ANGINA PECTORIS

Prepared by

Dr. Kamlesh P. Patel
Associate Professor
Department of Pharmacology
Smt. NHL Municipal Medical College
Ahmedabad

Angina pectoris

- O2 demand ≠ O2 supply
- Retrosternal chest pain
- Pressure like chest pain
- Radiate to left shoulder

Angina - Pathophysiology

- ↓ O_2 supply
- Coronary atherosclerosis
- Coronary vasospasm
- Coronary Thrombosis

↑O_2 demand

↑↑ HR

Ventricular Hypertrophy

↑↑ ventricular contractility and wall tension

TYPES OF ANGINA

- **CLASSICAL ANGINA**
- Attacks provoked by 3 E's :-
  - Exercise
  - Emotion
  - Eating
  - Stress
- Patho-physiology suggests presence of Severe Atherosclerosis of larger coronary artery Attacks relieved by sublingual nitrates

VARIANT / PRINZMETAL (VASOSPASTIC ANGINA)

- Attacks provoked at --- Sleep and/or Rest
- Patho – physiology --- recurrent coronary vasospasm
- Attack relieved by sublingual nitrates and / or oral calcium channel blockers

UNSTABLE ANGINA

- New onset of angina
- Attack occurs at …. Rest or during Exercise
- Patho – Physiology suggest superimposition of atherosclerosis and severe increase in tone of coronary arteries
- Severe sub-sternal pressing chest pain lasting for more than 15 minutes, not even relieved by sublingual nitrates…leads to Myocardial infarction (MI)
- Emergency condition…needs immediate Hospitalization.

ANGINA PECTORIS

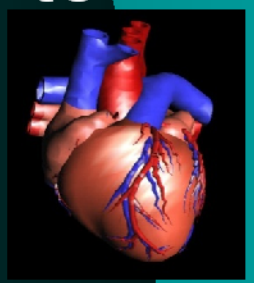
- **PRELOAD** (Ventricular End Diastolic Pressure): is a diastolic pressure which distends the already relaxed ventricular wall.
- Benefit:- ↓ Preload --- ↓ O2 demand, ↓ Heart work
- Drugs :- ↓ Preload are :-
- Nitrates (Glyceral Trinitrate)
- Nitrites (Amyl Nitrite)

ANGINA PECTORIS

- **AFTERLOAD :-** is the force distributed to the ventricular wall during ejection of blood & is related to the peripheral resistance.
- Benefit:- ↓ Afterload --- ↓ O2 demand, ↓ Heart work
- Drugs :- ↓ Afterload are :-
  - Calcium channel blockers
  - Phentolamine
  - Hydralazine
  - Nitrates

Drugs can help to correct imbalance by:

- ✓ **Decreasing** myocardial oxygen **demand** by reducing cardiac workload
  - Reducing heart rate
  - Reducing force of myocardial contraction
  - Reducing after load
- ✓ **Increasing** the **supply** of oxygen to ischemic myocardium



ANTI – ANGINAL DRUGS

- **(I) ORGANIC NITRATES**

(a) Short acting ► Nitroglycerine (NTG)

(b) Long Acting ► Isosorbide Dinitrate (S.L.)

► Isosorbide Mononitrate

(II) BETA BLOCKERS

► Propranolol

► Atenolol

► Metoprolol

ANTI – ANGINAL DRUGS

- **(III) CALCIUM CHANNEL BLOCKERS**

► Verapamil ► Nifedipine, Amlodipine, Nicardipine ► Diltiazem

(IV) POTASSIUM CHANNEL OPENERS

► Nicorandil

(V) ANTIPLATELET DRUGS

► Aspirin ► Clopidogrel

(VI) CYTOPROTECTIVE AGENT

► Trimetazidine

ORGANIC NITRATES– MOA

Nitrates

↓

Denitrated in the smooth muscle cell

↓

Release Nitric oxide (NO)

↓

↑ Guanyl Cyclase Enzyme → ↑ c GMP

↓

Dephosphorylation of Myosin Light Chain Kinase (MLCK)

↓

↓ iCa2+

↓

Vascular Smooth Muscle Relaxation

(Mainly venodilatation, arterial dilatation & Coronary vessels dilatation)

PHARMACOLOGICAL ACTIONS OF NITRATES

- **(A) HEMODYNAMIC ACTION**

VENODILATATION

↓

↑ Peripheral Pooling of blood

↓

↓ Venous return

↓

↓ End Diastolic Ventricular Pressure and Ventricular Size

↓

↓ Preload

↓

↓ Cardiac work Load

↓

↓ Oxygen Consumption (Demand)

