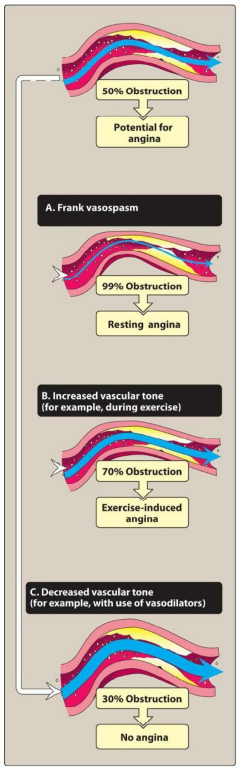
ANTI ANGINAL DRUGS

By: ZAKIRULLAH YOUSUFZAI
From: Dr. Najeeb Lectures

β-BLOCKERS
Atenolol TENORMIN
Bisoprolol GENERIC ONLY
Metoprolol LOPRESSOR, TOPROL XL
Propranolol INDERAL, INNOPRAN XL
CALCIUM CHANNEL BLOCKERS (DIHYDROPYRIDINES)
Amlodipine NORVASC
Felodipine PLENDIL
Nifedipine ADALAT, PROCARDIA
CALCIUM CHANNEL BLOCKERS (NONDIHYDROPYRIDINE)
Diltiazem CARDIZEM, CARTIA, TIAZAC
Verapamil CALAN, VERELAN
NITRATES
Nitroglycerin MINITRAN, NITRO-DUR, NITROSTAT
Isosorbide dinitrate DILATRATE-SR, ISORDIL
Isosorbide mononitrate GENERIC ONLY
SODIUM CHANNEL BLOCKER
Ranolazine RANEXA

20.1 Summary of antianginal drugs.



Angina angina is a central chest discomfort

angina is Reversible Myocardial ischemia

angina is one of the common symptom of Cardiac ischemia

clinically Feeling of angina is less like a pain & more like a weight on chest, sometime burning sensation occur.

* Sometime angina pain radiate to one arm or both arms, or to neck, or to Jaw or to epigastrium
* Sometime angina pain does not Radiate

Sometime felt only in the area of radiation b/c it is due to transiet ischemia of Myocardium.

when O_2 demand of Myocardium is increased but not fulfiled ~~the~~ such these complications occurs.

NOTE Typically angina should not lost more than 20 minutes.

Usually most of angina lost somewhere B/w 15 sec ——— 15 minutes

If svear chest/Myocardial ischemia lost more than 20 minutes Than it is called as **MI.**

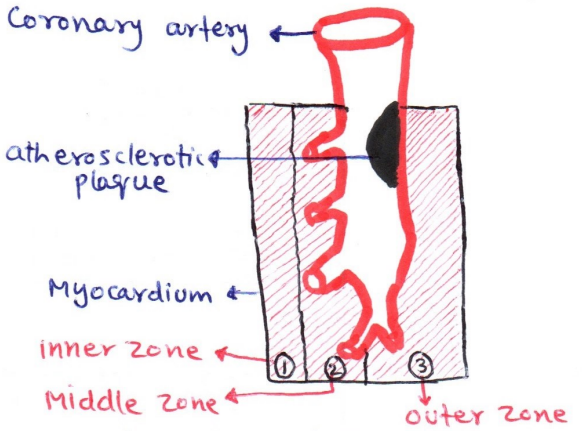
Angina is a Transiet, Reversible ischemia of Myocardium which does not lead to death of Myocardial cells.

ANGINA types

- classical angina OR Typical angina OR stable angina OR Exertional angina
- Prinzmetal angina OR varient angina OR coronary vessele spastic angina
- unstable angina

(1) Classical Angina

If atherosclerotic plaque obstruct 70% of lumen of artery, than artery supply blood which is enough for resting person, but if person undergo some exertion than O_2 need of tissue ↑es which is not fulfilled by such artery so this part of Myocardium become relatively ischemic so this is the source of anginal pain.



As this plaque is stable such anginal symptoms are also stable i.e

Pain is felt by exertion, exercise ----- etc, This type of angina is relived by Rest and giving Nitrates.

By using nitrates such pain is relived within minutes.

* If This obstruction become 90% than anginal pain occur at rest.

① innermost zone of Myocardium
② Middle " " "
③ outer " " "

1st ischemia start from innermost zone of Myocardium

First ischemia start from innermost zone b/c as ventricle contract this inner zone of Myocardium is compressed both from inner (by blood pressure) & from out (from plaque) or outer area

Than Microcirculation through this part also Compressed.

* even in normal heart outer Myocardium is better perfused & inner myocardium is poorly perfused.

(2) PRINZMETAL ANGINA:

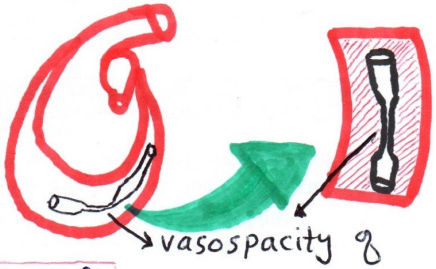
In this case plaque is not the symptomatology of angina The real problem is that coronary artery have **Fluctuating Tone.**

There is vasospasticity in artery lead to ischemia. This ischemia spread to inner, Middle even outer part of myocardium.

