Exercise-mediated reductions in oxidative stress and inflammation: Impact on vascular aging

LISA A LESNIEWSKI, PH.D.

UNIVERSITY OF UTAH, DEPARTMENT OF INTERNAL MEDICINE, DIVISION OF GERIATRICS

SALT LAKE CITY VETERAN’S AFFAIRS MEDICAL CENTER, GERIATRICS RESEARCH EDUCATION AND CLINICAL CENTER
Physical activity reduces mortality across individuals with a variety of risk factors.
Physical fitness reduces all cause mortality across all ages

Men (N=10244)  
Women (N=3120)

Blair et al. JAMA (1989)262:2395
Running reduces all cause and CVD mortality

Aging is a major risk factor for CVD

Increases in large artery stiffness and endothelial dysfunction characterize age-associated arterial dysfunction that is associated with increased CVD risk.

Adapted from Santos-Parker, LaRocca & Seals. *Advanc In Physiol Edu* (2014)
Aerobic exercise reduces CVD risk, but how?

Adapted from Santos-Parker, LaRocca & Seals. Advanc In Physiol Edu (2014)
Aerobic exercise reduces arterial stiffness in old mice

Citrate Synthase (mol/min/g)

<table>
<thead>
<tr>
<th></th>
<th>Young CC</th>
<th>Old CC</th>
<th>Young VR</th>
<th>Old VR</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 ± 1</td>
<td>21 ± 1</td>
<td>23 ± 1*</td>
<td>24 ± 1*†</td>
<td></td>
</tr>
</tbody>
</table>

Aerobic exercise reduces arterial stiffness in old mice

Aerobic exercise reduces arterial stiffness and collagen in the large elastic arteries of old mice
Aerobic exercise reduces arterial collagen contributing to decreased stiffness.
Aerobic exercise reduces CVD risk. What are the effects on endothelial function?

Adapted from Santos-Parker, LaRocca & Seals. *Advanc In Physiol Edu* (2014)
Aerobic exercise improves endothelial function in old mice

Durrant et al. J Physiol (2009)
Aerobic exercise reduces oxidative stress in arteries of old mice

Aerobic exercise reduces NADPH oxidase (oxidant) enzyme expression and activity in arteries of old mice
Aerobic exercise increases superoxide dismutase (antioxidant) activity in arteries from old mice

Durrant et al. J Physiol (2009)
Oxidative stress, via NADPH oxidase, suppresses endothelial function in old cage control mice

Improvement in dilation after reducing superoxide with a SOD mimetic

Improvement in dilation after inhibiting NADPH oxidase

Durrant et al. J Physiol (2009)
Aerobic exercise improves endothelial function in old mice by reducing NADPH oxidase derived superoxide

Durrant et al. J Physiol (2009)

Improvement in dilation after VR
Oxidative stress suppresses endothelial function with aging
Aerobic exercise improves arterial function in old mice by reducing oxidative stress.
Aging is also associated with a pro-inflammatory arterial phenotype.

Inflammation induces arterial oxidative stress via NADPH oxidase in old mice

Inflammation-associated superoxide production suppresses endothelial function in old mice

Superoxide mediated suppression of dilation absent after anti-inflammatory, salicylate treatment
Aerobic exercise improves arterial function in old mice by reducing oxidative stress.
Aerobic exercise reduces inflammatory cytokines in arteries of old mice

IL-1β

IL-6

IFN-γ

TNF-α

Lesniewski et al. AJP Heart (2011)
Aerobic exercise reduces macrophage infiltration in arteries from old mice

Lesniewski et al. AJP Heart (2011)
Aerobic exercise improves arterial function in old mice by reducing oxidative stress.
Similar reductions in oxidative stress and inflammation in endothelial cells from exercise trained older adults

**OXIDATIVE STRESS**

Nitrotyrosine

NADPH Oxidase

Superoxide Dismutase

**INFLAMMATION**

NFkB

Pierce et al. Aging Cell (2011)
Similar reductions in oxidative stress and inflammation in endothelial cells from exercise trained older adults were associated with improved endothelial function.

