Passive Leg Movement-Induced Vasodilation: Impact of Aging and Physical Activity

H. Jonathan Groot
Outline

• Cardiovascular Aging
  – Cardiovascular Disease (CVD) prevalence

• Attenuated Vascular Function with Age
  – Ach and SNP infusions
  – Flow-Mediated Vasodilation (FMD)

• The Passive Leg Movement (PLM) Model
  – Changes with age
  – Effect of physical activity
CVD Prevalence

• #1 cause of Morbidity/mortality in developed nations
  – Accounts for 1 in 3 deaths per year in the US

Go et al. (2013), Lakatta & Levy (2003), Lloyd-Jones et al. (1996), Lloyd-Jones et al. (2010)
Major Causes of Death in the USA

Lloyd-Jones et al. (2010) *Circulation*
CVD Prevalence

• #1 cause of Morbidity/mortality in developed nations
  – Accounts for 1 in 3 deaths per year in the US

• Rate of first CVD events increases 25 fold between the ages of 40 and 90

Go et al. (2013), Lakatta & Levy (2003), Lloyd-Jones et al. (1996), Lloyd-Jones et al. (2010)
Aging and CVD Prevalence

NHANES 2009

% US Population

Coronary  Hypertension  Stroke

- 18-44
- 45-64
- 65-74
- >75

- Coronary
- Hypertension
- Stroke
Vascular Function is an independent predictor of CVD risk

Heitzer et al. (2001), Lind et al. (2011), Van Sloten et al. (2014)
Endothelium Dependent Vascular Function Declines with advancing age
Infusion of Ach and SNP

Limitations

DeSouza et al. (2000) Circulation
Flow-Mediated Dilation (FMD)
Flow-Mediated Dilation (FMD)

Celermajer et al. (1994) *JACC*

Wray et al. (2012) *Hypertension*
Limitations of FMD

Green et al. (2013) *MSSE*
Vascular Function Assessed by Passive Leg Movement (PLM)
Ultrasound Doppler During PLM

PLM Begins

EXERCISE
Vasodilatory Response to PLM

Groot et al. (2013) *AJP Heart & Circ.*
Salt Lake City Inversion

Daily Average PM$_{2.5}$ Pollution in Salt Lake City Winter 2013-2014

- Unhealthy
- Unhealthy for Sensitive Groups
- Moderate
- Good

Data from epa.gov/aiodata

physioloco.blogspot.com
Pollution and PLM-Induced Dilation

Gifford et al.
Attenuated PLM-Induced Vasodilation With Age

McDaniel et al. (2010) *J Physiol*
NO-Mediated Vascular Function

Shear Stress, Insulin, Ach, estrogen, etc.

Endothelial Cell

Vessel Lumen

Ca²⁺

eNOS

Akt
AMPK
PKA
CaM K II

NO

GTP

GC

NO

cGMP

PKG

Ca²⁺

PKG

Akt
AMPK
PKA
CaM K II

Ca²⁺

Ca²⁺

Ca²⁺
NO is Antiatherogenic
PLM is Predominantly NO-Mediated

Attenuated NO-Mediated Vascular Function with Age

Trinity et al. (2015) AJP Heart & Circ
Postural alterations increase femoral perfusion pressure (FPP)

Mean FAP = 90 mmHg
Mean FVP = 5 mmHg
Femoral PP = 85 mmHg

Delta 8 mmHg

Mean FAP = 115 mmHg
Mean FVP = 22 mmHg
Femoral PP = 93 mmHg

Groot et al. (2013) *AJP Heart & Circ.*
Postural Alterations During PLM

Groot et al. (2015) Submitted
Effect of eNOS Inhibition

Groot et al. (2015) Submitted
Vasodilatory Reserve

Groot et al. (2015) Submitted
Rapid Vasodilation

Groot et al. (2015) Submitted
What We Know

• CVD prevalence increases with advancing age

• Vascular function, an independent predictor of CVD risk, decreases with advancing age

• The response to PLM, a novel method of assessing NO-mediated vascular function, is decreased with age
What We Don’t Know

What impact does physical activity have on the PLM response in human aging?
Subjects