This ischemia occurs throughout the wall of myocardium so it is called **Transmural angina.**

This type of angina is not related to exertion, BP, Tachycardia, & Not reliving by rest.

This type of angina is most common in ♀



(3) UNSTABLE ANGINA:

In this type of angina there is unstable block in coronary artery.

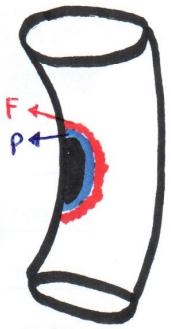
This Erythematous block is called Vulnerable block.

these are having very thin fibrin cap & alot of inflamatory activity occur within the plaque.

This plaque undergo svear acute changes:

e.g: this may undergo Fissioing, Erosion, ulceration, or intrablock hemorrhage.

Due to these acute changes surface of this plaque become irregular, and highly thrombogenic contents released from Erythoma.



Platlets stick on its surface and make aggregation & there is super added fibrin, whole the complex is called **Thrombus**

Than ischemia occur 1st in deeper parts of myocardium.

If this thrombus is occluded the whole lumen then this thrombus is called **Transmural thrombus.**

This plaque with super aded thrombi form **DYNAMIC OBSTRUCTION**. ie This thrombus & plaque keep on changing its shape & size, so degree of occlusion is also dynamic so this plaque is UNSTABLE.

If this obstruction/ischemia last more than 20minutes it lead to **INFARCTION.**

If treat within 20min then it is not leading to infaction

By definition this type of angina is very svear, recent angina, progressively increasing frequently.

This type of angina does not responded to **NITRATE** & **REST.**

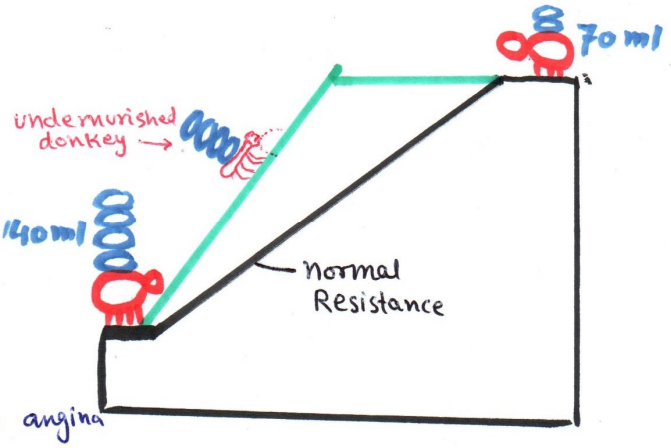
* if sublingual Nitrate is taken 3 times in 5 minutes & pain does not relived, its means it is unstable angina.

MANAGMENT OF ANGINA

Stable	Prinzmetal	unstable
It is presipitating by increasing work of Myocardium. ℞ Best therapy is to relive work of myocardium So O_2 demond will ted. in this case we do: ✓* PTCA (Percutaneous Transluminal Coronary angioplasty) OR ✓* CABG (coronary artery bypass Grafting)	℞ we give Coronary vasodialator ie: Nefidipine	There is ① atheroma → unstable ② platlet aggregation + Fibrin deposition = Thrombus ③ ± vasospasm ℞ * Antithrombolytic drug OR Antiplatlet drugs * O_2 therapy * ↓es work of heart * Coronary artery dialators

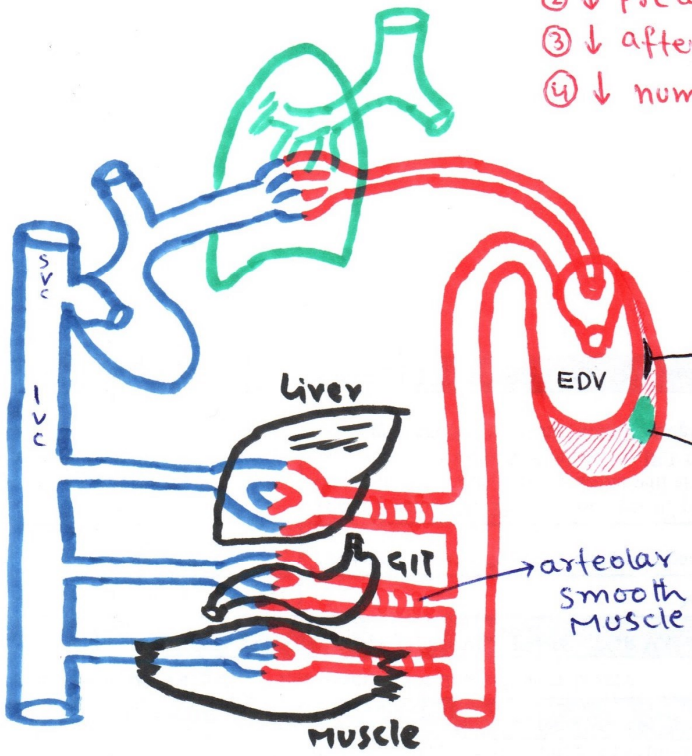
Work of HEART

* Consider heart is a donkey.
* Ischemic heart is like a donkey which is under nurished



