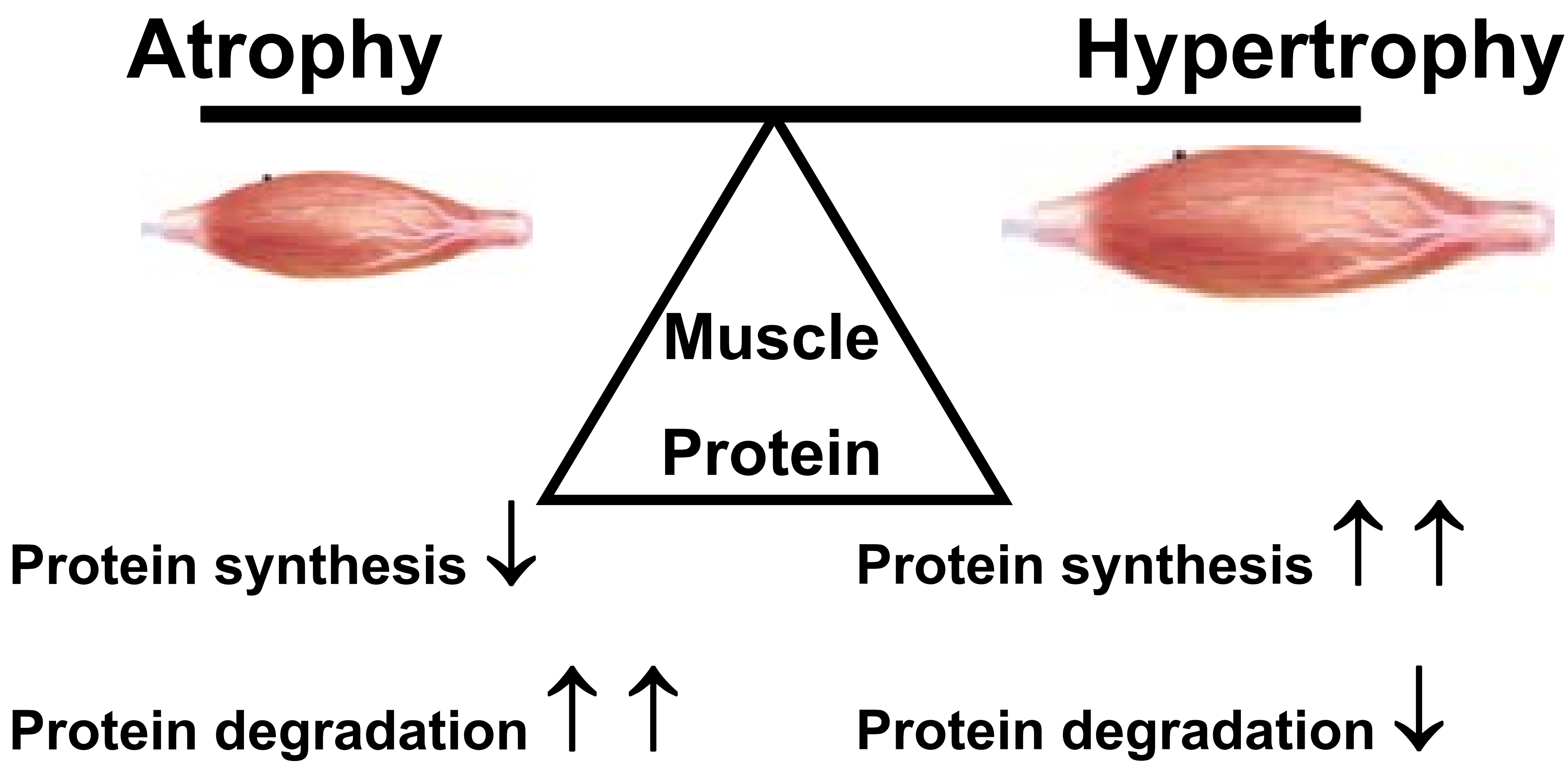
ROAD TRIP



Exercise-induced preconditioning against disuse skeletal muscle atrophy
1) Introduction disuse muscle atrophy
2) Ventilator-induced diaphragm dysfunction
3) Exercise-induced pre-conditioning against atrophy

Human Condition Resulting in Disuse Muscle Atrophy		Animal model
Mechanical Ventilation (Diaphragm inactivity)	→	Mechanical Ventilation
Limb Immobilization	→	Limb Immobilization
Space Flight	→	Hind-limb Suspension
Spinal Cord Injury	→	Denervation/Spinal Cord Isolation
Bed Rest	→	Hind-limb Suspension

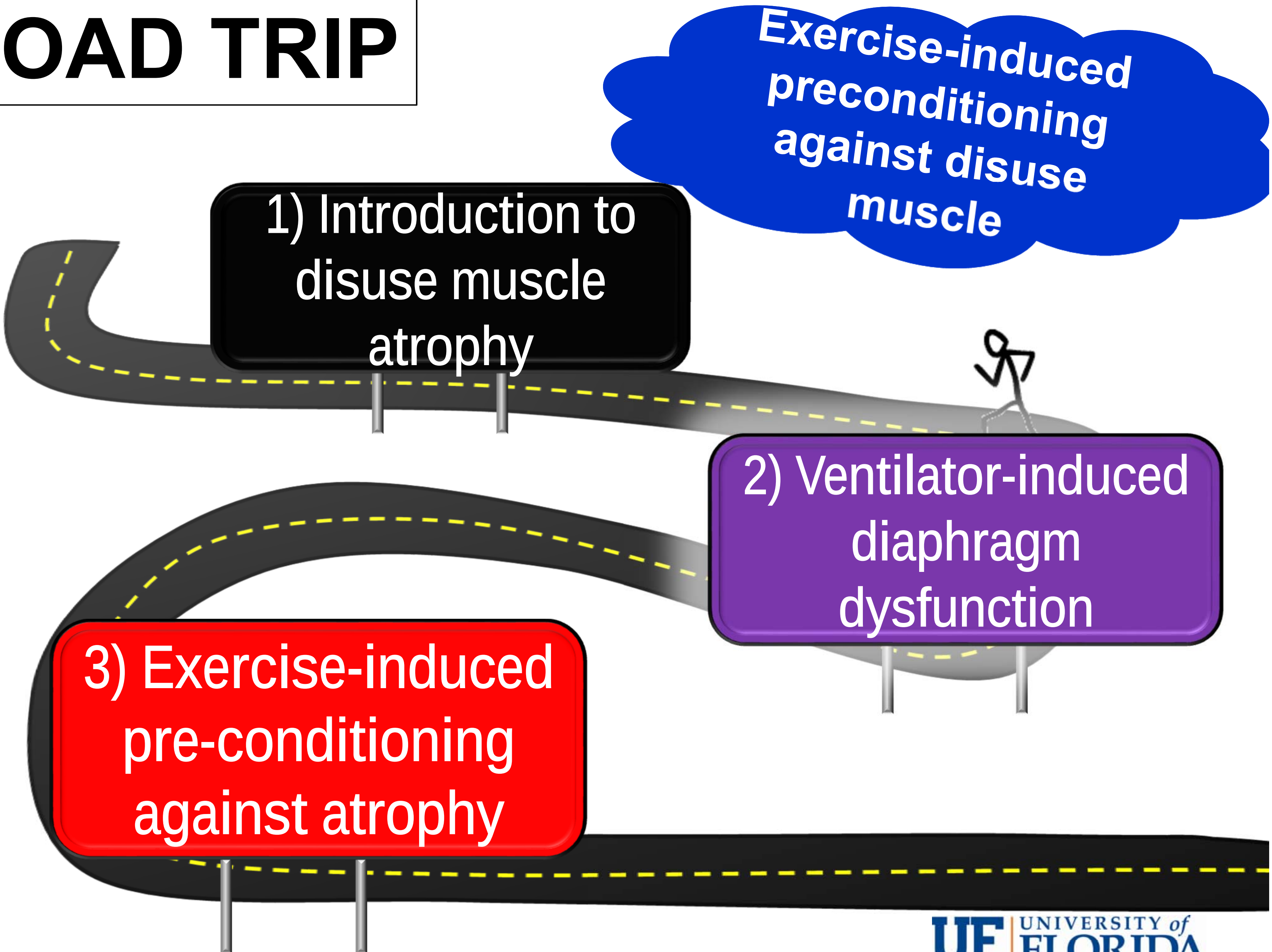
Skeletal muscle protein balance and muscle size



Importance of maintaining healthy skeletal muscle mass

- Healthy muscles are essential for breathing and locomotion
- Muscle is an endocrine organ and myokines are potential regulators of other organs
- Mortality rate of many diseases are associated with functional status and mass of skeletal muscles

