Pharmacotherapy of Angina Pectoris

Edward JN Ishac, Ph.D.

Smith Building, Room 742
eishac@vcu.edu
828-2127

Department of Pharmacology and Toxicology
Medical College of Virginia
Campus of Virginia Commonwealth University
Richmond, Virginia, USA

Angina Pectoris
- Chronic disease, intermittent attacks of chest pain, radiate through chest, shoulder & arm
- 3 million in USA (~ 1% pop.)

A. Typical (Stable, Effort) angina:
   - ↑ O₂ demand - fixed supply
B. Variant (Prinzmetal's) angina:
   - ↓ O₂ supply - unchanged demand
   - i.e. at rest, coronary spasm (PGs?)
C. Unstable angina:
   - ↓ O₂ supply, plaque, platelets, clot
D. Microvascular angina (Syndrome X):
   - atherosclerosis in small coronary a.

Angina - Pathophysiology

A. Normal
B. Stable angina
C. Unstable angina
D. Variant angina

Determinants of Oxygen Demand

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

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

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

Toni Braxton: Microvascular angina (Syndrome X)

Due to atherosclerosis in very small coronary arteries (5%)
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 – Coronary Occlusion

Lifestyle - Angina Risk Factors

Improving supply/demand ratio

a. Relaxation of resistance vessels (small arteries and arterioles) \( \downarrow \) TPR \( \rightarrow \) \( \downarrow \) BP \( \rightarrow \) \( \downarrow \) Afterload, \( \downarrow \) \( O_2 \) demand (Nitrites, calcium channel blockers and beta-blockers)

b. Relaxation of capacitance vessels (veins and venules) \( \downarrow \) Venous return, \( \downarrow \) heart size, \( \downarrow \) Preload, \( \downarrow \) \( O_2 \) demand (Nitrites)

c. Blockade or attenuation of sympathetic influence on the heart \( \downarrow \) Contactility, \( \downarrow \) HR, \( \downarrow \) \( O_2 \) demand (Beta-blockers)

d. Coronary vessel dilation
   - Important mechanism for relieving vasospastic angina
   - \( O_2 \) supply (Nitrites)

Nitroglycerin
Nitroprusside
Nitrites

Nitrates – Mechanism of Action

- Direct smooth m. relaxation
- High specificity vascular sm
- Vasodilation: vens > arteries
- \( \downarrow \) Preload \( \rightarrow \) \( \downarrow \) Afterload

a. Nitric oxide (NO) in endothelial cells involving sulfhydral (SH) groups
b. Interaction between NO and thiols in smooth m. to form nitrosothiols
c. Nitrosothiol activates guanylate cyclase and increased formation of cGMP

Tolerance: oxidation of SH groups and formation of disulfide bonds
- develops fast and recovers fast i.e. “Monday syndrome or Head”
Nitroglycerin - Routes of administration

1. Sublingual tablet
   - Avoids first-pass effect
   - Onset: 30 sec, Duration: 30 min
2. Buccal tablet
   - Tablet placed in buccal cavity
   - Adheres to mouth’s mucosal surface, NG released for 3-6 hrs
3. Oral (translingual) spray
   - Oral tablet - subject to first-pass effect
4. Topical
   a) ointment (paste)
      - Duration: 3-4 hrs, used in acute care setting
      - Inconvenient, messy, largely replaced by patch
   b) Transdermal system (patch)
      - Delivers NG over 24 hr period
      - Avoid continuous use to prevent tolerance (remove at night)

Nitroglycerin and Nitrates

<table>
<thead>
<tr>
<th>Nitroglycerin and Nitrates for Chronic Stable Angina</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compound</strong></td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td>Nitroglycerin</td>
</tr>
<tr>
<td>Nitroglycerin</td>
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<tr>
<td>Nitroglycerin</td>
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<tr>
<td>Nitroglycerin</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
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<tr>
<td>Isosorbide dinitrate</td>
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<tr>
<td>Isosorbide dinitrate</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
</tr>
<tr>
<td>Amyl nitrite</td>
</tr>
</tbody>
</table>

Other compounds have been developed with the intent of having a longer duration of action for prophylaxis

b. Isosorbide dinitrate [ISDN] – converted to ISMN
c. Isosorbide mononitrate [ISMN]
   - Active metabolite of ISDN
   - Not subject to first-pass metabolism
   - Greater bioavailability (100%)
   - Clinical efficacy not greater than ISDN

Both forms have: 30 min onset, 6 hr duration

Viagra (Sildenafil)

- phosphodiesterase type 5 inhibitor
- ↑NO release
- leads to ↑cGMP
- initially developed for angina
- CI with nitrates
Beta-Adrenoceptor Antagonists

