Drug therapy of Angina Pectoris
Coronary Artery Disease

- Coronary Artery Disease /Coronary atherosclerotic heart disease/ Ischaemic heart disease.
- Risk factors for CAD/CHD
- Clinical manifestations of CAD
Angina pectoris

◆ Definition

Angina pectoris is a primary symptom of myocardial ischemia, which is the severe chest pain that occurs when coronary blood flow is inadequate to supply the oxygen required by the heart.
Angina pectoris

◆ Typical Symptoms

a heavy strangulation or pressure-like sensation, sometimes may feel like indigestion, usually located in retrosternal area, often radiating to the left shoulder, left arm, jaw, neck, epigastrium or back.
Clinical Classifications of angina

- Stable angina pectoris
- Unstable angina pectoris
- Prinzmetal’s /Variant angina pectoris
1. Stable angina

- Is caused by narrowed arteries due to atherosclerosis
- Occurs when there is exertion /effort
- Episodes of pain tend to be alike
- Usually lasts a short time
- Is relieved by rest or antianginals
2. Prinzmetal, Variant, vasospastic angina

• Usually occurs at rest
• Tend to be severe
• Is caused by a transient spasm in a coronary artery
• Is relieved by anti-anginal drugs.
3. **Unstable angina**

- Often occurs at rest
- Is more severe and lasts longer than stable angina
- Episodes of pain tend to be changing in the character, i.e., increasing severity (cresendo angina), frequency, duration as well as precipitating factors
Acute Coronary Syndromes

• Is an emergency
• Occurs due to rupture of an atherosclerotic plaque & partial/complete thrombosis of a coronary artery.
• If thrombus occludes coronary vessel signif. --- necrosis of cardiac ms: MI
• May present as Unstable angina or Myocardial infarction.
Pathophysiology of angina

- An imbalance between the myocardial oxygen supply and demand.

\[ \text{O}_2 \text{ demand} > \text{O}_2 \text{ supply} \]
Factors affecting myocardial oxygen demand and oxygen supply

- Contractility
- Heart rate
- Wall tension

**O₂ demand** > **O₂ supply**

- The difference of Arteriovenous oxygen pressure
- Coronary blood flow

Angina

- Ventricular Pressure
- Ventricular Volume
- the duration of diastole
- Aortic Diastolic pressure
- Coronary Vascular resistance
Indirect measure of myocardial oxygen consumption

• **Double product:**
  heart rate $\times$ systolic blood pressure

• **Triple product:**
  systolic blood pressure $\times$ heart rate $\times$ ejection time
Treatment of angina pectoris

- **Lifestyle changes**
- **Drugs:**
  - Nitrates
  - β-blockers
  - Calcium channel blockers
  - Misc:
    - Potassium ch openers, Trimetazidine, Ranolazine, Ivabradine
- **Surgery:**
  - CABG (coronary artery bypass graft)
  - PTCA (percutaneous transluminal coronary angioplasty)
Organic Nitrates/ Nitrovasodilators

Nitroglycerine

Isosorbide dinitrate
Mechanisms of action

Nitrates → NO

NO → Guanylyl cyclase

Guanylyl cyclase → GTP → cGMP

GTP → PDE → GMP

cGMP → MLCK* → MLC

MLC → MLC-PO4

MLC-PO4 → MLC

MLC → Actin → Contraction

MLC → Relaxation

Ca^{2+} (intracellular)
Pharmacokinetics

**Absorption**  oral bioavailability 10-20%
ISMN- 100%

**Metabolism**  liver  by glutathione –organic nitrate reductase.

**Excretion**  kidney
<table>
<thead>
<tr>
<th>Drug &amp; Route</th>
<th>Dose (mg)</th>
<th>Onset (min)</th>
<th>Duration (hrs)</th>
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<tbody>
<tr>
<td>NITROGLYCERINE</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- Sublingual</td>
<td>0.5</td>
<td>2-5</td>
<td>0.25-0.5</td>
</tr>
<tr>
<td>- Oral*</td>
<td>5-15</td>
<td>20-30</td>
<td>4-8</td>
</tr>
<tr>
<td>- Ointment (2%)</td>
<td>-</td>
<td>15-30</td>
<td>3-8</td>
</tr>
<tr>
<td>- Transdermal</td>
<td>5-10 mg/24 hr</td>
<td>30-40</td>
<td>Max. 24 hr</td>
</tr>
<tr>
<td>ISOSORBIDE DINITRATE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Sublingual</td>
<td>5-10</td>
<td>5-15</td>
<td>1-2</td>
</tr>
<tr>
<td>- Oral*</td>
<td>10-20</td>
<td>30-60</td>
<td>2-4</td>
</tr>
<tr>
<td>ISOSORBIDE MONONITRATE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oral*</td>
<td>20-40</td>
<td>15-30</td>
<td>6-10</td>
</tr>
<tr>
<td>ERYTHRITYL TETRANITRATE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Sublingual</td>
<td>5-10</td>
<td>5-15</td>
<td>2-4</td>
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<tr>
<td>- Oral</td>
<td>10-30</td>
<td>30</td>
<td>2-6</td>
</tr>
<tr>
<td>PENTAERYTHRITOL TETRANITRATE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oral*</td>
<td>10-20</td>
<td>30</td>
<td>5-10</td>
</tr>
</tbody>
</table>

