## Treatment of Ischemic Heart Disease

### Ischemic Heart Disease

- **Mechanism**: Imbalance of the ratio of O2 Supply (Coronary Blood Flow) & O2 Demand (Work of the Heart)
  - **Factors of O2 Supply**: O2 extraction (%), coronary blood flow, aortic diastolic pressure, coronary arteriolar resistance, metabolic autoregulation, Endocardial-epicardial flow, coronary collateral blood flow, large coronary artery diameter
  - **Factors of O2 Demand**: Wall tension, ventricular volume, radius or heart size, ventricular pressure, systolic pressure (afterload), diastolic pressure (preload), heart rate, contractility

### Angina Categories

A. Transient coronary ischemia:
- **Fixed "Stable", Effort Angina** → Atherosclerosis
- **Unstable Angina** → Atherosclerosis + plaque rupture & platelet aggregations (can transform to MI)
- **Variant Angina “Primary Angina”** → Vasospasm

B. Coronary thrombosis:
- **Myocardial Infarction**
  - **Secondary**: Atherosclerosis
  - **Primary**: Vasospasm

### Control of SM Contraction

1. Influx of calcium through L-type channels
2. Ca²⁺ combines with calmodulin to form a complex that converts the enzyme myosin light-chain kinase to its active form (MLCK⁺)
3. MLCK⁺ phosphorylates myosin → myosin can now interact with actin → contraction

### β2-agonists (substances that → cAMP) cause relaxation in SM by accelerating the inactivation of MLCK and facilitating the expulsion of Ca²⁺ from the cell

---

### Drug Table

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Uses &amp; Desired Effects</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Adrenergic Blockers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| - Prevent actions of catecholamines, so more effective during exertion (stress)  
  - Work by decreasing heart rate and contractility → decreasing O2 demands  
  - Decreases the afterload   
  - ↑endocardial Blood flow, ↓epicardial BF | - Cause subjective and objective improvement: decreased number of anginal episodes, nitroglycerine consumption, enhanced exercise tolerance, and improved ECG |                                                   |                     |
| **Calcium Channel Blockers** |                                                                     |                                                                                        |                                                   |                     |
| Verapamil | - Block calcium channels  
  - Increases collateral vessel diameter  
  - Increases stenosis diameter  
  - Increase HR in the standing position, decrease it in the supine position (negative inotropic and chronotropic)  
  - Decreases the afterload but doesn’t affect the preload | - Particularly beneficial in vasospasm  
  - Can affect platelets aggregation | - Hypotension  
  - Headache, dizziness  
  - Flushing  
  - Peripheral edema | May be dangerous in the presence of heart failure and in patients susceptible to hypotension (because they are used in treatment of hypertension) |
| Diltiazem |                                                                     |                                                                                        |                                                   |                     |
| Nifedipine |                                                                     |                                                                                        |                                                   |                     |
| Nicardipine |                                                                     |                                                                                        |                                                   |                     |
| Amlodipine |                                                                     |                                                                                        |                                                   |                     |

Myocardial stunning is the reversible reduction of function of heart contraction after reperfusion not accounted for by tissue damage or reduced blood flow
# Treatment of Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Uses &amp; Desired Effects</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroglycerine (GTN)</td>
<td>♦ Releases NO → activation of guanylyl cyclase (nonspecific smooth muscle relaxant) → general dilation -Causes arteriolar dilation (↓ afterload) then venous dilation (↓ preload) -Increases endocardial blood flow and decreases epicardial blood flow -Increases collateral vessels diameter -Decreases preload (↓↓↓) -Decreases afterload (↓) -Decreases wall tension (↓↓↓)</td>
<td>-Treatment of Angina ♦ Potential beneficial effects: -Decreases O2 requirement by: -Decreasing ventricular volume -Decreasing arterial pressure -Decreasing ejection time -Relief of coronary artery spasm by: -Vasodilation of epicardial coronary arteries -Improves perfusion to ischemic myocardium by: -Increasing collateral flow -Improves subendocardial perfusion by: -Decreasing left ventricular diastolic pressure</td>
<td>♦ Headache -Hypotension and tachycardia -Increased intraocular and intracranial pressures -Methemoglobinemia -Tolerance: only for the arteriolar effects -Withdrawal: in workers in ammunition industry ♦ Potential deleterious effects: -Increases O2 requirement by the reflex tachycardia and increase in contractility -Decreases coronary perfusion by decreasing diastolic perfusion time due to tachycardia</td>
<td>♦ Arteriolar dilation: short lived (5-10 min): decreases systemic blood pressure (afterload) → can elicit the baroreceptor reflex to cause reflex tachycardia and increased contractility, and might increase MVO2 ♦ Venous dilation (Main): more intense, even with low doses, lasts for 30 minutes: decreases venous return (preload) &amp; decreases MVO2</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>Inhibits the uptake of adenosine and inhibits adenosine deaminase enzyme</td>
<td>-Increases the blood flow to the normal area (Coronary Steal Phenomenon: the normal area steals from the ischemic area) -Used as an antiplatelet (not better than aspirin)</td>
<td>-Thought to be a good coronary dilator</td>
<td></td>
</tr>
</tbody>
</table>

## Organic Nitrates
- Prototype, used for more than 150 years
- Action not antagonized by any known antagonist
- Usually administered sublingually by 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, breaks down the drug
- Amyl nitrite is an inhalant preparation

*If you want to memorize the preparations refer to slide 21*
Treatment of Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Nitrates Alone</th>
<th>Beta Blockers or Calcium Channel Blockers</th>
<th>Combined Nitrates with Beta Blockers or Ca-Channel Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>Reflex: increase</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Arterial pressure</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>End-diastolic volume</td>
<td>Decrease</td>
<td>Increase</td>
<td>Non or Decrease</td>
</tr>
<tr>
<td>Contractility</td>
<td>Reflex: increase</td>
<td>Decrease</td>
<td>Non</td>
</tr>
<tr>
<td>Ejection time</td>
<td>Decrease</td>
<td>Increase</td>
<td>Non</td>
</tr>
</tbody>
</table>

**Other Treatment of Ischemic Heart Disease**

- ACEI
- Anticoagulants and/or Thrombolytic Therapy
- Cholesterol Lowering Agents
- Angioplasty
- Surgery

**Newer Antianginal Agents**

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

Done by: Rama Abbady