Frontline, high clinical value
- ↓response elderly, Afro-Americans, smokers
Multiple mechanisms of action:
- i. block cardiac beta1-receptors: ↓HR →↓CO →↓BP
- ii. ↓myocardial O2 consumption by ↓HR and ↓force contraction, ↓CO
- iii. ↓BP →↓after-load, ↓pre-load

Clinical use – Beta-blockers

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>HT</th>
<th>Angina</th>
<th>Arth</th>
<th>MI</th>
<th>HF</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-selective β1/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carterolol</td>
<td>X</td>
<td>ISA</td>
<td>long acting; also for glaucoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>ISA, α-blocking activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labelolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>ISA, α-blocking activity</td>
<td></td>
</tr>
<tr>
<td>Nadololol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>long acting</td>
<td></td>
</tr>
<tr>
<td>Penbutolol</td>
<td>X</td>
<td>X</td>
<td>ISA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pindololol</td>
<td>X</td>
<td>X</td>
<td>ISA, MSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA; prototypical beta-blocker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotalolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Channel blocker</td>
<td></td>
</tr>
<tr>
<td>Timololol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>primarily used for glaucoma</td>
</tr>
</tbody>
</table>

β1-selective

<table>
<thead>
<tr>
<th>Drug</th>
<th>HT</th>
<th>Angina</th>
<th>Arth</th>
<th>MI</th>
<th>HF</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>ISA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>ISA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betaxolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esmololol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>MSA</td>
</tr>
</tbody>
</table>

β-Blockers: Untoward Effects, Cautions

- Supersensitivity: Abrupt withdrawal →Rebound HT, less with β-blockers with partial agonist (ie. pindolol).
- Cardiac: ↓reserve, fatigue, dizziness
- Asthma: Blockade of pulmonary β2-receptors leads to increase in airway resistance. β1-selective better
- Diabetes: Compensatory hyperglycemic effect of EPI in insulin-induced hypoglycemia is removed by block of β2-ARs in liver. β1-selective agents preferred
- Raynaud D: Decreased peripheral circulation
- CNS: nightmares, mental depression, insomnia
- Elderly: ↓Effectiveness, ↑adverse effects (ie. depression)

Angina – Beta Blockers

Table 5. Beta Blockers for Chronic Stable Angina

<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>β1</td>
<td>No</td>
<td>50-200 mg twice daily</td>
</tr>
<tr>
<td>Atenolol</td>
<td>β1</td>
<td>No</td>
<td>50-200 mg/day</td>
</tr>
<tr>
<td>Nadololol</td>
<td>None</td>
<td>No</td>
<td>40-80 mg/day</td>
</tr>
<tr>
<td>Timololol</td>
<td>None</td>
<td>No</td>
<td>10-20 mg twice daily</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>β1</td>
<td>Yes</td>
<td>200-600 mg twice daily</td>
</tr>
<tr>
<td>Beclomet</td>
<td>β1</td>
<td>No</td>
<td>10-20 mg/day</td>
</tr>
<tr>
<td>Esmololol (intravenous)</td>
<td>None</td>
<td>No</td>
<td>50-300 μg/kg/min</td>
</tr>
<tr>
<td>Labetalol</td>
<td>None</td>
<td>Yes</td>
<td>200-400 mg twice daily</td>
</tr>
<tr>
<td>Pindololol</td>
<td>None</td>
<td>Yes</td>
<td>25-75 mg 3 times daily</td>
</tr>
</tbody>
</table>

Calcium Channel Blockers

- frontline class, oral and generally well absorbed
- bind to L-type calcium channels in cardiac and vascular smooth muscle
- inhibition of calcium influx into cardiac and arterial smooth muscle cells
- minimal effect on venous capacitance vessels.
- dilate arterioles →↓TPR →↓BP (less verapamil, more nifedipine), ↓afterload
- negative inotropic action on heart (more verapamil, less nifedipine), ↓oxygen demand
- T½: most 2-5 hrs, bepridil 42 hrs, amlodipine 30-50- hrs
Calcium Channel Blockers

Non-dihydropyridines (non-DHPs):
- Verapamil, Diltiazem, Bepridil

Dihydropyridines (DHPs):[dipine]
- Nifedipine, Amlodipine, Nicardipine, Felodipine

Nifedipine:
- mainly arteriole vasodilation, little cardiac effect
- reflex tachycardia, flushing, peripheral edema

Verapamil:
- significant cardiac depression, constipation
- caution in digitalized patients (↑ digoxin levels)

Diltiazem:
- similar to Verapamil / Nifedipine (less)
- actions on cardiac and vascular beds