*Longer acting sustained release preparations are also available
Pharmacological actions of organic Nitrates

1. Dilate vascular smooth muscle, decrease myocardial oxygen consumption
   – dilate veins
   – dilate arteries (higher conc)
at minimal effective dose:

dilate veins $\rightarrow$ ↓ blood returning to heart $\rightarrow$

↓ preload $\rightarrow$ ↓ Ventricular volume $\rightarrow$ ↓ wall tension

at higher dose:

dilate arteries $\rightarrow$ ↓ peripheral resistance $\rightarrow$

↓ afterload $\rightarrow$ ↓ wall tension $\rightarrow$

↓ myocardial oxygen consumption.
2. Increase blood supply to ischemic area

- Increase subendocardium blood flow

- Redistribution of coronary blood flow
dilate veins $\rightarrow$ ↓ blood returning to heart

↓ LVEDV and LVEDP

dilate arteries $\rightarrow$ ↓ ventricular wall tension

blood flows from epicardium to endocardium
A. Control (no drug) in a patient with CAD

B. Effect of nitrate
- Collateral dilated
- Normal arteriolar tone
- Blood flow to normal area of myocardium
- Blood flow to ischaemic area of myocardium INCREASED

C. Effect of dipyridamole
- Collateral not dilated
- Fully dilated arterioles
- Blood flow to normal area INCREASED
- Blood flow to ischaemic area REDUCED
Nitrates...

3. Protect the ischemic cardiac myocytes, inhibit platelet aggregation and adhesion, decrease ischemic damage
Fig 20.3 Mechanism of Action of Calcium Channel Blockers (CCBs), Organic Nitrates and Potassium Channel Openers.

Key:
- MLCK*—Activated myosin light chain kinase
- MLC—Myosin light chain
- MLC • PO₄—Phosphorylated myosin light chain
- GC—Activated guanylyl cyclase
- PDE—Phosphodiesterase enzyme
- Contraction
- Relaxation
- Hyperpolarization
Clinical uses

- All types of angina
- Acute myocardial infarction
- Heart failure
- Cyanide poisoning
- Biliary colic
- Esophageal spasm
Haemoglobin → Sod. nitrite or Amyl nitrite → Methaemoglobin → CN⁻ → Cyanomethaemoglobin (unstable) → Sod. thiosulfate → Sod. thiocyanate → Excreted through urine

Cyanides (oral, inhalation) → CN⁻ → Chelates Fe³⁺ of cytochrome oxidase → Tissue anoxia, Seizures, Coma → Death
Nitrates : ADRs

Throbbing headache, Flushed appearance, Orthostatic hypotension, Tachycardia
Methemoglobinemia

Monday disease (M morning sickness)

Drug interactions

Sildenafil, Tadalafil, Vardenafil (PDE V inhibitors) potentiate axn : dangerous hypotension.
Nitrate Tolerance

The requirement for the dose of a drug becomes higher to achieve the same pharmacological effect. Develops rapidly when long acting prep. (oral, TTS) or continuous IV inf used for more than a few hrs without interruption.

Mechanism:

● Vascular SH depletion
● Free radical hypoth.: peroxynitrite
● Neurohormonal hypoth.: venodilation---compensatory vasoconstriction d/t activ. Of RAS
Tolerance: Prevention

“As is often true in matters of heart, absence makes the heart grow fonder” - Opie, 1991

Interval dosing with eccentric doses providing a nitrate-free interval of 10-12 hours should be observed to reduce or prevent tolerance.

• Others (less consistent effects): Co-therapy with ACE inhibitors, Carvedilol, hydralazine, vit C.
Antianginals: Beta-adrenoceptor Blocking Drugs

- Not vasodilators
- Nonselective $\beta$-blockers:
  - Propranolol, Pindolol, Timolol....
- Selective $\beta_1$-blockers:
  - Atenolol, Metoprolol, Acebutolol....
Beta-adrenoceptor Blockers

Antianginal actions

Decrease myocardial oxygen consumption

- block β- → decrease heart rate, contractility, and blood pressure → decrease myocardial oxygen consumption.