ROAD TRIP



UF UNIVERSITY of FLORIDA
The Foundation for The Gator Nation

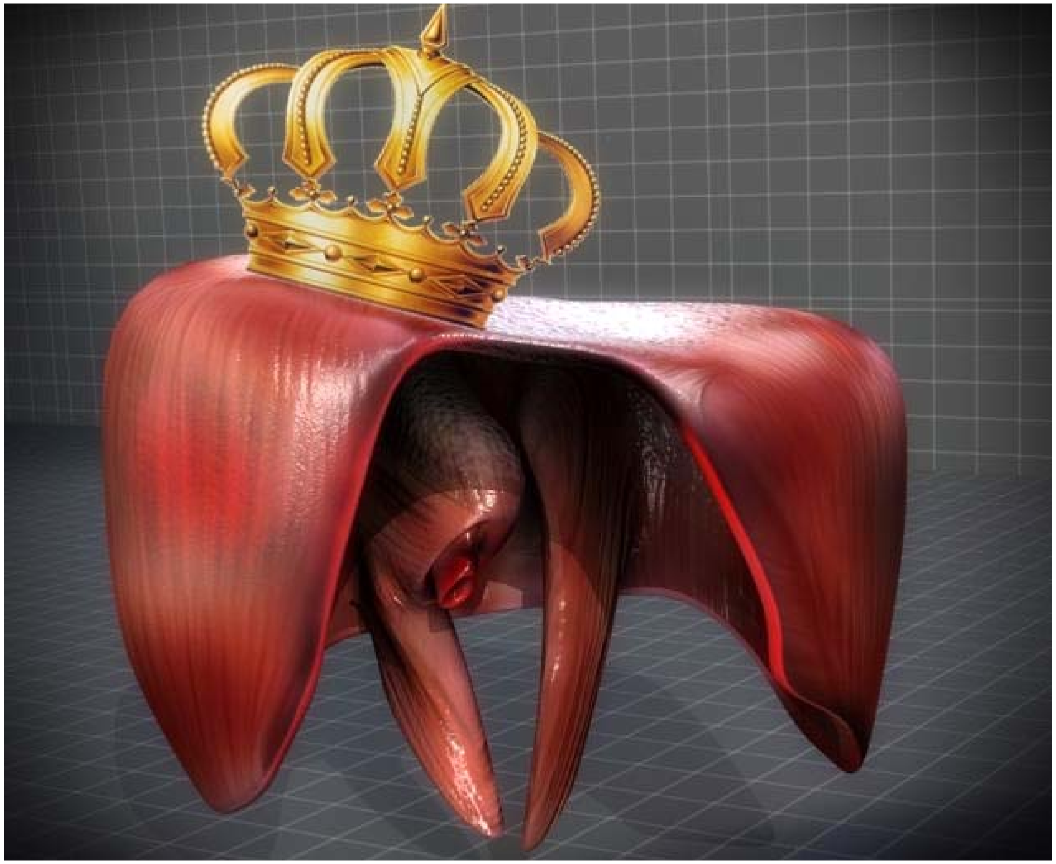
Mechanical Ventilation (MV)

- MV is used clinically to maintain adequate pulmonary gas exchange in patients who are incapable of maintaining sufficient alveolar ventilation

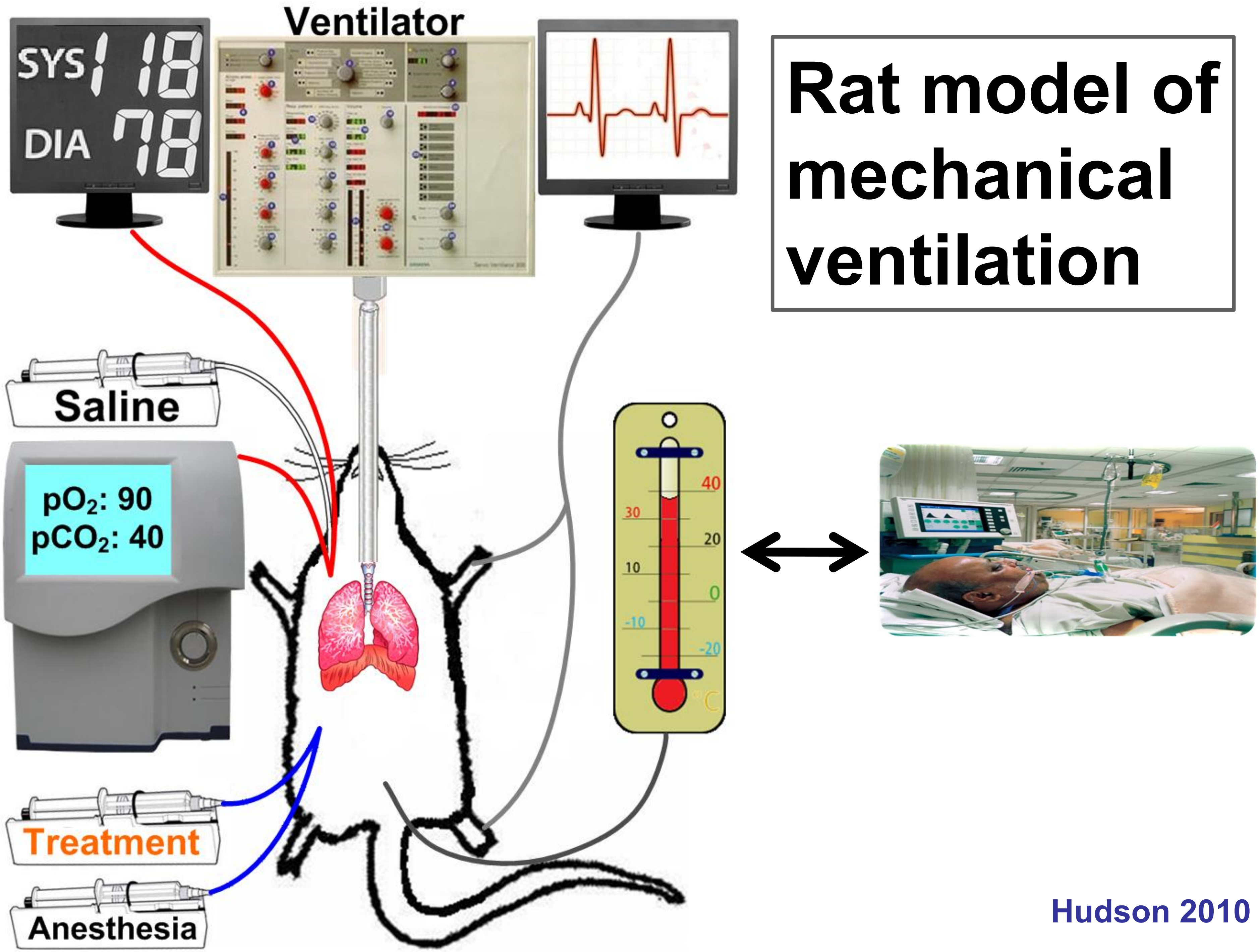
- <u>Common indications</u>: Respiratory failure, heart failure, neuromuscular diseases, drug overdoses, spinal cord injury, and surgery/post-surgical recovery

