Angina pectoris

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Angina pectoris

Chest pain due to ischemia of heart muscles

- Spasm/obstruction of coronary arteries
- Myocardial ischemia
- Reduced O_2 supply to myocardium
- Chest pain---Angina pectoris

- Weak relationship between severity of pain and degree of oxygen supply- there can be severe pain with minimal disruption of oxygen supply or no pain in severe cases

- Four types:

✔Stable angina

✔Unstable angina

✔Microvascular angina

✔Prinzmetal's angina

Stable angina:

- Also called “Effort Angina”
- Discomfort is precipitated by activity
- Minimal or no symptoms at rest
- Symptoms disappear after rest/cessation of activity

Unstable angina:

- Also called “Crescendo angina”
- Acute coronary syndrome in which angina worsens
- Occurs at rest
- Severe and of acute onset
- Crescendo pain- pain increases every time

Microvascular angina:

- Also called Syndrome X
- Cause unknown
- Probably due to poor functioning of the small blood vessels of the heart, arms and legs
- No arterial blockage
- Difficult to diagnose because it does not have arterial blockage
- Good prognosis

Prinzmetal's angina

- Prinzmetal's angina is a variant form of angina with normal coronary vessels or minimal atherosclerosis
- It is probably caused by spasm of coronary artery

- Symptoms
- What is the cause of ischemia ?

  either ↑ oxygen demand or ↓ oxygen supply
- Inadequate blood supply and decreased oxygen supply are directly related to blockade or narrowed vessels

Treatment:

- Aims:

✔Relief of symptoms

✔Slowing progression of the disease

✔Reduction of future events like myocardial infarction

Drugs:

