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

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Institute for Applied Life Sciences

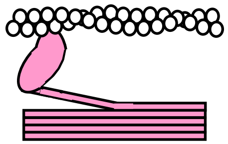
Advancing Life Sciences Research to Improve Human Health

Disclosure

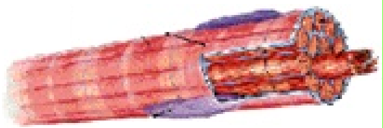
I have no actual or potential conflict of interest in relation to this presentation.

Areas of expertise

Molecular level



Single fiber level

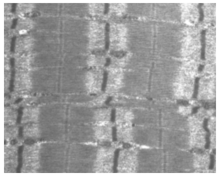


Whole muscle level

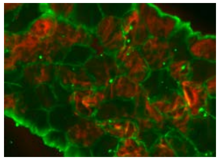
Whole body level

Muscle Function

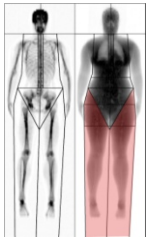
Myofibrillar level



Single fiber level



Whole muscle level



Muscle Structure

Previous studies

Aging

J Appl Physiol 115: 1004–1014, 2013.
First published July 25, 2013; doi:10.1152/japplphysiol.00563.2013.

Age-related slowing of myosin actin cross-bridge kinetics is sex specific and predicts decrements in whole skeletal muscle performance in humans

Mark S. Miller,[1] Nicholas G. Bedrin,[1] Damien M. Callahan,[2] Michael J. Previs,[1] Mark E. Jennings II,[2] Philip A. Ades,[2] David W. Maughan,[1] Bradley M. Palmer,[1] and Michael J. Toth[1,2]

Heart Failure

J Physiol 588.20 (2010) pp 4039–4053

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

Mark S. Miller[1], Peter VanBuren[1,2], Martin M. LeWinter[1,2], Joan M. Braddock[1], Philip A. Ades[2], David W. Maughan[1], Bradley M. Palmer[1] and Michael J. Toth[1,2]

Cancer

J Appl Physiol 114: 858–868, 2013.
First published February 14, 2013; doi:10.1152/japplphysiol.01474.2012.

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

Michael J. Toth,[1,2] Mark S. Miller,[2] Damien M. Callahan,[1] Andrew P. Sweeny,[1] Ivette Nunez,[1] Steven M. Grunberg,[1] Hirak Der-Torossian,[3] Marion E. Couch,[3] and Kim Dittus[1]

Knee Osteoarthritis (disuse model)

J Physiol 592.20 (2014) pp 4555–4573

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

Damien M. Callahan[1], Mark S. Miller[2], Andrew P. Sweeny[1], Timothy W. Tourville[3], James R. Slauterbeck[3], Patrick D. Savage[1], David W. Maugan[2], Philip A. Ades[1], Bruce D. Beynnon[3] and Michael J. Toth[1,2]

Heart Failure + Resistance training

J Physiol 590.5 (2012) pp 1243–1259

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

Michael J. Toth[1,2], Mark S. Miller[2], Peter VanBuren[1,2], Nicholas G. Bedrin[2], Martin M. LeWinter[1,2], Philip A. Ades[1] and Bradley M. Palmer[2]

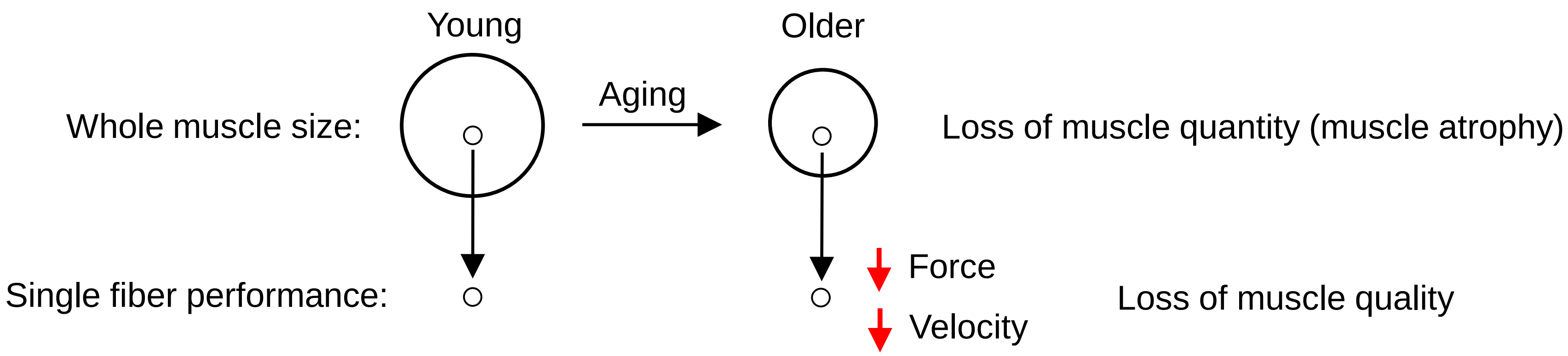
Knee Osteoarthritis + Resistance training (Submitted)

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

Power = Force × Velocity

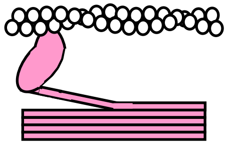


Are myosin-actin interactions affected by age?