- Prolonged MV results in inspiratory muscle weakness

Diaphragm is the principal muscle of inspiration in all mammals

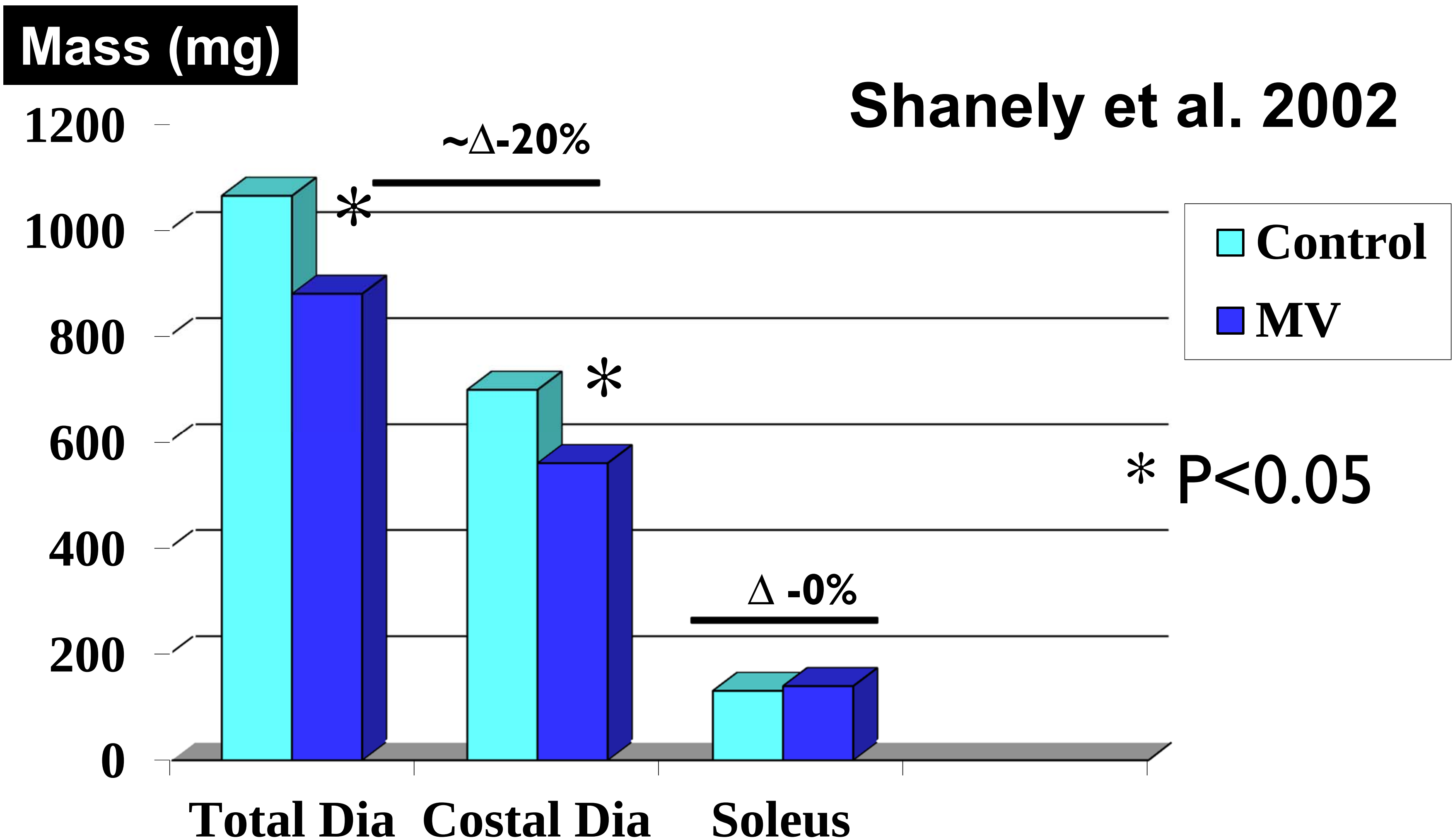


Rat model of mechanical ventilation

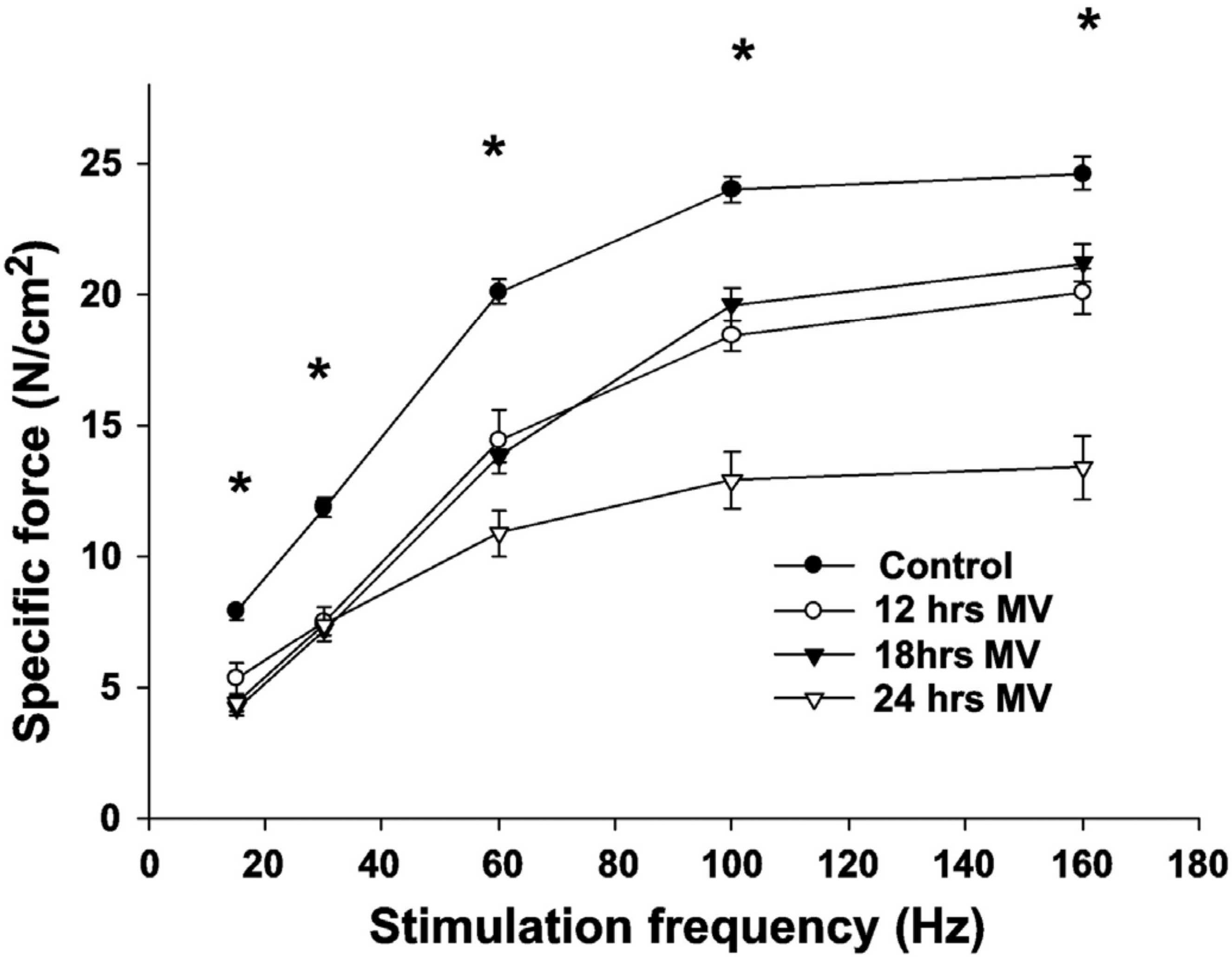


Hudson 2010

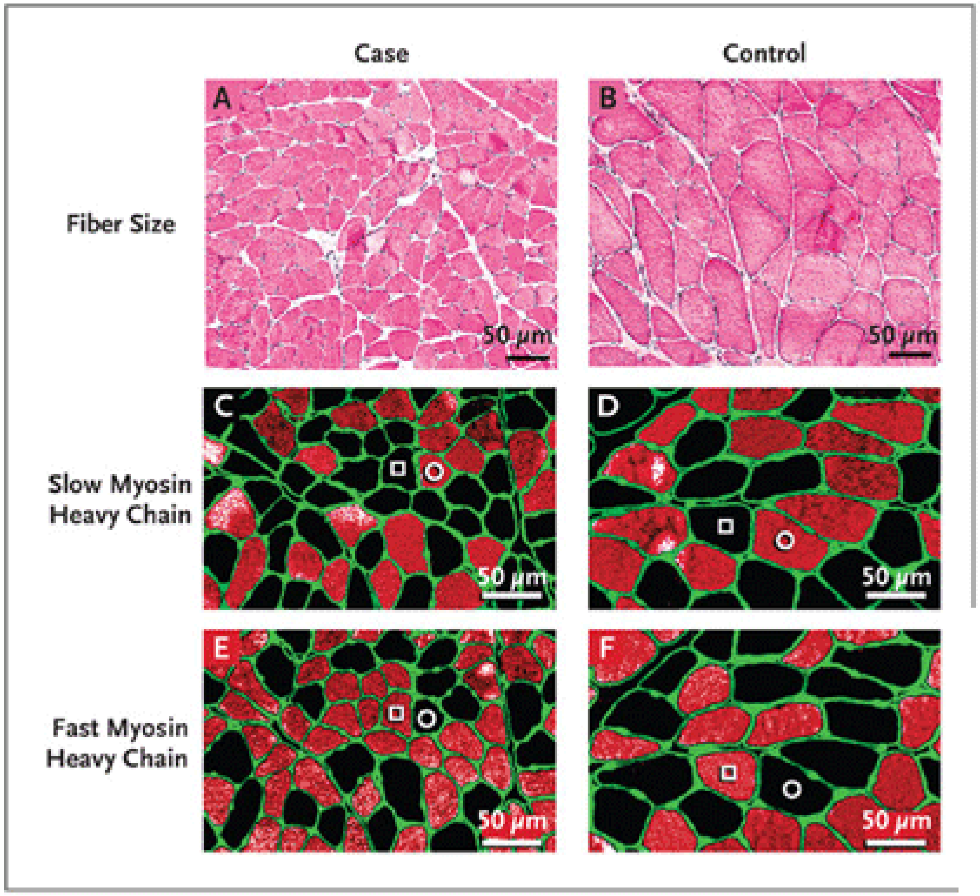
MV-induced diaphragmatic atrophy (18 hours)



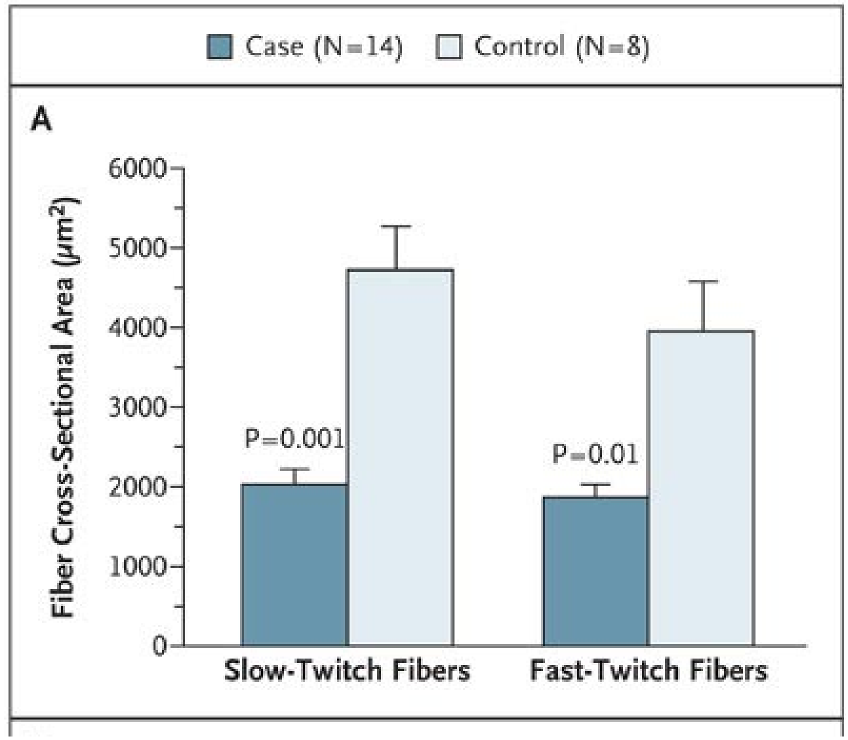
Prolonged MV promotes time-dependent decrease in diaphragmatic specific force



