Implications of Vascular Aging on Cardiovascular Disease Risk
I. Significance and Relevance

II. Arterial Structure / Stiffness

III. Endothelial Function

IV. Integrated Vascular Control
CVD is the Leading Cause of Death in the U.S.

A Total CVD  
B Cancer  
C Accidents  
D Chronic Lower Respiratory Diseases  
E Diabetes Mellitus  
F Alzheimer’s Disease  

Source: CDC/NCHS, 2002
Age-related incidence of Hypertension, Stroke, and CAD

Hypertension

Stroke

CAD
The Majority of CVD Deaths are Attributable to Vascular Complications

- Coronary Heart Disease: 53%
- Stroke: 18%
- Congestive Heart Failure: 6%
- High Blood Pressure: 5%
- Diseases of the Arteries: 4%
- Rheumatic Fever/Rheumatic Heart Disease: 13%
- Congenital Cardiovascular Defects: 6%
- Other: 0%
Vascular Aging a Major Risk Factor for Cardiovascular Disease

AGING: THE MAJOR RISK FACTOR FOR CARDIOVASCULAR MORBIDITY AND MORTALITY

Lakatta EG Circulation 2003
Aging Stats

• Population over 65 years of age will double from 12% to 22% from 2010-2040
• Prevalence of CVD will increase by 10% over the next 20 years
  • Additional 20 million with hypertension
  • 8 million with CHD
  • 3 million more with heart failure
  **Primarily due to increase in aging population
• Annual cost for people aged 65-79 years of age are projected to increase by 238% from $135B to $457B

Circulatory System

Diagram showing the circulatory system with labels for Aorta, Large Artery, Small Artery, Arteriole, Capillaries, Vein, Vena Cava, and Venules. The graph below the diagram illustrates the pressure changes across different vascular segments, from Aorta to Venules, with decreasing pressure as the blood flows from arteries to veins.
Arterial Structure
Structural Changes with Age

Carotid Intima Media Thickness (CIMT)

[Imagery showing a cross-sectional view of the carotid artery with annotations indicating the interior of the carotid artery and the intima media layer of the arterial wall.]

B

IMT and Age

- Intimal Media Thickness (cm)
- Age (years)

Najjar et al. Hypertension 2005
Mechanisms of Arterial Wall Thickening

**Immune System Infiltration**

<table>
<thead>
<tr>
<th>Age (m)</th>
<th>8</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCR2</td>
<td></td>
<td></td>
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<tr>
<td>18s rRNA</td>
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</tbody>
</table>

Other potential influences:

- ↑ Increased Blood Pressure
- ↑ Increased growth factors
- ↓ Endothelial function

Aging is Associated with Elevated SBP and Pulse Pressure

**Graphs:**

- **C:** Systolic BP (mm Hg) vs. Age (30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84).
  - SBP: 160+, 140-159, 120-139, <120.

- **D:** Diastolic BP (mm Hg) vs. Age.
  - <120.

- **B:** Scatter plot of Pulse Pressure (mm Hg) vs. Age (years).
  - Male and Female.

*Lakatta E G, Levy D. Circulation 2003;107:139-146*
Aging and Aortic Stiffness

PWV = $\frac{\Delta L}{\Delta t}$

Common carotid artery
Thoracic aorta
Abdominal aorta
Femoral artery
Iliac artery

Pulse Wave Velocity (cm/sec)

AGE (years)

Female
Male

$r = 0.61, p = 0.0001$
$r = 0.58, p = 0.0001$

Lakatta EG Circulation 2003
Aging and Large Artery Compliance

Carotid Artery Compliance (U)

- Sedentary
  - Young: 0.20
  - Middle: 0.15
  - Older: 0.10

- Endurance-Trained
  - Young: 0.25
  - Middle: 0.20
  - Older: 0.15

*Tanaka et al. Circulation 2000*

Normal Artery Expansion and Contraction with Heartbeat

During Diastole
Normal arterial walls expand as the heart pumps blood thru them.
Mechanisms of Arterial Stiffness