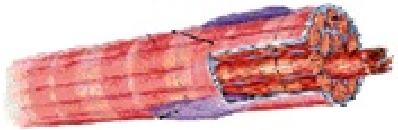
If so, can these altered myosin-actin interactions explain reductions in whole muscle power output?

Age-related changes in muscle function

Molecular level



Single fiber level



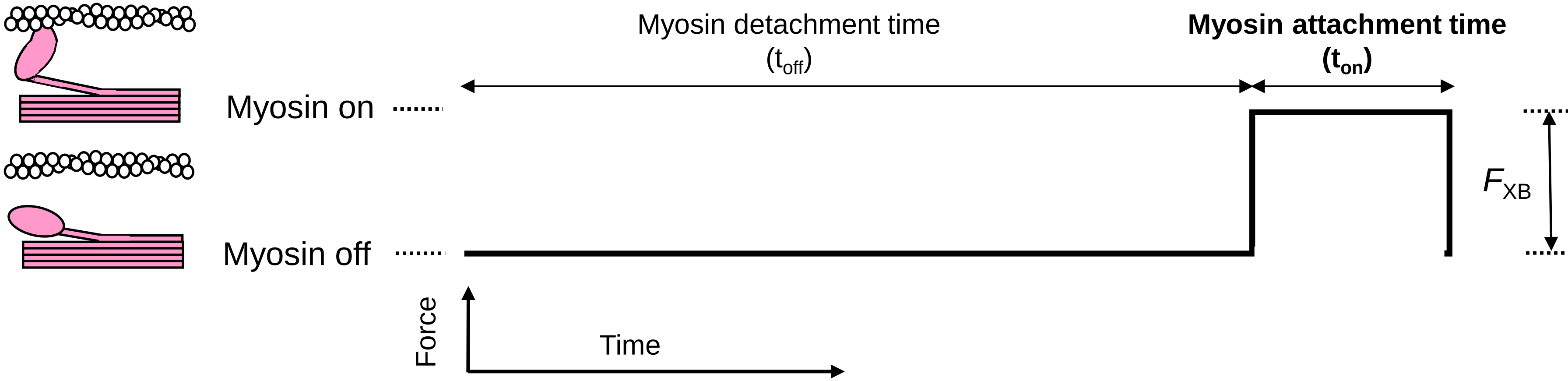
Whole muscle level

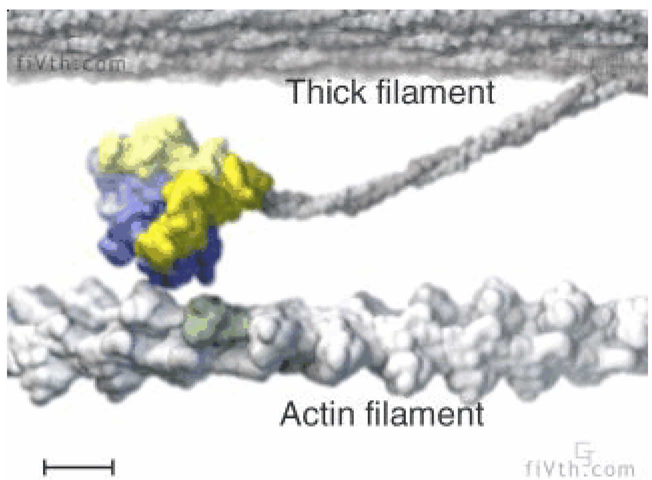
Whole body level

↔ Physical activity

↓ Functional performance (peak O_2 consumption)

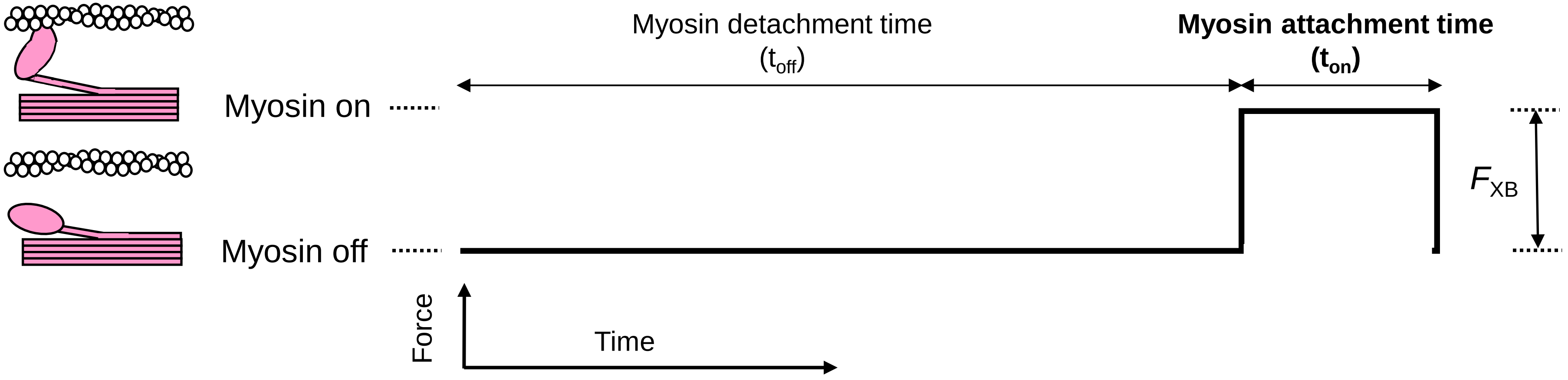
Myosin-actin interactions or cross-bridge kinetics