1. For treatment of acute attacks:

Organic nitrates/nitrites

2. For prophylaxis:

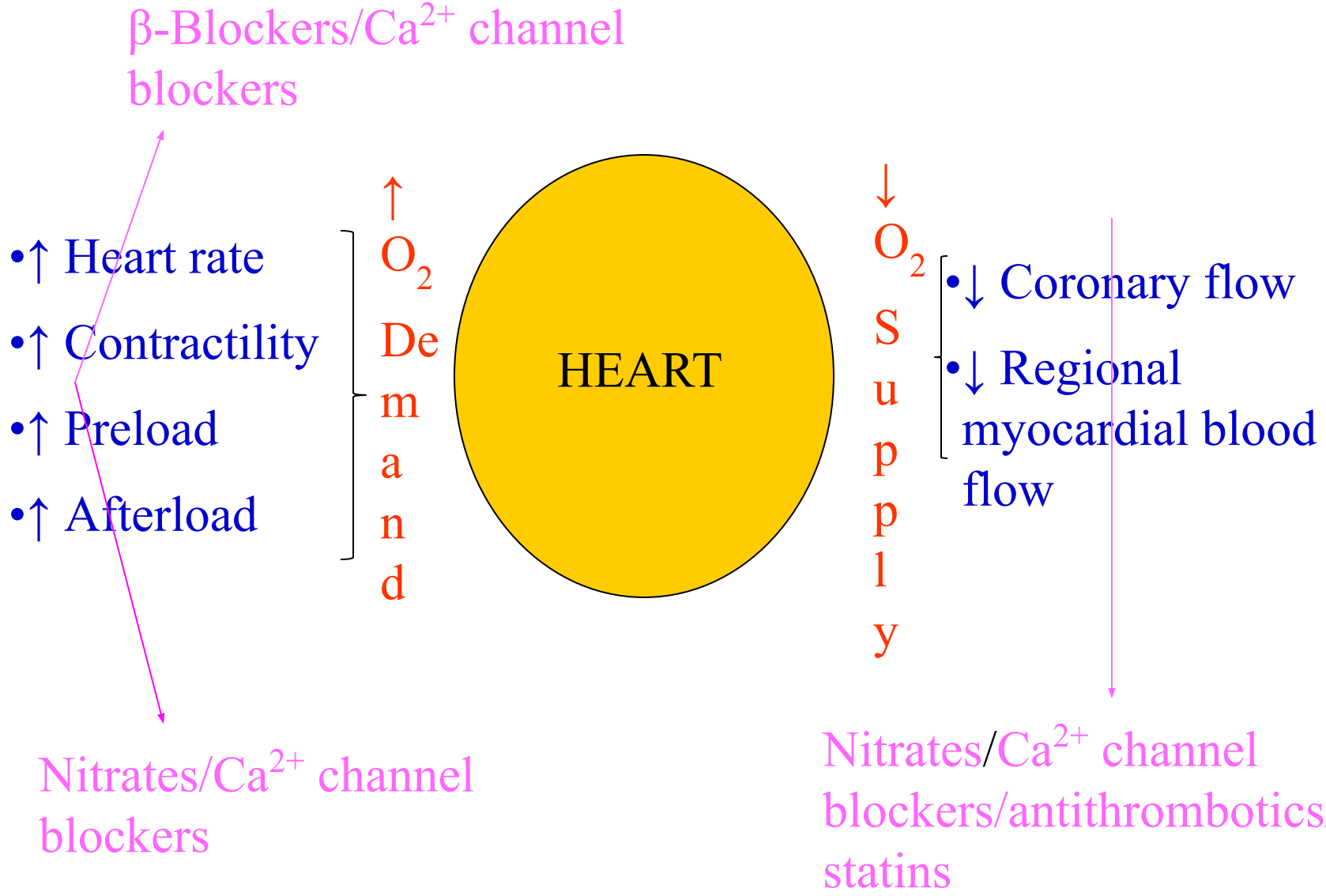
Organic nitrates

Beta blockers

Calcium channel blockers

Ranolazine

K^+ channel opener- Nicorandil


β-Blockers/Ca2+ channel blockers
•↑ Heart rate
•↑ Contractility
•↑ Preload
•↑ Afterload
↑ O2 Demand
HEART
↓ O2 Supply
•↓ Coronary flow
•↓ Regional myocardial blood flow
Nitrates/Ca2+ channel blockers
Nitrates/Ca2+ channel blockers/antithrombotics/ statins

