Antianginal drugs

Nitrates
β blockers
Ca^{++} channel blockers
Metabolism modifiers

What is the cause of angina?

- Coronary insufficiency
- **Angina occurs when O_2 demand exceeds O_2 supply**
    1. **Prerload**
    2. **Afterload**
    3. Heart Rate & cardiac contractility

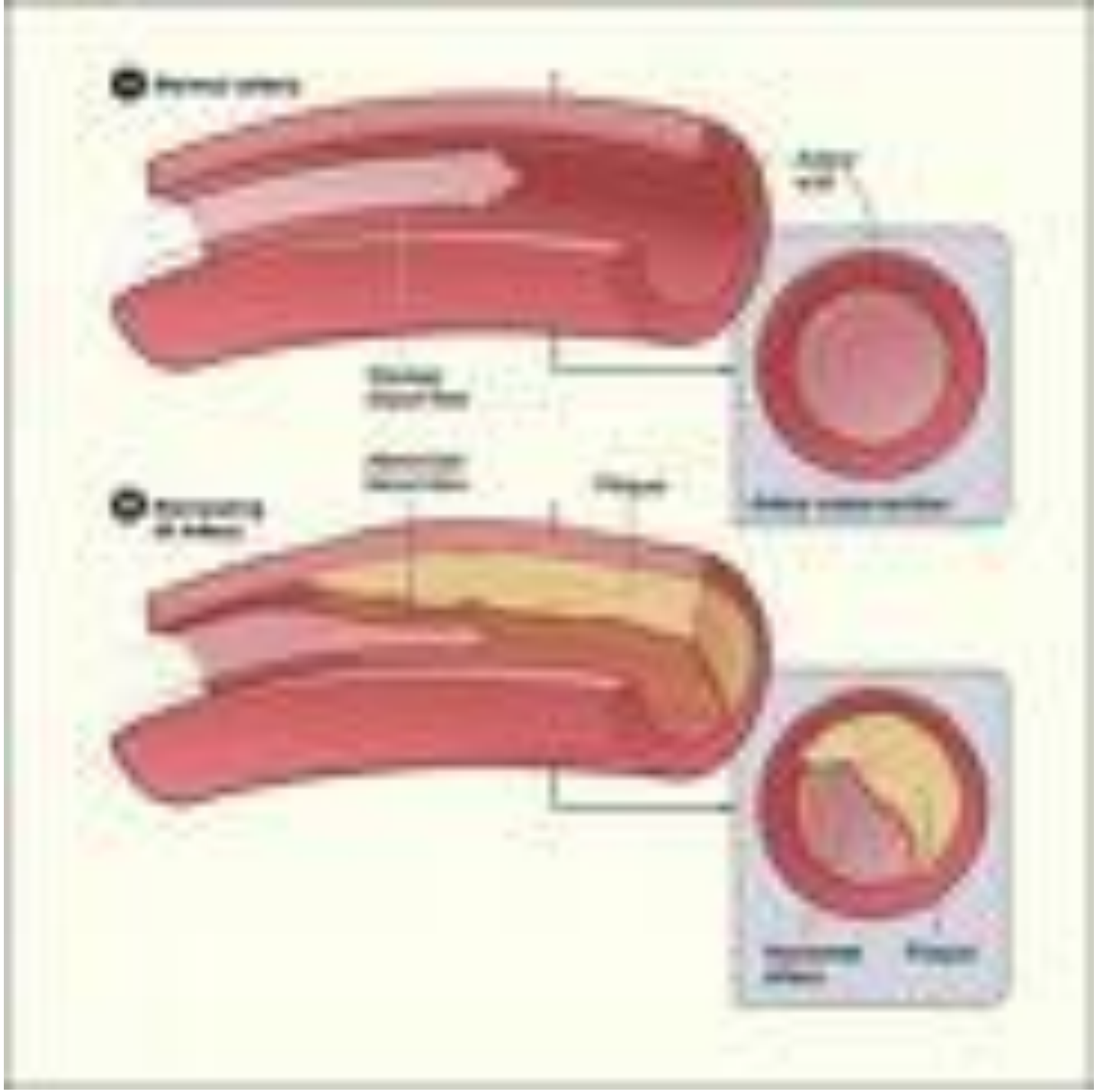
- **Preload** (diastolic filling pressure)
  - Blood volume
  - Venous tone---controlled by **sympathetic outflow**
- **Afterload**
  - Peripheral resistance
  - Arterial stiffness, Arterial BP
- Heart rate --- At faster rate
  - Diastole is abbreviated --- coronary flow is ↓
  - Fiber spend more time at systolic tension levels