Improve blood supply to the ischemic area

- decrease myocardial oxygen consumption, promote the blood supply to the compensative dilating ischemic area
- decrease heart rate, increase diastolic perfusion time, blood flow from epicardium to endocardium
Beta blockers: Antianginal action

Also decrease myocardial free fatty acid production → improve myocardial metabolism

These agents decrease mortality of pt with recent MI & improve survival & prevent stroke in pt of HT.

Better outcomes than CCBs in pt with stable angina.
Disadvantages

• 1. decrease contractility $\rightarrow$ eject time $\uparrow$, ventricular volume $\uparrow$ $\Rightarrow$ $O_2$ consumption $\uparrow$

• 2. block $\beta_2$-R on coronary artery $\Rightarrow$ coronary artery contract $\Rightarrow$ coronary blood flow $\downarrow$

• These deleterious effects are balanced by using nitrates concomitantly
Clinical uses

- Stable and unstable angina
- Myocardial infarction
  Combined with nitroglycerin
- Variant angina pectoris: CI
- Other Contraindications:
- Adverse Effects:
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Nitrates</th>
<th>β-Blockers</th>
<th>Combined Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heart rate</td>
<td>↑</td>
<td>↓</td>
<td>± or ↓</td>
</tr>
<tr>
<td>2. Contractility</td>
<td>↑</td>
<td>↓</td>
<td>±</td>
</tr>
<tr>
<td>3. Arterial pressure</td>
<td>↓</td>
<td>↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>4. End-diastolic volume</td>
<td>↓</td>
<td>↑</td>
<td>±</td>
</tr>
<tr>
<td>5. Ejection time</td>
<td>↓</td>
<td>↑</td>
<td>±</td>
</tr>
<tr>
<td>6. Coronary blood flow</td>
<td>↑</td>
<td>↓</td>
<td>± or ↑</td>
</tr>
<tr>
<td>7. Subendocardial ischaemic area blood flow</td>
<td>↑</td>
<td>± or ↑</td>
<td>↑</td>
</tr>
<tr>
<td>8. Collateral blood flow</td>
<td>↑</td>
<td>±</td>
<td>↑</td>
</tr>
<tr>
<td>9. Myocardial wall tension</td>
<td>↓</td>
<td>±</td>
<td>↓</td>
</tr>
<tr>
<td>10. Ventricular volume</td>
<td>↓</td>
<td>↑</td>
<td>±</td>
</tr>
<tr>
<td>11. Heart size</td>
<td>↓</td>
<td>↑</td>
<td>±</td>
</tr>
</tbody>
</table>
Factors Influencing the Development of Angina Pectoris: Targets for Therapy

Heart Rate → Diastolic Time

Contractility → Oxygen Demand

Wall Tension → Oxygen Demand

Systolic Pressure → Ischemia

Volume → Ischemia

Oxygen Supply

Coronary Blood Flow → Collaterals

AoP – LVED Gradient

LVEDP

Ao Dias. Pressure

Spasm/Autoreg.

Adapted from Morrow, Gersh, Braunwald. Chronic Coronary Artery Disease. In Heart Disease, 7th Ed. Zipes, Libby, Bonow, Braunwald, eds.
Calcium channel blockers

- Phenilalkylamines
  - Verapamil
- Benzothiazepines
  - Diltiazem
- Dihydropyridines
  - 1st generation
    - Nifedipine
  - 2nd generation
    - Isradipine
    - Nicardipine
    - Felodipine
  - 3rd generation
    - Amlodipine
Calcium channel-blocking drugs
Mechanisms of Antianginal actions

- Decrease myocardial oxygen consumption
  - Decrease heart rate and contractility; vasodilation; antisympathetic action
- Improve the blood supply to the ischemia
  - Dilate coronary artery, decrease the platelet aggregation
- Protect ischemic cardiac myocytes
- Antiatherosclerosis
Inhibition of cardiac functions

Sinus node

Impulse generation
Heart rate ↓
Reflex tachycardia with nifedipine

AV-node

Impulse conduction
AV-conduction ↓

Ventricular muscle

Electromechanical coupling
Contractility ↓
Clinical uses

Antianginal effect is similar to $\beta$-blockers,

- Suited for the anginal patient with asthma
- **Variant angina** first choice
- Suited for the anginal patient with surrounding blood vessel spasm
Dihydropyridines

- Hypertension
- Angina pectoris
Nifedipine

● Variant angina strongest action
● Stable angina

Combined with β-blokers
Verapamil and Diltiazem

- Supraventricular arrhythmias
  - Atrial fibrillation
  - Atrial flutter
  - Paroxysmal supraventricular tachycardia