44 healthy men

- 12 young sedentary (18-25 yrs)
- 12 older sedentary (65+ yrs)
- 10 older physically active (65+ yrs)
- 10 older endurance trained (65+ yrs)

• No CVD or metabolic disease, non-smokers
<table>
<thead>
<tr>
<th>Subject Characteristics</th>
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Table 1: Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Old Sedentary</th>
<th>Old Active</th>
<th>Old Trained</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Age (y)</td>
<td>23 ± 1</td>
<td>73 ± 2#</td>
<td>71 ± 2#</td>
<td>72 ± 1#</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>176 ± 2</td>
<td>176 ± 1</td>
<td>180 ± 2</td>
<td>177 ± 1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75 ± 3</td>
<td>82 ± 4</td>
<td>77 ± 3</td>
<td>71 ± 1§</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.2 ± 0.9</td>
<td>26.4 ± 1.1</td>
<td>24.0 ± 0.6</td>
<td>22.6 ± 0.4§</td>
</tr>
<tr>
<td>Thigh Vol (dL)</td>
<td>70 ± 3</td>
<td>65 ± 3</td>
<td>66 ± 3</td>
<td>67 ± 2</td>
</tr>
<tr>
<td>FA Diameter (cm)</td>
<td>0.90 ± 0.02</td>
<td>1.01 ± 0.05</td>
<td>1.10 ± 0.06#</td>
<td>1.15 ± 0.04#</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>72 ± 3</td>
<td>73 ± 3</td>
<td>81 ± 3</td>
<td>90 ± 4#§</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>163 ± 12</td>
<td>182 ± 8</td>
<td>178 ± 8</td>
<td>197 ± 11</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>114 ± 29</td>
<td>93 ± 11</td>
<td>73 ± 6</td>
<td>56 ± 2§†</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>45 ± 3</td>
<td>50 ± 3</td>
<td>54 ± 4#</td>
<td>86 ± 5#§†</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>101 ± 9</td>
<td>117 ± 7</td>
<td>113 ± 7</td>
<td>111 ± 6</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>15.8 ± 0.3</td>
<td>15.3 ± 0.2</td>
<td>15.0 ± 0.4</td>
<td>14.7 ± 0.3#</td>
</tr>
<tr>
<td>WBC (K/ul)</td>
<td>5.7 ± 0.2</td>
<td>5.5 ± 0.3</td>
<td>5.9 ± 0.4</td>
<td>5.9 ± 0.4</td>
</tr>
<tr>
<td>Neutrophil (K/ul)</td>
<td>3.0 ± 0.2</td>
<td>3.2 ± 0.2</td>
<td>3.6 ± 0.3</td>
<td>3.5 ± 0.3</td>
</tr>
<tr>
<td>Lymphocyte (K/ul)</td>
<td>2.0 ± 0.1</td>
<td>1.7 ± 0.2</td>
<td>1.6 ± 0.1#</td>
<td>1.8 ± 0.1</td>
</tr>
<tr>
<td>Monocyte (K/ul)</td>
<td>0.52 ± 0.02</td>
<td>0.48 ± 0.03</td>
<td>0.49 ± 0.03</td>
<td>0.50 ± 0.05</td>
</tr>
</tbody>
</table>

#p<0.05 compared to Young
§p<0.05 compared to Old Sedentary
†p<0.05 compared to Old Active
Physical Activity

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<tbody>
<tr>
<td>Category</td>
<td>Sedentary</td>
<td>Active</td>
<td>Trained</td>
<td></td>
</tr>
<tr>
<td>Counts per Minute</td>
<td></td>
<td></td>
<td></td>
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</table>
Fitness (VO$_2$peak)
Supine PLM

#p<0.05 compared to Young
§p<0.05 compared to Old Sedentary
†p<0.05 compared to Old Active
Upright-seated PLM

#p<0.05 compared to Young
§p<0.05 compared to Old Sedentary
†p<0.05 compared to Old Active
Vasodilatory Reserve

#p<0.05 compared to Young
§p<0.05 compared to Old Sedentary
†p<0.05 compared to Old Active
Rapid Vasodilation

![Graph showing leg vascular conductance over time for different age and activity groups.](image)
Conclusions

- Physical activity augments the PLM response in older individuals, likely due to increased NO bioavailability.