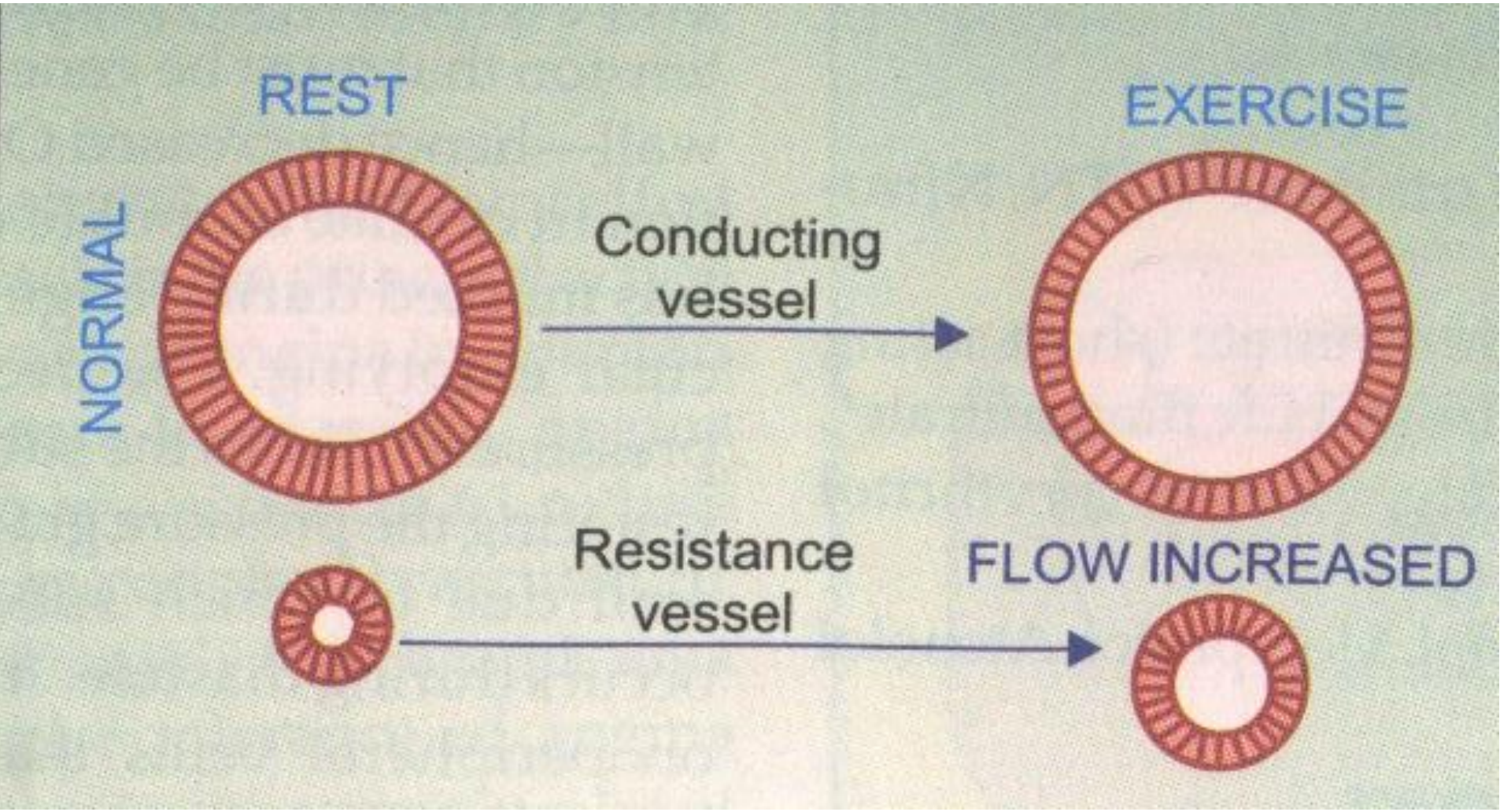
TYPES OF ANGINA

1. ATHEROSCLEROTIC ANGINA
   (Atheromatous plaques occlude coronary arteries)

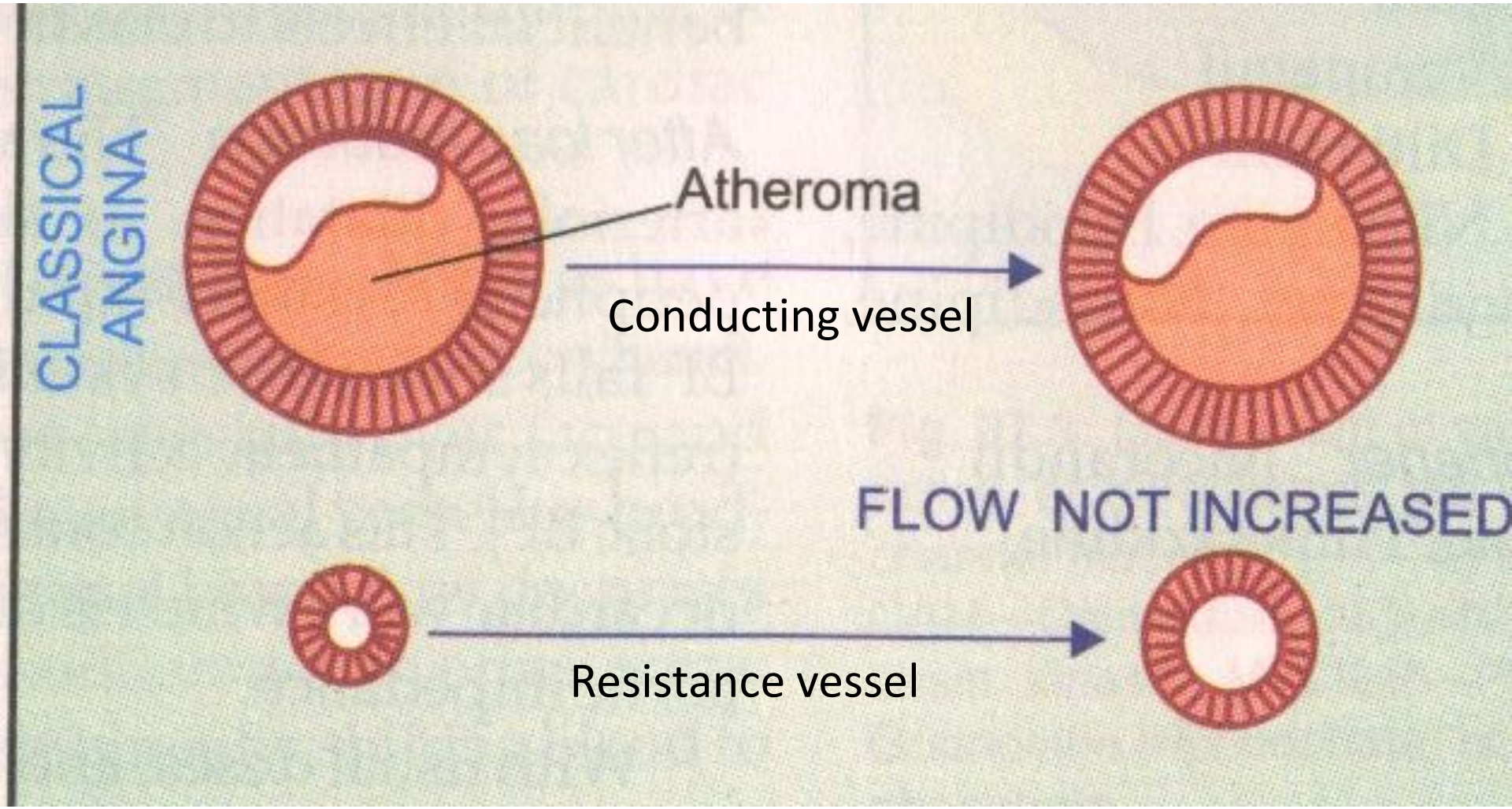
2. VASOSPASTIC ANGINA --- VARIANT ANGINA
   (Constriction of coronary arteries)

3. UNSTABLE ANGINA
   (Thrombus with atherosclerosis and vasospasm
   of coronary arteries)

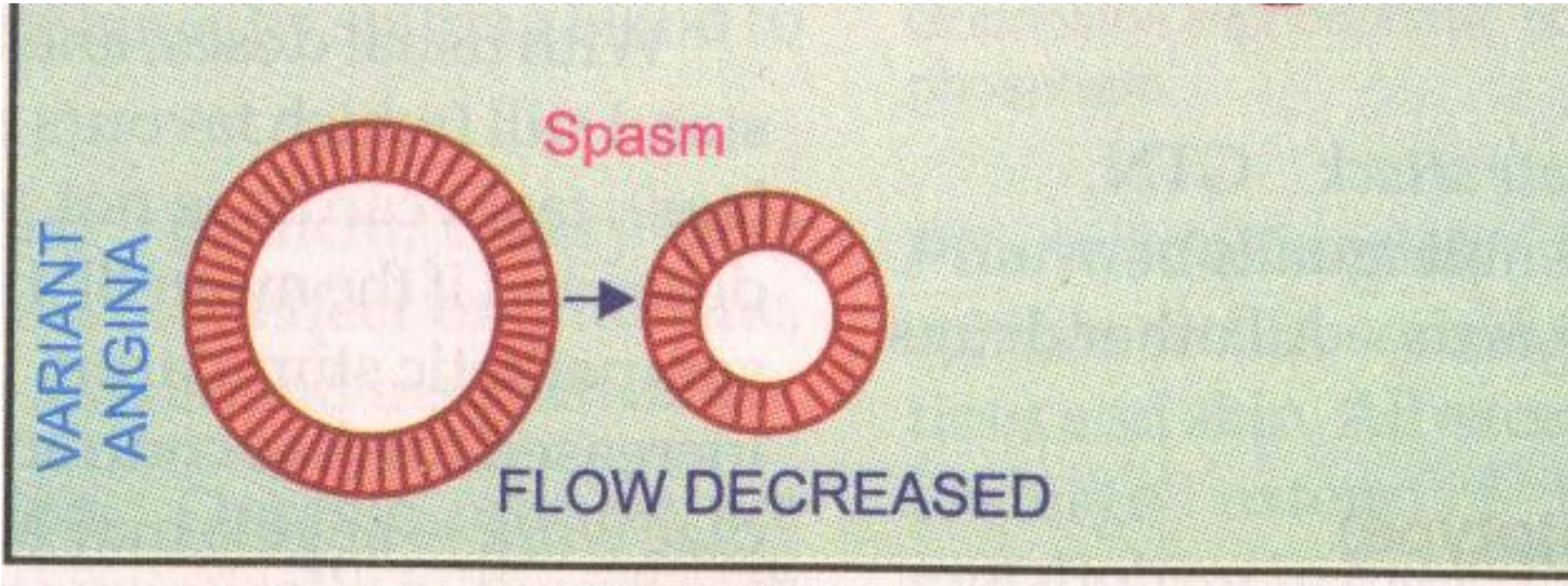



REST
EXERCISE
NORMAL
Conducting vessel
Resistance vessel
FLOW INCREASED

Rest Exercise



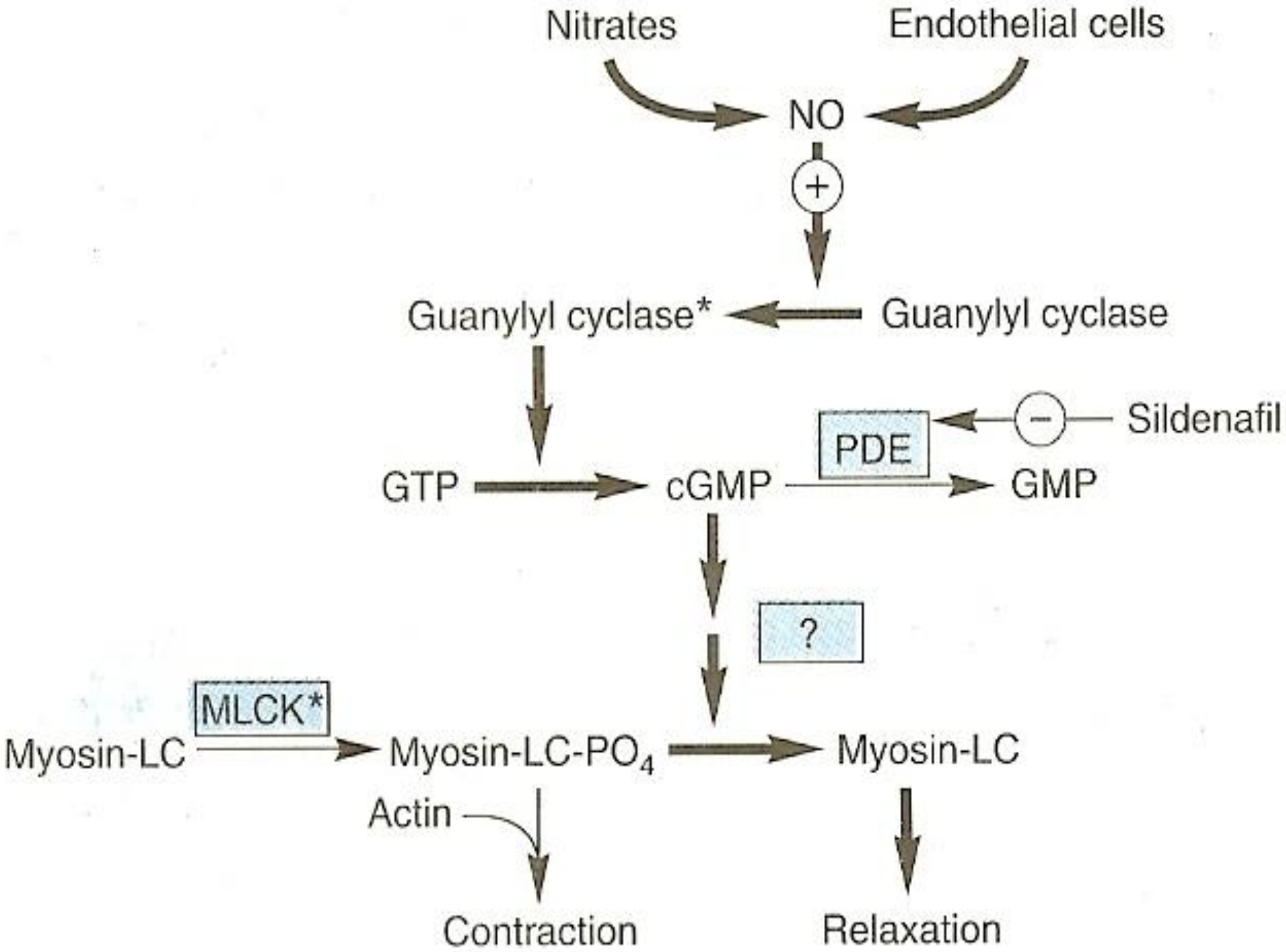
ATHEROSCLEROTIC ANGINA
(Atheromatous plaques occlude coronary arteries)