Organic nitrates

Pro drugs ⟶ release NO

↓

↑ Levels of intracellular cGMP

↓

Dephosphorylation of mysosin light chain

↓ Cytosolic calcium

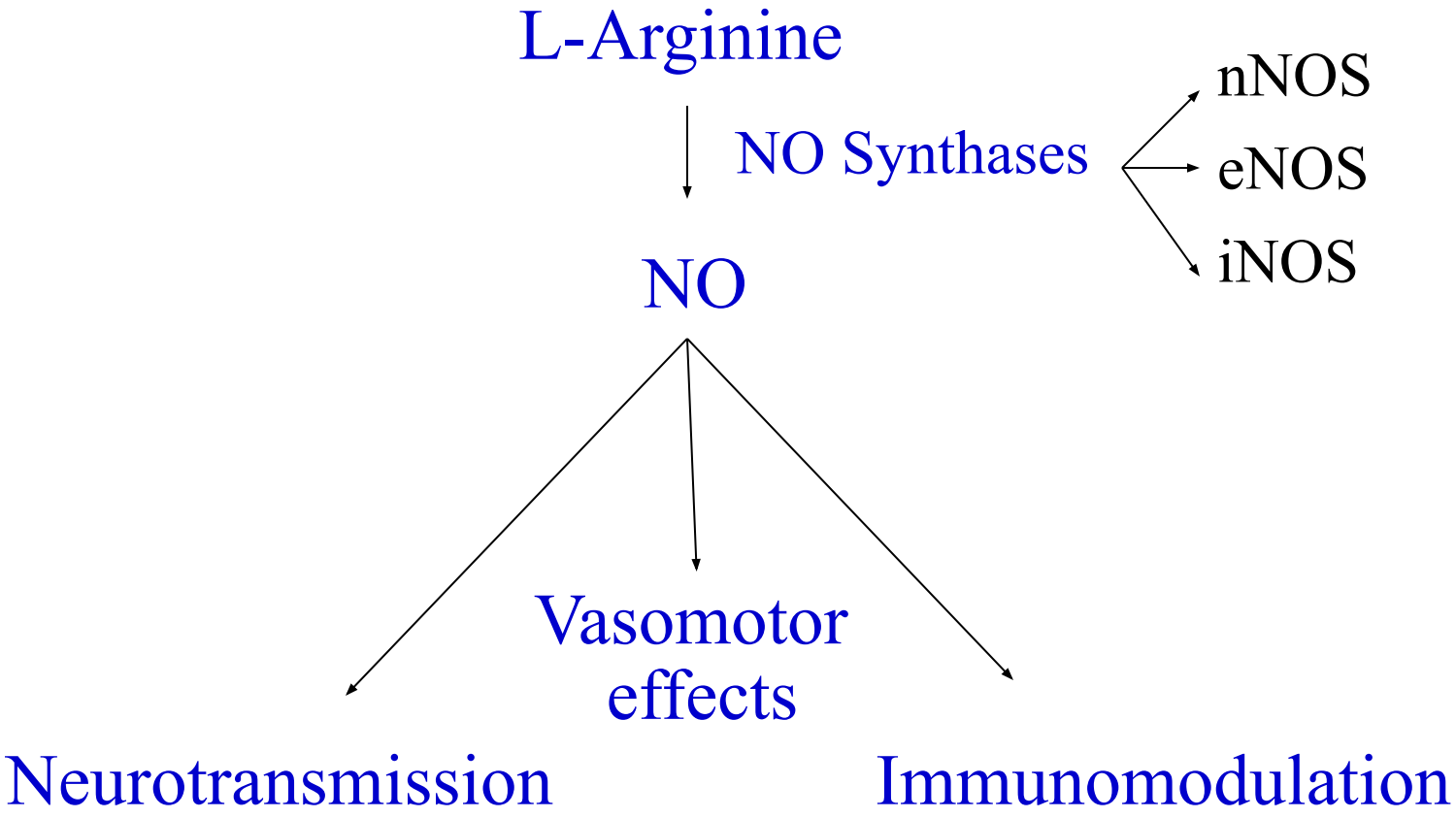
↓

Relaxation of smooth muscle

EDRF –endothelium derived relaxing factor is NO

- Relaxation of vascular smooth muscles- vasodilatation
- NO-mediated guanylyl cyclase activation inhibits platelet aggregation
- Relaxation of smooth muscles of bronchi and GIT

Endogenous NO pathway



Three different forms of NO synthase are found in humans:

1. Neuronal NOS (nNOS or NOS1)- found in nervous tissue, skeletal muscle- involved in cell communication

2. Inducible NOS (iNOS or NOS2) found in immune system and cardiovascular system- involved in immune defense against pathogens

3. Endothelial NOS (eNOS or NOS3 or cNOS) found in endothelium- responsible for vasodilation

CVS Effects:

- Vasodilatation- low concentrations preferably dilate veins
- Venodilatation→ decreases venous return to heart
- Decreased chamber size and end-diastolic pressure of ventricles
- Systemic vascular resistance changes minimally
- Systemic BP may fall slightly
- Dilatation of meaningeal vessels can cause headache

- HR-unchanged or may increase slightly (reflex tachycardia)
- Cardiac output slightly reduced
- Even low doses can cause dilatation of arterioles of face and neck causing flushing
- Higher doses may cause fall in systemic BP due to venous pooling and decreased arteriolar resistance
- Reflex tachycardia and peripheral arteriolar constriction occur which tend to restore the systemic BP