Powers et al. 2002



Prolonged MV results in rapid diaphragmatic atrophy in humans



Levine et al. NEJM (2008)

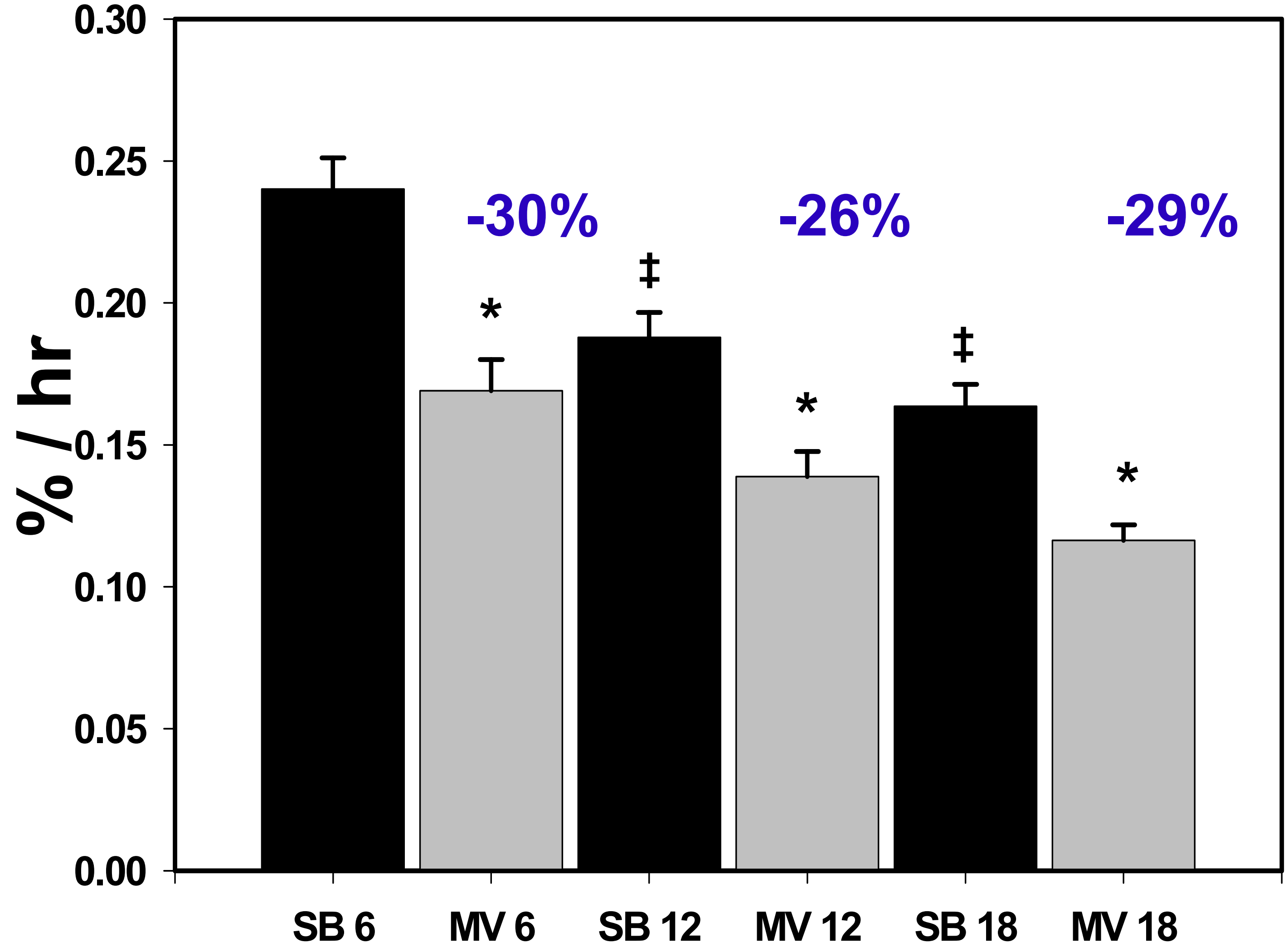
UF UNIVERSITY of FLORIDA
The Foundation for The Gator Nation

Why study VIDD?

- ~30% patients exposed to prolonged MV experience difficult weaning
- Failure to wean results in extended stays in ICU
- Diaphragmatic weakness predicted to be major risk factor for difficult weaning

Mechanisms responsible for the rapid development of ventilator-induced diaphragm atrophy?

Fractional Rate of Mixed Muscle Protein Synthesis-diaphragm



Shanely et al. 2004

- **All major proteolytic systems are activated in diaphragm during prolonged MV**
- **Proteolysis plays a dominant role in the development of VIDD during the first several days of MV**

Oxidative stress is required for mechanical ventilation-induced protease activation in the diaphragm

Melissa A. Whidden, Ashley J. Smuder, Min Wu, Matthew B. Hudson, W. Bradley Nelson and Scott K. Powers

J Appl Physiol 108:1376-1382, 2010. First published 4 March 2010;
doi:10.1152/japplphysiol.00098.2010

Free Radical Biology & Medicine 46 (2009) 842–850

ELSEVIER

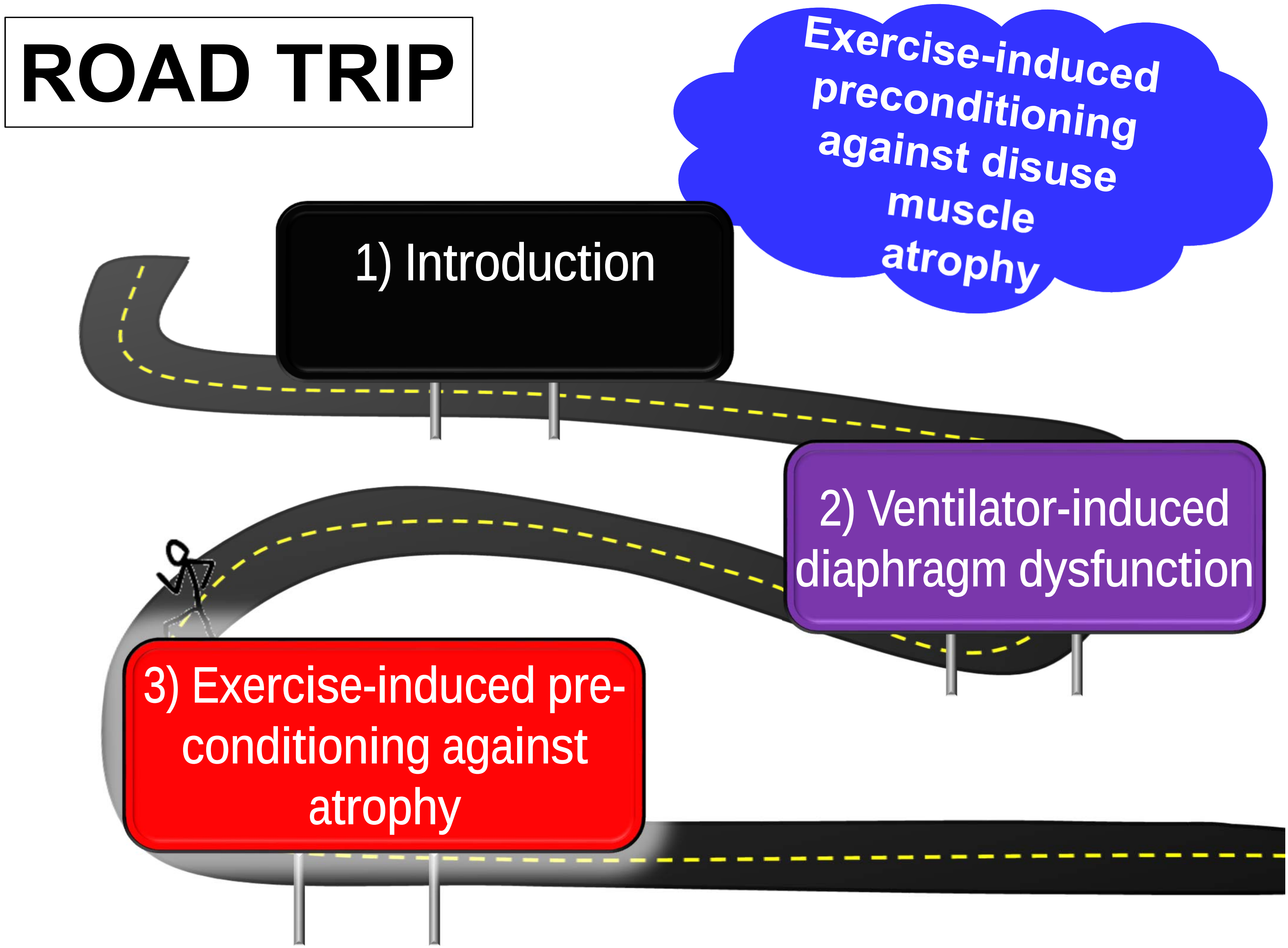
Contents lists available at ScienceDirect

Free Radical Biology & Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Mitochondria-targeted antioxidants protect against mechanical ventilation-induced diaphragm weakness*

Scott K. Powers, PhD, EdD; Matthew B. Hudson, MS; W. Bradley Nelson, MS; Erin E. Talbert, BS; Kisuk Min, MS; Hazel H. Szeto, MD, PhD; Andreas N. Kavazis, PhD; Ashley J. Smuder, MS


ROAD TRIP
Exercise-induced preconditioning against disuse muscle atrophy
1) Introduction
2) Ventilator-induced diaphragm dysfunction
3) Exercise-induced pre-conditioning against atrophy

Strategies to protect against VIDD?

