Cardiovascular disease physiology

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Bioscience in the 21st Century
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Content

• Introduction – The number 1 killer in America
  – Some statistics
  – Recommendations
• The disease process
  – Damage
  – Current treatments
• Control of vascular tone
• Some research at Lehigh
Heart Disease is number 1 in deaths in 2011:

- Heart Disease
- Cancer
- Chronic respiratory disease
- Stroke
- Accidents
- Alzheimer's disease
- Diabetes
- Kidney disease
- Influenza and Pneumonia

Preliminary Data from the CDC

Some Good news.

In many western developed countries, deaths from coronary heart disease have decreased steadily as treatment options have improved, and as people have made lifestyle changes.

NHLBI.NIH
# Direct and Indirect Economic Costs of Illness by Major Diagnosis, U.S., 2010

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Direct Costs*</th>
<th>Morbidity**</th>
<th>Mortality†</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Disease</td>
<td>$324.1</td>
<td>$41.7</td>
<td>$137.4</td>
<td>$503.2</td>
</tr>
<tr>
<td>Subtotal</td>
<td>453.0</td>
<td>74.4</td>
<td>177.4</td>
<td>704.8</td>
</tr>
<tr>
<td>Diseases of the Digestive System</td>
<td>227.4</td>
<td>12.6</td>
<td>30.6</td>
<td>270.6</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>102.8</td>
<td>20.9</td>
<td>140.1</td>
<td>263.8</td>
</tr>
<tr>
<td>Mental Disorders</td>
<td>180.8</td>
<td>32.4</td>
<td>12.5</td>
<td>225.7</td>
</tr>
<tr>
<td>Diseases of the Nervous System</td>
<td>157.7</td>
<td>9.6</td>
<td>16.4</td>
<td>183.7</td>
</tr>
<tr>
<td>Total</td>
<td>2,176.6</td>
<td>244.9</td>
<td>679.3</td>
<td>3,100.8</td>
</tr>
</tbody>
</table>

NHLBI numbers: Categories above $100 billion are listed

Source: Estimates by NHLBI; data from the NCHS, the CMS, the Bureau of the Census, and the Institute for Health and Aging, University of California.
Risk Factors

• High blood pressure (above 120/80 mm Hg)
• Serum cholesterol [aim for below 100 mg/dL LDL cholesterol and above 50 mg/dL HDL, or aim for total cholesterol below 200 mg/dL]
• Body Mass Index (BMI) [above 30]
• Smoking
• Drinking
• Diabetes
Chart 3-6. Ten year risk for CHD by risk factors

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>5</td>
<td>8</td>
<td>25</td>
<td>37</td>
</tr>
<tr>
<td>Women</td>
<td>5</td>
<td>13</td>
<td>20</td>
<td>27</td>
</tr>
</tbody>
</table>

A: BP, mm HG
- 120/80
- 140/90
- 140/90
- 140/90

B: mg/dL, Total Cholesterol
- 200
- 240
- 240
- 240

C: Mg/dL HDL cholesterol
- 50
- 50
- 40
- 40

D: Diabetes
- No
- No
- Yes
- Yes

Cigarettes
- No
- No
- No
- Yes

Rosamond, W. et al.
Circulation 2007;115:e69-e171
Metabolic Syndrome

• Central obesity (excessive fat tissue in and around the abdomen)
• Atherogenic dyslipidemia (blood fat disorders — mainly high triglycerides and low HDL cholesterol)
• Insulin resistance or glucose intolerance (the body can’t properly use insulin or blood sugar)
• Prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor in the blood)
• Raised blood pressure (130/85 mmHg or higher)
• Proinflammatory state
Diet
Portion size
Physical Activity
Genes

Fat as an endocrine tissue
  – Makes leptin – lowered desire to eat, more use of stored fat
  – Makes inflammatory signaling molecules
  – Decreases synthesis of signals that in turn cause a decrease in blood pressure
  – with the result being increased blood pressure
Recommendations