VASOSPASTIC ANGINA
(Constriction of coronary arteries)

Nitrates are potent vasodilators

- **Dilation of the large veins -------This reduces preload** (venous return) and reduces the work of the heart
  - ↓ myocardial oxygen demand/consumption because of ↓ cardiac work
- Dilates coronary vessels
  - ↓coronary vasoconstriction or vasospasm and ↑ perfusion of myocardium


Nitrates
Endothelial cells
NO
+
Guanylyl cyclase*
Guanylyl cyclase
−
Sildenafil
PDE
GTP
cGMP
GMP
?
MLCK*
Myosin-LC
Myosin-LC-PO4
Myosin-LC
Actin
Contraction
Relaxation

Toxicity/ precaution

- Vasodilation
  - Tachycardia (baroreceptor reflex)
  - Orthostatic hypotension (effect of vasodilation)
  - Throbbing headache (meningeal artery vasodilation), facial flushing
  - Precautions with other hypotensive agents
- Sildenfil potentiate the action of nitrates
  - Synergestic relaxation of vascular smooth muscle with potential dangerous hypotension and hypoperfusion of critical organ
  - Sidenafil (or other PDE5 inhibitors) should not be given with nitrates

Tolerance

- Develops rapidly
  - Loss of effect of a nitrate vasodilator when exposure is prolonged beyond 10 to 12 hours
- A daily **“Nitrate free interval”** to restore sensitivity to drug
  - Typically 10 to 12 hours interval, usually at night
- In patients of variant angina Nitrate-free interval should occur in the late afternoon
  - Variant angina worsen early in the morning (↑ catecholamine surges)

β blockers

- Reduce work and myocardial O2 demand, both at rest and especially on exertion
  - -Ve ionotropic effect and -Ve chronotropic effect
  - Low heart rate is associated with an increase in diastolic perfusion time of myocardium
- Cardioselective β blockers are preferred
  - Atenolol , Metoprolol
  - All β blockers are nonselective at high doses
  - Agents with intrinsic sympathomimetic activity (e.g., Pindolol) are less effective and should be avoided in angina

β blockers

- β blockers are of **no value in an acute attack**
- Used for **prophylactic therapy** of angina
  - Effective in preventing **exercise induced angina**
  - **Reduce the frequency and severity of anginal attacks**
- **Ineffective in against the vasospastic angina**
  - **May aggravate coronary artery spasm**
- **β blockers + nitrate combination is useful --- undesirable effects of nitrates (tachycardia) are reduced by the β blockers**

β blockers

- Used in secondary prevention
  - Drugs of choice in patients with previous MI and has been shown to prolong survival
- **It is important not to discontinue β blockers therapy abruptly**
- **The dose should be gradually tapered off over 5 to 10 days to avoid rebound angina or hypertension**

β blockers + Nitrates

- Increase exercise duration and tolerance
- Tachycardia due to nitrate is blocked by the β blockers
- The tendency of β blockers to cause ventricular dilatation is counteracted by nitrates
- The tendency of β blockers to reduce total coronary flow is opposed by nitrates

Contraindications

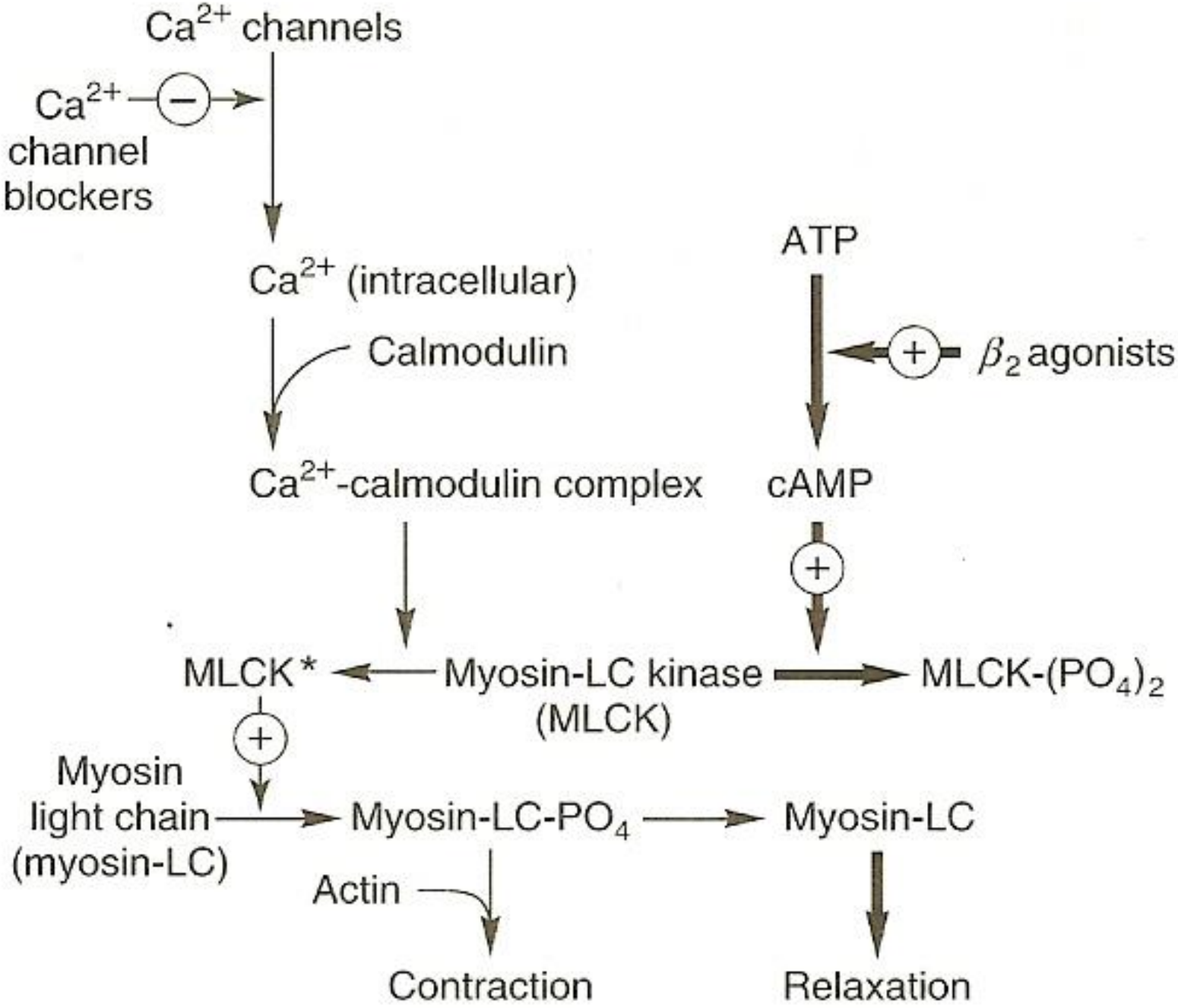
- Bradycardia
- AV block
- Asthma/COPD
- Peripheral vascular disease