Other potential influences:

↑ Arterial Collagen Content

↓ Arterial Elastin Content

↓ Endothelial function

PHYSIOLOGICAL AGING

Mechanisms

**Structural**

Elastin:
- ↑ fragmentation
- ↓ density

Collagen:
- ↑ concentration
- △ phenotype
- ↑ cross-linking
- ↑ AGEs
- VSM cell hypertrophy
- ↑ growth factors

**Functional**

- ↑ VSM cell tone

Subclinical atherosclerosis
(↑ MCP-1, CCR2)

Age-gene interactions

Effects

Large elastic artery remodeling
- ↑ internal diameter
- ↑ IMT

- ↓ aortic and carotid arterial compliance (↑ stiffness)
- ↑ aortic PWV
- ↑ systolic pulse augmentation (↑ carotid AI)

Consequences

- ↑ SBP and PP systolic hypertension
- ↑ aneurysms, stroke

- Endothelial damage
- ↑ atherosclerosis
- ↑ MI, thrombosis
- ↑ CAD, PAD, etc.

- ↑ aortic impedance
- ↑ LV wall tension
- ↑ LV hypertrophy (↑ CHF)
- ↑ LV work, VO$_2$
prolonged contraction
- ↓ early diastolic filling

- ↓ LV systolic reserve
- peak LV ESV
- peak LV EF
Healthy, Normally Functioning Vascular Endothelium

Anti-Atherosclerotic Phenotype

- Anticoagulant surface
- Low leukocyte adhesivity
- Produces nitric oxide
- Basal endogenous anti-inflammatory and vasodilator properties
“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 and Endothelial Dependent Dilation

Brachial Artery

Celemajer et al., JACC 1994

Taddei et al., Hypertension 1996
Aging and Endothelial Independent Dilation

Brachial Artery

Glyceryl Trinitrate Induced Dilation

Brachial FMD Model

Normotensive Males (n=36)

Forearm Blood Flow Model

Maximal FBF response to Sodium Nitroprusside

Celermaier et al., JACC 1994

Taddei et al., Hypertension 1996
Aging, Endothelial Dilation and NO

Age related EDD deficit is explained by reduced NO

Endurance trained individuals have augmented EDD via greater NO

Vascular endothelial dysfunction and risk of CVD with aging

Douglas R. Seals, Kristen L. Jablonski and Anthony J. Donato; Clinical Science 2011 120, 357-375
Hypothesized Role of Reactive Oxygen Species in Reduced NO

NAD(P)H oxide
Xanthine oxidoreductase
Cyclooxygenase
eNOS
Mitochondrial respiration
Reduced intracellular antioxidants

Reactive oxygen species (O2^•-, H2O2, •OH, ••OH)

NO-Mediated actions

Endothelial dysfunction

Vasoconstriction and altered vascular tone

Matrix production, vascular collagen, and protein synthesis

Platelet aggregation

Inflammation, leukocyte adhesion

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Oxidative Stress a Mechanism Contributing to Endothelial Dysfunction with Aging
Acute Vitamin C Infusion Restores Brachial Artery FMD in Older Sedentary Men

Eskurza et al., J Physiol, 2004
Endothelial nitrotyrosine and EDD with aging in men

Donato et al., Circ Res 100:1659-66, 2007
1. Age-related EDD deficit is explained by reduced NO

2. Older adults can ameliorate NO mediated EDD by blocking oxidative stress
NADPH p47 phox, a subunit of an oxidant protein, is increased in endothelial cells from older sedentary adults.

No age-related changes in antioxidant protein expression.