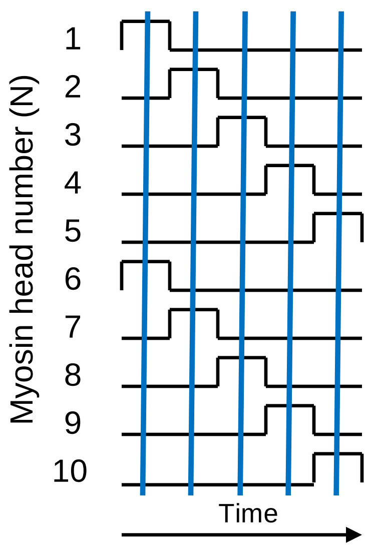


Vale and Milligan (2000) *Science*

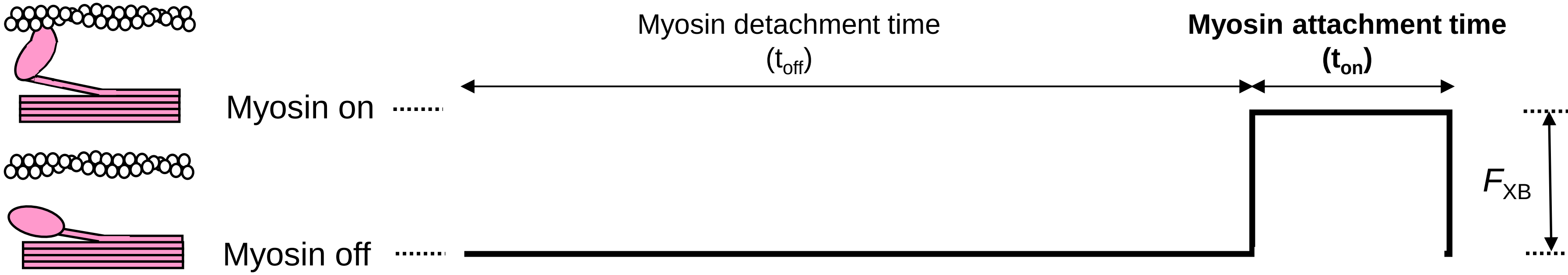
Myosin-actin cross-bridge kinetics



Force: **2 myosin heads**



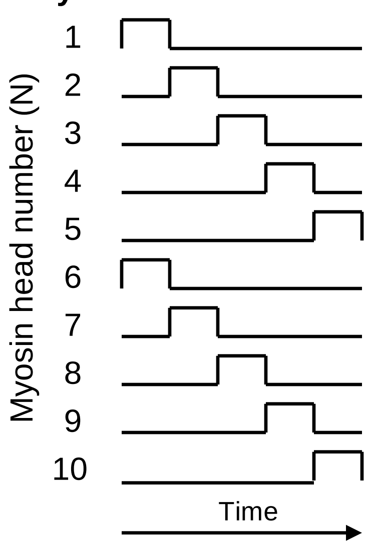
Myosin-actin cross-bridge kinetics



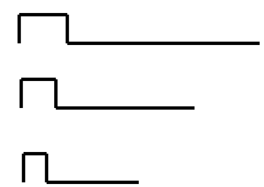
Isometric force (F_{Iso}): $F_{Iso} = \left[\dfrac{t_{on}}{t_{on} + t_{off}} \right] N\, F_{XB}$ Velocity $\propto \dfrac{1}{t_{on}}$