If we ↑es resistance the Ischemic donkey will cry which is angina

we help this donkey by giving ① ↑ Perfusion
② ↓ Preload
③ ↓ after load (Resistance)
④ ↓ number of visit (ie: HR↓)



$P \propto \frac{T}{R\downarrow}$

as we ↓ing the radius of ventricle it become more efficient

- EDV is load in ventricle before Myocardial contraction.
- ↑ed EDV or EDP ↑ Stretch on myocardium, as more strongly myocardium strech, there is ↑ demond (oxygen) & more Compression on inner Myocardium. To such patients we give VENODIALATOR DRUGS (To↓ Preload) & ARTERIOLODIALATOR (To ↓ after load) & -ve chronotropic drugs (To inhibit SA-node→↓HR)

Venodialator → ↑ blood in perephry (pooling) → ↓ venous return → ↓EDV → ↓ Preload → ↓ Pre strech → ↓ O_2 demond → ↓ Compression on deep parts of Myocardium → even less flow will cause enough perfusion to deeper parts.

All those drugs which are venodialator are preload reducer.

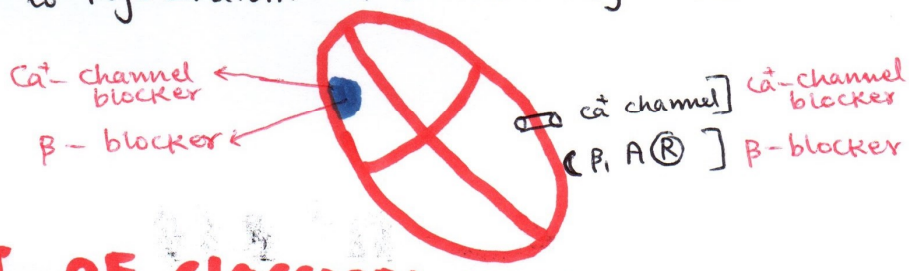
All Those drugs which are arteriodialator are after load reducer.

Best arteriolodialator is Ca^+ channel blocker

-ve chronotropic drugs inhibit SA-node (to ↓HR), by blocking Ca^+-channel of SA-node.

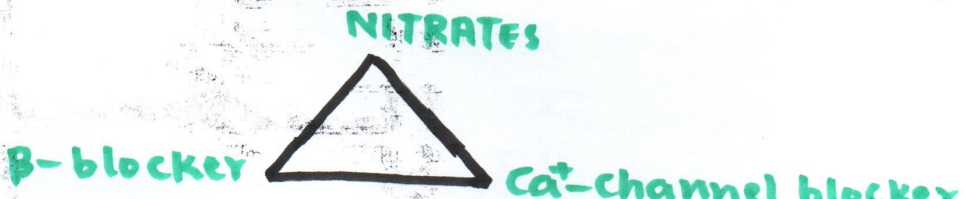
* we have to also protect SA-node from endogeneous Epi/Nor Epineprine, which act on β_1 Adrenergic receptor, we block β_1 AR by giving β-blockers.

* β_1 receptor & Ca^+-channel load Myocardial cells with Ca^+, so: by ↓Ca^+ loading to Myocardium ⟶ ↓ Contractility ⟶ ↓ SV.



MANAGMENT OF CLASSICAL ANGINA

There are 3 types of drugs for classical Angina



long term managment of angina

① Modify the Risk factor for atherosclerosis
ie→ smoking, DM, hyperlipidemia ..... etc

② Plaque stabilizer ⟶ STATINS → stabilize unstable plaque.

③ Anti platlet/Anti thrombolytic drugs.

DRUGS

(1) NITRATES

also called Nitrovasodialator drugs.

① Glyceride Trinitrate / Nitroglycerine
② Isosorbid Dinitrate
③ Iso Sorbid Mononitrate

Glyceride Trinitrate

- Sublingual OR Buccal Spray
  - Action start in 1-2 min
  - Duration of action = 30 min
- Oral sustained Released Tablet
  - Action start in = 30 min
  - Duration of action = 6 hr
- Transdermal application
  - Action in = 30 min
  - Duration of action = 8-12 hr

* Patient with occasionaly angina should need to have Nitroglycerine tablet with themself & take the tab as required.
* If patient is regullarly angina patient, he need to take Nitroglycerine regullarly on daily basis.

Isosorbid Dinitrate

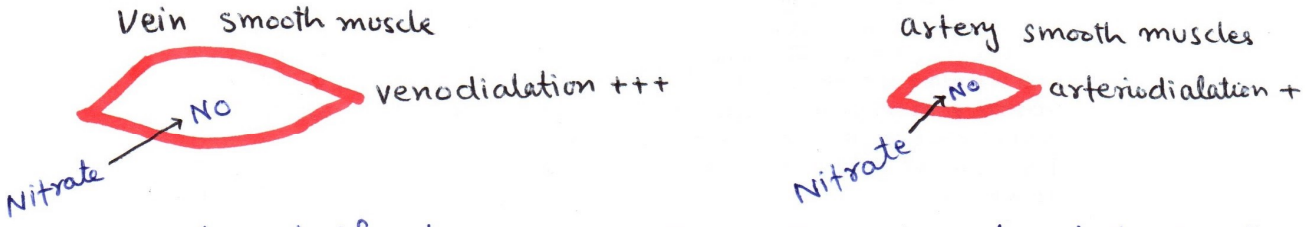
- Sublingual
  - Action start in = 5 min
  - duration of action = 1 hr
- orally Slow release
  - Start action in = 30 min
  - Duration of action = 8 hr

Isosorbid Mononitrate

- Oral Extended release
  - Start action in = 30 min
  - Duration of action = 12 hr

If nitrate are taken for longer time they looses their action.