Role of Reactive Oxygen Species in Reduced NO with Aging

- NAD(P)H oxide
- Xanthine oxidoreductase
- Cyclooxygenase
- eNOS
- Mitochondrial respiration
- Reduced intracellular antioxidants

NAD(P)H oxidase → Xanthine oxidoreductase → Cyclooxygenase → eNOS → Mitochondrial respiration → Reduced intracellular antioxidants

Reactive oxygen species (O2•−, H2O2, •OH, •OH) → NO-Mediated actions

Endothelial dysfunction

- Vasoconstriction and altered vascular tone
- Platelet aggregation
- Inflammation, leukocyte adhesion
- Matrix production, vascular collagen, and protein synthesis
Fibrinolysis - The Clot Buster

Normal endothelial cell

EDRF
Inhibits platelet adhesion
Promotes vasodilatation
Controls shear
Prevents leukocyte adhesion

Normal t-PA:PAI-1
Promotes fibrinolysis

Dysfunctional endothelial cell in hypercholesterolemia and atherosclerosis

Decrease in EDRF
Promotes platelet adhesion
Promotes vasoconstriction
Increases shear
Promotes leukocyte adhesion

Decrease in t-PA:PAI-1
Promotes thrombosis

Increase in adhesion molecules
Promotes monocyte or macrophage retention

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Aging and Fibrinolysis

Smith et al. *J Physiol* 2002
Risk Factors, Endothelial Dysfunction, Atherogenesis, and Progression to Cardiovascular Events

- Aging
- Smoking
- Diabetes
- Hypertension
- Dyslipidemia
- Estrogen withdrawal
- Homocysteine
- Infection/inflammation
- Sedentary lifestyle

Endothelial dysfunction

- Decreased NO
  - Vasodilation
  - Platelet adhesion
  - VSMC proliferation
  - Leukocyte adhesion
- Other vasoactive agents
  - \( \downarrow \) Prostacyclin
  - Endothelin
  - EDHF
  - Carbon monoxide
- Decreased t-PA:PAI-1
  - Impaired fibrinolysis
  - Other procoagulants
- Adhesion molecules expression
  - Monocyte adhesion
  - Foam cell formation
  - Plaque inflammation
  - Other inflammatory cytokines

Atherosclerotic lesion formation and progression
- Plaque activation and rupture
- Decreased blood flow due to thrombosis and vasospasm

Coronary events and stroke

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Another Issue with Aging

“What doesn’t kill you, makes you a burden.”
Percent of Elderly with Physical Limitations

• With increasing life expectancy, physical limitations become more prevalent.

• This creates an expensive burden on health care systems and individual families.

• The decline in cardiovascular function with aging contributes to these limitations.

[Bar chart showing percent of elderly with physical limitations from 1992 to 1998.]

CDC NSDB 2003
Blood Flow Regulation

- A delicate balance of vasoconstrictor and vasodilator influences determines vessel caliber and thereby vascular resistance and blood flow.

Vasoconstrictor (+) and vasodilator (−) influences acting upon arterioles and other pre-capillary resistance vessels. The state of vessel tone is a balance between constrictor and dilator influences.
Aging and Resting Leg Blood Flow

Dinenno et al. Circulation 1999

Femoral Blood Flow

Young Adults

Older Adults

Femoral Vascular Resistance

Young Adults

Older Adults
Aging and Exercise Leg Blood Flow

Leg Blood Flow (L/min)

Leg Vascular Conductance (ml/min/mmHg)

Donato et al. *AJP Heart Circ.* 2006
Conclusions

Healthy Sedentary aging is associated with:
- Lumen enlargement
- Medial wall thickening
- Large artery stiffening
- Generalized endothelial dysfunction due to
  - Decreased NO bioavailability
  - Augmented oxidative stress

- A pro-constrictor resistance vasculature resulting in an attenuated resting and exercise leg blood flow
Questions??
Structural Changes in Resistance Arteries

Behnke, B. J. et al. J Physiol (Lond) 2006
1. Aging attenuates vasodilation to isoproterenol in arterioles without a functional endothelium

2. The magnitude of vasodilation is not reduced after denuding the endothelium, thus adrenergic vasodilation is due to VSM-mediated dilation in arterioles

Donato et al. *J physiol* 2007
Aging and cAMP Mediated Dilation

Resistance artery -endothelium

Donato et al. *J physiol* 2007