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

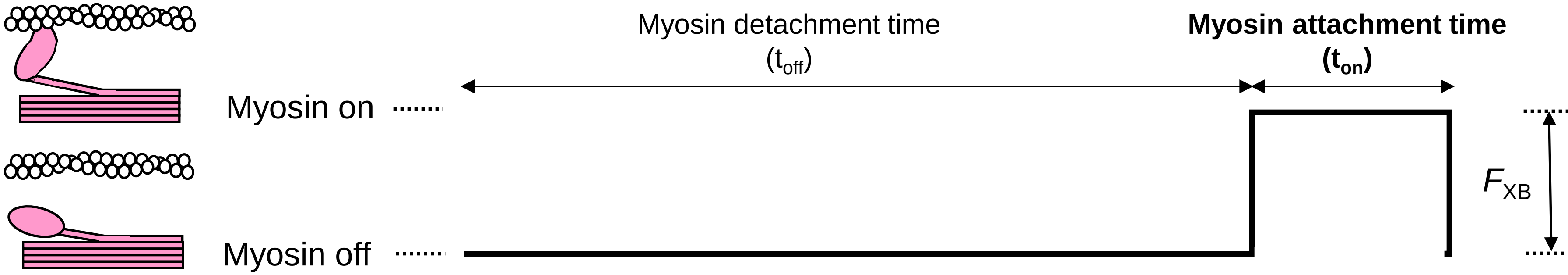
Velocity: **1.0 ML/s**



	Shortening Velocity
MHC I	Slow
MHC IIA	Fast
MHC IIX	Fastest



Myosin-actin cross-bridge kinetics



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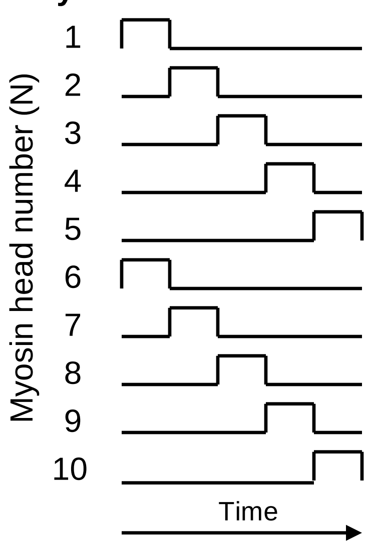
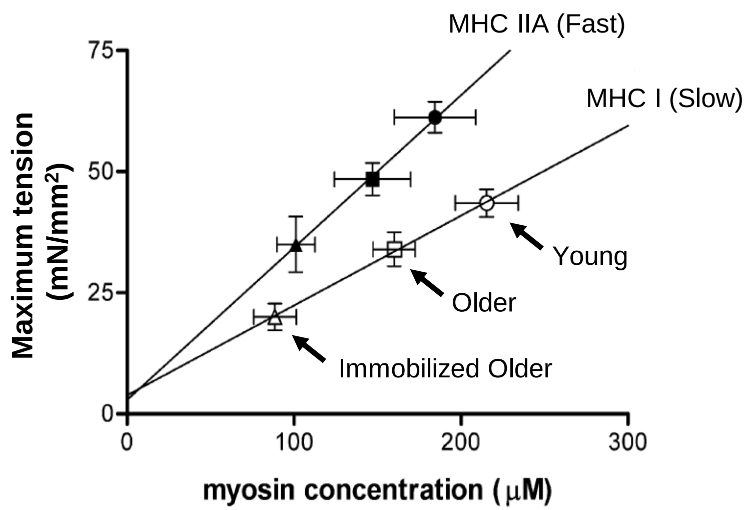
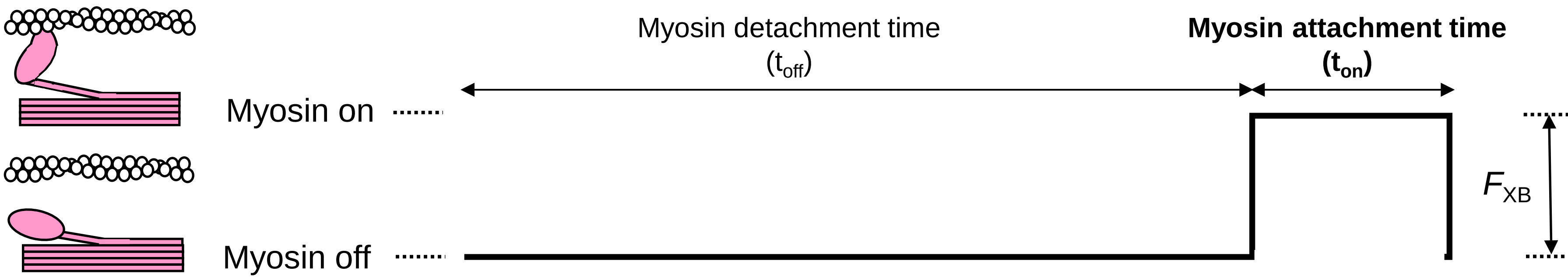