Calcium channel blockers

- Reduce oxygen demand of myocardium
  - Relax coronary arteries
  - Reduce **afterload** by causing peripheral vasodilatation
  - Reduce force of LV contraction
- The non-dihydropyridines (diltiazem and verapamil) also reduce heart rate
  - Particularly useful antianginal agents, but should be used with caution in combination with beta blockers
  - Verapamil + β blocker combination is contraindicated

Calcium channel blockers -- Nifedipine

- Short acting dihydropyridines (nifedipine) can cause reflex tachycardia
  - High dose nifedipine is associated with adverse effects
  - Slow release preparations + 3rd generation agents(amlodipine)
    - have smooth profile of action
    - No significant effect on heart rate
    - No significant negative ionotropic effect


Ca^{2+} channels
Ca^{2+} channel blockers
Ca^{2+} (intracellular)
Calmodulin
Ca^{2+}-calmodulin complex
ATP
β_2 agonists
cAMP
MLCK*
Myosin-LC kinase (MLCK)
$MLCK-(PO_4)_2$
Myosin light chain (myosin-LC)
$Myosin-LC-PO_4$
Myosin-LC
Actin
Contraction
Relaxation

Calcium channel blockers

- Ca^{++} channel blockers do not reduce the risk of MI in unstable angina
- The use of ditiazem or verapamil should be reversed for patients resistant to treatment with beta blockers
- Sudden withdrawal of calcium channel blockers may be associated with an exacerbation of angina
  - Rebound worsening of angina on withdrawal is less than with beta blockers

Uses -- Angina pectoris, arrhythmia

- Safe to be used in patients with
  - COPD and peripheral vascular diseases in whom beta blockers are contraindicated
- Arrhythmia --- verapamil
  - (ditiazem to a lesser extent) is highly effective in PSVT and
  - for control of ventricular rate in supraventricular (VT) arrhythmias

Rational drug combinations

- When monotherapy is unable to provide adequate relief, 2 or more drugs may be given
- β blockers + long acting nitrate
- Slow acting DHP+β blockers
  - Contraindicated ---- β blockers + verapamil
  - To be used with caution β blockers + diltiazem
- **Nitrates + CCBs**
  - **Especially useful in vasospastic angina**

Nicorandil

- Nicorandil has two components
  - K+ channel activator
  - Nitrate component
- It has both arterial and venous dilating properties
- Not used as first-line drug
  - Used when there are contraindication to use of other drugs and
  - In refractory unstable angina

Metabolism modifiers (trimetazidine)

- Used as **additional medication to conventional therapy in angina and post MI**
- Improves cellular tolerance to ischemia
    - Decrease fatty acid metabolism and increasing glucose metabolism in mitochondria by inhibiting mitochondrial lon chain 3 ketoacyl Co A(3KAT) thiolase
    - Limit intracellular acidosis and Na^{+}, Ca^{++} accumulation during ischemia
    - Protect against O+ free radical induced membrane damage

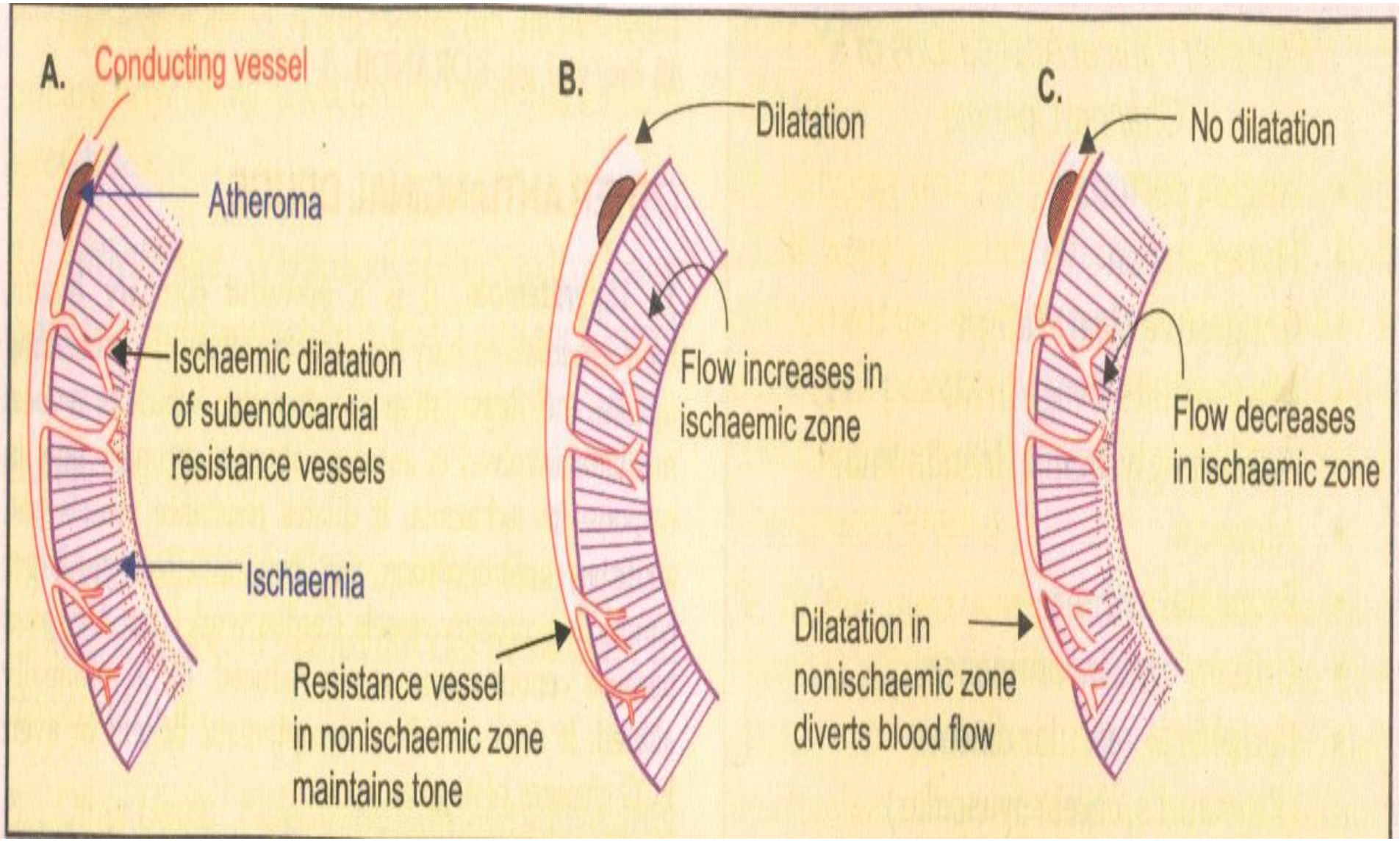
Dipyridamole

- A powerful coronary dilator, increases total coronary flow
- It inhibits platelets aggregation
  - By potentiating PGI2 and increasing cAMP in platelets
- **Dipyrimidole – The pharmacological success but therapeutic failure**
- **Coronary steal**
  - By dilating resistance vessels in non ischemic zone as well, it diverts the already reduced blood flow from the ischaemic zone

Angina pectoris

Nitrates

Coronary steal by Dipyridamol



Treatment of angina

- Risk factor evaluation and correction
  - Smoking, hypercholestrolaemia
  - Weight reduction, regular exercise
- Management of coexistent conditions
  - DM, HTN
- **Medical therapy**
- Revascularization
  - CABG
  - Angioplasty

Medical treatment

- Prognostic therapies
  - **Aspirin --- 75 mg daily**
  - **Lipid lowering therapy**
    - Low fat diet
    - **Statins** (HMG-Co A reductase inhibitors)
    - **Fibrate** (if TGs >3.5 mmol/l)
- Symptomatic treatment
  - **Nitrates**
  - **β blockers** **- C C Bs,**
  - **Nicorandil** **- Trimetazidine**

Medical treatment

Prognostic therapies

- **Aspirin**
  - **75 - 300 mg daily**
- **Lipid lowering therapy**
  - Low fat diet
  - **Statins** (HMG-Co A reductase inhibitors)
  - **Fibrate** (if TGs >3.5 mmol/l)

Symptomatic treatment

- **Nitrates**
- **β blockers**
- **C C Bs,**
- **Nicorandil**
- **Trimetazidine**

Treatment of angina with concomitant disease

- None
  - Long acting **nitrates, β blockers, C C Bs**
- Recent MI
  - Long acting **nitrates, β blockers**
- Asthma/COPD
  - Long acting **nitrates, C C Bs**

