Drug Treatment of Ischemic Heart Disease

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Categories of Ischemic Heart Disease

Fixed "Stable", Effort Angina
Variant Angina “Primary Angina”
Unstable Angina
Myocardial Infarction
<table>
<thead>
<tr>
<th>Secondary Angina</th>
<th>Primary Angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>Variant (Prinzmetal’s)</td>
</tr>
<tr>
<td>Angina of Effort</td>
<td>Angina at Rest</td>
</tr>
<tr>
<td>Typical</td>
<td>Atypical</td>
</tr>
<tr>
<td>1768</td>
<td>1957</td>
</tr>
<tr>
<td>Small vessels</td>
<td>Large vessels</td>
</tr>
<tr>
<td>Single or multiple</td>
<td>Single</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Vasospasm</td>
</tr>
<tr>
<td>ST depression</td>
<td>ST elevation</td>
</tr>
</tbody>
</table>
EFFORT ANGINA
Ople 2008

Ischemic cascade

- dyspnea
- ECG
dyspnea
- systolic dysfunction
- diastolic dysfunction
- ischemia

Effort

Symptoms

- pain relief
- ECG normal
- systolic recovery starts

- stunning

Full recovery

Stops effort

$\text{seconds} \quad \text{minutes} \quad \text{? hours}$
**Stunning?:**

- **Myocardial stunning** is the reversible reduction of function of heart contraction after reperfusion not accounted for by tissue damage or reduced blood flow.
Control of smooth muscle contraction

► Contraction is triggered by influx of calcium through L-type 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*).

► MLCK 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 and by facilitating the expulsion of calcium from the cell.
Control of vascular smooth muscle contraction

\[ \text{Ca}^{2+} \]

- \text{Ca}^{2+} \text{ channel blockers}

- \text{Calmodulin}

- \text{Ca}^{2+} - \text{Calmodulin complex}

- \text{MLCK}^*

- \text{Myosin-LC kinase (MLCK)}

- \text{Myosin-LC-PO}_4

- \text{Actin}

- \text{Contraction}

\[ \text{ATP} \]

- \text{\(\beta_2\) agonists}

- \text{cAMP}

- \text{MILK(PO}_4)_2

- \text{cGMP}

- \text{Myosin-LC}

- \text{Relaxation}

Vascular smooth muscle cell

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Mechanism of IHD

Due to an imbalance of the ratio:

\[ \frac{O_2 \text{ Supply (Coronary Blood Flow)}}{O_2 \text{ Demand (Work of the Heart)}} \]
**Major Determinants of Myocardial Oxygen Supply and Demand**

<table>
<thead>
<tr>
<th>Oxygen supply</th>
<th>Oxygen demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen extraction (%)</td>
<td>Wall tension</td>
</tr>
<tr>
<td>Coronary blood flow</td>
<td>Ventricular volume</td>
</tr>
<tr>
<td>Aortic diastolic pressure</td>
<td>Radius or heart size</td>
</tr>
<tr>
<td>Coronary arteriolar resistance</td>
<td>Ventricular pressure</td>
</tr>
<tr>
<td>Metabolic autoregulation</td>
<td>Systolic pressure (afterload)</td>
</tr>
<tr>
<td>Endocardial-epicardial flow</td>
<td>Diastolic pressure (preload)</td>
</tr>
<tr>
<td>Coronary collateral blood flow</td>
<td>Heart rate</td>
</tr>
<tr>
<td>Large coronary artery diameter</td>
<td>Contractility</td>
</tr>
</tbody>
</table>
Pharmacological modification of the major determinants of myocardial O$_2$ supply

Agents decreasing O$_2$ demand

- Heart rate
- Contractility
- Preload
- Afterload

β Adrenergic antagonists
Some Ca$^{2+}$ entry blockers

Agents increasing O$_2$ Supply

- Coronary blood flow
- Regional myocardial blood flow

Coronary blood flow

Vasodilators (esp. Ca$^{2+}$ entry block)

Also statins, anti-thrombotics

BALANCE

O$_2$ Demand > O$_2$ Supply

ISCHEMIA

Source: Brunton LL, Chabner BA, Knollmann BC: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition: www.accessmedicine.com
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19.1 Simplified diagram of atherosclerosis, angina and myocardial infarction, and drugs used in treatment.
Drug effects on vascular smooth muscle contraction.