D'Antona et al. (2003) *J Physiol*

Myosin-actin cross-bridge kinetics



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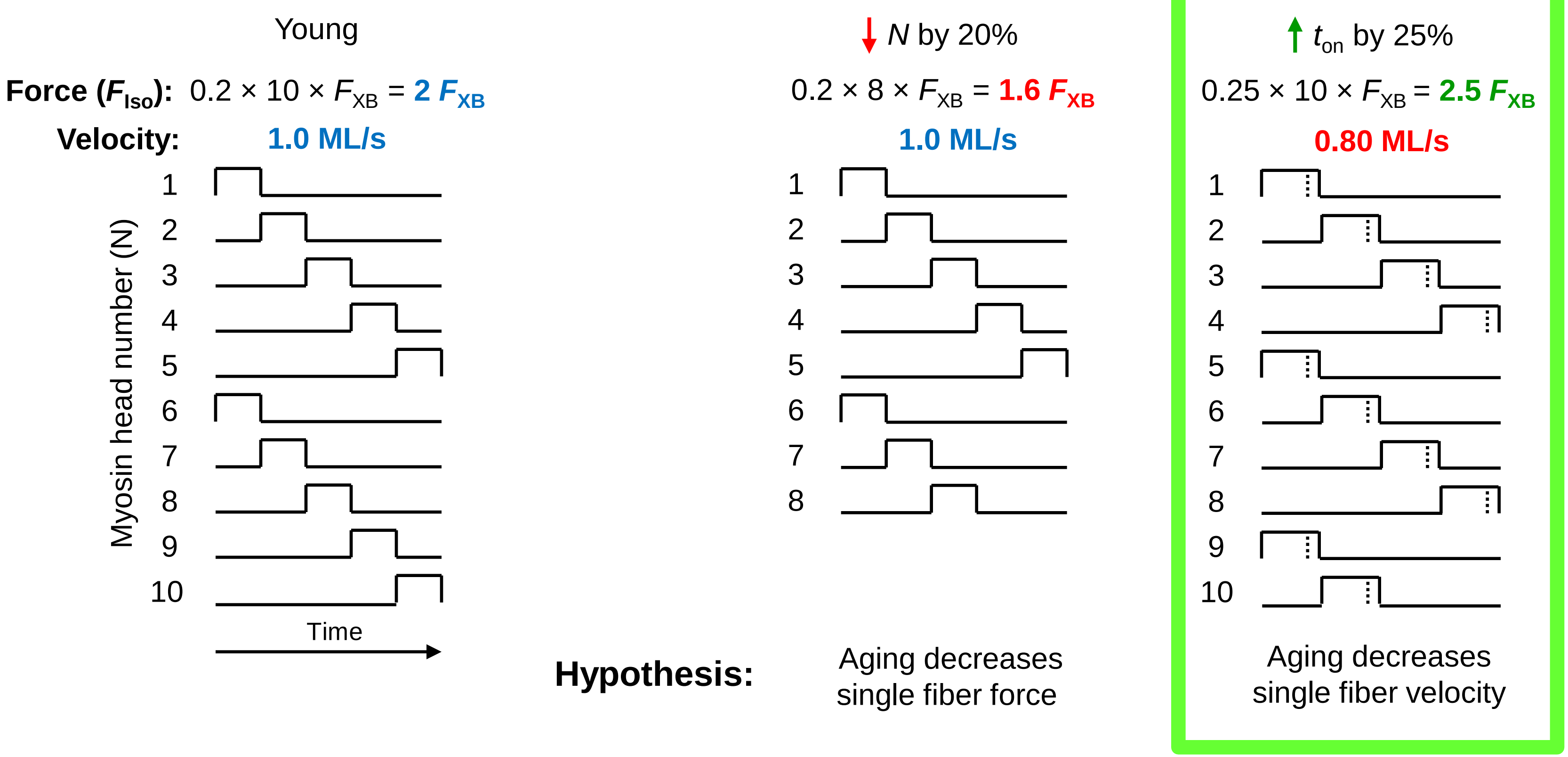
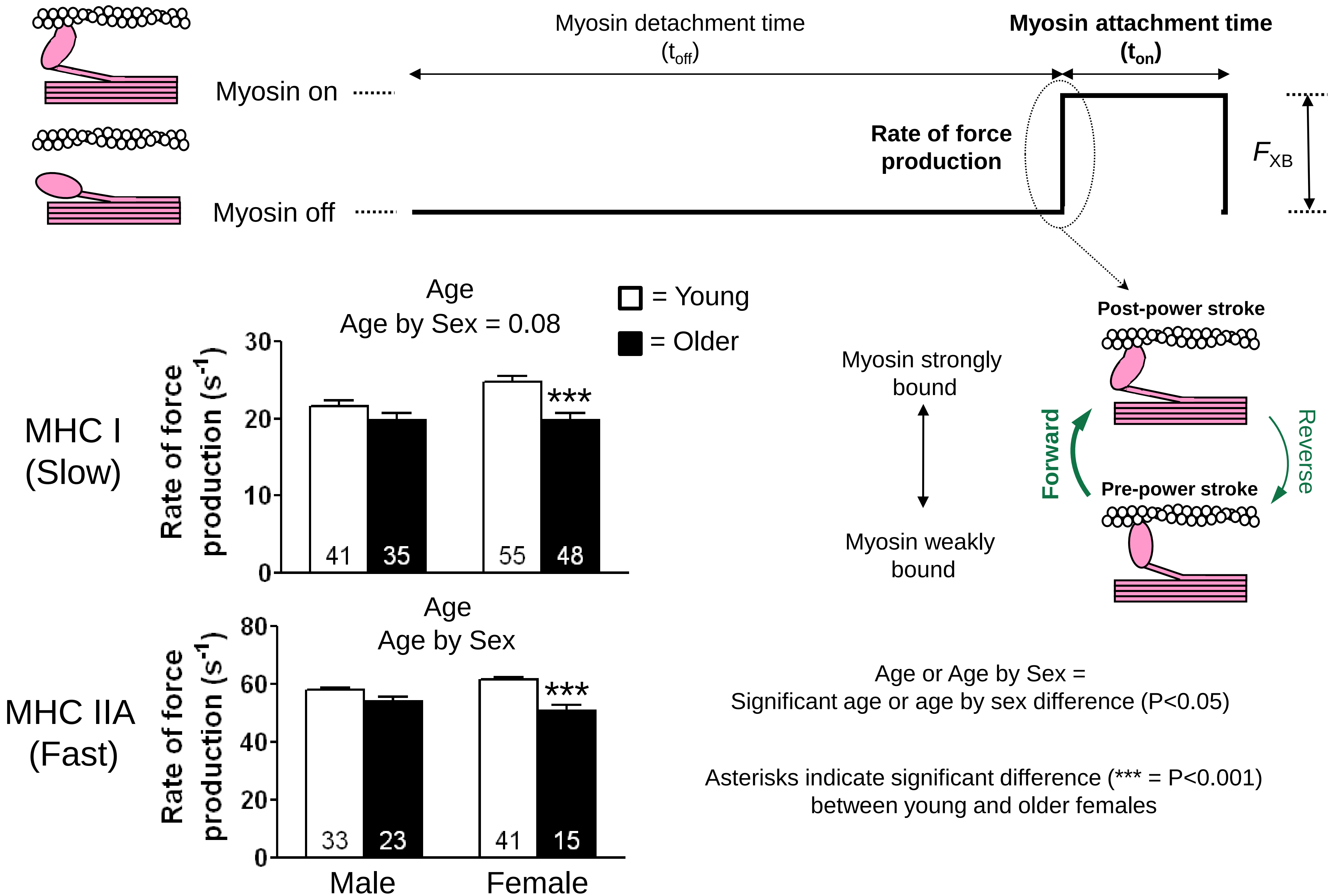