Mechanism of action of nitrate



* nitrate itself have no action, when it enter into smooth muscle, NITRIC OXIDE release from it, which cause vasodialation.
* There is more venodialation occur than arteriodialation, under the influence of Nitric oxide.

NITRATE —ENZYME→ Nitric oxide (NO)

14— 15 hr Continue supply of Nitrate, than enzyme stop working to release NO from nitrate.
This enzyme need gap of 6—8hr daily to restart its action, otherwise nitrate tolerence develop, so to prevent this tolerence we need to give our patient Nitrate with a gap of 6— 8hr.

we give nitrate with β-blocker, where if angina is frequent. In this condition person is not protected by nitrate but protected by β-blocker

* person with Exertional angina have more risk at day time so nitrate free interval should be at Night → ie: keep patch for 12h in day time & remove at bed time.
* prinzmetal angina is more at morning, when adrenaline level in blood is high → For them nitrate free interval should be at evening time
→ They take tablet before sleeping & just after get up.

MONDAY DISEASE

(2nd world war)

most of workers in Explosive factories should take rest at weakened, after weakend when they come at monday & inhale nitrate in factory, so at monday & Tuesday they develope nitrate tolerence.

But next of all the days they have no complications, so every monday they develope *Headach * Flushing *dizzeness & *postural hypotention.

NITRATE DEPENDENCY

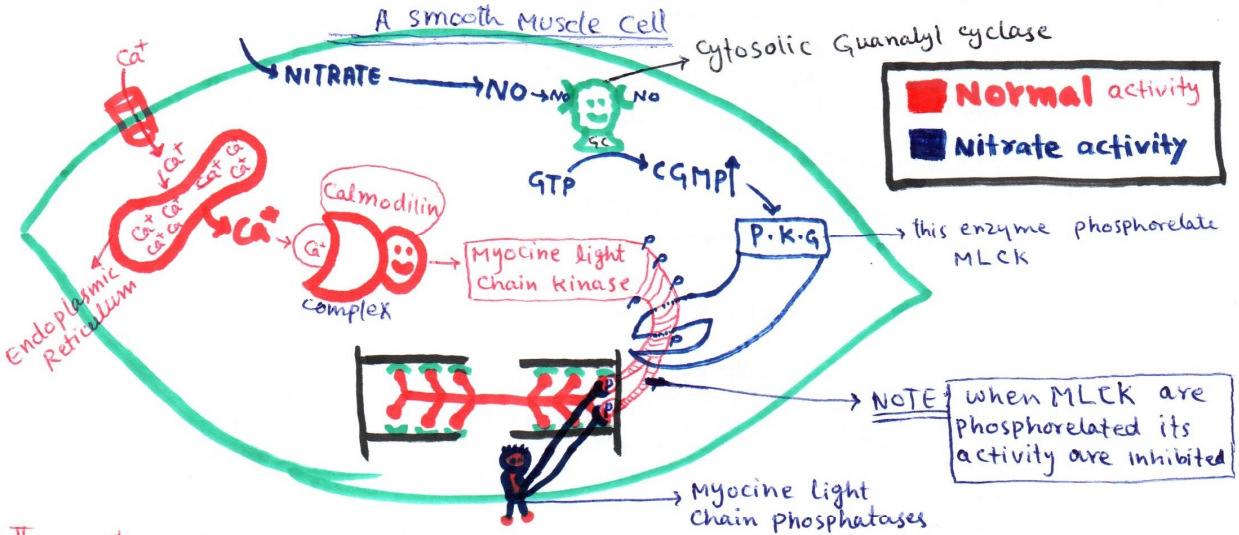
In this Condition patient develop angina at weekened.

How normal smooth muscle work

(i) Contraction:

(a) Ca^+ come into cell, & alot of Ca^+ release from ER.

(b) that Ca^+ bind with Calmodulin & Ca^+-calmodulin complex are formed.



(c) The Ca^+ — calmodulin complex stimulate Myocine light chain kinase, which phosphorelate the light chain, so actin — Myocine bind & contraction occur.

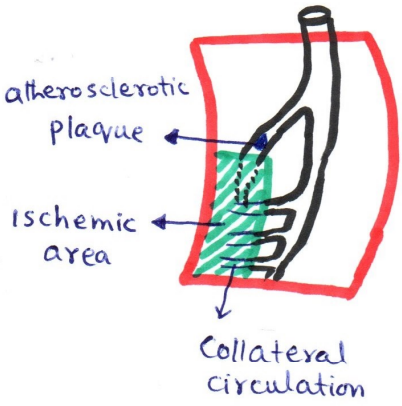
(ii) Relaxation

* Myocine light chain phosphatase remove phosphate from light chain, so relaxation of smooth muscle occur.