► Calcium influx is inhibited by CCBs, leading to muscle relaxation.

► Organic nitrates release nitric oxide, which activates guanylyl cyclase and increases formation of cyclic guanosine monophosphate.
  ▪ cGMP causes smooth muscle relaxation by activating kinases that increase myosin phosphatase activity and decrease myosin phosphate levels.

► α 1-Adrenoceptor agonists activate phospholipase C (PLC), which increases formation of inositol triphosphate (IP 3) from phosphatidylinositol bisphosphate (PIP 2), leading to increased release of calcium from the sarcoplasmic reticulum.

► β 2-Adrenoceptor agonists increase formation of cyclic adenosine monophosphate (cAMP), which activates kinases that inhibit myosin light-chain kinase.
Organic Nitrates

 ► Nitroglycerine (GTN):
   ► Prototype, used for more than 140 years.
   ► Nonspecific smooth muscle relaxant.
   ► Action not antagonized by any known antagonist.
Nitrates, nitrites, and other substances that increase the concentration of nitric oxide (NO) in vascular muscle

Source: Katzung BG, Masters SB, Trevor AJ. Basic & Clinical Pharmacology.
Nitroglycerine (GTN)

► Usually administered sublingually.
► Can be administered by various routes.
► Fast onset of action (1-3 minutes, Peaks at 10 minutes).
► Short duration (15-30 minutes).
► Reductase enzyme in liver will breakdown the drug.
Nitroglycerine (GTN)

► Causes general vasodilation:

► Arteriolar dilation: short lived (5-10 min)
  ▪ Decreases systemic blood pressure (afterload) and causes reflex tachycardia and increased contractility, might increase MVO2.

► Venous dilation: more intense, even with low doses, lasts for 30 minutes.
  ▪ Decreases venous return (preload) and decreases MVO2.
Figure 19-2
A schematic drawing indicating the major actions of the nitrates on the ischemic heart and peripheral circulation. ↓ = decrease; ↑ = increase; → = unchanged; ‡ = variable effect.

(↓ ) Afterload

Preload (↓↓↓)

(→↑) Heart rate

(→↑) Contractility

(↓↓↓) Wall tension

Collateral vessel diameter(↑↑)

Stenosis diameter (↑)

Site of occlusion

Ischemic area

Transmural blood flow
(epicardial ↓)
(endocardial ↑)
<table>
<thead>
<tr>
<th>Effect</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potential beneficial effects</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased ventricular volume</td>
<td>Decreased myocardial oxygen requirement</td>
</tr>
<tr>
<td>Decreased arterial pressure</td>
<td></td>
</tr>
<tr>
<td>Decreased ejection time</td>
<td></td>
</tr>
<tr>
<td>Vasodilation of epicardial coronary arteries</td>
<td>Relief of coronary artery spasm</td>
</tr>
<tr>
<td>Increased collateral flow</td>
<td>Improved perfusion to ischemic myocardium</td>
</tr>
<tr>
<td>Decreased left ventricular diastolic pressure</td>
<td>Improved subendocardial perfusion</td>
</tr>
<tr>
<td><strong>Potential deleterious effects</strong></td>
<td></td>
</tr>
<tr>
<td>Reflex tachycardia</td>
<td>Increased myocardial oxygen requirement</td>
</tr>
<tr>
<td>Reflex increase in contractility</td>
<td>Increased myocardial oxygen requirement</td>
</tr>
<tr>
<td>Decreased diastolic perfusion time due to tachycardia</td>
<td>Decreased coronary perfusion</td>
</tr>
</tbody>
</table>
Nitroglycerine (GTN)

► **Side Effects:**

► Headache.