Hypothesis: Aging decreases single fiber force

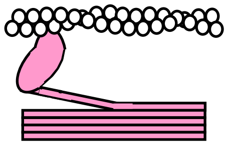
Aging decreases single fiber velocity

Myosin-actin cross-bridge kinetics



Age-related changes in muscle function

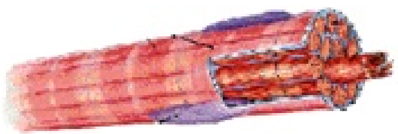
Molecular level



↓ Rate of force production
↑ Myosin attachment time

Slower cross-bridge kinetics with age

Single fiber level



↑ Isometric tension

↓ Contractile velocity **(Predicted)**

Correlated

Whole muscle level

↔ Isometric torque

↓ Isokinetic power

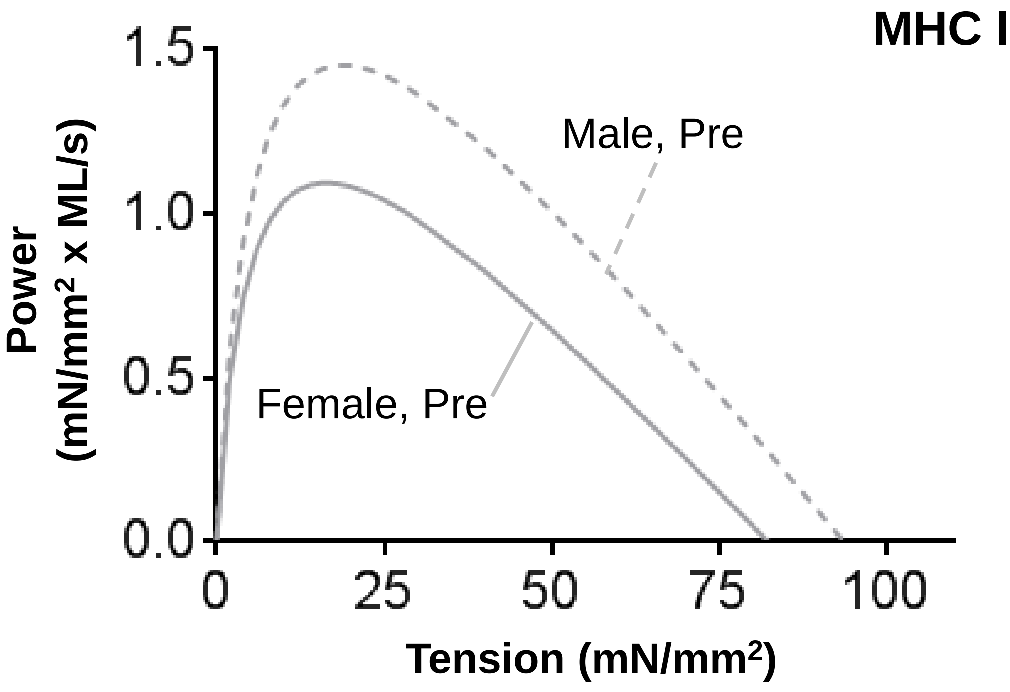
Power = Force x Velocity

Whole body level

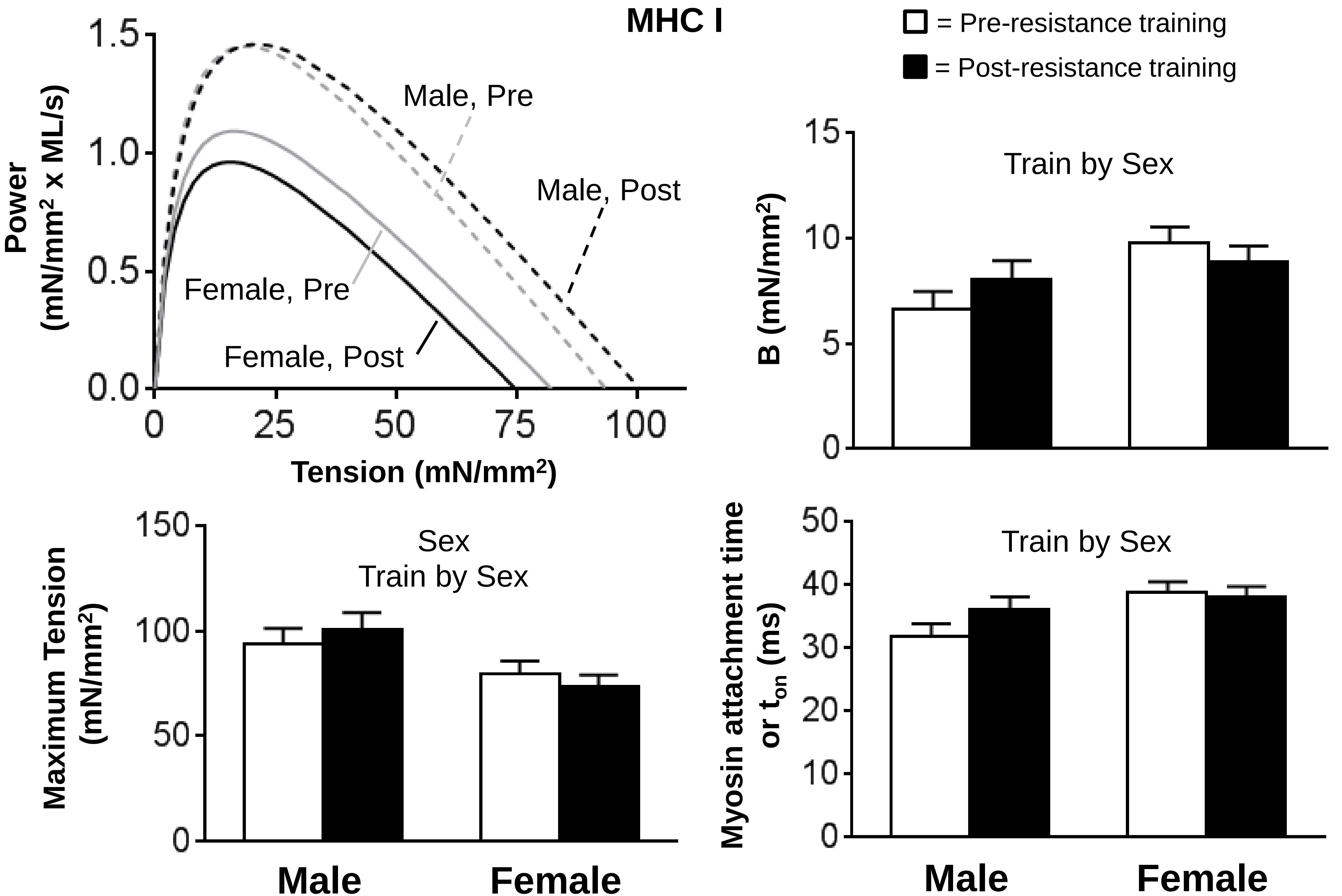
↔ Physical activity

↓ Functional performance (peak O_2 consumption)