PHARMACOLOGICAL ACTIONS OF NITRATES

- **(A) HEMODYNAMIC ACTION**

ARTERIODILATATION

↓

↓ Total Peripheral Resistance

↓

↓ B.P. (SBP>DBP)

↓

↓ Cardiac Output

↓

↓ Ventricular Systolic Wall Tension

↓

↓ Aortic Impedance (Resistance)

↓

↓ Cardiac Work Load -→ ↓ Afterload

↓

↓ Oxygen Demand / Consumption

PHARMACOLOGICAL ACTIONS OF NITRATES

(B) REDISTRIBUTION OF BLOOD :-

Dilatation of large coronary arteries

↓

Dilatation of collateral blood vessels

↓

Redistribution of coronary blood flow to ischaemic areas

↓

Improves perfusion of ischaemic subendocardial region

↓

Development of inter-cardial anastomosis within myocardium.

↓ Cardiac Output -→ ↑ Oxygen supply

↑ Survival rates (Useful in Variant / Prinzmetal Angina)

(C) EXERCISE THRESHOLD

↓ Oxygen consumption of the heart

↓

↑ Exercise Tolerance without increasing Anginal Index (HRxSBP)

PHARMACOLOGICAL ACTIONS OF NITRATES

- **(D) EXTRACARDIAC EFFECTS**

(1) ***Cerebral Vessels :-***

- Vasodilatation
- ↑ intracranial pressure
- Throbbing Headache

(2) ***Cutaneous (skin) Vessels :-***

- Flushing on face and neck
- Vasodilatation

(3) ***Other Smooth Muscles :-***

- ***R***elaxes smooth muscles of :-
- Bronchi , Biliary Tract , Renal

ROUTES OF ADMINISTRATION OF NITRATES

(1) SUBLINGUAL :-

(i) Tablet :- NTG (Nitroglycerine) ; Isosorbide Dinitrite

(ii) Spray :- NTG

(2) ORAL :-

(i) Tablet :- Isosorbide Mono / Dinitrite

(ii) SR/TR Tablet :- NTG

(iii) Chewable:- Isosorbide Dinitrite

(iv) Buccal Tablet:- NTG

(3) INHALATION :-

(i) Amyl Nitrite

(4) SKIN :-

(i) Ointment – NTG

(ii) Trans-Dermal Patch :- NTG

(5) INJECTION – NTG (I.V.)

THERAPEUTIC USES OF NITRATES

- (1) Acute attack of Angina Pectoris
- (2) Prophylaxis against Angina Pectoris
- (3) Paroxysmal Nocturnal Dyspnoea-Acute Left Ventricular Failure (LVF)
- (4) Chronic LVF due to IHD
- (5) Acute Myocardial Infarction (AMI)
- (6) Cyanide Poisoning
- (7) Biliary colic

Treatment of Cyanide Poisoning

Haemoglobin (Non – toxic)

↓

Amyl Nitrite Inhalation or I.V. Sodium Nitrate

↓

Methaemoglobin

↓

Cyanomethaemoglobin

↓

I.V. Sodium Thiosulphate

↓

Convert cyanide to Sodium Thiocyanate
(Rapidly excreted in urine)

ADVERSE EFFECTS OF NITRATES

- Throbbing Headache
- Postural Hypotension
- Giddiness , Weakness
- Flushing
- Methaemoglobinemia
- Tolerance
- Reflex Tachycardia
- Cold , Sweats , N, V.
- Monday Morning Phenomenon

BETA-BLOCKERS IN ANGINA
MECHANISM OF ACTIONS

BETA – BLOCKERS (Atenolol, Metoprolol)

↓

Blocks B-1 Adrenoceptors on Heart

↓

↓ Sympathetic stimulation of Heart

↓

↓ Heart Rate (-ve chronotropic effect)

↓

↓ Myocardial contractility (-ve ionotropic effect)

↓

↓ Arterial Blood Pressure

↓

↓ Myocardial oxygen requirement
(during rest and exercise)

ADVERSE EFFECTS OF B-BLOCKERS

- **Hypotension**
- **Severe Syncope with nitrates**
- **Bradycardia (Decrease in Heart Rate)**
- **Abrupt stoppage ….. Sudden precipitation of anginal attack**
- **Precipitation or aggravation of CHF…..(use Digitalis)**
- **↑ Ejection time due to ↑ in end diastolic volume → ↑ O2 requirement → Blunt BB effect as monotherapy.**

ADVANTAGES OF B-BLOCKERS

- Decreases Nitroglycerin (NTG) Requirement
- Prevents……. Exercise / Stress – induced cardiac arryhthmias
- With nitrates …..used for chronic prophylaxis of angina
- ↓ Frequency of attacks + ↑ Exercise tolerance → Useful in Classical or Angina of Efforts.