► Hypotension and tachycardia.

► Increased intraocular and intracranial pressures.

► Methemoglobinemia.

► Tolerance: only for the arteriolar effects.

► Withdrawal: in workers in ammunition industry.
# Nitrate and Nitrite Drugs Used in the Treatment of Angina.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting:</strong></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin, sublingual</td>
<td>10–30 minutes</td>
</tr>
<tr>
<td>Isosorbide dinitrate, sublingual</td>
<td>10–60 minutes</td>
</tr>
<tr>
<td>Amyl nitrite, inhalant</td>
<td>3–5 minutes</td>
</tr>
<tr>
<td><strong>Long-acting:</strong></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin, oral sustained-action</td>
<td>6–8 hours</td>
</tr>
<tr>
<td>Nitroglycerin, 2% ointment, transdermal</td>
<td>3–6 hours</td>
</tr>
<tr>
<td>Nitroglycerin, slow-release, buccal</td>
<td>3–6 hours</td>
</tr>
<tr>
<td>Nitroglycerin, slow-release patch,</td>
<td>8–10 hours</td>
</tr>
<tr>
<td>transdermal</td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate, sublingual</td>
<td>1.5–2 hours</td>
</tr>
<tr>
<td>Isosorbide dinitrate, oral</td>
<td>4–6 hours</td>
</tr>
<tr>
<td>Isosorbide dinitrate, chewable oral</td>
<td>2–3 hours</td>
</tr>
</tbody>
</table>
Beta Adrenergic Blockers

► Prevent actions of catecholamines, so more effective during exertion.
► Do not dilate coronary arteries.
► Do not increase collateral blood flow.
► Cause subjective and objective improvement: decreased number of anginal episodes, nitroglycerine consumption, enhanced exercise tolerance, and improved ECG.
**Figure 19-3**

A schematic drawing indicating the major actions of the β-blockers on the ischemic heart and peripheral circulation. For key, see Fig. 19-2.
Calcium Channel Blockers

Particularly beneficial in vasospasm.
Can affect platelets aggregation.
May be dangerous in heart failure and in patients susceptible to hypotension.
### Properties of Several Recognized Voltage-Activated Calcium Channels.

<table>
<thead>
<tr>
<th>Type</th>
<th>Channel Name</th>
<th>Where Found</th>
<th>Properties of the Calcium Current</th>
<th>Blocked By</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>Ca(<em>{v})1.1–Ca(</em>{v})1.3</td>
<td>Cardiac, skeletal, smooth muscle, neurons (Ca(_{v})1.4 is found in retina), endocrine cells, bone</td>
<td>Long, large, high threshold</td>
<td>Verapamil, DHPs, Cd(^{2+}), -aga-IIIA</td>
</tr>
<tr>
<td>T</td>
<td>Ca(<em>{v})3.1–Ca(</em>{v})3.3</td>
<td>Heart, neurons</td>
<td>Short, small, low threshold</td>
<td>sFTX, flunarizine, Ni(^{2+}), mibefradil(^1)</td>
</tr>
<tr>
<td>N</td>
<td>Ca(_{v})2.2</td>
<td>Neurons, sperm(^{2})</td>
<td>Short, high threshold</td>
<td>Ziconotide,(^{3}) gabapentin,(^{4}) -CTX-GVIA, -aga-III, Cd(^{2+})</td>
</tr>
<tr>
<td>P/Q</td>
<td>Ca(_{v})2.1</td>
<td>Neurons</td>
<td>Long, high threshold</td>
<td>-CTX-MVIIC, -aga-IVA</td>
</tr>
<tr>
<td>R</td>
<td>Ca(_{v})2.3</td>
<td>Neurons, sperm(^{2})</td>
<td>Pacemaking</td>
<td>SNX-482, -aga-III</td>
</tr>
</tbody>
</table>

\(^1\) mibefradil is not shown in the image.

