Angina Pectoris

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Angina Pectoris

- Chronic disease
- Intermittent attacks of chest pain that radiates through the chest, left shoulder and arm
- 3 million in USA (approx. 1% population)

A. Typical (Stable, Effort) angina:
   - ↑ O₂ demand - fixed supply

B. Variant (Unstable, Prinzmetal's) angina:
   - ↓ O₂ supply - unchanged demand
   - ie. at rest, coronary spasm (PGs?)
Determinants of Oxygen Demand

Need to improve ratio
Coronary blood flow / cardiac work
or
Cardiac O₂ Supply / Cardiac O₂ Requirement

Angina – Coronary Occlusion

When a clogged artery keeps the heart from getting enough blood and oxygen, angina can occur.
Coronary Circulation vs Other Circulation

- most tissues can increase $O_2$ extraction with demand
- heart extracts near maximal amount of $O_2$ at rest
- therefore can only increase $O_2$ delivery by increasing coronary blood flow

Angina – Surgical Treatment
(Coronary bypass, angioplasty, stents)
Stents

Angina Risk Factors

- Obesity
- $\text{Na}^+$ intake
- Physical inactivity
- Smoking
- Hypertension
- Stress
- High blood cholesterol
- Age
- Gender
- Family history

(can regulate)

(inherent)
Cholesterol Levels

- Total cholesterol less than 200 mg/dl – desirable
- 200 – 239 mg/dl – borderline high
- 240 mg/dl and over – high

- HDL cholesterol greater than 35 mg/dl is desirable, the higher the better
- LDL cholesterol less than 130 mg/dl – desirable
- 130-159 mg/dl – borderline
- 160 mg/dl or higher – high

- Ratio LDL:HDL < 3 is desirable

Improving supply/demand ratio

a. Relaxation of resistance vessels (small arteries and arterioles)
   $\downarrow$TPR $\rightarrow$ $\downarrow$BP $\rightarrow$ $\downarrow$Afterload
   (Nitrites, calcium channel blockers and beta-blockers)

b. Relaxation of capacitance vessels (veins and venules)
   $\downarrow$Venous return, $\downarrow$heart size, $\downarrow$Preload
   (Nitrites and calcium channel blockers)

c. Blockade or attenuation of sympathetic influence on the heart
   $\downarrow$Contactility, $\downarrow$HR, $\downarrow$O$_2$ demand
   (Beta-blockers)

d. Coronary Dilation
   - Important mechanism for relieving vasospastic angina
   - $\uparrow$O$_2$ supply
   (Nitrites)
Nitrates and Nitrites

- Formation of Nitric oxide (NO) → activation of guanylate cyclase
- $\uparrow$ Ca$^{++}$ uptake SR

Tolerance: frequency / dose dependence (absence periods)

Absorption and disposition: well absorbed, first-pass metabolism with oral administration

Toxicity: headache, flushing, hypotension, possible circulatory collapse

a. Nitroglycerin
   • Sublingual (duration 30min), buccal (4hr)
   • Oral spray (30min), oral tablets (6hr)
   • Topical: ointment (4hr), transdermal patches (8hr)
   • Intravenous: instant action
b. Isosorbide dinitrate: sublingual (2hr), oral (4hr)
c. Isosorbide mononitrate: oral (8hr)
d. Amyl nitrite, butyl nitrite: volatile, "recreational use/abuse"

Nitrates – Mechanism of Action

[Diagram of Nitrates – Mechanism of Action]

- Nitrates
- Endothelial cells
- Nitrosodiol
- Guanylate cyclase
- GTP
- cGMP
- MLCK
- Myosin-LC
- Actin
- Contraction
- Relaxation
### Nitroglycerin and Nitrates

#### Table 1. Nitroglycerin and Nitrates for Chronic Stable Angina

<table>
<thead>
<tr>
<th>Compound</th>
<th>Route</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerin</td>
<td>Sublingual</td>
<td>0.3-0.6 mg up to 1.5 mg</td>
<td>15-30 min</td>
</tr>
<tr>
<td></td>
<td>Spray</td>
<td>0.4 mg as needed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ointment</td>
<td>2/6 x 6 in 15 x 15 cm, 7.5-45 mg</td>
<td>Effect up to 7 h</td>
</tr>
<tr>
<td></td>
<td>Transdermal</td>
<td>0.2-0.8 mg/8 h every 12 h</td>
<td>8-12 h during intermittent therapy</td>
</tr>
<tr>
<td></td>
<td>Oral sustained</td>
<td>2.5-13 mg</td>
<td>4-8 h</td>
</tr>
<tr>
<td></td>
<td>release</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Buccal</td>
<td>1.3 mg, 3 times daily</td>
<td>3-5 h</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>50 mg/30 min</td>
<td>Tolerance in 7-8 h</td>
</tr>
<tr>
<td>Isosorbide</td>
<td>Sublingual</td>
<td>2.5-15 mg</td>
<td>Up to 60 min</td>
</tr>
<tr>
<td>Nitrate</td>
<td>Oral</td>
<td>5-90 mg 2-3 times daily</td>
<td>Up to 8 h</td>
</tr>
<tr>
<td></td>
<td>Spray</td>
<td>1.25 mg daily</td>
<td>2-3 h</td>
</tr>
<tr>
<td></td>
<td>Chewable</td>
<td>5 mg</td>
<td>2-2.5 h</td>
</tr>
<tr>
<td></td>
<td>Oral slow release</td>
<td>40 mg x 1-2 times daily</td>
<td>Up to 8 h</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>100 mg/4 h</td>
<td>Tolerance in 7-8 h</td>
</tr>
<tr>
<td></td>
<td>Ointment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosorbide</td>
<td>Oral</td>
<td>20 mg twice daily</td>
<td>12-24 h</td>
</tr>
<tr>
<td>Mononitrate</td>
<td>Oral</td>
<td>50-240 mg once daily</td>
<td></td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Sublingual</td>
<td>10 mg as needed</td>
<td>Not known</td>
</tr>
<tr>
<td>Tartrate</td>
<td>Oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>Sublingual</td>
<td>5-10 mg as needed</td>
<td>Not known</td>
</tr>
<tr>
<td>Nitrate</td>
<td>Oral</td>
<td>10-30 mg, 3 times daily</td>
<td>Not known</td>
</tr>
</tbody>
</table>

