May 20th, 11:15 AM

Skeletal Muscle Function Changes with Aging and Exercise: From the Myosin Molecule to the Whole Muscle

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Skeletal Muscle Function Changes with Aging and Exercise:
From the Myosin Molecule to the Whole Muscle

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Disclosure

I have no actual or potential conflict of interest in relation to this presentation.
Areas of expertise

- Molecular level
  - Myofibrillar level
  - Single fiber level
  - Whole muscle level
  - Whole body level

Muscle Function

Muscle Structure
Previous studies

Aging

Chronic heart failure decreases cross-bridge kinetics in single skeletal muscle fibres from humans

Heart Failure

Mark S. Miller¹, Peter VanBuren¹,², Martin M. LeWinter¹,², Joan M. Braddock¹, Philip A. Ades², David W. Maughan¹, Bradley M. Palmer¹ and Michael J. Toth¹,²

Cancer

Molecular mechanisms underlying skeletal muscle weakness in human cancer: reduced myosin-actin cross-bridge formation and kinetics

Knee Osteoarthritis

Muscle disuse alters skeletal muscle contractile function at the molecular and cellular levels in older adult humans in a sex-specific manner

Knee Osteoarthritis + Resistance training

Resistance training alters skeletal muscle structure and function in human heart failure: effects at the tissue, cellular and molecular levels

Heart Failure + Resistance training

Knee Osteoarthritis + Resistance training (Submitted)
Why study myosin-actin interactions in aging skeletal muscle?

- Whole skeletal muscle power output decreases with age, which leads to functional limitations and disability
- Understanding mechanisms behind muscle power loss will aid in developing pharmacological and/or exercise countermeasures

\[
\text{Power} = \text{Force} \times \text{Velocity}
\]

Are myosin-actin interactions affected by age?
If so, can these altered myosin-actin interactions explain reductions in whole muscle power output?
Age-related changes in muscle function

Molecular level

Single fiber level

Whole muscle level

Whole body level

Physical activity

Functional performance (peak O₂ consumption)
Myosin-actin interactions or cross-bridge kinetics

Myosin attachment time \( (t_{on}) \)

Myosin detachment time \( (t_{off}) \)

Time

Force

Myosin-actin cross-bridge kinetics

Myosin head number (N)

Force: 2 myosin heads
Myosin-actin cross-bridge kinetics

Myosin detachment time ($t_{off}$)
Myosin attachment time ($t_{on}$)

Isometric force ($F_{iso}$): $F_{iso} = \left[ \frac{t_{on}}{t_{on} + t_{off}} \right] N F_{XB}$
Velocity $\propto \frac{1}{t_{on}}$

Force ($F_{iso}$): $0.2 \times 10 \times F_{XB} = 2 F_{XB}$

Velocity: 1.0 ML/s

Myosin head number (N)

Shortening Velocity

MHC I Slow
MHC IIA Fast
MHC IIX Fastest
Myosin-actin cross-bridge kinetics

Myosin attachment time \((t_{on})\)

Myosin detachment time \((t_{off})\)

Isometric force \((F_{iso})\):

\[
F_{iso} = \left[ \frac{t_{on}}{t_{on} + t_{off}} \right] N F_{XB}
\]

Velocity \(\propto \frac{1}{t_{on}}\)

Myosin-actin cross-bridge kinetics

Force \((F_{iso})\): \(0.2 \times 10 \times F_{XB} = 2 F_{XB}\)

Velocity: \(1.0\) ML/s

Myosin head number (N)

1 2 3 4 5 6 7 8 9 10

Time

Maximum tension (mN/mm²)

myosin concentration (µM)

D’Antona et al. (2003) J Physiol
Myosin-actin cross-bridge kinetics

Isometric force ($F_{\text{iso}}$): $F_{\text{iso}} = \left[ \frac{t_{\text{on}}}{t_{\text{on}} + t_{\text{off}}} \right] N F_{\text{XB}}$

Velocity $\propto \frac{1}{t_{\text{on}}}$

Young

Force ($F_{\text{iso}}$): 0.2 × 10 × $F_{\text{XB}} = 2 F_{\text{XB}}$

Velocity: 1.0 ML/s

- Myosin on
- Myosin off

Hypothesis: Aging decreases single fiber force

Aging decreases single fiber velocity
Myosin-actin cross-bridge kinetics

Myosin attachment time ($t_{on}$)
Myosin detachment time ($t_{off}$)

Rate of force production

F$_{XB}$

---

Myosin strongly bound
Myosin weakly bound

---

MHC I (Slow)
MHC IIA (Fast)

Age
Age by Sex = 0.08

---

Age or Age by Sex = Significant age or age by sex difference (P<0.05)

Asterisks indicate significant difference (*** = P<0.001) between young and older females.
Age-related changes in muscle function

Molecular level

- Rate of force production
- Myosin attachment time

Single fiber level

- Isometric tension
- Contractile velocity (Predicted)

Whole muscle level

- Isometric torque
- Power = Force x Velocity

Whole body level

- Physical activity
- Functional performance (peak O₂ consumption)

Slower cross-bridge kinetics with age
Preliminary findings from knee osteoarthritis + training study

![Graph showing power (mN/mm² x ML/s) vs tension (mN/mm²) for MHC I, with curves for Male, Pre and Female, Pre.]
Preliminary findings from knee osteoarthritis + training study

MHC I

- Male, Pre
- Male, Post
- Female, Pre
- Female, Post

Train by Sex

- Bar graphs showing changes in MHC I expression before and after training.

Power (mN/mm² x ML/s) vs. Tension (mN/mm²)

- Graphs illustrating the change in power output with tension before and after training.

Sex Train by Sex

- Graphs showing the effect of sex and training on maximum tension.

Myosin attachment time or t⁻ on (ms)

- Graphs displaying the myosin attachment time before and after training for both males and females.
Future Directions

PT = Power Training, RT = Resistance Training

Previously measured

This is a novel approach in that exercise programs would be developed for clinical applications by correcting the fundamental molecular and cellular pathology of aging and disease.
Acknowledgments

Volunteers
Joan Braddock
Damien Callahan
Rich Lachapelle
Michael Previs
Bertrand Tanner
Kimberly Ward
Katie Bedard
Nicholas Bedrin*
James Berking*
Hilary Kulakowski
Mariel Maling
Andrew Sweeney*
Juliana Yellin

CRC Staff
Philip Ades
Michael Toth
Brad Palmer
David Maughan
Jim Vigoreaux

* indicates individuals who were under the age of 18 at the time of the event.
Isolate and “skin” single muscle fiber.

Mount fiber with t-clips to force transducer and servo motor.

Measure elastic modulus, viscous modulus, and work output by oscillating the muscle from 0.125 to 200 Hz (sinusoidal analysis).

Expose fiber to exposed to different Ca$^{2+}$ conditions.

Use sinusoidal analysis and curve fitting parameters to calculate a myosin attachment time ($t_{on}$).

Palmer et al. (2007) Biophys J
Curve fitting parameters for sinusoidal analysis data

\[ Y(\omega) = A(i\omega)^k - B \left( \frac{i\omega}{2\pi b + i\omega} \right) + C \left( \frac{i\omega}{2\pi c + i\omega} \right) \]

\((2\pi c)^{-1}\) is equivalent to myosin attachment time \((t_{on})\)

Palmer et al. (2007) Biophys J