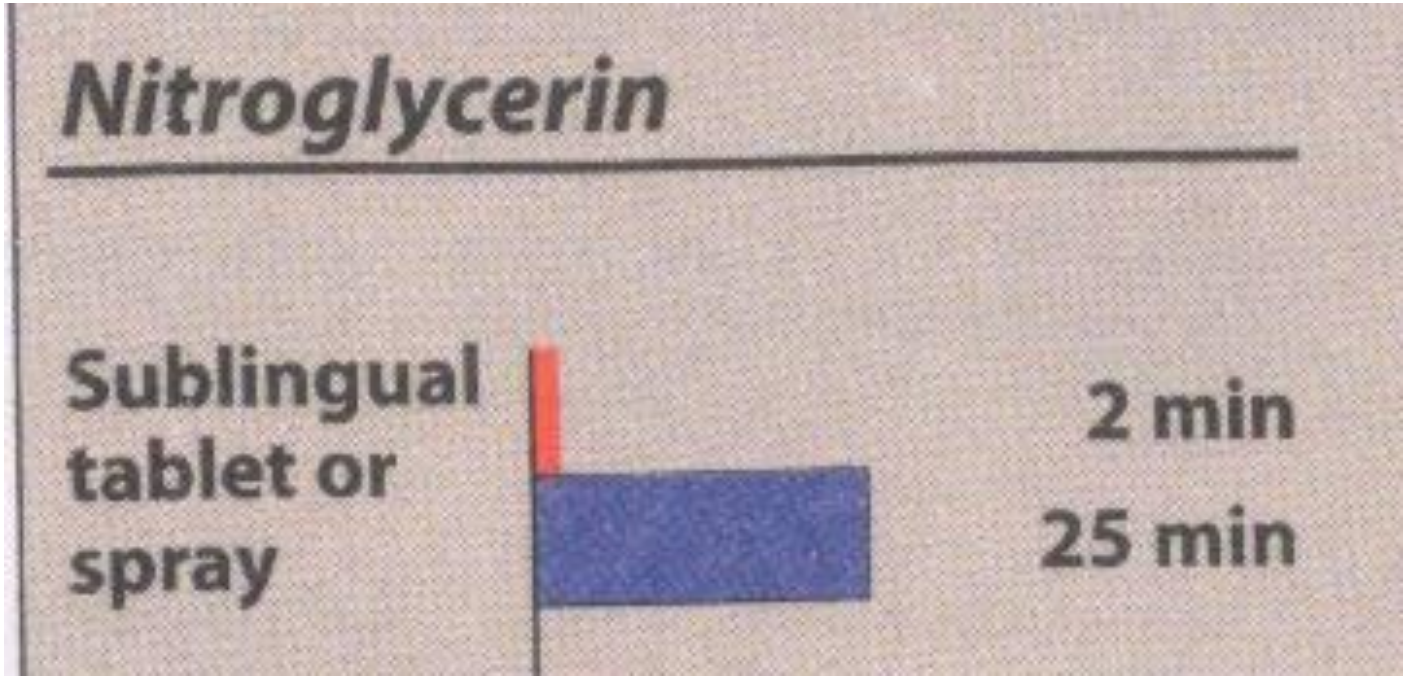
Treatment of angina with concomitant disease

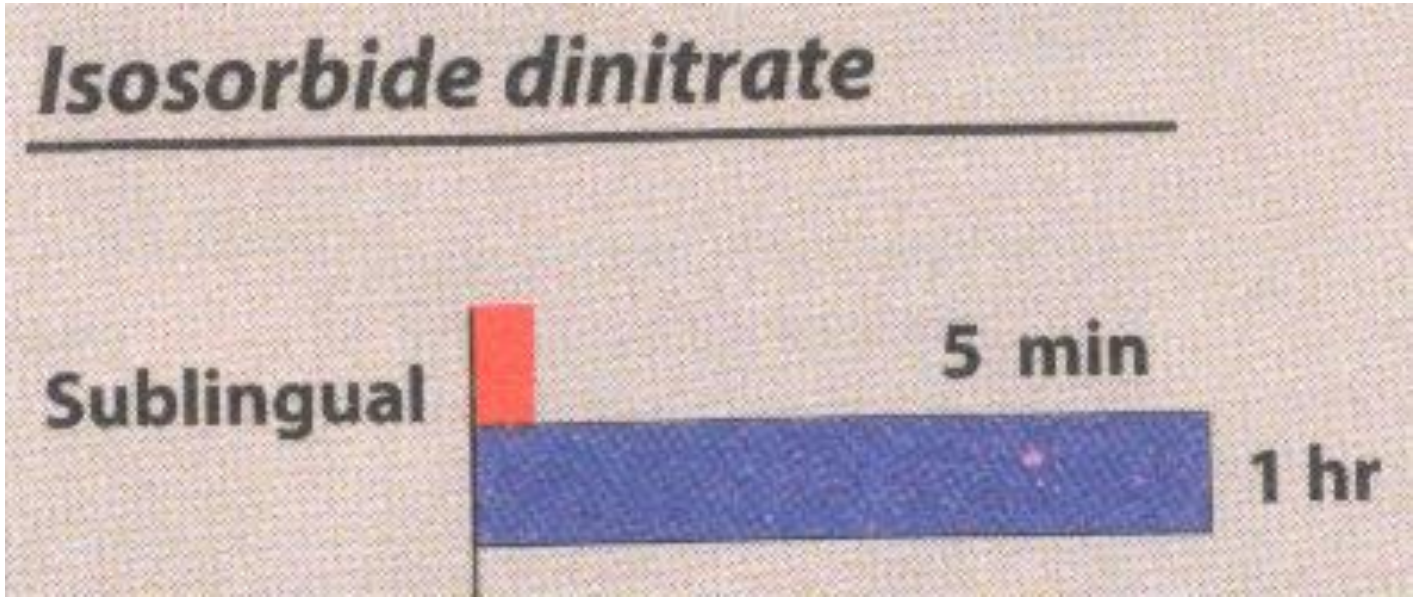
- HTN
  - **β blockers, C C Bs**
  - Long acting **nitrates (less effective)**
- DM
  - Long acting **nitrates, C C Bs**
- CRF
  - Long acting **nitrates, C C Bs**
  - **β blockers (less effective)**

Treatment of acute anginal pain

- **Sublingual** --- Tablets or spray
- **S/L nitroglycerine is the drug of choice**
- For prompt relief of an acute attack of angina precipitated by exercise or emotional stress