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Nov-14

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Calcium channel blockers

- Phenylalkylamines
  - Verapamil

- Benzothiazepines
  - Diltiazem

- Dihydropyridines
  - 1st generation
    - Nifedipine
  - 2nd generation
    - Isradipine
    - Nicardipine
  - 3rd generation
    - Felodipine
    - Amlodipine
Figure 19-4
A schematic drawing indicating the major actions of the calcium antagonists on the ischemic heart and coronary circulation. For key, see Fig. 19-2.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Bioavailability (%)</th>
<th>Half-Life (hours)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dihydropyridines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>65–90</td>
<td>30–50</td>
<td>Angina, hypertension</td>
</tr>
<tr>
<td>Felodipine</td>
<td>15–20</td>
<td>11–16</td>
<td>Hypertension, Raynaud's phenomenon</td>
</tr>
<tr>
<td>Isradipine</td>
<td>15–25</td>
<td>8</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>35</td>
<td>2–4</td>
<td>Angina, hypertension</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>45–70</td>
<td>4</td>
<td>Angina, hypertension, Raynaud's phenomenon</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>13</td>
<td>1–2</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>&lt; 10</td>
<td>6–12</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>10–30</td>
<td>5–12</td>
<td>Investigational</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>40–65</td>
<td>3–4</td>
<td>Angina, hypertension, Raynaud's phenomenon</td>
</tr>
<tr>
<td>Verapamil</td>
<td>20–35</td>
<td>6</td>
<td>Angina, hypertension, arrhythmias, migraine</td>
</tr>
</tbody>
</table>
Calcium Channel Blockers

**Side Effects:**

- Hypotension.
- Headache, dizziness.
- Flushing.
- Peripheral edema.
# Effects of Nitrates Alone and with Beta Blockers or Calcium Channel Blockers in Angina Pectoris.

<table>
<thead>
<tr>
<th></th>
<th>Nitrates Alone</th>
<th>Beta Blockers or Calcium Channel Blockers</th>
<th>Combined Nitrates with Beta Blockers or Calcium Channel Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate</strong></td>
<td>Reflex(^1) increase</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td><strong>Arterial pressure</strong></td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td><strong>End-diastolic volume</strong></td>
<td>Decrease</td>
<td>Increase</td>
<td>Non or decrease</td>
</tr>
<tr>
<td><strong>Contractility</strong></td>
<td>Reflex(^1) increase</td>
<td>Decrease</td>
<td>Non</td>
</tr>
<tr>
<td><strong>Ejection time</strong></td>
<td>Decrease</td>
<td>Increase</td>
<td>Non</td>
</tr>
</tbody>
</table>
Dipyridamole

- Inhibits the uptake of adenosine and inhibits adenosine deaminase enzyme.
- Thought to be a good coronary dilator.
- Increases the blood flow to the normal area i.e. "Coronary Steal Phenomenon".
- Still used as an antiplatelet drug (in TIAs), but not better than aspirin.
Others

► ACEI.

► Anticoagulants and/or Thrombolytic Therapy.

► Cholesterol Lowering Agents.

► Angioplasty

► Surgery.
Stent addresses the existing lesion but not future lesions.

Bypass grafting addresses the existing lesion and also future culprit lesions.


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Newer Antianginal Drugs

► Metabolic modulators: Ranolazine.
► Direct bradycardic agents: Ivabradine.
► Potassium channel activators: Nicorandil.
► Rho-kinase inhibitors: Fasudil.
► Sulfonylureas: Glibenclamide.
► Thiazolidinediones.
► Vasopeptidase inhibitors.
► Nitric oxide donors: L-arginine.
► Capsaicin.
► Amiloride.