Preliminary findings from knee osteoarthritis + training study

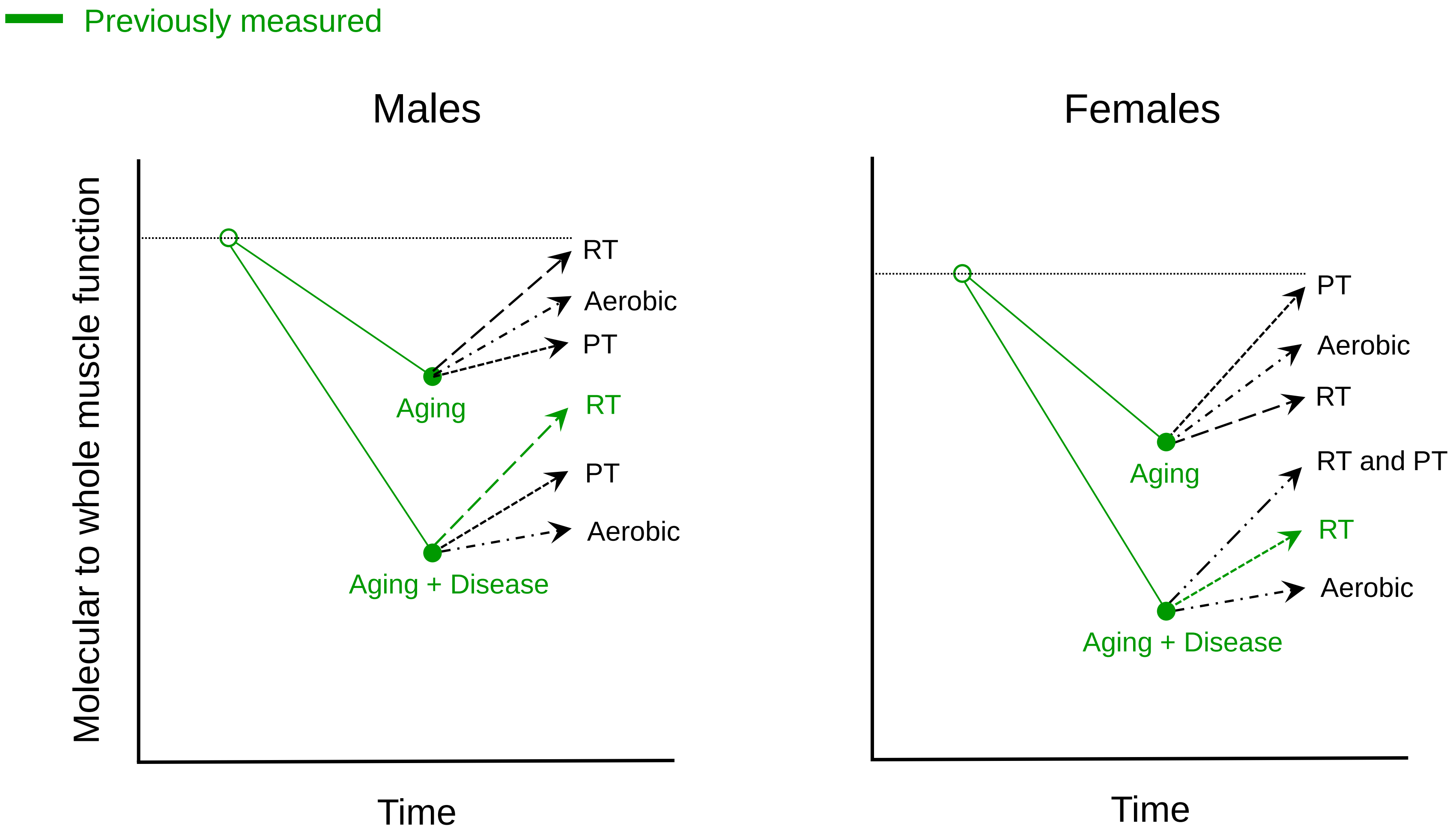


Preliminary findings from knee osteoarthritis + training study



Future Directions

PT = Power Training, RT = Resistance Training



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

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Philip Ades
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Brad Palmer
David Maughan
Jim Vigoreaux