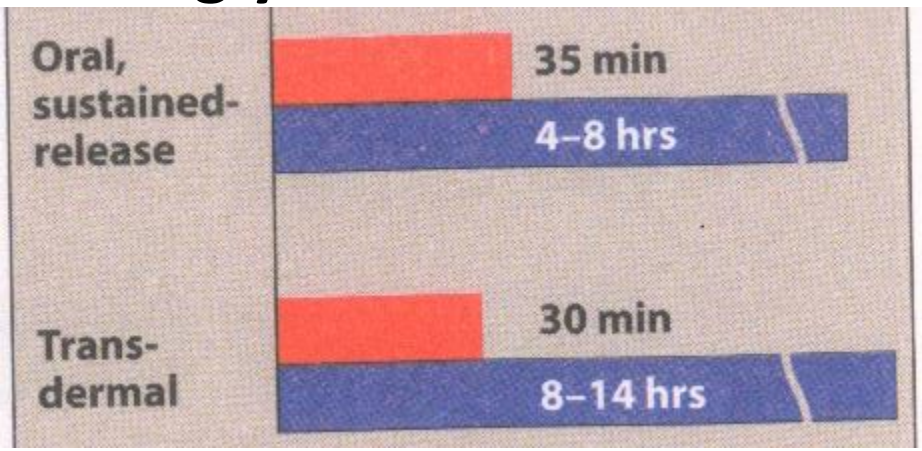
Onset of action + duration of action



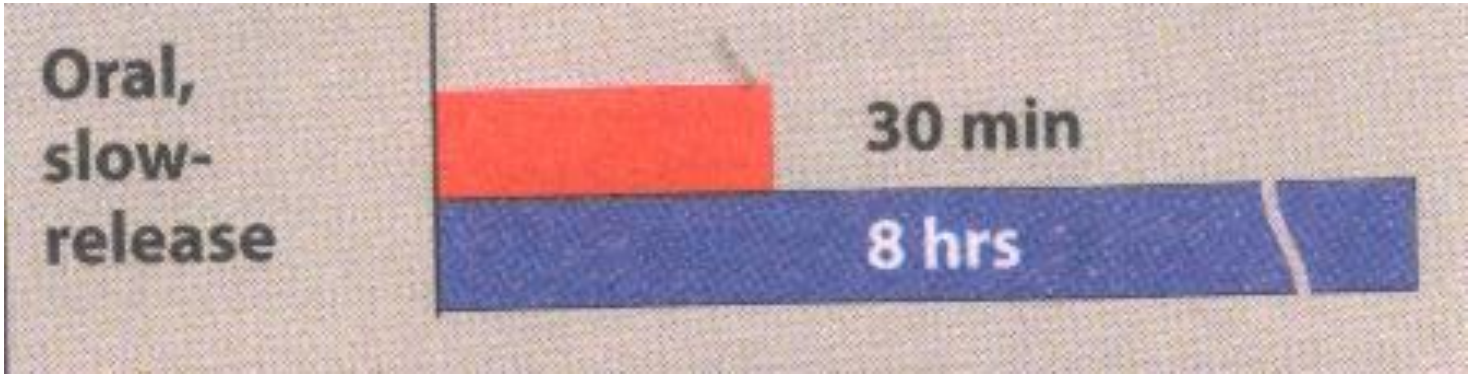


Chronic stable angina

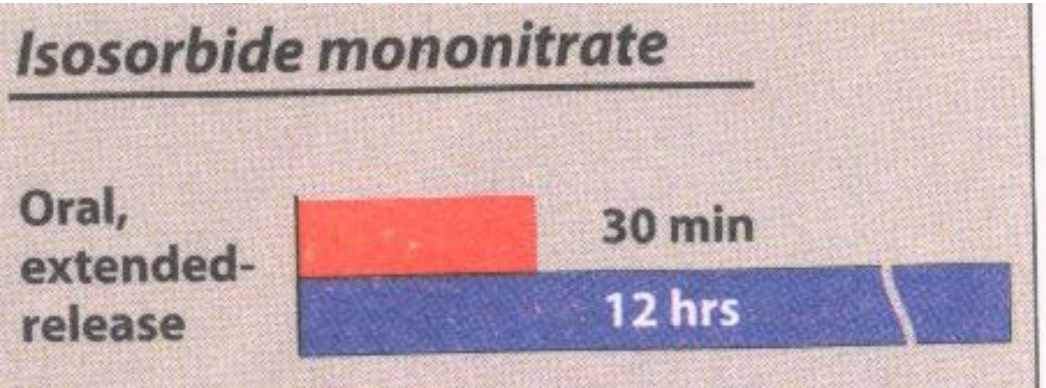
Nitroglycerine



Isosorbide dinitrate



Isosorbide mononitrate



Treatment of angina

- **Transdermal GTN** (ointmenr or patch) last up to 24 hours
  - Symptomatic relief & Prophylactic therapy
  - Tolerance develops after 8-10 hours
  - Patch to be removed after 10-12 hours to allow recovery of sensitivity to the drug
- Long acting nitrates(Isosorbide mononitrate)
  - Once daily preparation are available
  - Smooth phamacokinetic profile and avoid the problem of tolerance

Rational drug combinations

- When monotherapy is unable to provide adequate relief, 2 or more drugs may be given
- β blockers + long acting nitrate
- Slow acting DHP+β blockers
  - Contraindicated ---- β blockers + verapamil
  - To be used with caution β blockers + diltiazem
- Nitrates + CCBs
  - Especially useful in vasospastic angina

Severe and resistant cases of angina

- Nitrates + β blockers + CCBs
- Nitrates decrease preload
- CCBs reduce afterload + ↑ coronary flow
- β blockers decrease cardiac work by –Ve ionotropic and chronotropic action on heart
  - Verapamil and diltiazem is to be avoided in such combinations

Acute coronary syndromes

ST-elevation MI (STEMI)

Non ST-elevation MI (NSTEMI)

Unstable angina

ACS

- O2
- Aspirin/clopidogril
- Opioid analgesic
- Morphine 10-20 mg I/V
- β blockers
- GTN
- plaque stabilization /ventricular remoduling
  - HMG Co A reductase inhibitors
  - ACE I

ACS-(For non-STEMI)

- Anti-thrombin
  - Low molecular weight heparin
- Glycoprotein IIB/IIIA
  - Abciximab
  - Eptifibatide
  - tirofiban

ACS-(For STEMI)

- Thrombolysis
  - **Streptokinase**

    or
  - Alteplase (rt-PA)

    or
  - Tenecteplase (TNKase)

    or
  - Reteplase

Pharmacological therapy in acute coronary syndromes

- O2 therapy 6- 10 liters / minute
  - 35-50 %
- Antiplatelet
  - **Aspirin**
    - Chewable or soluble
    - 150 -300 mg stat then 75-100 mg daily
  - **Clopidogril**
    - Loading dose 300 mg orally
      Then 75 mg daily

Analgesia

- **Opioid analgesic + antiemetic**
- Morphine
  - 10-20 mg I/V or
- Pathedine or
  - 50-100 mg I/V
- antiemetic, **metoclopramide** 10 mg I/V

Myocardial energy consumption(β blockers)

- **Atenolol**
  - 5 mg I/V repeated after 15 minutes, then
  - 25-50 mg p.o. daily or
- **Metoprolol**
  - 5 mg I/V repeated to a maximum of 15 mg, then
  - 25 -50 mg p.o. daily
- Contraindications
  - Avoid in asthma, COPD, heart failure, hypotension, bradyarrhythmias

Coronary vasodilatation

- Glyceryl trinitrate
- 2-10 mg I/V infusion, or sublingual
- Maintain systolic BP > 90 mm Hg

Plaque stabilization / ventricular remodelling

- Statins (HMG-Co A reductase inhibitors)
  - Simavastatin 20-40 mg P.O. daily
  - Pravastatin 20-40 mg P.O. daily
  - Atorvastatin 80 mg P.O. daily
- ACR I
  - Ramipiril 2.5-10 mg P.O. daily
  - Lisinopril 5-10 mg P.O. daily
  - Monitor renal function

Plus for NSTEMI

- **Antithrombin**
  - Low molecular weight heparin
  - Enoxaparin 1mg/ Kg S.C twice daily
- **Glycoprotein IIB/IIIA inhibitors**
- If coronary intervention likely within 24 hours
- **Abciximab**
  - 0.25 mg/Kg I/V bolus, then 0.125 mg/Kg /min up to 10 mg / minute I/V for 12 hours
- Indicated in high risk patients managed without coronary intervention or during PCI
- **Eptifibatide**
  - 180 mg/Kg I/v bolusthen 2 mg /Kg /minute I/V for 72 hours
- **Tirofiban**
  - 0.4 mg/Kg/min I/V for 30 min, then 0.1 mg/Kg /min for 48-108 hours

Plus for ST- elevation myocardial infarction (thrombolysis)

- Streptokinase or
- Alteplase (rt-PA) or
- Tenecteplase (TNKase) or
- Reteplase
- **Streptokinase**
  - 1.5 mega units (1,500,000) I/V over 60 minutes
  - Antibodies appear after 4 days, which reduce effectiveness

Contraindications to thrombolysis

- Absolute
  - Haemorhagic stroke
  - Ischaemic stoke in preceding 6 months
  - CNS neoplasm
  - Recent(3months) major trauma, surgery, head injury
  - GIT bleeding within the last month
  - Known bleeding disorder
  - Aortic dissection

Contraindications to thrombolysis

- Relative
  - TIA in preceding 6 months
  - Oral anticoagulant therapy
  - Pregnancy or within one week postpartum
  - Refractory HTN(systolic BP > 180 mmHg)
  - Advance liver disease
  - Infective endocarditis
  - Non-compressible punctures
  - Traumatic resuscitation

Vasoconstrictor drugs

Vasoconstrictor drugs

- Sympathomimetic amines
  - (direct and indirect)
- Peptides
  - Angiotensin II
  - Antidiuretic Hormones (ADH) and
  - Endothelin (no clinical use)
- 5-HT_{1D} receptor agonists
  - Dihydroergotamine
  - Triptans
- Eicosanoids (thrombaxone A2)- no clinical use

Clinical uses -- vasoconstrictors

- Local application
  - Nasal decongestion
  - Coadministration with local anesthetics
- Circulatory shock
  - Sympathetic amines
- Anaphylactic shock & cardiac arrest
  - Adrenaline
- To stop esophageal bleeding in patients with portal hypertension caused by CLD
  - **ADH (**A posterior pituitary hormone**)**
  - Octreotide ---- a long acting analogue of somatostatin

