I. Angina Pectoris

Angina pectoris is a chronic disease affecting 3 million in the USA (approx. 1% of population) characterized by intermittent attacks of chest pain which radiates to the left arm, shoulder, and jaw. Attacks of typical (effort, stable) angina are associated with exertion, excitement and other factors which increase cardiac work. The development of the disease is not fully understood, but it probably involves the following sequence:

![Coronary Atherosclerosis → Coronary Narrowing → Coronary Insufficiency → Myocardial Hypoxia → Angina Pectoris]

A less common form, variant (Prinzmetal's) angina is characterized by attacks occurring during rest and is caused by coronary artery spasm possibly involving prostaglandins.

A. Typical (Stable, Effort) angina: increased O₂ demand - fixed supply
B. Variant angina (Unstable): decreased O₂ supply - unchanged demand (spasms, PGs?)

II. Pharmacologic approaches to treatment angina pectoris

A. Since angina is due to imbalance between the oxygen requirement of the heart and oxygen supplied via the coronary arteries, the crucial consideration is improvement of the ratio.

\[
\frac{\text{coronary blood flow}}{\text{cardiac work}} \quad \text{or} \quad \frac{O_2 \text{ supply}}{O_2 \text{ requirement}}
\]

1. The primary determinants of myocardial O₂ supply are:
   a. Coronary blood flow
   b. O₂ content of the blood
   c. O₂ extraction by the myocardium

2. The primary determinants of myocardial O₂ consumption are:
   a. Ventricular systolic pressure (afterload)
   b. Heart size (preload)
   c. Heart rate
   d. Myocardial contractility

Note: Heart extracts near maximal O₂ at rest, therefore to increase O₂ supply need to increase coronary blood flow.
3. **Risk factors:**

- Obesity
- Na\(^+\) intake
- Physical inactivity
- Smoking
- Stress
- Age
- Gender
- Family history
- Hypertension
- High blood cholesterol

4. **Possible mechanisms for altering supply/demand ratio:**

a. Relaxation of resistance vessels (small arteries and arterioles) leading to decreased peripheral resistance and a decrease in systemic blood pressure (reduction in afterload). Nitrates and calcium channel blockers have such effects.

b. Relaxation of capacitance vessels (veins and venules) leading to decreased venous return and decreased heart size (reduction in preload). Nitrates and calcium channel blockers have such effects.

c. Blockade or attenuation of sympathetic influence on the heart. This would decrease O\(_2\) demand in the myocardium as a result of decreased heart rate and contractility. Beta-blockers, such as propranolol would have this effect.

d. Coronary Dilation - Important mechanism for relieving vasospastic angina. Nitrates have such effects.

III. **Classification of drugs used to treat angina**

A. **Nitrates and Nitrites** (vasodilation via direct smooth muscle relaxation)

2. Mechanism of action (see figure next page):

a. the formation of nitric oxide (NO) in endothelial cells in a reaction involving tissue sulfhydryl (SH) groups

b. interaction between NO and thiols in the smooth muscle cell to form nitrosothiols

c. nitrosothiol activation of guanylate cyclase and increased formation of cGMP

d. with increased cGMP there is:

1) increased calcium uptake by SR
2) less calcium to interact with calmodulin
3) less activation of MLCK by calcium and calmodulin
4) decreased phosphorylation of MLC
5) decreased smooth muscle tone
Figure 1. Control of smooth muscle contraction and site of action of calcium channel-blocking drugs. Contraction is triggered by influx of calcium (which can be blocked by calcium channel blockers) through transmembrane calcium channels. The calcium combines with calmodulin to form a complex that converts the enzyme myosin light chain kinase to its active form (MLCK*). The latter phosphorylates the myosin light chains, thereby initiating the interaction of myosin with actin. Beta2 agonists (and other substances that increase cAMP) may cause relaxation in smooth muscle by accelerating the inactivation of MLCK (heavy arrows) and by facilitating the expulsion of calcium from the cell (not shown).

Figure 2. Mechanism of action of nitrates, nitrites and other substances that increase the concentration of nitric oxide (NO) in smooth muscle cells. MLCK*: activated myosin light chain kinase. Guanylate cyclase*: activated guanylate cyclase. ?: Unknown intermediate steps. Steps leading to relaxation are shown with heavy arrows.
3. Development of tolerance:

Tolerance can develop to the pharmacological effects of nitrates if large amounts are administered frequently. Tolerance disappears if the drug is discontinued for a short period of time. Tolerance may be due to oxidation of SH groups and formation of disulfide bonds.

4. Absorption and disposition:

Nitrates are well absorbed. Disposition is primarily by hepatic reductases. There is considerable first-pass metabolism of most nitrates with oral administration.