(But not in Vasospastic angina).

ADVANTAGES OF B-BLOCKERS

- ↓ Total Coronary Blood Flow
- But, ↑ Blood flow to subendocardial ischaemic region + ischaemic areas distal to severe coronary arteries stenosis
- ** favourable redistribution
- ** ↓ HR,& Ventricular walltension
- ** ↑ Diastolic perfusion time.
- Inhibits platelet aggrtegation

CALCIUM CHANNEL BLOCKERS ADVERSE EFFECTS

- **(1) Verapamil :-**

  Bradycardia , Heart Block , Hypotension.

(2) Nifedipine :-

Tachycardia , Orthostatic hypotension

(3) Diltiazem :-

Bradycardia , Myocardial depression.

CALCIUM CHANNEL BLOCKERS IN ANGINA (MOA)

- Blocks calcium channels
- Decrease intra-cellular Ca2+ enrty
- Decrease intra-cellular Ca2+ levels
- Potent vasodilator ……dilates large coronary arteries and small intra- myocardial coronary arteries …… (Improve coronary artery flow)

CALCIUM CHANNEL BLOCKERS IN ANGINA (MOA)

- Potent arteriodilator ….↓ total peripheral resistance → ↓ B.P. → ↓ cardiac workload → ↓ O2 requirement → ↓ After load …… (useful in vasospatic / variant / prinzmetal angina)

- CCBs are Indicated in :-

(i) Vasospastic angina with nitrates.

(ii) Angina of efforts

RATIONALE OF COMBINATION THERAPY IN ANGINA PECTORIS

- **(I) <u>L.A. NITRATES + B – BLOCKERS</u>**

  (a) B.B blocks Tachycardia produced by L.A. Nitrates

  (b) L.A..N. counteracts ventricular dilatation induced by B. Blockers

  (c) L.A..N. opposes reduction in total coronary blood flow induced by B. Blockers

(Therefore, the above combination is useful in Classical & Resistant cases of Classical Angina)

RATIONALE OF COMBINATION THERAPY IN ANGINA PECTORIS

- **(II) DHP - C.C.B .s + B – BLOCKERS**

  (a) B.B blocks Tachycardia produced by Nifedipine

  (b) DHP - CCB (Nifedipine) counteracts ventricular dilatation induced by B. Blockers

  (c) DHP – CCB opposes reduction in total coronary blood flow induced by B. Blockers

  (d) DHP – CCB do not produce –ve chronotropic effect (↓ HR) , therefore do not aggravates bradycardia produce by Beta - Blockers.

RATIONALE OF COMBINATION THERAPY IN ANGINA PECTORIS

- **(III) <u>L.A. NITRATES + C C B s</u>**

  (a) Nitrates reduces Preload

  (b) C.C.B. s reduces Afterload

  (c) Combination reduces cardiac workload, therefore useful in Resistant Variant (vasospastic) Angina.

RATIONALE OF COMBINATION THERAPY IN ANGINA PECTORIS

- **(IV) L.A. NITRATES + B. B. +C C B s**

(a) Nitrates reduces Preload
(b) C.C.B. s reduces Afterload
(c) B.B. reduces cardiac workload
(d) Combination produces supra -additive effect by different mechanisms…. therefore useful in severe Resistant Variant (vasospastic) Angina.

Treatment of Angina Pectoris

- Maintain Balance Between O_2 supply & O_2 demand
- ***↓ O_2 Demand :-***
- By reducing workload on heart :---
- (i) ↓ Preload (mainly) : Nitrates
- (ii) ↓ Afterload : CCBs, K + channel opener
- (iii) ↓ HR & contractility : Beta - Blockers

Treatment of Angina Pectoris

- **↑ O_2 Supply :-**

1) Relieve atheromatous plaque :-

- **(a) Percutaneous transluminal coronary angioplasty (PTCA)**
- **(b) Coronary artery bypass graft (CABG)**

