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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
- Whole muscle level
- Whole body level

Single fiber level
- Whole muscle level
- Whole body level

Whole muscle level

Muscle Function
- Single fiber level

Muscle Structure
- Whole muscle level
- Whole body level
Previous studies

Aging

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

Heart Failure

Knee Osteoarthritis (disuse model)

Cancer

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

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

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

Myosin detachment time ($t_{off}$)

Myosin attachment time ($t_{on}$)

Time

Force

$F_{XB}$

Myosin-actin cross-bridge kinetics

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

Myosin on  .........  Myosin off  .........

Force  Time

2 myosin heads

Time
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

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

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

Velocity: 1.0 ML/s

Myosin head number (N)

Myosin on

Myosin off

Shortening Velocity

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

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

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

Myosin detachement 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 \( \propto \frac{1}{t_{on}} \)

Hypothesis:
Aging decreases single fiber force
Aging decreases single fiber velocity

Young

Force (F_{iso}): \( 0.2 \times 10 \times F_{XB} = 2 F_{XB} \)
Velocity: 1.0 ML/s

\begin{align*}
\text{Myosin head number (N)} & \\
1 & \uparrow \\
2 & \uparrow \\
3 & \uparrow \\
4 & \uparrow \\
5 & \uparrow \\
6 & \uparrow \\
7 & \uparrow \\
8 & \uparrow \\
9 & \uparrow \\
10 & \uparrow \\
\end{align*}

\begin{align*}
\text{Time} & \\
1 & \uparrow \\
2 & \uparrow \\
3 & \uparrow \\
4 & \uparrow \\
5 & \uparrow \\
6 & \uparrow \\
7 & \uparrow \\
8 & \uparrow \\
9 & \uparrow \\
10 & \uparrow \\
\end{align*}

Down N by 20%

\( 0.2 \times 8 \times F_{XB} = 1.6 F_{XB} \)

\begin{align*}
\text{Velocity} & \\
1.0 \text{ ML/s} & \uparrow \\
0.80 \text{ ML/s} & \uparrow \\
\end{align*}

\begin{align*}
\text{Myosin head number (N)} & \\
1 & \uparrow \\
2 & \uparrow \\
3 & \uparrow \\
4 & \uparrow \\
5 & \uparrow \\
6 & \uparrow \\
7 & \uparrow \\
8 & \uparrow \\
9 & \uparrow \\
10 & \uparrow \\
\end{align*}

\begin{align*}
\text{Time} & \\
1 & \uparrow \\
2 & \uparrow \\
3 & \uparrow \\
4 & \uparrow \\
5 & \uparrow \\
6 & \uparrow \\
7 & \uparrow \\
8 & \uparrow \\
9 & \uparrow \\
10 & \uparrow \\
\end{align*}

\begin{align*}
\text{Aging decreases single fiber force} & \\
\text{Aging decreases single fiber velocity} &
\end{align*}
Myosin-actin cross-bridge kinetics

Myosin attachment time ($t_{on}$)

Myosin detachment time ($t_{off}$)

Rate of force production

$F_{XB}$

Myosin weakly bound

Myosin strongly bound

Forward

Post-power stroke

Pre-power stroke

Reverse

Age by Sex = 0.08

Age

Age by Sex

$= $ Young

$= $ Older

Asterisks indicate significant difference (*** = P<0.001) between young and older females

MHC I (Slow)

Rate of force production (s$^{-1}$)

Age

Age by Sex

Female

Male

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

MHC IIA (Fast)
Age-related changes in muscle function

Molecular level
- Rate of force production
  ↓
- Myosin attachment time
  ↑
  \[\text{Slower cross-bridge kinetics with age}\]

Single fiber level
- Isometric tension
  ↑
- Isometric torque
  ←
- Contractile velocity
  ↓
  \(\text{Predicted}\)

Whole muscle level
- Isokinetic power
  ↓
  \[\text{Power} = \text{Force} \times \text{Velocity}\]

Whole body level
- Physical activity
  ←
- Functional performance
  ↓
  \(\text{peak} \ O_2 \ \text{consumption}\)
Preliminary findings from knee osteoarthritis + training study

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

**MHC I**

- Pre-resistance training
- Post-resistance training

Myosin attachment time or $t_{on}$ (ms)

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

**Power**

- Maximum Tension (mN/mm²)

- Train by Sex

- B (mN/mm²)

- Male
- Female

- Myosin attachment time or $t_{on}$ (ms)

- Male
- Female
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.
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Turning Discovery Into Health
Single skinned fiber muscle mechanics (sinusoidal analysis)

1. Isolate and “skin” single muscle fiber.
2. Mount fiber with t-clips to force transducer and servo motor.
3. Measure elastic modulus, viscous modulus, and work output by oscillating the muscle from 0.125 to 200 Hz (sinusoidal analysis).
4. Expose fiber to different Ca\(^{2+}\) conditions.
5. 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*