* To Relax the smooth muscle we need to inhibit Myocine light chain kinase, so Light chain is no more be phosphorelated. This inhibition is caused by NITRATES

Nitrate → NO → bind with Guanylyl cyclase → (GTP) CGMP↑ → protein kinase G → phosphorelation of MLCK, & thus inhibition occur → Muscle Relax b/c actin & Myosin does not attached to one another.

How angina is Terminated by Nitrates



nitrate cause dialation of collateral vessele, so blood supply to Ischemic area ↑es.

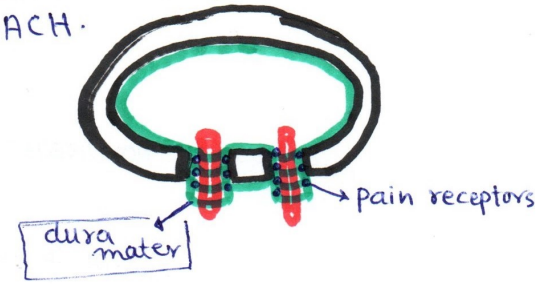
1. Venodialator
2. Better Perfusion
3. dialation of Coronary vessele (collateral dialation)
4. Some Extent Arteriolodialation.

Side effects of NITRATE

(i) HEADACH: most common side effec

All Those drugs which are vasodialator produce headach, this is called THROBBING HEADACH.

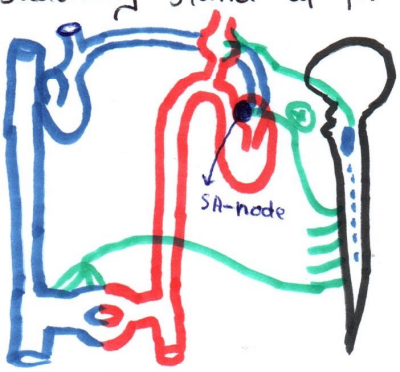
when vasodialation occurs, vessele are Pressed against bone, & the dura around the vessele have pain receptor, so headach occur.



(ii) Facial Flushing: due to dialation of facial artery.

(iii) Postural hypotention: (most important side effects)

Normal normally when a person ~~by~~ lay down & suddenly stand up for a short while venous return is less b/c blood is pumped in lower part of body So ↓es venous Return → ↓EDV → ↓ Cardiac output → ↓ B.P → Baroreceptor → CNS (Medulla vasomotor Center) → sympathetic out flow → squees & venocontraction → So volume retention should be maintained & CO should be maintained



If patient is on NITRATE

* when person stand up from lying position → ↓venous return → ↓EDV → ↓CO → ↓BP → Baroreceptors activated → CNS → sympathetic stimulation →

→ So as nitrate are working on smooth muscles of venules, so sympathetic does not cause significant venoconstriction So venous return can't be maintained → so when such a person standup, he feel fall in BP.

From lying down posture to standing posture, he develop postural hypotention; This type of hypotention is called ARTHROSTATIC HYPOTENTION

ARthrostatic: In which neurovenous mechanism can't constrict The veins on standing, They can't maintained venous return and Cardiac output.

So blood flow to CNS ↓es, & person feels Dizziness, & vertigo. if blood flow become too less, blood can't reach to cerebral Cortex, so person become UNCONSCIOUS.

Such antihypertensive drug which interfere sympathetic outflow & venoconstriction, lead to postural hypotention.

But this sympathetic system is able to stimulate SA-node.

(iv) Reflex Tachycardia: This occur due to overstimulation of SA-node & the patient feels palpitation

Palpitation ⇒ unplacent awarness of cardiac activity.

If we give β-blocker it prevent reflex Tachycardia caused by nitrates.

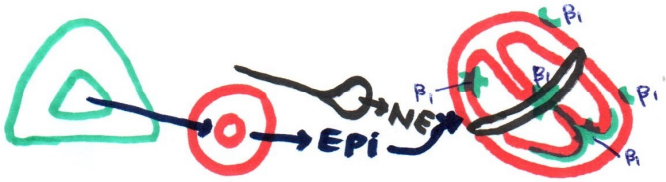
(2) β-blockers & Angina

β-blockers block reversibly or competitively Adrenergic receptors.

Adrenergic receptors

- αAR
- βAR
  - β_1AR
  - β_2AR

β_1AR are present in the heart



β_2AR are present in

① Bronchial smooth muscle → cause bronchial dialation

② in Liver → to ↑ glycogenolysis

③ in Pancrease → Release glucagon to ↑ gluconeogenesis in Liver

β_1 action

- SA-node ⟶ +ve chronotropic action → (↑ HR)
- AV-node ⟶ +ve dromotropic action → (↑ conduction)
- Myocardium → +ve inotropic action ⟶ (↑ contractility)

β-blockers

Non-selective

$\beta_1 + \beta_2$

e.g: Propranolol

Selective (also called Cardioselective β-blocker)

β_1

e.g Atenelol
Acebutolol
Metoprolol

NOTE: High dose of these drugs losses its β_1 selectivity & than also Block β_2 slightly

when β-blocker are given in angina, sympathetic action on heart will be lost so they produce:

① −ve chronotropic action (↓HR)
② −ve dromotropic action (↓ conductivity)
③ −ve inotropic action (↓ contractility)

β-blocker les electrical as well as Mechanical activity of heart.