- Hypertension

- Angina
Verapamil

- Weaker for dilating peripheral vessels
- Inhibit the heart
- Used for stable angina and variant angina combined with other drugs
- Contraindications:
  - heart failure
  - atrioventricular blockade
Diltiazem

- Moderate, used for all types of angina
- Anginal patient with heart failure, atrioventricular blockade caution
Misc. Antianginal Drugs

• **Potassium channel openers:**
  
  • **Types of K ch:** *Voltage gated* \{vascular & other SM\}, *Ca activated*, *ATP activated* \{cardiac ms & Beta cells of pancreas: opening causes hyperpolariz & relaxn of cardiac SM; others\}
  
  • **Nicorandil:** Newer agent, Activates ATP sensitive K ch (\(K_{\text{ATP}}\)) & hyperpolarizes VSM. Decreases pre- & afterload & prod coronary dilation. Has nitrate –like moiety, also exerts nitrate like effect. Thus arteriodilator + venodilator. But no tolerance.
Nicorandil...

- Simulates “ischaemic preconditioning” d/t activ of mitochondrial K$_{ATP}$ Ch.
- **PK**: Well absb PO, almost completely metab in liver, biphasic elimin. Used in vasospastic & chronic stable angina. Dose: 10-20 mg BD PO
- **A/E**: flushing, palpitations, dizziness, headache, stomatitis, N,V, apthous ulcers
- **DI**: Not to be used with sildenafil
- **CI**: pt in cardiogenic shock, Hypotension
Cytoprotective agents

- **Trimetazidine**: Acts non-haemodynamically, prevents degradation of membrane unsaturated fatty acids by lipid peroxidation—reduces myo O2 demand- pFOX inhibitor
- Also inhibits superoxide cytotoxicity- protects myo from harmful effects of ischaemia.
- **PK**: Absb PO, partly metab in liver , mainly excreted unchanged in urine.
- **A/E**: GI irritation, fatigue, dizziness, reversible parkinsonism in elderly. Use: stable angina,
Ranolazine

- **Main axn:** inhibition of late inward Na current \( (\text{late } I_{Na}) \) in myo. during ischaemia. Ca load in cardiac ms is reduced indirectly thru Na–Ca exchanger: cardioprotective; also inhibits fatty acid oxidation
- No effect on HR & BP prolongs exercise tolerance to angina but no effect on HR, BP.
- **PK:** BA- 30-50%, metab mainly in liver by CYP3A4, excreted in urine. T1/2 is 7hrs
Ranolazine is an Inhibitor of Late $I_{Na}$

Calcium overload causes:
- Electrical instability
- Contractile dysfunction
- Consumption ATP

Ranolazine.....

- **Dose** 500mg BD PO. Can be combined with CCBs?, BB or nitrates
- **A/E**: dizziness, weakness, constipation, postural hypotension, dyspepsia, Headache, prolongation of QTc
- **DI**: Metab by CYP3A4: caution with drugs like verapamil. Diltiazem, ketoconazole, macrolides, PI
Ivabradine

- Direct bradycardic agent or ‘pure’ HR lowering agent
- Blocks hyperpolarization-activated current ($I_f$) thru Na ch present in SA node which get activated during early part of slow distoloc depolariz(Ph4) during ischaemic episodes.---HR decreased– myo oxygen demand decreases.

No negative inotropic or lusitropic effect effect or fall in BP
Ivabradine...

PK: Well absb PO, BA-40%, metab by CYP3A4, Excreted in urine, t1/2 is 2 hrs

Use: Chr stable angina in pt with sinus rhythm who can’t tolerate BB or where BB are CI A/E ; disturbance in nocturnal vision with flashing lights, excess bradycardia, H D N CI : HR < 60, Sick sinus synd, CYP3A4 inhibitors
Ivabradine: Specific and Selective Inhibitor of the $I_f$ Ion Channel

Channel principally responsible for the SA Node Pacemaker Current

Unstable Angina

- In patients with unstable angina, anticoagulant and antiplatelet drugs play a major role in therapy. Aggressive therapy with antilipid drugs, heparin, and antiplatelet agents is recommended.

- In addition, therapy with nitroglycerin and β-blockers should be considered; calcium channel blockers should be added in refractory cases.
Treatment of peripheral artery disease

• d/t atherosclerosis of large & medium periph. arteries.
• S/S: Intermittent claudication: LL
• Trt.: directed at reversal or control of atherosclerosis & trt of hyperlipidemia ,HT, DM, smoking cessation.
• Antiplatelet agents
• Pentoxyphilline-xanthine deriv-dec. blood viscosity
• Cilostazol: PDE 3 inhib : sel antiplatelet & vasodilating axn. Both drugs increase exercise tolerance