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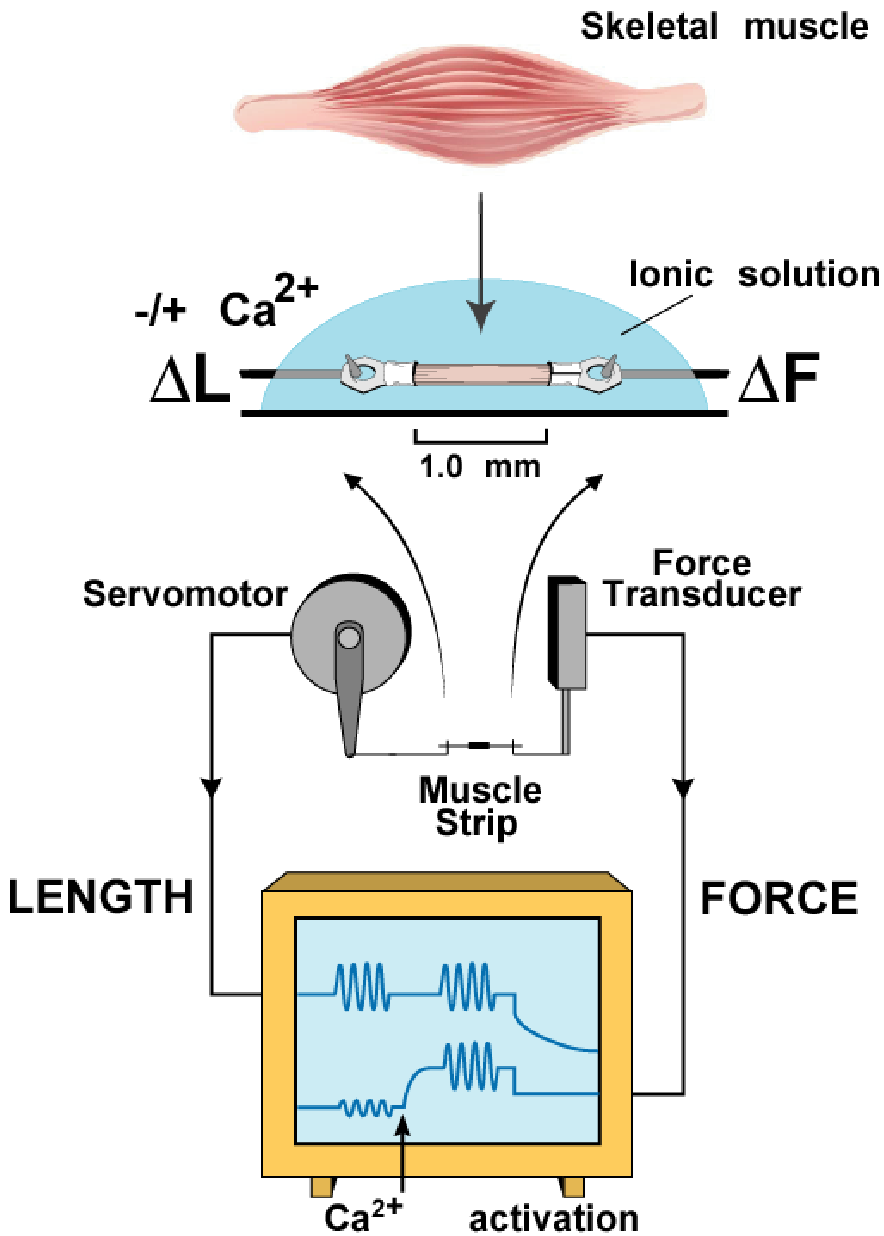
Rich Lachapelle
Michael Previs
Bertrand Tanner
Kimberly Ward

Katie Bedard
Nicholas Bedrin*
James Berking*
Hilary Kulakowski
Mariel Maling
Andrew Sweeney*
Juliana Yellin

Single skinned fiber muscle mechanics (sinusoidal analysis)



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

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

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

Palmer et al. (2007) *Biophys J*