Vasopressin – ADH

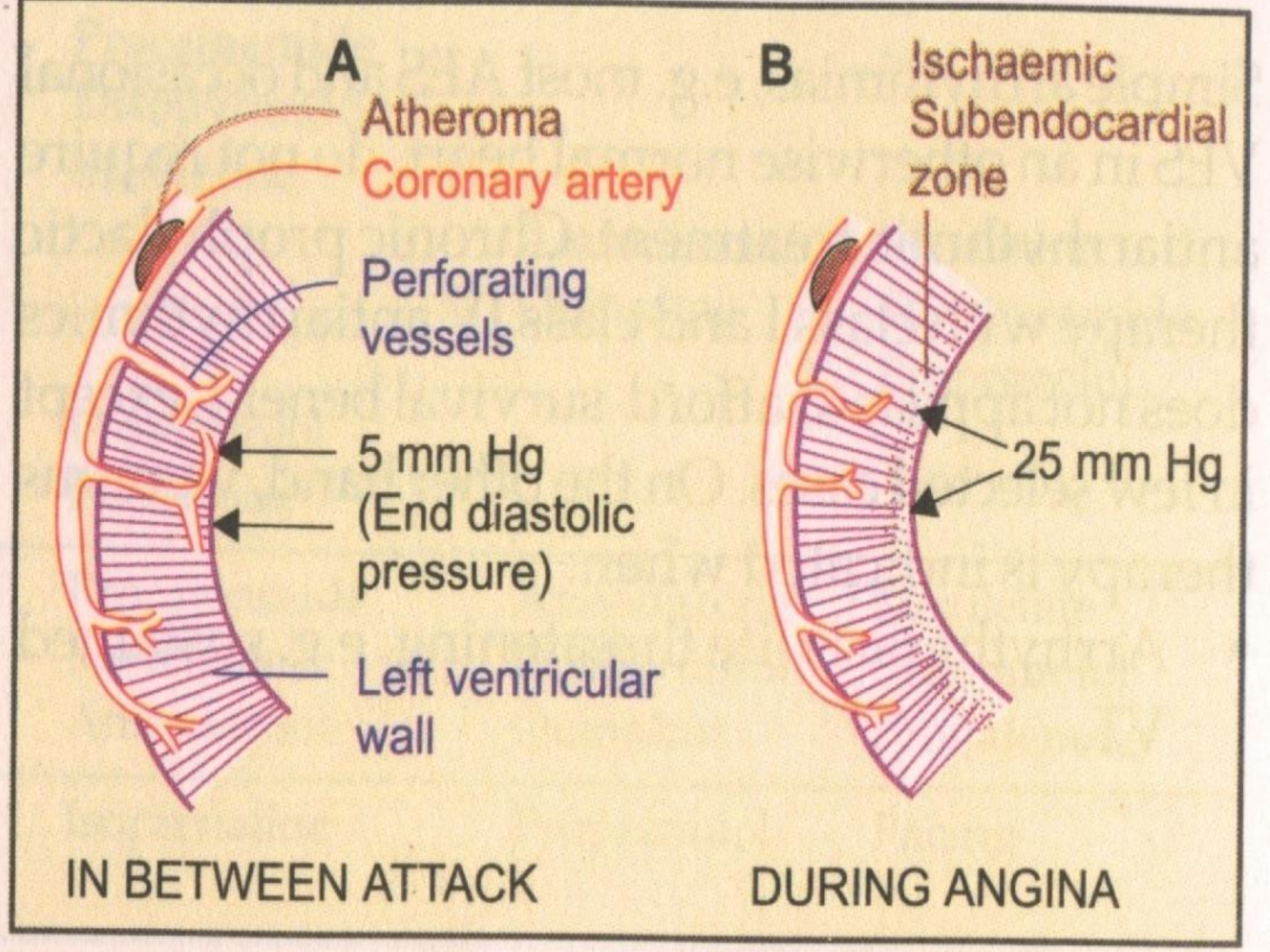
- **Antidiuretic action on the kidney**
  - Mediated via **V_2** receptors and involve Activation of adenylate cyclase in renal collecting ducts
  - Occurs at low plasma concentration of ADH
- **A powerful vasoconstrictor ---** generalized vasoconstriction
  - Mediated through **V_1** receptors
  - Require higher concentration and involve activation of **phospholipase C**
  - Used to treat patients with bleeding **esophageal varices and portal hypertension**
  - It also affects other smooth muscles – GIT and uterine – **abdominal cramps**

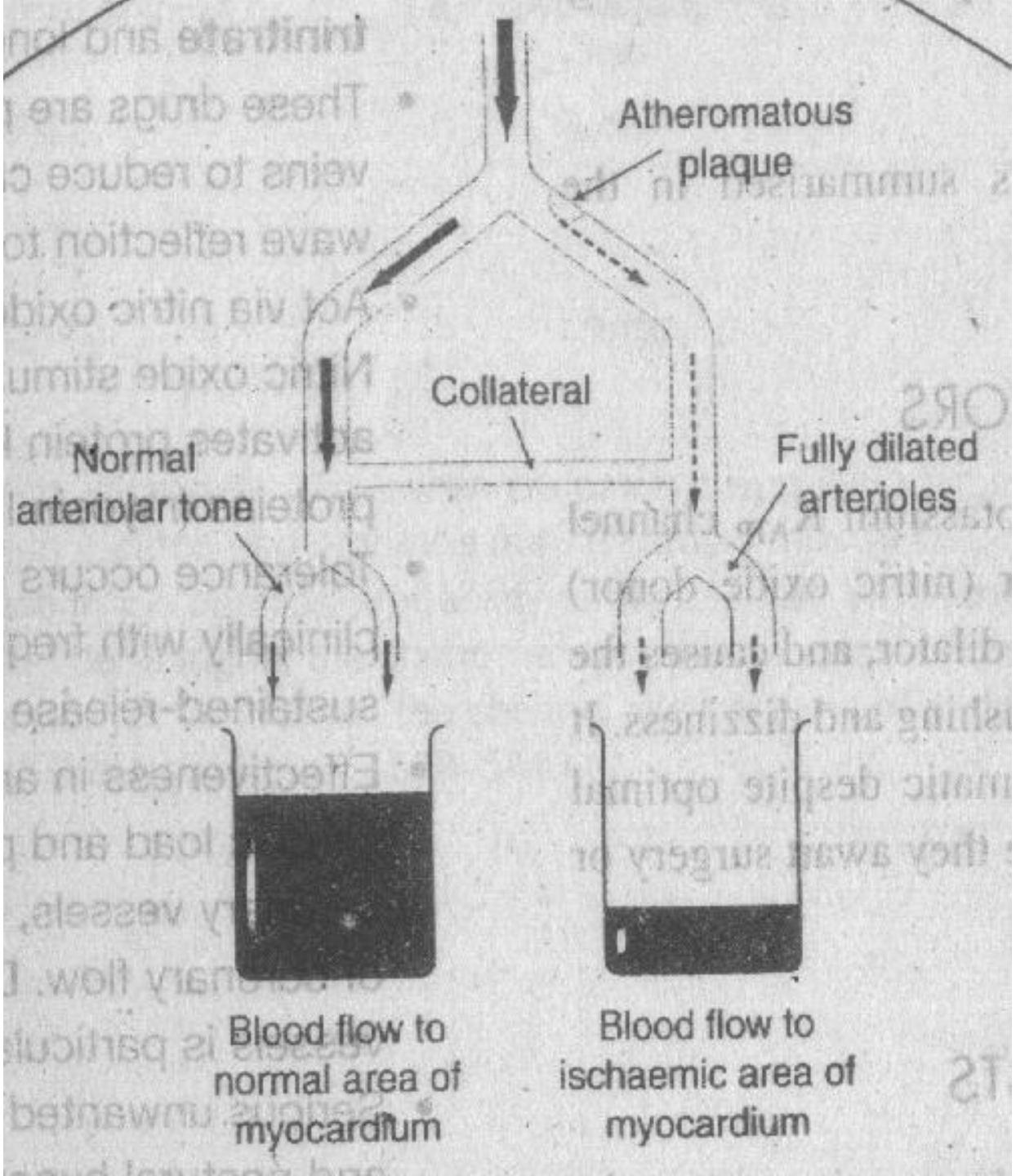
Vasodilators

- Arteriolar dilators (↓ after-load)
  - **Hydralazine, Minoxidil, Ca^{++} channel blockers**
  - Fenoldopam (dopamine D1 receptor activator)
- Venodilators (↓ pre-load)
  - **Nitrates**
- Mixed dilators(↓ pre and after load)
  - **ACE inhibitors, ARB**
  - **Nitroprusside**

Main uses of vasodilators

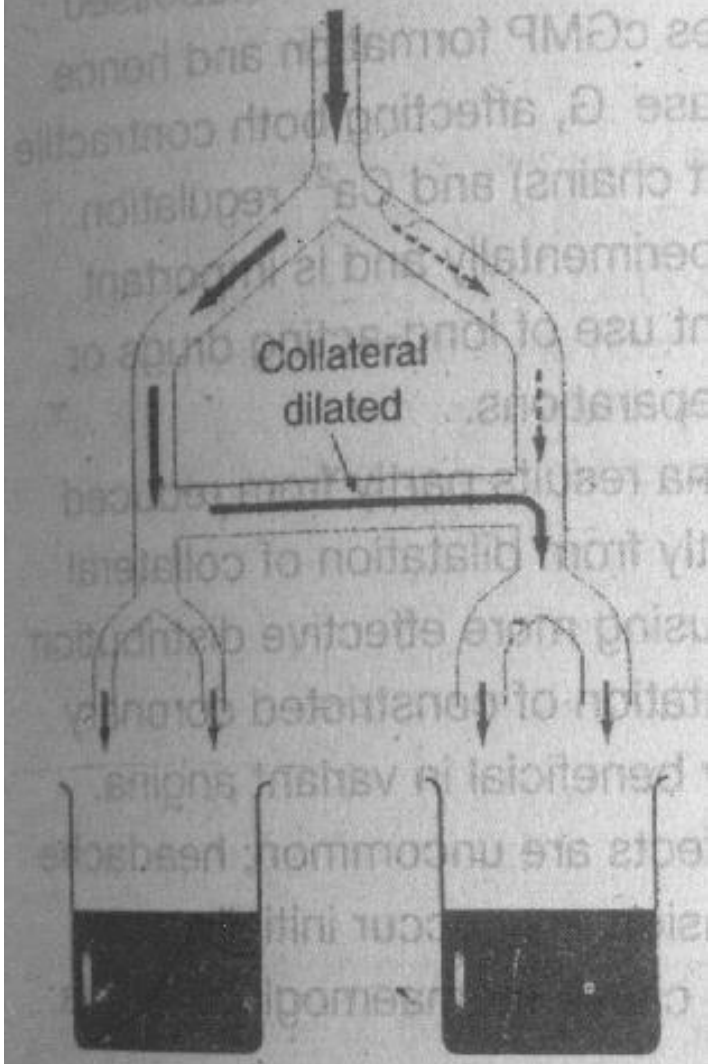
- **Antihypertensive** therapy
  - ACE I, AT_1 antagonists (ARB), CCB and α_1 antagonists
- Treatment and prophylaxis of **angina pectoris**
  - CCB, Nitrates
- Treatment of **cardiac failure**
  - ACE I, ARB