2) Relieve the vasospasm by drugs : CCBs / Nitrates

3) Break the thrombi using Thrombolytic agents : Streptokinase/Urokinase

4) Prevent thrombi using antiplatelet drugs :-

(a) low –dose aspirin (b) Clopidogrel

PRINCIPLES OF TREATMENT OF ANGINA PECTORIS

- Relief from attack (↑ O2 supply , ↓ O2 demand)
- Prevention of recurrent attacks
- **Chronic prophylaxis :-**
  - (i) Take L.A. Nitrates , B1-Blockers / C.C.B. s , Statins
  - (ii) Antiplatelets (Aspirin, Clopidogrel)
  - (iii) Moderate Physical Exercise
  - (iv) Control emotion, smoking, alcohol
  - (v) Induce weight reduction
  - (vi) Avoid sympathomimetics

TREATMENT OF ACUTE MI

- (I) **PRE – HOSPITALIZATION :**
- ***(A) Pain Relief :-***
- (i) Mild Pain :- Sublingual NTG (0.5 mg q 5 mins . Max. 3 dose)
- (ii) Persistent Pain :- I.V. NTG
- (iii) Severe Pain :- I.V. Morphine (repeat after 30 mins).
- ***(Advantages of Morphine) :-*** Rapid Pain Relief , Relieve Pulmonary Congestion , Minimizes shock
- ***(Adverse effect of Morphine) :-*** Hypotension
- ***(C/I of Morphine) :-*** Bradycardia, Resp. depression

TREATMENT OF ACUTE MI

- (II) <u>OXYGENATION :-</u>
- 100% 2-5 L/min with face mask
- Bed rest

- (III) **ANTIPLATELET :-**
- 4 tablets stat of 75 mg each of Aspirin or Clopidogrel.

TREATMENT OF ACUTE MI

- (II) **HOSPITALIZATION :-**
- (1) Oxygenation and Bed Rest
- (2) I.V. Thrombolytic Therapy with either:
- ► Streptokinase I.V. 1.5 MU bolus over 60 mins, then same dose slow i.v. infusion over 24 hrs. (or)
- ► Urokinase I.V. 5000 IU / kg in 10 mins followed by slow I.V. Infusion over 24 hrs. (or)
- ► rtPA I.V. 10 mg over 2 mins with I.V. heparin, followed by 50 mg slow I.V. over 1 hr

TREATMENT OF ACUTE MI

- (III) I..V. BETA BLOCKER
- (1) Metoprolol : 5 mg I.V. over 2 min q 5 min (Max. 3 Doses).
- Followed by 50-100 mg of Tab. Metoprolol orally in two divided doses daily. (or)
- Tab. Atenolol 25-100 mg orally in two divided doses daily

TREATMENT OF ACUTE MI

- **ADVANTAGES OF BETA – BLOCKERS :**
- ***Start therapy within 6 hrs and continue life long***
- ***Restore perfusion***
- ***Reduce infarct size***
- ***Prevent post-MI sudden death during 1st year due to its anti-arryhthmic property***
- ***Reduces mortality***
- ***Increases Quality of Life (QOL)***

TREATMENT OF ACUTE MI

- (IV) **ACE – INHIBITORS :-**
- Enalapril 5mg / Ramipril 5mg once a day
- Start within 24 hrs and give life long
- ***Advantages:-***
- *(1) Decrease LV Dysfunction*
- *(2) Decrease LV Hypertrophy*
- *(3) Decrease B.P.*
- *(4) Decrease progression of HF*

TREATMENT OF ACUTE MI

- (V) **ANTICOAGULANTS :-**
- Heparin (I.V.) or Low Molecular Weight Heparin (LMWH)-S.C.in Patient with LV Dysfunction, to prevent venous thrombosis and/or pulmonary embolism
- (VI) **GENERAL MEASURES :-**
- **I.V Diazepam (for sedation)**
- **Liquid diet**
- **Correct constipation with liquid Cremaffin**
- **Anti-arrhthymic drugs – I.V. lignocaine**
- **Improve Pump Failure by I.V. Dopamine, Dobutamine, Milrinone**

TREATMENT OF ACUTE MI

- (VI) **POST-HOSPITALIZATION :-**
- *Aspirin 150 mg daily life long*
- *B1 blockers 25-100 mg in d.d doses life long*
- *ACE-I 5 mg (Ramipril) O.D. life long*
- *Atorvastatin 20 mg O.D. life long*
- *Mild exercise, cholestrol free diet*
- *Quit smoking, tobacco chewing*
- *Live stress free life*
- *Regular check up, ECG follow up.*