• Limit your saturated fat intake (trans fat too)
• Consume less than 200 (300) mg/day cholesterol
• Eat fish regularly
• Limit your salt intake (less than 2300 mg/day)
• Consume vegetables and whole grains
• Diet options for lowering cholesterol
  • Plant sterols and/or soluble fiber
• Eat only enough calories to maintain weight (or reach a healthy weight)
• At least 30 min of moderate physical activity/day
• http://www.americanheart.org
Progression of Vascular Disease

1. Normal cross-section of artery
2. Tear in artery wall
3. Fatty material is deposited in vessel wall
4. Narrowed artery becomes blocked by a blood clot

Stent

Aspirin

MedlinePlus Medical Encyclopedia
Atherosclerosis

- Leads to narrowing/blocking of arteries
  - Blocked flow to the heart
    - Myocardial Infarction (heart attack)
  - Blocked flow to the brain
    - Ischemic Stroke

Bypass
Atherosclerosis is Geometrically Focal

Smooth Flow Region

“Non-Sticky” ECs

Intact Endothelium

Disturbed Flow Region

“Sticky” ECs

Inflammed vasculature

“Leaky” Endothelium

Flow, along with other factors, contributes to risk.

Meron Mengistu
Contraction of blood vessels

- Angiotensin is a major contraction signal that increases blood pressure transiently

Diuretics, Ace inhibitors, β-blockers, Calcium channel blockers
Relaxation of blood vessels

• NO (nitric oxide) and atrial natriuretic factor both cause increases in cGMP
PKG Signaling

Nitric Oxide

Nitric Oxide Synthase

Soluble guanylate cyclase

GTP

phosphodiesterases

cGMP

Protein Kinase G

Myosin phosphatase

Smooth muscle relaxation

VASP

Platelet inhibition

Transcription factors

Changes in gene expression

http://www.reading.ac.uk/cellmigration/cgmp.htm
• But cGMP is typically rapidly degraded by proteins called PDEs

\[ \text{cGMP} \quad \rightarrow \quad \text{GMP} \]

• PDE3 is primarily in cardiac muscle
• PDE6 is primarily in the retinas
• PDE5 is primarily in vascular smooth muscle
Sildenafil citrate

• Blocks PDE5 80 to 4000 times more effectively than it blocks other PDE isoforms (except PDE6)
• Therefore in vascular smooth muscle cells cGMP remains elevated longer.

• Viagra is a trade name for sildenafil citrate
Fluid Shear Stress and Atherosclerosis

- FSS plays an essential role in maintaining vascular homeostasis

\[ \tau_w \geq 15 \text{ dynes/cm}^2 \]  
Atheroprotective Areas

Intact Endothelium

\[ \tau_w \leq 4 \text{ dynes/cm}^2 \]  
Atheroprone Areas

“Leaky” Endothelium Plaque formation!
FSS-Induced Actin Realignment

No Flow

5’ – 15’ ↑FSS

30’ ↑FSS

60’ – 120’ ↑FSS

Time Zero

Phase 1

Phase 2

Phase 3

Flow

Actin

A Mechanosensing Complex

Adapted from Conway D. and Schwartz MA 2012 with established links to actin added.
Stress Kinase Inhibitors Disrupt Barrier Integrity

VE-cadherin

No Inhibitor

JNK + SP600125

p38 + SB203580

Slee JB & Lowe-Krentz LJ. 2013
Lipid Raft Signaling

Shear Stress

Caveolae $\uparrow$

NO $\uparrow$

Caveolae

Cholesterol-rich membranes

Ca$^{2+}$

TRPC1,3,4,6

TRPV4, MSC

K$_{Ca}$ 3.1

K$_{Ca}$ 2.3

K$^+$

Ca$^{2+}$

Na$^+$

Ca$^{2+}$

DAG

PLC

eNOS

K$^+$

Ca$^{2+}$

Na$^+$

Gav-1

Source: http://web.uni-marburg.de/sfb593/all.html
TMEM184A is Present in Vascular Cells

A

B

Our Antibody TMEM184A-NTD

Slee JB & Lowe-Krentz LJ. In Review, Y. Li, unpublished
TMEM184A co-localizes with Cav-1

A TMEM184A-

INT Cav-1 Merge Merge - 4X

RAOSMC

BAOEC

Slee JB & Lowe-Krentz LJ. In Review