- Coronary blood flow may initially increase transiently
- Subsequently, due to decreased BP, may decrease
- Nitrates have dilating effect on large coronary vessels
- Increase collateral flow to ischemic areas
- Tend to normalize blood flow to subendocardial regions of heart- *redistribution of blood*
- Dilate stenoses and reduce vascular resistance in ischemic areas

- Reduction in myocardial O_2 consumption is caused by:

✔Peripheral pooling of blood- reduced preload

✔Arteriolar dilatation- reduced afterload

✔ ↓ in end diastolic volume and LV filling pressure

- In platelets increases cGMP: inhibits aggregation
- Strongest factor for nitrate effect is peripheral pooling

✔Nitrates infused into coronary artery- no effect

✔Sublingual- produces effect

✔Venous phlebotomy mimics effect of nitrates

How myocardial O_2 consumption can be determined?

Double product: HR × systolic BP- approximate measure of myocardial O_2 consumption

Triple product: Aortic pressure × HR × Ejection time- roughly proportional to myocardial O_2 consumption

- Angina occurs at the same value of triple product with or without nitrates, therefore;
- The beneficial effects of nitrates appear to be due to decrease in oxygen consumption rather than increase in oxygen supply
- Relax all smooth muscles-GIT, biliary, bronchial etc

Pharmacokinetics:

- Orally ineffective because of high first pass metabolism
- Administered sublingually to avoid first pass matabolism

Tolerance:

- Repeated doses lead to tolerance
- Dose spacing is necessary
- Reasons for tolerance:

✔↓ Capacity of vascular smooth muscle to convert nitrates to NO – called true vascular tolerance

✔Pseudotolerance- due to other reasons

ADRs:

- Headache- may be severe

✔ May disappear after continued use or,

✔ Decrease dose

- Transient episodes of dizziness, weakness, pallor etc- symptoms of postural hypotension
- Rash
- PDE5 inhibitor (sildenafil) and nitrates given simultaneously can produce severe hypotension
- Uses: Angina pectoris, CHF, MI

Administration of nitrates:

- Sublingual
- Oral: For prophylaxis, require high doses due to first pass metabolism, isosorbide dinitrate (20 mg or more) every 4 h or mononitrate (20 mg or more) OD or BD
- Cutaneous:

✔Ointment (2%) applied to 2.5-5 cm patch of skin

- ✔Transdermal nitrogycerine discs impregnated with nitroglycerine polymer- gradual absorption and 24 h plasma nitrate concentration
- ✔Onset is slow
- ✔Peak concentration in 1-2 h
- ✔Interrupt therapy for at least 8 h a day to prevent tolerance

Ca^{2+} antagonists:

- ↓ Ca^{2+} influx
- Negative iono and chronotropic effects
- Peripheral vasodilatation
- Used in variant angina (spasm), exertional angina, unstable angina, MI, hypertension, antiarrhythmic

β-Blockers:

- Effective in reducing severity and frequency of exertional angina
- May worsen vasospastic angina- contraindicated
- Reduce myocardial O_2 demand by reducing cardiac work (-ve iono and chrono effects; decrease in BP during rest and exercise)
- All β-blockers are equally effective

Ranolazine:

- Reserve agent for treatment of chronic, resistant angina
- Inhibits cardiac late Na^+ current
- Effects the Na^+ dependent Ca^{2+} channels and prevents Ca^{2+} overload that causes cardiac ischemia
- Decreases cardiac contractility
- No change in HR, BP
- Prolongs QT interval so it is contraindicated with drugs that increase QT interval

Nicorandil

- Vasodilatory drug used to treat angina pectoris
- It has dual properties of a nitrate and ATP sensitive K^+ channel opener
- Nitrate action dilates the large coronary arteries at low plasma concentrations
- At high concentrations it reduces coronary artery resistance which is associated with opening of ATP sensitive K^+ channels
- Nicorandil has cardioprotective effect which appears to be due to activation of ATP sensitive K^+ channels
- ADRs: Flushing, palpitation, headache, mouth ulcers, nausea and vomiting