Cardiovascular disease, studies at the cellular and molecular level

Linda Lowe-Krentz
Bioscience in the 21st Century
November 14
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 180 mg/dL]
- Body Mass index (BMI) [between 18.5 and 24.9]
- Smoking
- Drinking
- Diabetes
Compare to Metabolic Syndrome

• Abdominal obesity
• High blood pressure
• High fasting blood glucose
• High triglycerides
• Low HDL
Statistics

• Compiled and presented in the Journal Circulation – published by the American Heart Association
Chart 2-1 Trends in the age-adjusted prevalence of health conditions
US adults ages 20 to 74


Chart 2-3. CVD without including hypertension

Chart 2-6. CVD deaths vs cancer deaths by age. (2004)

Chart 3-6. Ten year risk for CHD by risk factors

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

<table>
<thead>
<tr>
<th></th>
<th>BP, mm Hg</th>
<th>mg/dL Total Cholesterol</th>
<th>Mg/dL HDL cholesterol</th>
<th>Diabetes</th>
<th>Cigarettes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>120/80</td>
<td>200</td>
<td>50</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>B</td>
<td>140/90</td>
<td>240</td>
<td>50</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>C</td>
<td>140/90</td>
<td>240</td>
<td>40</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>D</td>
<td>140/90</td>
<td>240</td>
<td>40</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Recommendations

• Eat less than 7% of your calories from sat. fat
• Consume less than 200 mg/day cholesterol
• Eat 25-35% of your daily calories in fat
• 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
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
Cut-section of artery

- Tear in artery wall
- Macrophage cell
- Cholesterol deposits
- Red blood cell
- Macrophage foam cell
- Fat deposits

MedlinePlus Medical Encyclopedia
Contraction of blood vessels

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

Ace inhibitors, β-blockers
Relaxation of blood vessels

- NO (nitric oxide) and atrial natriuretic factor both cause increases in cGMP

[Diagram showing the relationship between NO, atrial natriuretic factor, and increased 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 the trade name for sildenafil citrate
Cell proliferation and wound repair

- Lack of contact, damaging chemicals, etc.
- Growth factors, Angiotensin
- Immune system
Excessive damage

• Occurs where physical stress from blood flow also is present
• Occurs when excessive chemical agents damage cells (e.g. high cholesterol)
• Occurs if there is constant infiltration by cells from the immune system
• How can the cells stop the injury cycle?
Effects of flow on cell morphology

- Models helpful in the study of molecular events in cell culture

12 to 24 hours
Cultured Endothelial cells

Actin Staining
Chemical treatments

TNFα for 15 min
Flow induced changes

Flow for 15 min
Actin Remodeling Under Shear Stress

**Low shear flow for 60’**

- Cells and their actin filaments begin to align in the direction of flow after 60’ of high shear flow exposure.
- No change under low shear stress

**High shear flow for 60’**

- Flow
- F-Actin starts to align in the direction of flow
Flow with an inhibitor