A
Atheroma
Coronary artery
Perforating vessels
5 mm Hg
(End diastolic pressure)
Left ventricular wall
IN BETWEEN ATTACK
B
Ischaemic Subendocardial zone
25 mm Hg
DURING ANGINA

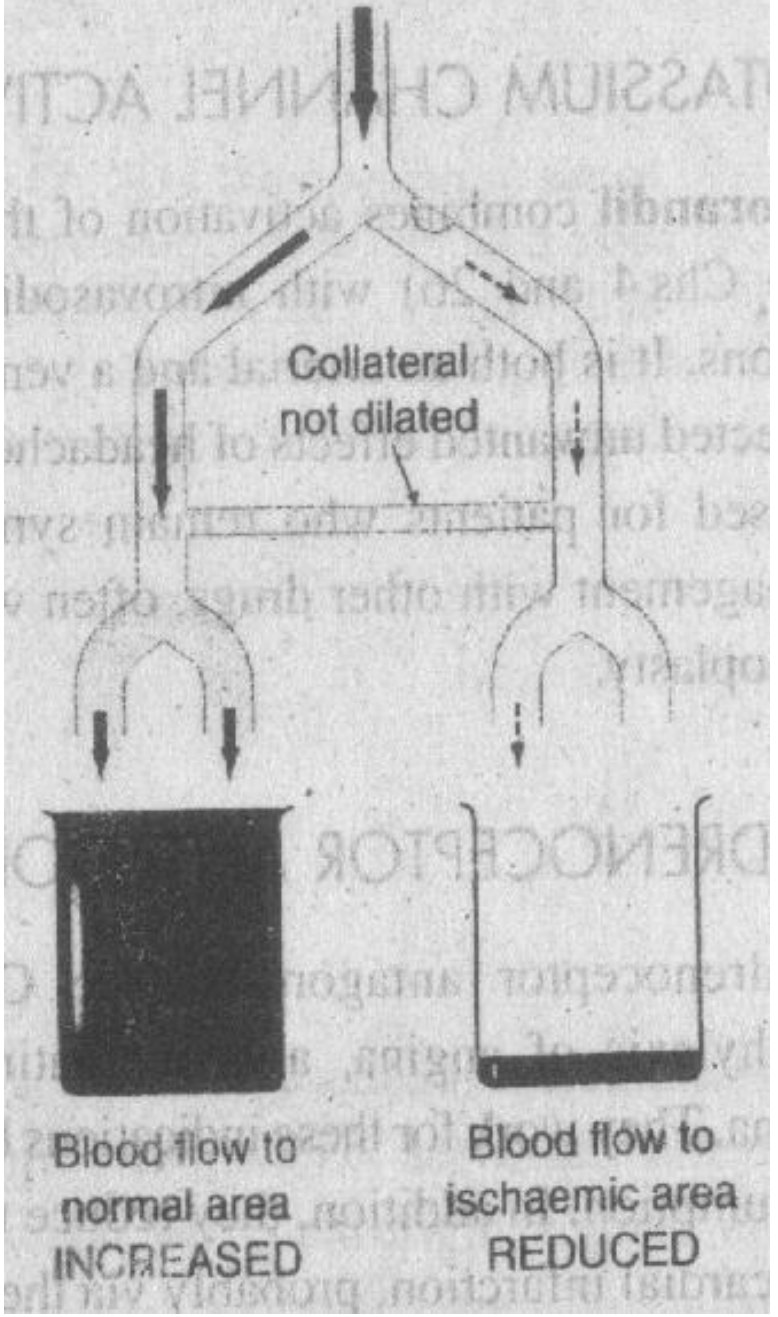

Atheromatous plaque
Collateral
Normal arteriolar tone
Fully dilated arterioles
Blood flow to normal area of myocardium
Blood flow to ischaemic area of myocardium

B

Effect of nitrate

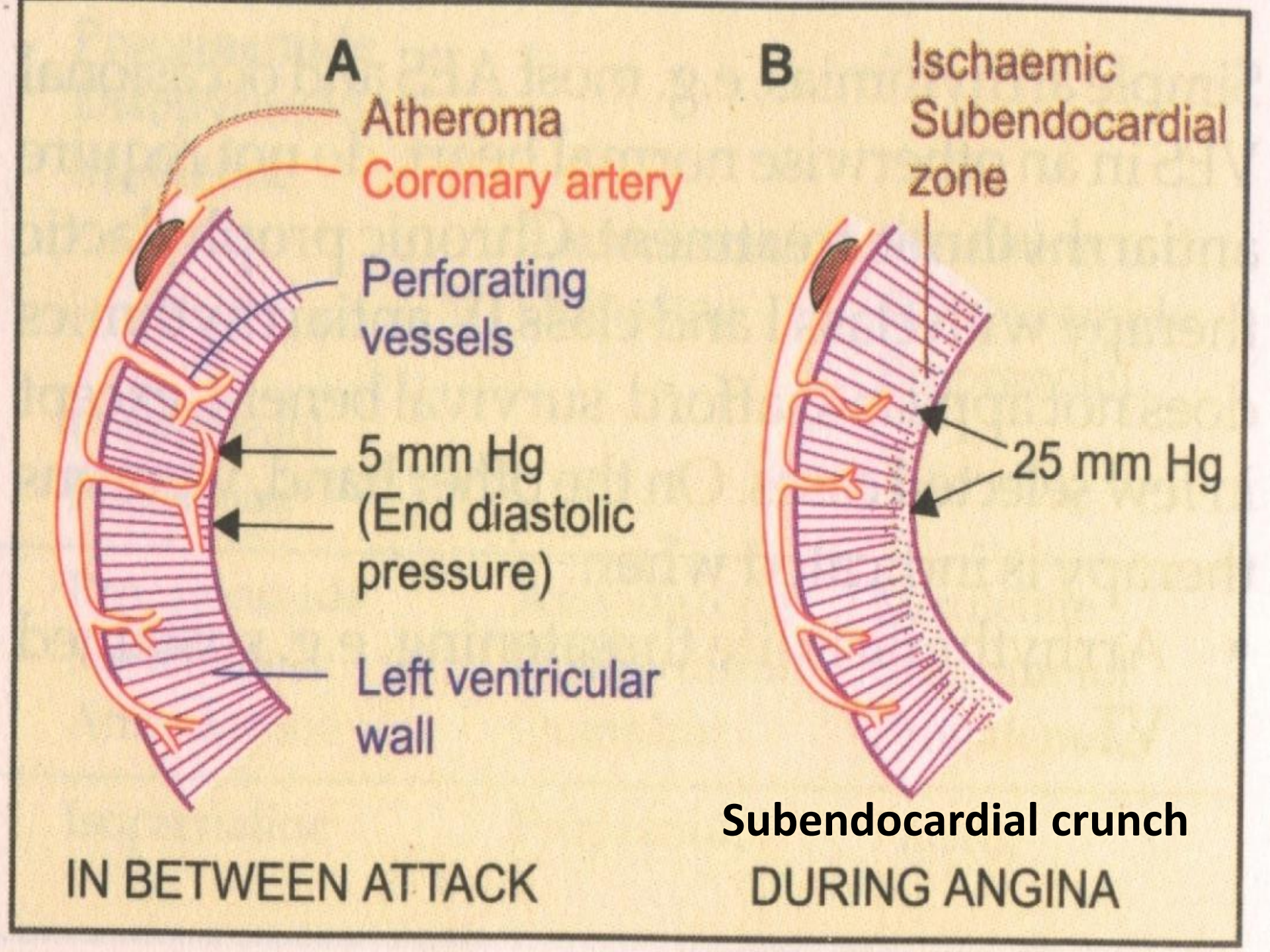


Effect of dipyridamole



Subendocardial crunch

- Blood flow to the subendocardial region occurs only during diastole
- Due to inadequacy of ischemic L V, the end diastolic L V pressure rises from 5 to about 25 mmHg ----produces subendocardial crunch during diastole



Subendocardial crunch