Regular bouts of endurance exercise has been shown to achieve all of these goals in trained skeletal muscle

Does exercise training result in diaphragmatic adaptations that protect against VIDD?

Two exercise experiments

1) Continuous aerobic exercise (Endurance exercise)
10 days of exercise training (60 min/day, ~70% VO_{2max})

2) High intensity interval training (HIIT)
10 days of HIIT training (60s x 5 intervals, ~100% VO_{2max})

- MV initiated 24 hours after last exercise bout

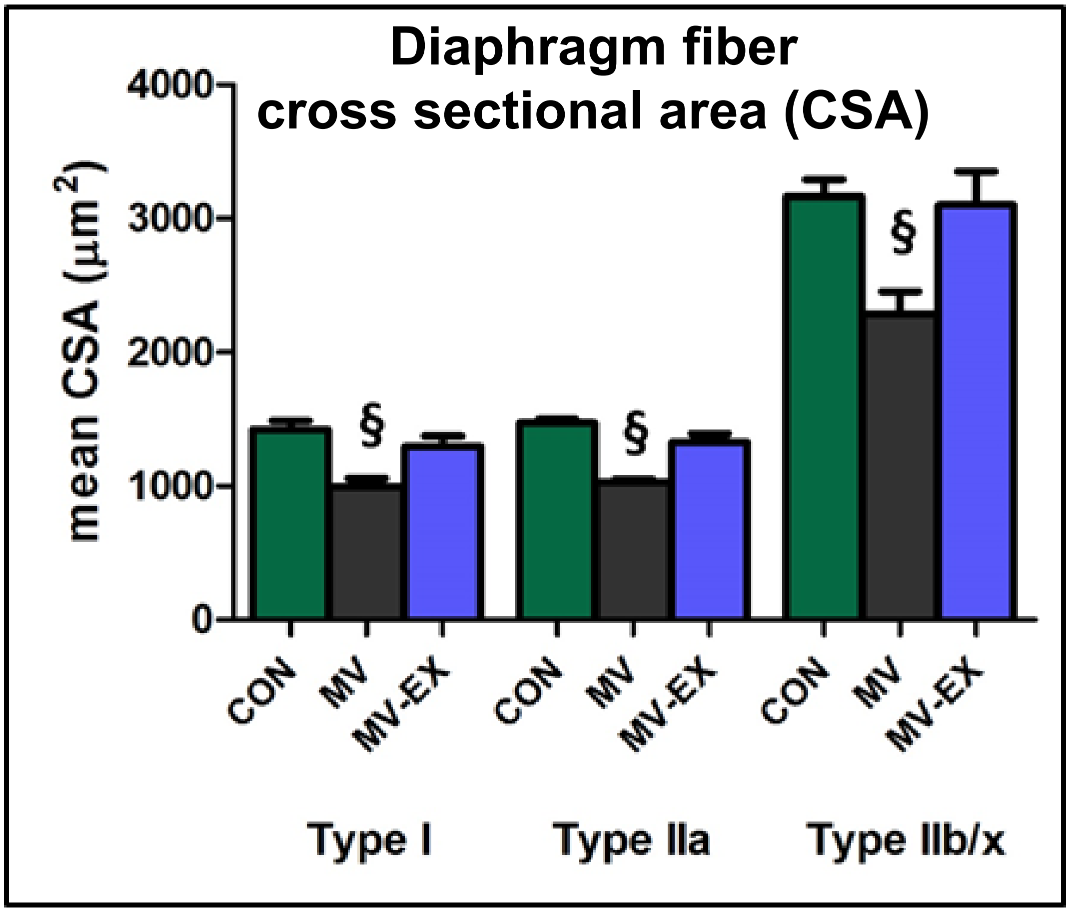
J Appl Physiol 112: 501–510, 2012.
First published November 10, 2011; doi:10.1152/japplphysiol.01086.2011.

Endurance exercise attenuates ventilator-induced diaphragm dysfunction

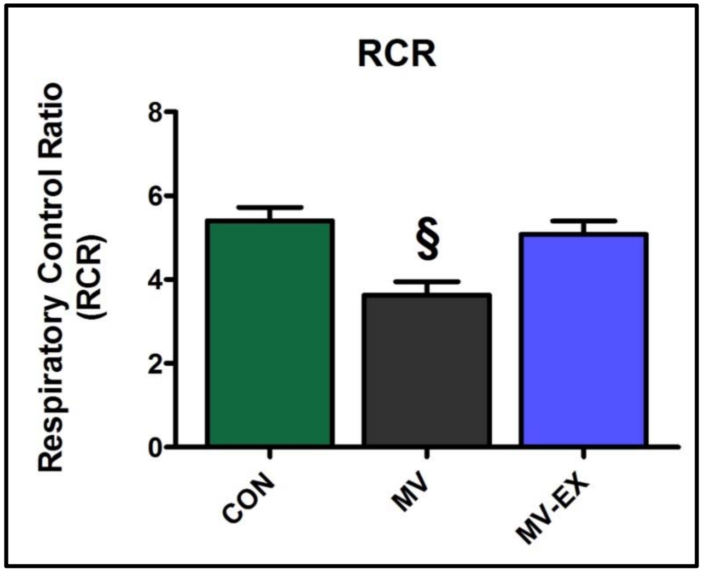
Ashley J. Smuder,[1] Kisuk Min,[1] Matthew B. Hudson,[1] Andreas N. Kavazis,[2] Oh-Sung Kwon,[1] W. Bradley Nelson,[1] and Scott K. Powers[1]

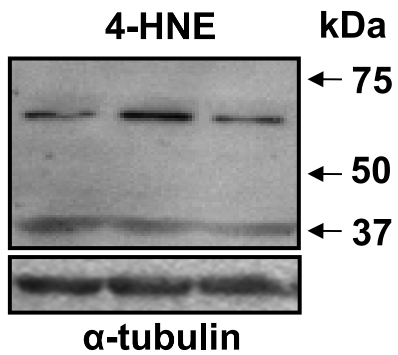
[1]*Department of Applied Physiology and Kinesiology, Center for Exercise Science, University of Florida, Gainesville, Florida; and* [2]*Department of Kinesiology, Mississippi State University, Mississippi State, Mississippi*

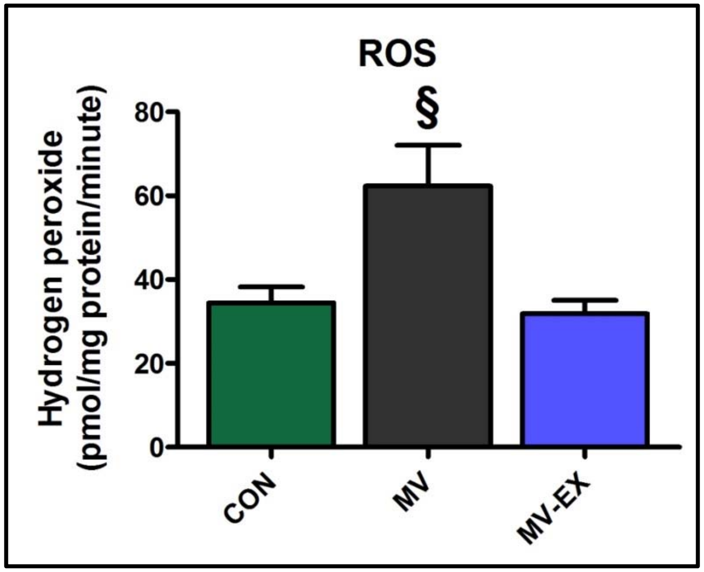
Submitted 31 August 2011; accepted in final form 6 November 2011

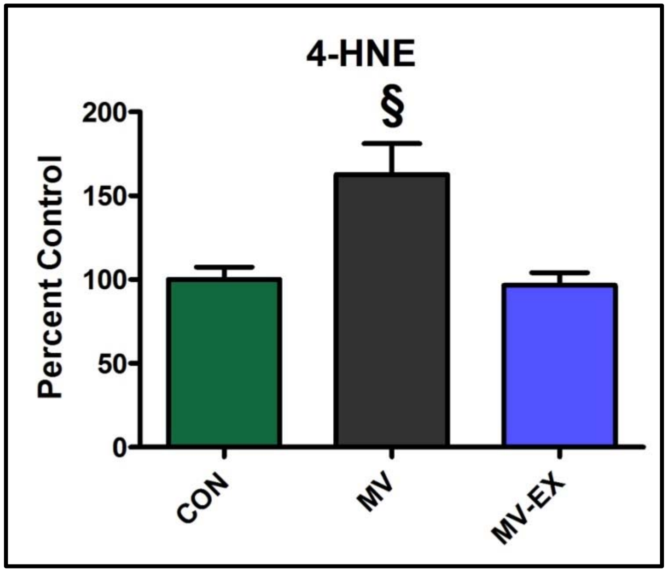


Exercise training maintains mitochondrial function and decreases ROS production during MV





