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 (hypertension)

• Some research at Lehigh
Cardiovascular disease (CVD) and other major causes of death: total, <85 years of age, and ≥85 years of age.

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.
Heart Disease Death Rates, 2008-2010
Adults, Ages 35+, by County

Rates are spatially smoothed to enhance the stability of rates in counties with small populations.

Data Source:
National Vital Statistics System
National Center for Health Statistics
Projected total (direct and indirect) costs of total cardiovascular disease by age (2012 $ in billions).

Projected direct costs of total cardiovascular disease by type of cost (2012 $ in billions).

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

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Direct Costs* (Billions)</th>
<th>Morbidity** (Billions)</th>
<th>Mortality† (Billions)</th>
<th>Total (Billions)</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

Age-standardized prevalence estimates for poor, intermediate, and ideal cardiovascular health for each of the 7 metrics of cardiovascular health in the American Heart Association 2020 goals among US adults aged ≥20 years, National Health and Nutrition Examination Survey 2009 to 2010.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Poor</th>
<th>Intermediate</th>
<th>Ideal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Smoking</td>
<td>3.2</td>
<td>35.8</td>
<td>61.0</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>20.5</td>
<td>48.2</td>
<td>31.3</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>10.9</td>
<td>40.9</td>
<td>48.2</td>
</tr>
<tr>
<td>Healthy Diet Score*</td>
<td>72.5</td>
<td>7.0</td>
<td>20.5</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>39.7</td>
<td>47.0</td>
<td>13.3</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>44.6</td>
<td>41.5</td>
<td>13.9</td>
</tr>
<tr>
<td>Fasting Plasma Glucose</td>
<td>34.4</td>
<td>57.5</td>
<td>8.1</td>
</tr>
</tbody>
</table>

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**

[http://stateofobesity.org/adult-obesity/](http://stateofobesity.org/adult-obesity/)
Obesity

- 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

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

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
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
• But cGMP is typically rapidly degraded by proteins called PDEs

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

• 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
Flow, along with other factors, contributes to risk.
Model of Heparin Receptor Mediated Anti-growth Effects in VSMCs and Anti-inflammatory Effects in Endothelial cells

Questions:
Identification of the Receptor
  a. Protein identity
  b. Validation
  c. Heparin binding ability
1. Does the signal go through eNOS?
2. What are the inflammatory targets in endothelial cells?
3. What are the gene expression changes?
And what about angiogenesis?
Where do we go from here?

• How can research dissociate components of diet from their effects on heart disease?
• What types of communication/education can lead to improved activity levels, diet, etc?
• Current treatment of vascular diseases is increasing life-span, but at significant cost. Can we slow development of vascular disease and increase the time until expensive interventions are required?