- Ageing appears to create a ceiling effect that increasing levels of physical activity cannot overcome.
Utah Vascular Research Laboratory

UVRL.org

National Institute of Health
American Lung Association
American Heart Association
Parker B. Francis Foundation
Stein Institute For Aging Research
Tobacco Related Disease Research Program
Association Francaise contre les Myopathies
Office of Rural Health VAMC
Rehabilitation Research and Design VAMC
Supplemental Slides
Aging, Oxidative Stress & Vascular Function

Oral Antioxidant Cocktail (AOC)

Wray et al. (2012) Hypertension
Purpose

• We will seek to determine the impact of acute AOC supplementation on vasodilatory function assessed by PLM in young and old subjects
Hypotheses

• Due to elevated oxidative stress and NO scavenging in the old,
  – The AOC supplementation will rescue the decreased PLM-induced vascular function in the old in both body postures
  – AOC supplementation will restore the vasodilatory reserve in the old
  – AOC supplementation will have no effect on hemodynamic parameters in the young
Methods

Subjects

• 30 Subjects
  – 15 young men and women (18-25 yrs)
  – 15 old men and women (65+ yrs)

• Healthy
  – No overt signs of CVD or metabolic disease
  – Non-smokers

• Sedentary to low physical activity level
Antioxidant Supplementation

- 2 doses separated by 30 min
  - First dose 90 min prior to PLM protocol, second dose 60 prior to PLM protocol
- Dose 1
  - 500 mg Vit C, 200 IU Vit E, 300 mg α-lipoic acid
- Dose 2
  - 500 mg Vit C, 400 IU Vit E, 300 mg α-lipoic acid
Measurements
Statistical Analysis

• Student’s t-tests
  – Subject Characteristics

• 2x2x2 Repeated Measures ANOVA
  – Baseline and Peak Change in HR, SV, CO, MAP, LBF, and LVC

• 2x2 Repeated Measures ANOVA
  – Vasodilatory reserve

• Data expressed as mean ± SEM
Preliminary Results
Training Restores Vascular Function with Age

DeSouza et al. (2000) *Circulation*
Vascular Effects of Estrogen

Attenuated PLM-Induced Vasodilation With Age

McDaniel et al. (2010) *J Physiol*

Groot et al. (2013) *AJP Heart & Circ.*
Attenuated PLM-Induced Vasodilation With Age

Groot et al. (2013) AJP Heart & Circ.
NO-Mediated Vascular Function

Shear Stress, Insulin, Ach, estrogen, etc.

Vessel Lumen

Endothelial Cell

Vascular Smooth Muscle Cell

Ca^2+ \rightarrow \text{Ca}^{2+}\cdot\text{CaM}

\text{CaM K II} \rightarrow \text{Akt AMPK PKA}

\text{eNOS} \rightarrow \text{NO}

\text{BH}_4 \rightarrow 2 \text{NADPH L-Arginine L-Citrulline}

\text{L-Citrulline} \rightarrow 2 \text{NADP}^+ \rightarrow 2 \text{H}_2\text{O}

\text{NO} \rightarrow \text{GC}

\text{GTP} \rightarrow \text{cGMP} \rightarrow \text{PKG}

\text{Akt AMPK PKA} \rightarrow \text{Ca}^{2+}\cdot\text{CaM} \rightarrow \text{Cam K II}

? \rightarrow \text{Ca}^{2+} \rightarrow \text{Ca}^{2+}
Free Radical Quenching of NO

Vessel Lumen

Endothelial Cell

Vascular Smooth Muscle Cell

Shear Stress, Insulin, Ach, estrogen, etc.

Ca\(^{2+}\)

CaM

Ca^{2+}\cdot\text{CaM}

CaM K II

Akt

AMPK

PKA

Ca^{2+}

Akt

AMPK

PKA

Ca^{2+}

CaM

K II

BH\(_4\)

L-Arginine

L-Citrulline

2 NADPH

2 NADP\(^{+}\)

2 H\(_2\)O

\text{NO}

\text{GTP}

\text{cGMP}

\text{PKG}

\text{GC}

OONO\(^{-}\)

\text{O}_2^{-}
Aging and CVD Prevalence


Preliminary Results