Beta-Blockers

**Propranolol, Atenolol, Nadolol**

- \( \downarrow \text{myocardial O}_2 \text{ consumption by} \ \downarrow \text{HR and} \ \downarrow \text{force contraction,} \ \downarrow \text{CO} \)

- \( \downarrow \text{BP} \rightarrow \downarrow \text{after-load,} \ \downarrow \text{pre-load} \)
Mechanism of Action

![Mechanism of Action Diagram]

Angina – Beta Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Selectivity</th>
<th>Partial Agonist Activity</th>
<th>Usual Dose for Angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>None</td>
<td>No</td>
<td>20-80 mg twice daily</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>$\beta_1$</td>
<td>No</td>
<td>50-200 mg twice daily</td>
</tr>
<tr>
<td>Atenolol</td>
<td>$\beta_1$</td>
<td>No</td>
<td>50-200 mg/day</td>
</tr>
<tr>
<td>Nadolol</td>
<td>None</td>
<td>No</td>
<td>40-80 mg/day</td>
</tr>
<tr>
<td>Timolol</td>
<td>None</td>
<td>No</td>
<td>10 mg twice daily</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>$\beta_1$</td>
<td>Yes</td>
<td>200-500 mg twice daily</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>$\beta_1$</td>
<td>No</td>
<td>10-20 mg/day</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>$\beta_1$</td>
<td>No</td>
<td>10 mg/day</td>
</tr>
<tr>
<td>Esmolol (intravenous)</td>
<td>$\beta_1$</td>
<td>No</td>
<td>50-300 $\mu$g/kg/min</td>
</tr>
<tr>
<td>Labetalol*</td>
<td>None</td>
<td>Yes</td>
<td>200-600 mg twice daily</td>
</tr>
<tr>
<td>Pindolol</td>
<td>None</td>
<td>Yes</td>
<td>25-75 mg 3 times daily</td>
</tr>
</tbody>
</table>

*Labetalol is a combined alpha and beta blocker.

Ca++ Channel Blockers

Main: Verapamil, Diltiazem, Nifedipine
Others: Nicardipine, Bepridil

↓Ca++ influx → ↓TPR → ↓afterload (also ↑ coronary flow)

Toxicity

a. Hypotension
b. Effects related to vasodilation (dizziness, flushing, headache)
c. Gingival hyperplasia
d. Constipation, especially with verapamil
e. Cardiac depression with verapamil and diltiazem
f. Tachycardia with nifedipine and nicardipine
g. Arrhythmias and agranulocytosis with bepridil

Intracellular Action of Calcium
**Drug Choices in Angina**

**A. Effort:**
- nitrates, calcium blockers, beta blockers

**B. Variant:**
- nitrates, calcium blockers, beta blockers, aspirin, anticoagulants, thrombolytics

**Aims in the use of antianginal drugs:**

a. **Treatment of acute attack** - nitroglycerin very effective (i.v., sublingual, oral spray)

b. **Short term prophylaxis** - taking nitroglycerin prior to anticipated physical or emotional stress may prevent attack

c. **Long term prophylaxis** - objective is to reduce frequency of anginal attacks. Many options are now available i.e. long-acting nitrates, Ca++-blockers, β-blockers, aspirin, anticoagulants, thrombolytics
Angina Drug Treatment

Aspirin to Prevent MI and Death

- Aspirin 75 to 325 mg daily should be used routinely to all patients with acute and chronic ischemic heart disease in the absence of contraindications
  - aspirin exerts an antithrombotic effect by inhibiting cyclo-oxygenase and synthesis of platelet thromboxane A₂
  - in patients with stable angina, aspirin reduces the risk of adverse cardiovascular events by 33%
  - in patients with unstable angina, aspirin decreases the short and long-term risk of fatal and nonfatal MI
  - aspirin (325 mg), given on alternate days to asymptomatic persons, associated with a decreased incidence of MI

BMJ 1995;308:81-106