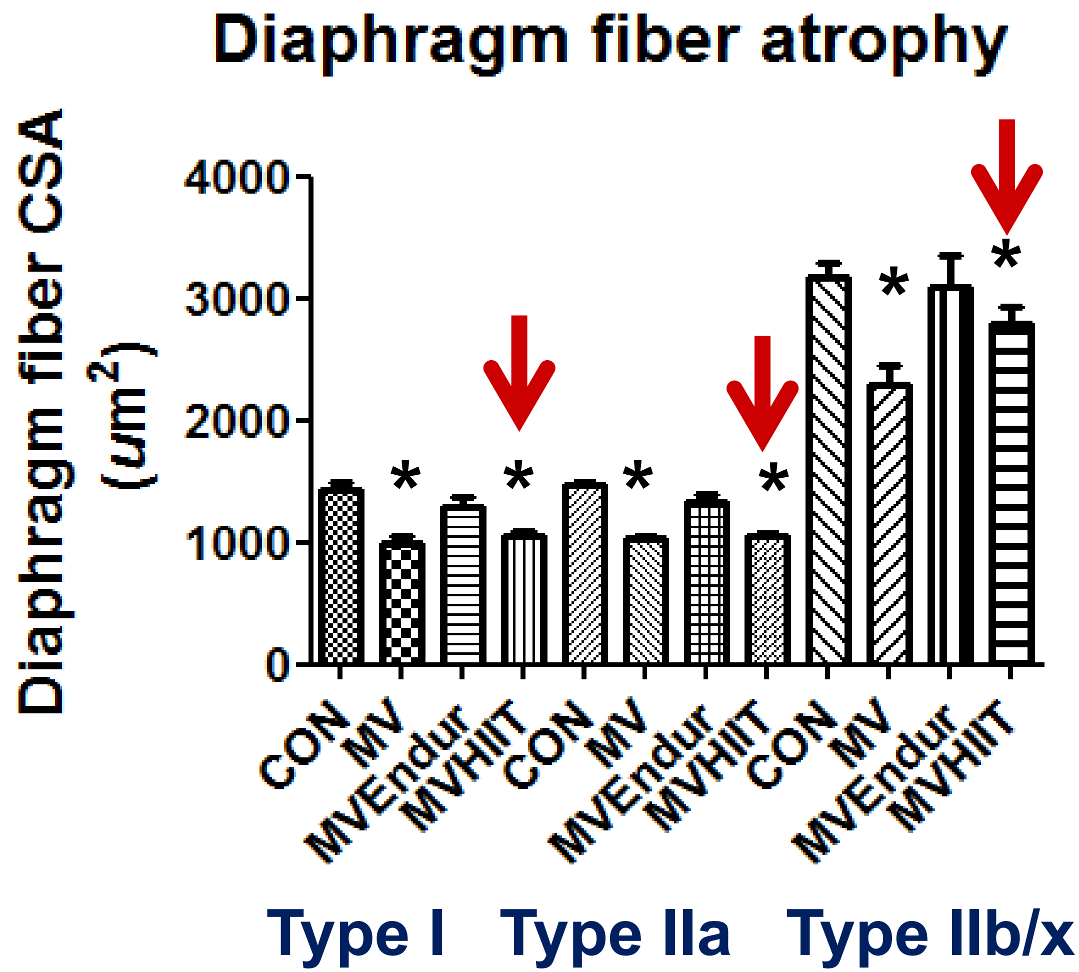




Smuder et al. *J Appl Physiol* 2012

§ MV vs. all groups

High intensity interval training does not prevent mechanical ventilation-induced diaphragmatic atrophy



Smuder et al (2012)

Are animals with a high intrinsic aerobic capacity protected against VIDD?

Physiol Genomics
5: 45–52, 2001.

Artificial selection for intrinsic aerobic endurance running capacity in rats

LAUREN GERARD KOCH AND STEVEN L. BRITTON
Functional Genomics Laboratory, Medical College of Ohio, Toledo, Ohio 43614-5804