5. Toxicity

acute - headache, flushing of the face, hypotension, possible circulatory collapse

6. Individual compounds

a. Nitroglycerin - Routes of administration:

- effective for all forms of angina, for prompt relief (oral spray or sublingual)

1) sublingual tablet (Nitrostat)
2) buccal tablet (Nitrogard)
3) oral (translingual) spray (Nitrolingual)
4) oral tablet (Nitro-Bid)
5) topical
   a) ointment (Nitrol and Nitro-Bid)
   b) transdermal system (Transderm-Nitro, Nitrodisc, Nitro-Dur, others).
6) intravenous (Nitrostat IV, Nitro-Bid IV)

Sublingual administration of nitroglycerin is preferred for treatment of acute attacks of angina because of its rapid onset of action. Other forms (except for intravenous) are intended to have a longer duration of action and are used for anginal prophylaxis.

b. Isosorbide dinitrate [ISDN] (Isordil)
c. Isosorbide mononitrate [ISMN] (Ismo)
d. Pentaerythritol tetranitrate (Peritrate)
e. Erythrityl tetranitrate (Cardilate)
f. Volatile nitrites used as “recreational drugs”

1) amyl nitrite
2) butyl nitrite
B. Beta-adrenergic Blockers

1. Propranolol (Inderal)
2. Atenolol (Tenormin)
3. Nadolol (Corgard)

By blocking cardiac beta receptors, propranolol and similar drugs decrease myocardial O\textsubscript{2} consumption through reduction in heart rate and contractility. Several studies have reported a reduction in the frequency of anginal attacks with propranolol.

C. Calcium Blockers

1. Mechanism of Action

These agents inhibit calcium movement through channels (primarily L-type) in membranes of muscle cells. In vascular smooth muscle, the reduction in intracellular calcium results in a decrease in muscle tone. All blockers are dihydropyridines except verapamil, diltiazem and bepridil which bind to different receptors in the channel.

2. Cardiovascular Effects

The decrease in vascular muscle tone results in primarily arteriolar dilation and a fall in peripheral resistance and afterload. Coronary dilation and an increase in coronary flow can occur in patients with variant angina. Verapamil and diltiazem have stronger direct effects on the heart and are used to suppress cardiac arrhythmias. They also cause cardiac depression as an adverse effect. All drugs are vasodilators and can reduce blood pressure.

3. Pharmacokinetics

a. Administration: oral - generally well absorbed
b. Disposition: metabolism > renal
c. Half-life: 2-5 hours, except bepridil (42 hr) & amlodipine (40 hr)

4. Toxicity

a. Hypotension
b. Other effects related to vasodilation (dizziness, flushing, headache)
c. Constipation, especially with verapamil
d. Cardiac depression with verapamil and diltiazem
e. Tachycardia with nifedipine and nicardipine
f. Arrhythmias and agranulocytosis with bepridil
g. Gingival hyperplasia
5. Individual agents
   a. Verapamil (Isoptin, Calan)
   b. Diltiazem (Cardizem)
   c. Bepridil (Vascor)
   d. Nifedipine (Procardia, Adalat)
   e. Nicardipine (Cardene)  Dihydropyridines
   f. Amlodipine (Norvasc, Lotrel)

IV. Summary of Effects of Antianginals on Primary Determinants of Myocardial O2 Consumption

<table>
<thead>
<tr>
<th></th>
<th>Nitrates</th>
<th>Beta Blockers</th>
<th>Calcium Blockers</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSP (Afterload)</td>
<td>↓</td>
<td>0-↓</td>
<td>↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Heart Size (Preload)</td>
<td>↓↓</td>
<td>0-↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>↑(R)</td>
<td>↓</td>
<td>0-↓</td>
<td>↑(R)</td>
</tr>
<tr>
<td>Contractile Force</td>
<td>0↑(R)</td>
<td>↓</td>
<td>↓</td>
<td>0</td>
</tr>
</tbody>
</table>

R = Reflex

V. Use of Drugs in Different Forms of Angina
   A. Stable/Effort - nitrates, calcium blockers, beta blockers
   B. Variant (Unstable) - nitrates, calcium blockers, beta blockers, aspirin, anticoagulants, thrombolytics

VI. Aims in use of antianginal drugs
   A. Treatment of acute attack - nitroglycerin very effective
   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. Long-acting nitrates, beta-blockers, calcium antagonists.
VII. Angina treatment summary

![Diagram showing drugs commonly used in treating angina]

Figure 18.4
Treatment of angina in patients with concomitant diseases. COPD, chronic obstructive pulmonary disease.

VIII. References