<table>
<thead>
<tr>
<th>Brachial artery function</th>
<th>Young Sedentary (n=20)</th>
<th>Older Sedentary (n=28)</th>
<th>Older Exercising (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline diameter (mm)</td>
<td>4.0 ± 0.09</td>
<td>4.1 ± 0.1</td>
<td>3.8 ± 0.09</td>
</tr>
<tr>
<td>Baseline shear rate (sec⁻¹)</td>
<td>---</td>
<td>14 ± 2</td>
<td>18 ± 7</td>
</tr>
<tr>
<td>Flow-mediated dilation (%Δ)</td>
<td>7.1 ± 0.5</td>
<td>4.9 ± 0.4*</td>
<td>6.3 ± 0.5†</td>
</tr>
<tr>
<td>Flow-mediated dilation (mm Δ)</td>
<td>0.28 ± 0.02</td>
<td>0.20 ± 0.01*</td>
<td>0.24 ± 0.02†</td>
</tr>
<tr>
<td>Peak shear rate during FMD (sec⁻¹)</td>
<td>---</td>
<td>104 ± 5</td>
<td>109 ± 9</td>
</tr>
<tr>
<td>Dilation to sublingual GTN (%Δ)</td>
<td>25 ± 2 (n=16)</td>
<td>25 ± 1 (n=18)</td>
<td>27 ± 2 (n=8)</td>
</tr>
<tr>
<td>Dilation to sublingual GTN (mm Δ)</td>
<td>0.97 ± 0.07 (n=16)</td>
<td>0.99 ± 0.05 (n=18)</td>
<td>1.02 ± 0.06 (n=8)</td>
</tr>
</tbody>
</table>

Data are mean ± standard error.

Pierce GL et al. Aging Cell (2011)
Blunted inflammation and oxidative stress in endothelial cells from exercise trained older adults

Blunted inflammation and oxidative stress in endothelial cells from exercise trained older adults were associated with improved endothelial function

Summary

Aging

- Upward arrow for collagen
- Upward arrow for oxidative stress
- Upward arrow for inflammation

Arterial Dysfunction

- Downward arrow for endothelial function

Aerobic Exercise

- Upward arrow for arterial stiffness
- Upward arrow for antioxidants & downward arrow for oxidants
- Downward arrow for cytokines, macrophages, & inflammatory signaling
Integrative Physiology of Aging Laboratory, University of Colorado at Boulder

Douglas Seals, Ph.D.
Jessica Durrant, D.V.M.
Melanie Connell, M.S.
Bradley Fleenor, Ph.D.
Molly Nowlan, M.S.
Brooke Lawson, M.S.
Brian Folian, M.S., J.D.
Alexander Black, M.S.
Martin Anderson, M.S.
Kurt Marshall, M.S.
Gary L. Pierce, Ph.D.
Thomas J. LaRocca, Ph.D.
Iratxe Eskurza, M.D.
Annemarie E. Silver, Ph.D.

Translational Vascular Physiology Laboratory, University of Utah and SLC-VAMC GRECC

TVP Laboratory
Anthony Donato, Ph.D.
Ashley Walker, Ph.D.
Grant Henson, M.S.

Funding: NIH
AG006537  AG000279
AG013038  AG033196
AG029337  AG033755
AG039210  UL1 RR025780
CVD is the Leading Cause of Death in the U.S.

Source: American Heart Association
Aging is a \textit{the} major risk factor for CVD

Majority of CVD deaths due to vascular disorders

Source: American Heart Association
Aerobic exercise reduces immune cell infiltration in arteries from old mice
Arterial stiffness increases in the large elastic arteries with advancing age

- Large elastic arteries buffer pulse wave after blood is ejected from the heart
- Expand and recoil of these arteries:
  - Maintains constant blood flow to periphery
  - Reduces pulse wave reaching periphery
- Assessing stiffness in animal models:
  - *In vivo*: Pulse wave velocity
  - *Ex vivo*: Passive mechanical properties

Santos-Parker, LaRocca & Seals, Advan In Physiol Edu 2014
Arterial stiffness increases in the large elastic arteries with advancing age

**In Vivo**

- Pulse Wave Velocity (cm/s)
  - YC
  - YHF
  - OC
  - OHF

**Ex Vivo**

- Diameter normalized to 100 mmHg
- Incremental Stiffness (AU)
  - Young
  - Old

---

*Henson et al. Physiol Reports 2014*

*Lesniewski et al. J Gerontol Biol Sci 2009*
Increased arterial stiffness in old mice is associated with structural changes
Aging increases large artery stiffness

Adapted from Santos-Parker, LaRocca & Seals. Advanc In Physiol Edu 2014
Healthy, normally functioning vascular endothelium

Anti-Atherosclerotic Phenotype
“Vascular Endothelial Dysfunction”: generalized alteration in endothelial cell function

Impaired vascular endothelium-dependent dilation (EDD), characterized by the loss of endothelium-derived nitric oxide (NO) production, is the central feature of endothelial dysfunction.
Aging is associated with endothelial dysfunction
Aging is associated with endothelial dysfunction

Aging is associated with oxidative stress and inflammation-mediated endothelial dysfunction.
Aging is associated with oxidative stress and inflammation-mediated endothelial dysfunction

Aging is associated with oxidative stress and inflammation-mediated endothelial dysfunction.