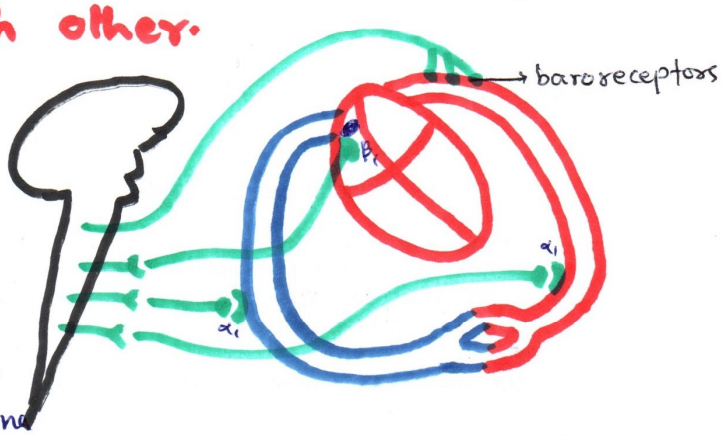
β-blocker ↓ HR & Contractility

ie ↓HR × ↓SV ⇒ ↓ CO ⇒ ↓ Cardiac work ⇒ ↓ O_2 demand

Person on β-blockers have ↓HR on resting position.

β-blocker not only protect heart at resting position, But also protect heart during physical Exertion & emotion & HR les only slightly, so total episode of angina is led.

When nitrate is given with β-blockers they will ↓es advantages of each other & cancel side effect of each other.



when nitrate is given:

venodialation

↓ venous return

↓ EDV

↓ CO → ↓ cardiac work

so it is good for angina

But if nitrate is given too much cardiac output ↓es too much it stimulate reflex tachycardia → it stimulate reflex venoconstriction → it stimulate reflex arteriocontriction → ↑ HR → ↑ SV → ↑ work on heart,

But nitrate keeps the veins dialated, so reflex venoconstriction will not occur.

If β-blocker are given they cancel the Reflex pathway stimulated by Nitrate.

on this way nitrate induced Tachycardia is ↓ed by β-blockers.

so β-blocker ↓ side effect of nitrate.

Any drug which ↓ HR will ↑es filling time of heart (ie Diastole)

so β-blocker ↑es filling time of heart. ie (↑EDV)

by ↓ SV β-blocker also ↑es EDV. so one of disadvantage of β-blocker is that it increase EDV. so it is bad for angina patient.

In this case nitrates are helpful by causing venodialation it will ↓es venous return inspite of ↑ Diastolic filling & ↓es contratility

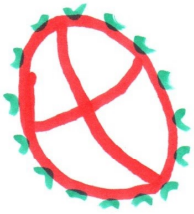
so on this way both drugs help each other.

Side effects + Contra indication of β-blocker

(1) Never ever stop β-blocker abruptly

B/c when patient is treating with β-blocker for longer time, than upregulation of such receptor occur (↑ receptors) & drug if stop abruptly the action of Catecholamin on heart

Increase → ↑HR → ↑ contractility → ↑ Cardiac work → ↑ O_2 demond → Ischemia → MI



NOTE: Discontinue β-blocker in 7—14 days.

(2) Fatigue

If β-blocker are given perephral β_2-mediated venodialation will be lost & person do some exertion he will fatigued easily

(3) Sleep disturbance

(4) Depression

(5) Impotence (failure to maintain enough erection)

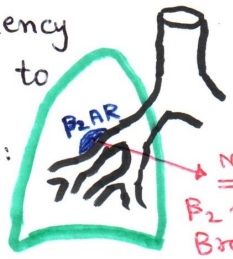
Normal Person
- α_1 mediate Veno constriction
- β_2 mediated Vasodialation

Conditions in which β-blocker should not be given OR we are very very careful | caution.

(i) COPD

They have tendency to develop obstruction to Air way.

These patients may be:
- Asthma
- Chronic bronchitis
- Emphysemia (loss of lung elasticity)
- Bronchictasis



Normally β_2 mediated Bronchodialation

If β-blocker is given to normal person, there will not be bronchodiala But it is not serious

If to such patients given β-blocker (propranolol) the β_2 mediated bronchodialation will lost, which is fatal

in COPD we also not giving β_1- selective, b/c these also slightly block β_2, so we can't get risk.

(ii) D·M

Insulin Dependant DM → such a person even sometime normally develop hypoglycemia, if to such person is given insulin injection, they develop hypoglycemia.

Conditions in which hypoglycemia develop in DM Patient.

1. Taking insulin but not taking food
2. Taking insulin but vomiting
3. Taking insulin but excessive physical activity
4. Extra amount intake of insulin

If such hypoglycemia occur than how body is activated?

↓GLUCOSE

(a) activation of sympathetic outflow

Sympathetic Nervous system produce warning sign (symptoms)

e.g → Tachycardia
→ Tremor
→ sweating

These symptoms are very helpful for DM patient to take glucose.

