Cardiovascular disease, studies at the cellular and molecular level

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Bioscience in the 21\textsuperscript{st} Century
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Content

• Introduction
  – Some statistics
  – Recommendations

• The disease process
  – Damage
  – Current treatments

• Control of vascular tone

• Control of endothelial damage
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 2-1 Trends in the age-adjusted prevalence of health conditions
US adults ages 20 to 74


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>
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<tbody>
<tr>
<td>BP, mm HG</td>
<td>120/80</td>
<td>140/90</td>
<td>140/90</td>
<td>140/90</td>
</tr>
<tr>
<td>mg/dL, Total Cholesterol</td>
<td>200</td>
<td>240</td>
<td>240</td>
<td>240</td>
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<tr>
<td>Mg/dL HDL cholesterol</td>
<td>50</td>
<td>50</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Statins

Rosamond, W. et al.
Circulation 2007;115:e69-e171
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/presenter.jhtml?identifier=851
Progression of Vascular Disease
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

“Leaky” Endothelium

Flow, along with other factors, contributes to risk.

Meron Mengistu
Vessel Anatomy

diagram showing layers of the vessel with labels:
- endothelium
- internal elastic lamina
- fibrocollagenous tissue
- tunica intima
- smooth muscle
- tunica media
- fibrocollagenous tissue with external elastic lamina
- fibrocollagenous tissue
- tunica adventitia

Source: greenfield.fortunecity.com
Contraction of blood vessels

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

Angiotensin II (ANG II) • Ace inhibitors, β-blockers
Relaxation of blood vessels

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

Nitrolycerin
• But cGMP is typically rapidly degraded by proteins called PDEs

![cGMP → GMP](image)

• 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
Cell proliferation and wound repair

- Lack of contact, damaging chemicals, etc.
- Growth factors, Angiotensin
- Immune system
Effects of flow on endothelial cell morphology

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

12 to 24 hours
Stress Fiber Alignment

• High Fluid shear stress exposure results in three phases of cell changes:
  – (1) increase in stress fiber formation
  – (2) dense cortical band formation of actin cytoskeleton
  – (3) stress fiber alignment in the direction of flow

No Flow 5’ – 15’ ↑FSS 30’ ↑FSS 60’ – 120’ ↑FSS
Phase 1 Phase 2 Phase 3

Meron Mengistu
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.
Effect of Flow Exposure on Endothelial Cells

% Elongation of Long-axis

- 15 min
- 30 min
- 60 min
- 120 min

σ_{eff} 0 7000 15000

4 dyn/cm²  15 dyn/cm²

ADINA models

control  15 min  30 min  60 min  120 min

Jamie Maciaszek, Shannon Alejandro, Josh Slee, Samir Ghadiali