Intracellular Action of Calcium

Calcium channels:
- Type: L, T, N
- L: dominant in cardiac and smooth muscle

L-Type channel contains several receptors:
- Dihydropyridines (ie. nifedipine) and verapamil/diltiazem bind to different receptors in L channel to decrease calcium influx

Calcium-Blockers: Adverse effects

- constipation (more likely with non-DHPs)
- non-DHPs: cardiac depression, bradycardia, AV block
- non-DHPs are contraindicated with beta-blockers
- mostly DHPs: hypotension, reflex tachycardia, flushing, headache, edema
- hypotension (more likely with DHPs)
- gingival hyperplasia (nifedipine, 10%)
- CHF non-DHPs contraindicated, DHPs not recommended
- CYP3A4 inhibitors: grapefruit, verapamil, diltiazem
- CYP3A4 substrates: amlodipine, verapamil

CCBs: Cardiovascular & renal actions:

<table>
<thead>
<tr>
<th></th>
<th>Diltiazem</th>
<th>Verapamil</th>
<th>Nifedipine (DHPs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↓</td>
<td>↓</td>
<td>↑ (reflex)</td>
</tr>
<tr>
<td>Myocardial</td>
<td>↓</td>
<td>↓</td>
<td>↓ or ↑ (reflex)</td>
</tr>
<tr>
<td>contractility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal conduction</td>
<td>↓</td>
<td>↓</td>
<td>↑ (reflex)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>vasodilation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Calcium blockers - Gingival Hyperplasia

- Calcium blockers – especially nifedipine (10%)
- Phenytoin (Dilantin) – for seizures (40%)
- Cyclosporine – immunosuppressant (30%)

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>Nifedipine</td>
<td>Immediate release</td>
<td>Short</td>
<td>Hypotension, dizziness, flushing, muscle cramps, edema</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>5-10 mg q.d.</td>
<td>Long</td>
<td>Headache, edema</td>
</tr>
<tr>
<td>Felodipine</td>
<td>5-10 mg q.d.</td>
<td>Long</td>
<td>Headache, edema</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>20-40 mg q.d.</td>
<td>Short</td>
<td>Headache, dizziness, flushing, muscle cramps</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>20 mg q.d.</td>
<td>Short</td>
<td>Headache, edema</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Immediate release</td>
<td>Short</td>
<td>Hypotension, dizziness, flushing, muscle cramps</td>
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<td>Felodipine</td>
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<td>Immediate release</td>
<td>Short</td>
<td>Hypotension, dizziness, flushing, muscle cramps</td>
</tr>
</tbody>
</table>

Other Agents
1. Dipyridamole (Persantin)
   - inhibitor of thromboxane synthase (↓TXA2)
   - decrease platelet aggregation
2. Aspirin (low dose)
   - also an inhibitor of platelet aggregation
3. Ranolazine (Ranexa)
   - reserve agent for chronic, resistant angina
   - inhibits cardiac late Na current, ↓Ca
   - ↓cardiac contractility, [metabolic action]
   - ↑QT interval, no change in HR, BP
   - CI with other agents that ↑QT (ie. quinidine)

Antianginals on Primary Determinants of Myocardial O₂ Consumption

<table>
<thead>
<tr>
<th>Calcium Blockers</th>
<th>Nitrates</th>
<th>Beta-Blockers</th>
<th>Verapamil/Dimazem Non-DHPs</th>
<th>DPHs</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSP (Afterload)</td>
<td>↓</td>
<td>0-1</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Heart Size (Preload)</td>
<td>↓</td>
<td>0-1</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>↑ (R)</td>
<td>↓</td>
<td>0-1</td>
<td>↑ (R)</td>
</tr>
<tr>
<td>Contractile Force</td>
<td>0-1 (R)</td>
<td>↓</td>
<td>↑</td>
<td>0</td>
</tr>
</tbody>
</table>

Drug Choices in Angina
A. Effort: nitrates, calcium blockers, beta blockers
B. Variant: nitrates, calcium blockers
C. Unstable: nitrates, calcium blockers, beta blockers, aspirin, anticoagulants, thrombolytics

Aims in the use of antianginal drugs:
- Treatment of acute attack - nitroglycerin very effective (i.v., sublingual, oral spray)
- Short term prophylaxis - taking nitroglycerin prior to anticipated physical or emotional stress may prevent attack
- Long term prophylaxis - objective is to reduce frequency of angina attacks. Many options are now available ie. long-acting nitrates, Ca++-blockers, β-blockers, aspirin, anticoagulants, thrombolytics

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

Angina Drug Treatment

Determinants of Myocardial Oxygen Supply and Demand

Figure 6.1. Major determinants of myocardial oxygen supply and demand. P, ventricular systolic pressure; r, resistance ratio; Q, ventricular diastolic work.