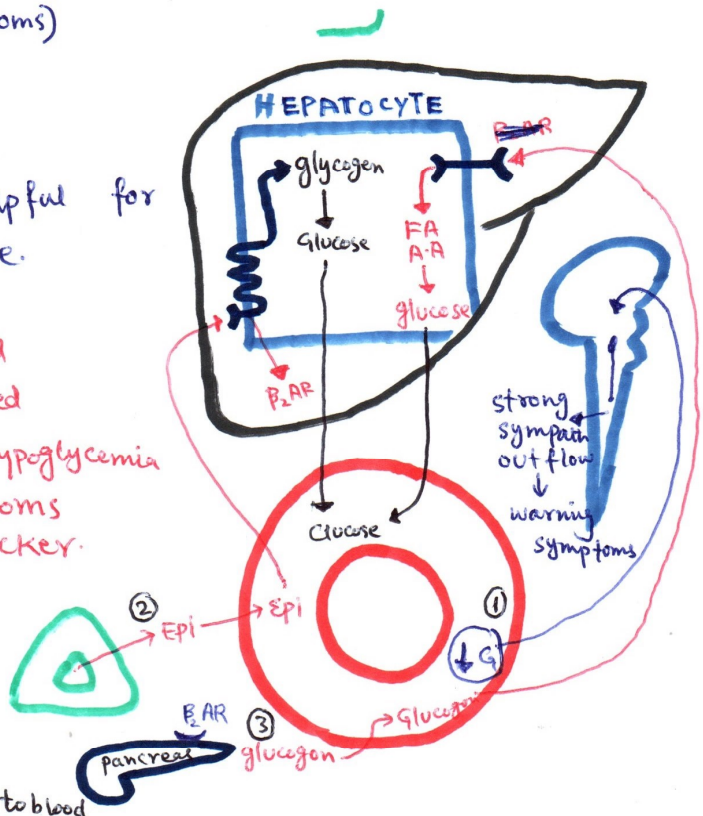
patient on β-blocker develop

(1) No Tachycardia → β_1 blocked

(2) No Tremor b/c → β_2 blocked

So such in DM patient on hypoglycemia no sympathetic warning symptoms are produced when use β-blocker.

(b) normally sympathetic activation Release Epinephrin from adrenal medulla → which acts on β_2AR of hepatocytes & increase glycogenolysis → as a result alot of glucose enter to blood



(c) Pancreas Release glucagon, which cause gluconeogenesis in liver.

* β-blocker ↓ the release the glucagon, So no gluconeogenesis occur. So DM patients on β-blockers develop svear hypoglycemeia.

(iii) Raynauds

In This Condition perephral vessele Especially that of hands develop vasospasTicity, so hand become

* cold
* pale
* Reactive cyanosis &
* Reactive hyperemia

if such patients are given β-blockers perephral vasodialation is lost.

(iv) Brady arrythmias

HR
awake 60 BPm
sleep 50 BPm
Bradycardia

Epi, Nor Epi normaly stimulate SA-Node & Av-node

e.g Nodal block

If sinus bradycardia patient is given β-blocker, so action of Epinephrin & Nor-Epinephrine are blocked, so bradycardia is converted into Bradyarrythmias.

NOTE we give β-blocker in congestive heart failure, but if patient have very svear acute CHF & ~~bradycardia~~ β-blocker should not be given.

(v) Depression

β-blocker should not be given b/c when β-blocker are given activity in the CNS is further depressed, so patient do sucide.

(3) Ca^+-channel blockers & Angina

These are competitive inhibitor of voltage gated (L-Type Ca^+-channel) blocker.

There are many types of Ca^+-channel in the body ie in CNS, in Endocrine..... In Cardiac problems we only block Ca^+-channel of heart.

Ca^+ channel blocker

- NEFIDIPINE
- Diltiazem
- Verapamil
- Bepridil

* SA-node & AV-node + purkinji are also Myocardial tissue but they are specialized Myocardium.
* The atrial+ventricular Myocardium is called generalized myocardium

* Cause Coronary artery dialation
* Block Na^+–K^+ channel

(SA-node) Specialized myocardium loss the tendency to Contract but they have automaticity

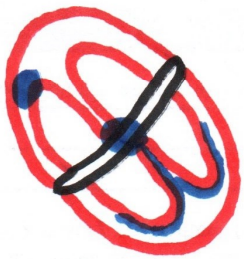
AV-node loss the tendency to contract but they have conductivity.

① SA-node depolarization is Ca^+ dependant.

② AV-node depolarization is Ca^+ dependant.

③ Myocardial depolarization

- Ca^+ dependant depolarization
  - SA-node
  - AV-node
- Na^+ dependant depolarization
  - atrial Myocardium
  - Ventricular Myocardium
  - Purkinji fiber



Atrial+ventricular depolarization is Na^+ dependant But their contractility is Ca^+ dependant.