Received 8 November 2000; accepted in final form 5 January 2001

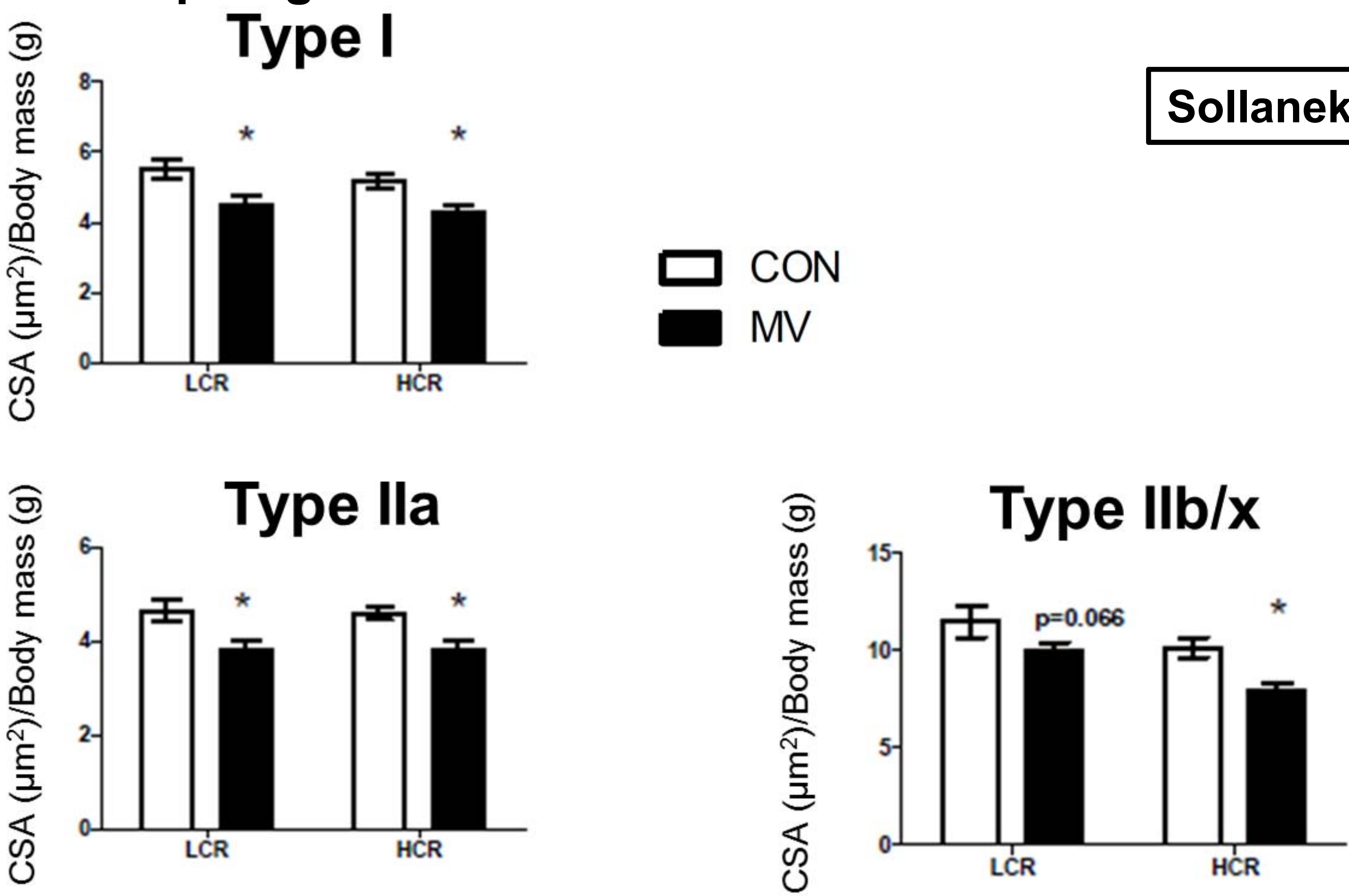
Low capacity runners
LCRs

High capacity runners
HCRs

High intrinsic aerobic capacity does not protect against VIDD

Diaphragm muscle fibers cross sectional areas

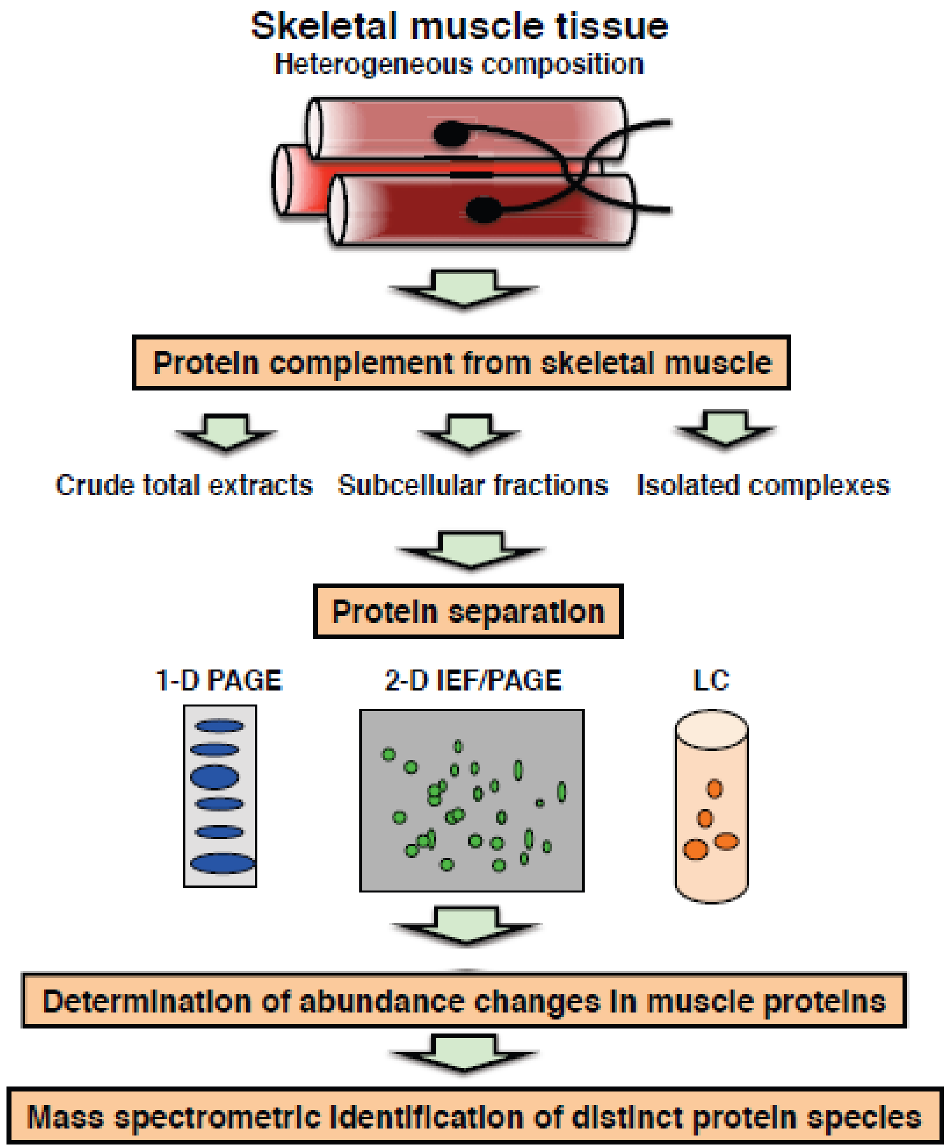
Sollanek et al. 2015



***P<0.05, MV significantly different from control within strain**

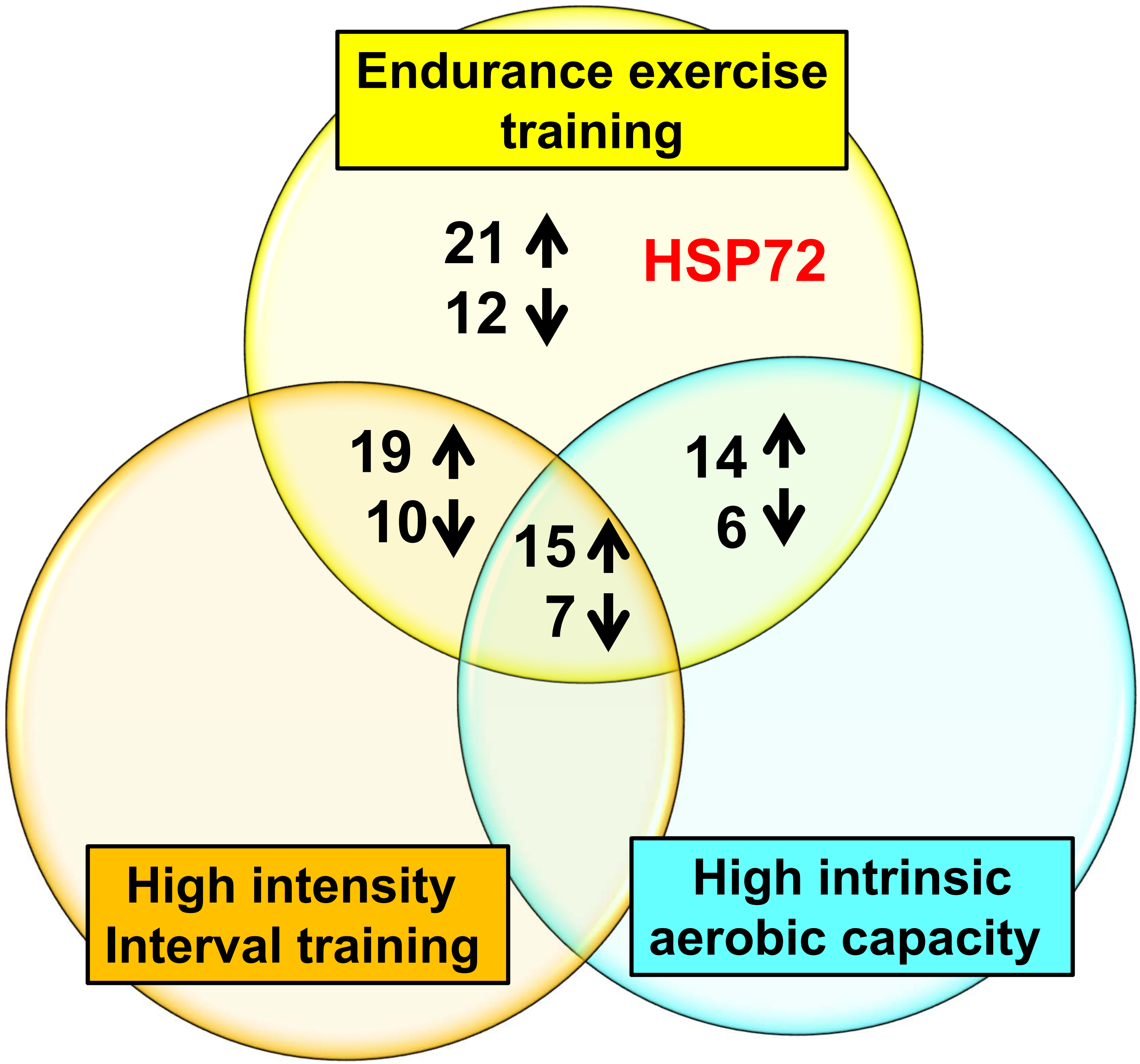
The question now becomes……

What are the exercise-induced changes in the diaphragm that contribute to pre-conditioning protection against disuse muscle atrophy



Proteomics approach

Ohlendieck 2011, *Skeletal muscle*

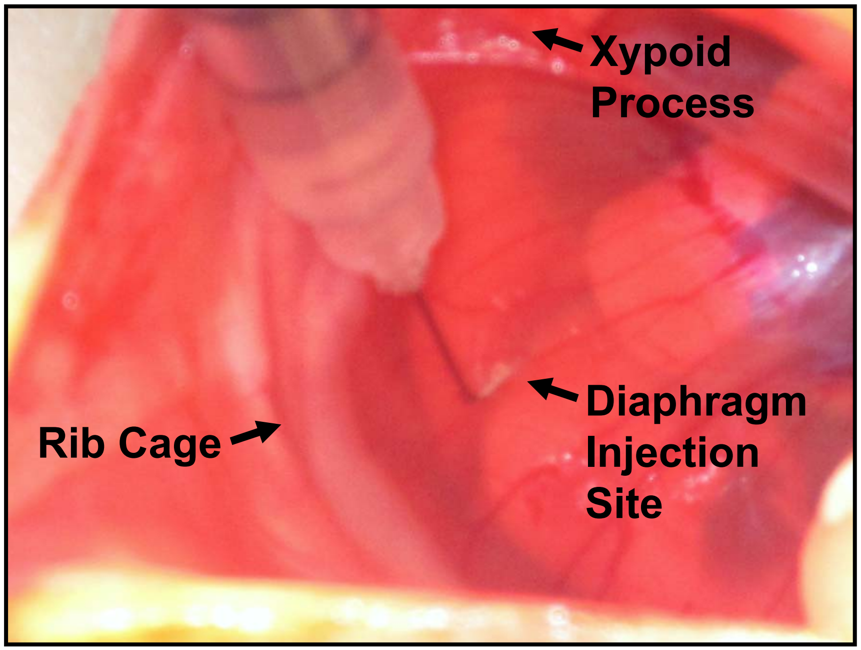

Endurance exercise training
21 ↑
12 ↓
HSP72
19 ↑
10 ↓
14 ↑
6 ↓
15 ↑
7 ↓
High intensity Interval training
High intrinsic aerobic capacity

Experimental strategy

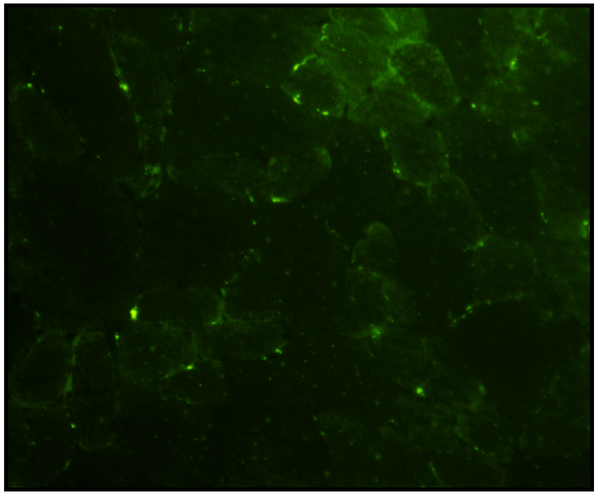
Phase 1- Transfect and overexpress single protein of interest in diaphragm; Determine if overexpression of single protein is sufficient to protect against VIDD

Phase 2- Gene silencing to prevent exercise-induced expression of protein; Determine if exercise-induced expression of protein is required to protect against VIDD

