Exercise-induced preconditioning in skeletal muscles

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1) Introduction
disuse muscle atrophy

2) Ventilator-induced
diaphragm dysfunction

3) Exercise-induced pre-conditioning against atrophy

Exercise-induced preconditioning against disuse skeletal muscle atrophy
Human Condition Resulting in Disuse Muscle Atrophy

- 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

Animal model
Skeletal muscle protein balance and muscle size

Atrophy

Protein synthesis ↓

Protein degradation ↑

Hypertrophy

Protein synthesis ↑↑

Protein degradation ↓
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
1) Introduction to disuse muscle atrophy

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Mechanical Ventilation (MV)

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

- **Common indications**: 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)

Shanely et al. 2002

* P<0.05

~Δ-20%

Δ -0%
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)
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
doi:10.1152/japplphysiol.00098.2010

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

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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$_{2\text{max}}$)

2) High intensity interval training (HIIT)
   10 days of HIIT training (60s x 5 intervals, ~100% VO$_{2\text{max}}$)

➢ MV initiated 24 hours after last exercise bout
Endurance exercise attenuates ventilator-induced diaphragm dysfunction

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Submitted 31 August 2011; accepted in final form 6 November 2011
Exercise training maintains mitochondrial function and decreases ROS production during MV


4-HNE

α-tubulin

§ 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?

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
High intrinsic aerobic capacity does not protect against VIDD

Diaphragm muscle fibers cross sectional areas

Type I

Type Ila

Type IIb/x

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

Sollanek et al. 2015
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*
High intrinsic aerobic capacity

Endurance exercise training

High intensity Interval training

HSP72
**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

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

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
Thank you for your attention