Angina Pectoris

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- 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

Coronary Circulation vs Other Circulation

- most tissues can increase O₂ extraction with demand
- heart extracts near maximal amount of O₂ at rest
- therefore can only increase O₂ delivery by increasing coronary blood flow

Coronary – Surgical Treatment

(Coronary bypass, angioplasty, stents)

Angina – Coronary Occlusion

When a regionally sensitize the heart from getting enough blood and oxygen, angina can occur.
**Stents**

**Angina Risk Factors**
- Obesity
- Na$^+$ intake
- Physical inactivity
- Smoking
- Hypertension
- Stress
- High blood cholesterol
- Age
- Gender
- Family history

**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
- 160mg/dl or higher – high
- Ratio LDL:HDL < 3 is desirable

**Improving supply/demand ratio**
- a. Relaxation of resistance vessels (small arteries and arterioles)
  \[ \text{TQI} \rightarrow \text{JBP} \rightarrow \text{JAfterload} \]
  (Nitrates, calcium channel blockers and beta-blockers)
- b. Relaxation of capacitance vessels (veins and venules)
  \[ \text{Venous return, Jheart size, JPreload} \]
  (Nitrates and calcium channel blockers)
- c. Blockade or attenuation of sympathetic influence on the heart
  \[ \text{JContactility, JHR, JO$_2$ demand} \]
  (Beta-blockers)
- d. Coronary Dilation
  Important mechanism for relieving vasospastic angina
  \[ \text{TQI supply} \]
  (Nitrates)

**Nitrites and Nitrates**
- Formation of Nitric oxide (NO) → activation of guanylate cyclase
- ↑ Ca$^{2+}$ 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)
  - Intravaginal: 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**

Nitric oxide (NO) activates guanylate cyclase, leading to the formation of cGMP, which relaxes smooth muscle cells and reduces blood pressure. This relaxation improves the blood flow to the heart, helping to relieve angina. The mechanism involves the relaxation of resistance vessels and the blockade of sympathetic influence on the heart.
Nitroglycerin and Nitrates

<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>0.3-3 mg</td>
<td>up to 3 mg</td>
</tr>
<tr>
<td></td>
<td>Spray</td>
<td>0.1 mg</td>
<td>even dose</td>
</tr>
<tr>
<td></td>
<td>Intraoral</td>
<td>2.5-10 mg</td>
<td>1.5-3 mg</td>
</tr>
<tr>
<td></td>
<td>Transdermal</td>
<td>0.0-0.08 mg</td>
<td>0.03-0.08 mg</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>1.5-3 mg</td>
<td>up to 3 mg</td>
</tr>
</tbody>
</table>

- Beta-Blockers

**Propranolol, Atenolol, Nadolol**

- ↓ myocardial O₂ consumption by ↓ HR and ↓ force contraction, ↓ CO
- ↓ BP → ↓ after-load, ↓ pre-load

Mechanism of Action

- ↓ cns sympathetic outflow
- ↓ BP
- ↓ preload

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

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>None</td>
<td>No</td>
<td>50-200 mg twice daily</td>
</tr>
<tr>
<td>Atenolol</td>
<td>None</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>None</td>
<td>Yes</td>
<td>200-400 mg twice daily</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>None</td>
<td>Yes</td>
<td>10-20 mg/day</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>None</td>
<td>No</td>
<td>10 mg/day</td>
</tr>
<tr>
<td>Esmolol (nicardipine)</td>
<td>None</td>
<td>No</td>
<td>50-200 μg/hour</td>
</tr>
<tr>
<td>Labetalol²</td>
<td>None</td>
<td>Yes</td>
<td>200-400 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>

²Labetalol is a combined alpha and beta blocker.

Intracellular Action of Calcium
Angina – Calcium Antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose</th>
<th>Duration of Action</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem (Diltiazem HCl)</td>
<td>Immediate release</td>
<td>Short</td>
<td>Hypotension, dizziness, flushing, rash, constipation, edema</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>5-10 mg oral</td>
<td>Short</td>
<td>Headache, edema</td>
</tr>
<tr>
<td>Felodipine</td>
<td>5-10 mg oral</td>
<td>Short</td>
<td>Headache, edema</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>20-40 mg oral</td>
<td>Short</td>
<td>Headache, dizziness, flushing, edema</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>30 mg oral or tablet</td>
<td>Medium</td>
<td>Similar to nifedipine</td>
</tr>
</tbody>
</table>

| Table 6. Calcium Antagonists for Chronic Stable Angina |

**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

**Anginina 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 cyclooxygenase 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

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