Ca^+-channel dependant Cardiac activity

① SA + AV-nodes depolarization

② Atrial + ventricular contraction

Mechanisim of Action of Ca^+ channel blocker

① SA-node → -ve chronotropic action (Reduce automacity)
② AV-node → -ve dromotropic action (decrease conductivity)

↓HR → sinus bradycardia
→ sinus arrest

If this inhibition increases lead to:
heart block / Nodal block / junctional block

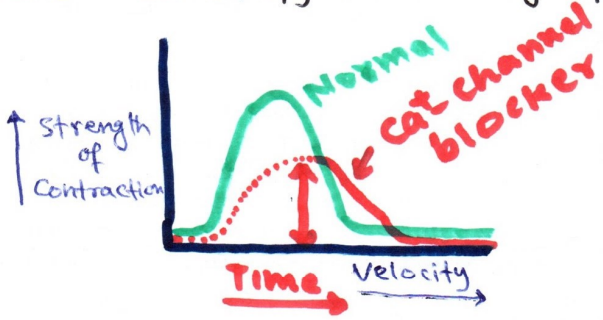
→ I° → II°] Partial heart block
→ III°] Complete heart block.

* Sinus bradycardia → ↓HR 60bpm due to SA-node inhibition.
* sinus arrest → SA-node activity is totally blocked.

③ When Ca^+ channel blockers is given, influx of Ca^+ during plautaue phase is blocked → ↓es Triggered Ca^+ → ↓ release of Ca^+ from sarcoplasmic → ↓ interaction of Actin & myosin → so Muscle contractility ↓es,

The term which is used as:

-ve inotropy → ↓ strength of Contraction
-ve clinotropy → ↓ velocity of Contraction

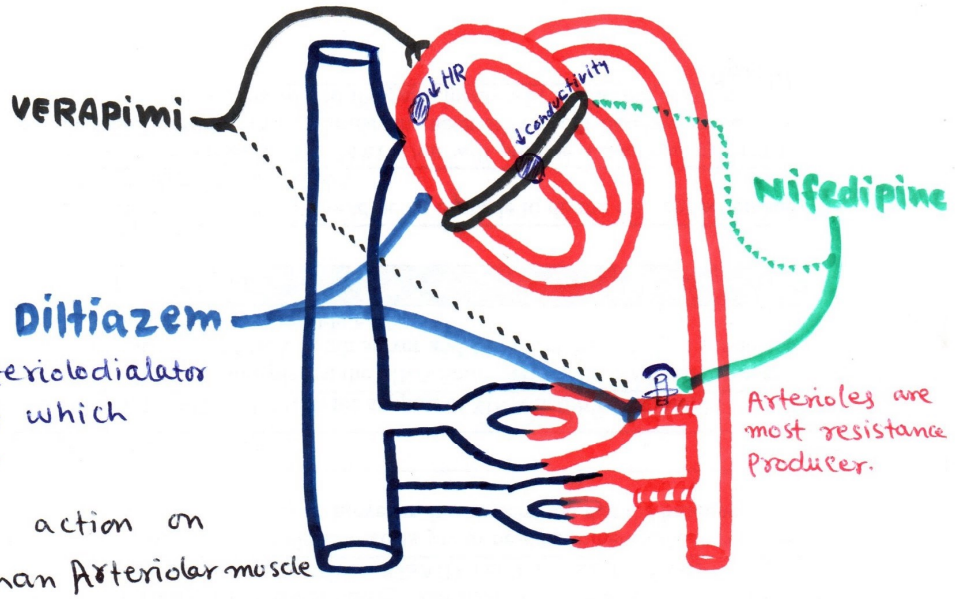


all these -ve effects lead to
- decrease CO
- ↓ Cardiac work
- ↓ O_2 demond

when Ca^+ channel of arteriole is blocked, so arterial muscle contract poorly, as resistance to blood flow decreases from arterial toward venous side.

ie ↓ Total perephral resistance.

* **Nifedipine is Dihydropyridine derivative**



* Nifedipine work more on smooth muscle of arteriole than heart muscle

They are primirily arteriolodialator so ↓ Resistance against which heart has to pump.

* verapamil has more action on heart smoothmuscle than Arteriolar muscle
* Diltiazem has same action on heart & Arterioles.

* Nifedifine is best drug for prinzmetal angina, b/c there is coronary artery spasm, & nifedipin dialate them
* **In classic angina all of drugs can be used.**

As nitrate cause venodialation & ↓BP & Reflex Tachycardia
Nifedipine cause arteriolodialation & ↓B & reflex Tachycardia

If nitrate is used with verapamil, the reflex tachycardia of nitrate will be canceled, b/c verapamil is heart Inhibitor.

* verapamil precipitate sinus bradycardia, nodal bradycardia & Cardiac failure.

uses of Ca^+ — channel blockers

Angina
- classic → Nifidipine + β-blocker
- prinzmetal → Nifedipine

Bepridil → block Na^+ & K^+ channel + Coronary artery dialation

when there is Na^+ & K^+ channels are blocked there is special type of Arrythmias called Torsa – D – Pontus (T·D·P).

↳ Twisted QRS – complex

angina + T·D·P
⇓
Bepridil

* side effects of nipidepin is like nitrate side effects

* side effects of verapamil is like β-blocker

Nifidepin Cause Headach → mechanis is same like other vasodialators.

End of Anginal drugs.

By: Zakirullah Yousufzai.

From: Dr. Najeeb video lectures.