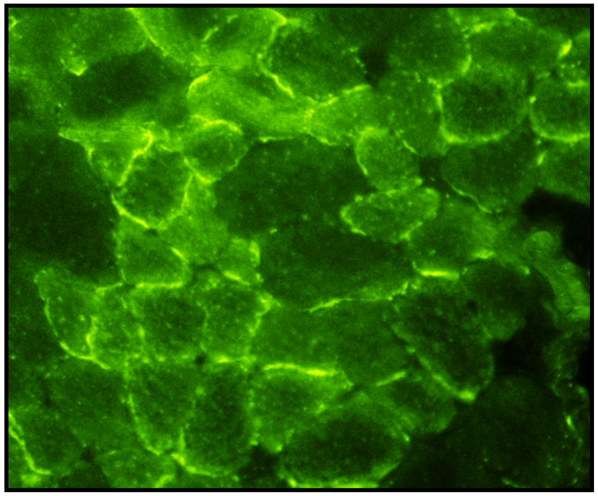
Diaphragm AAV9 injections



SHAM

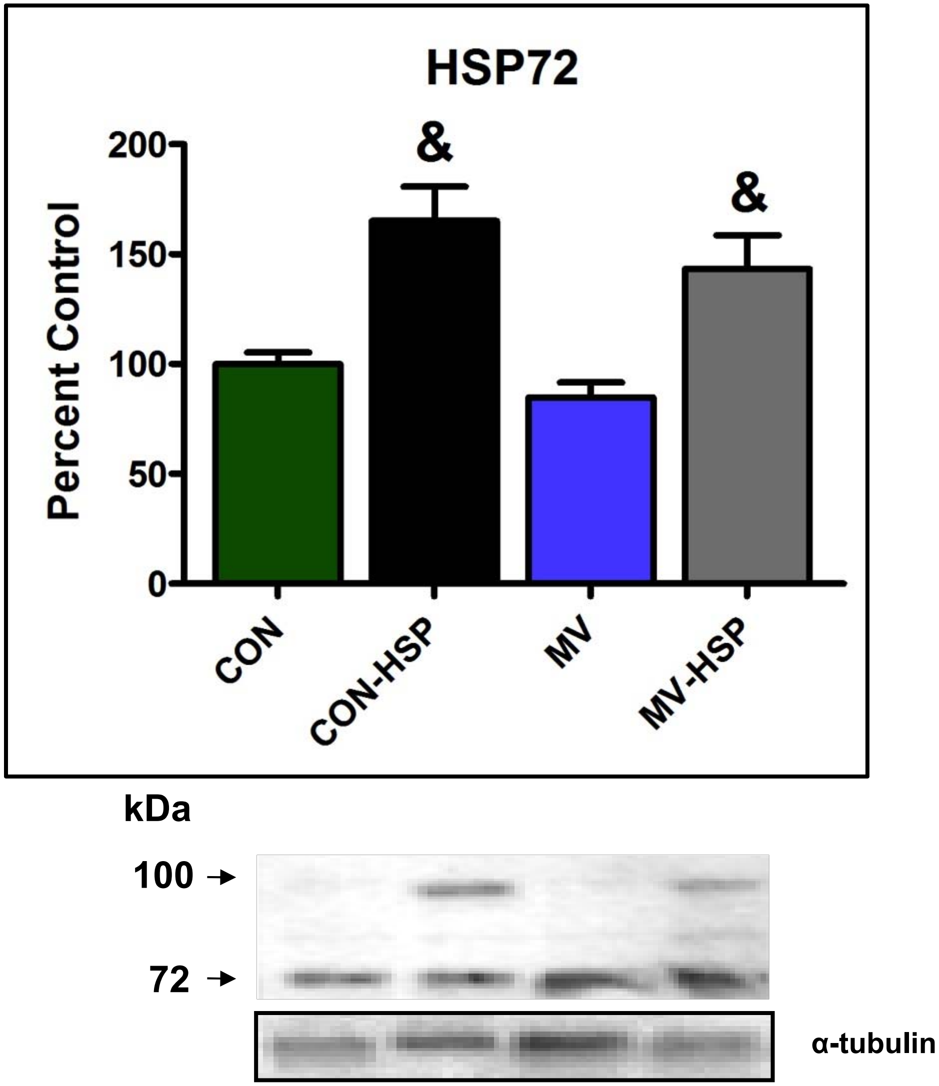


GFP



Smuder et al. *Hum Gene Ther Methods* 2013

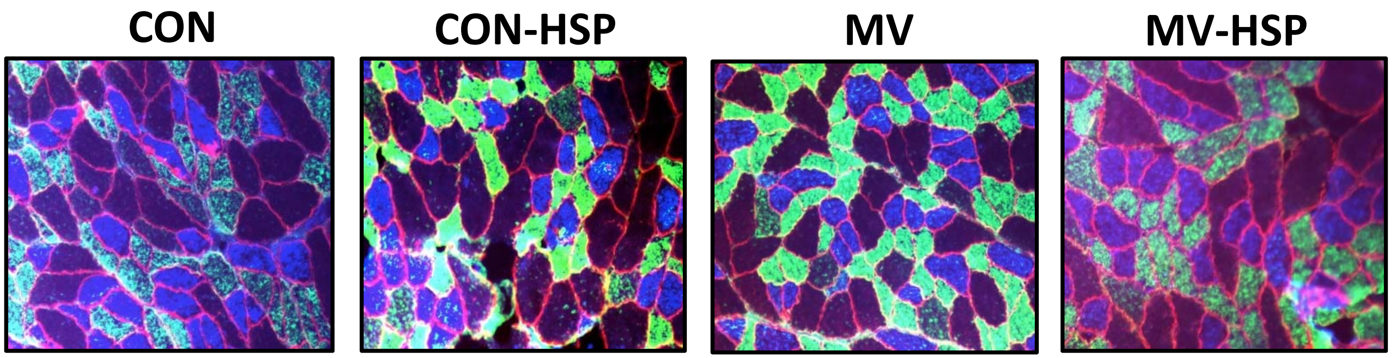
HSP72 overexpression in the diaphragm

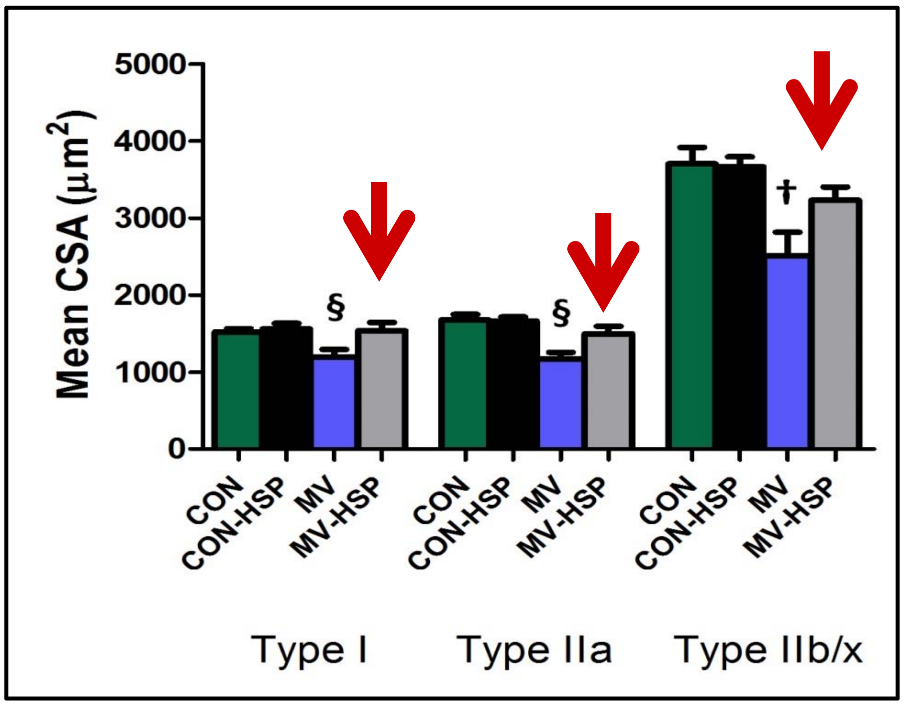


Smuder et al. (unpublished)

& sig diff vs. CON and MV

HSP72 overexpression protects against MV-induced diaphragm atrophy





Smuder et al. (unpublished)

† MV vs. CON and CON-HSP
§ MV vs. CON, CON-HSP and MV-HSP

What happens to exercise-induced protection against VIDD when exercise-mediated expression of HSP 72 is prevented?

Work in progress…..

Summary

1. MV-induced diaphragmatic atrophy occurs rapidly –major risk factor for difficult weaning
2. Endurance exercise training protects against MV-induced diaphragmatic atrophy in rodents-exercise is an experimental tool for treatment discovery
3. Exercise-induced increases in diaphragmatic HSP72 may play a key role in exercise-induced preconditioning of diaphragm

Acknowledgements

University of Florida

Joe McClung, PhD
Andy Shanely, PhD
Ashley Smudder, MS
Darin Van Gammeren, PhD
Darin Falk, PhD
Melissa Deering, PhD
Keith DeRuisseau, PhD
Andreas Kavazis, PhD
Matt Hudson, MS
Brad Nelson, MS
Kisuk Min, MS
Erin Talbert, BS
Oh-Sung Kwon, MS
Kurt Sollanek, PhD
Michael Wiggs, PhD

University of Pennsylvania

Sanford Levine, MD

Cornell University

Hazel Szeto, MD, PhD

UC-Irvine

Catherine Sassoon, MD

Acknowledgements (International)

Leuven University

Marc DeCramer, MD, PhD
Ghis Gayan-Ramirez, PhD
Karen Maes, PhD

University of Queensland

Jeff Coombes, PhD

Hacepette University

Haydar Demirel, MD, PhD
Murat Zergeroglu, MD, PhD

Jutendo University

Hisashi Naito, PhD

Porto University

Jose Duarte, MD, PhD

NATIONAL INSTITUTES OF HEALTH

AMERICAN LUNG ASSOCIATION. Fighting for Air

American Heart Association Learn and Live.

U.S. Department of Health and Human Services

Supported by the NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

UF UNIVERSITY of FLORIDA The Foundation for The Gator Nation

Thank you for your attention

Special thanks to:

U.S. Department of Health and Human Services

Supported by the

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases