DRUGS USED IN CARDIAC FAILURE

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Frank starling law

when ventricles are fill more (strech) they contract more.

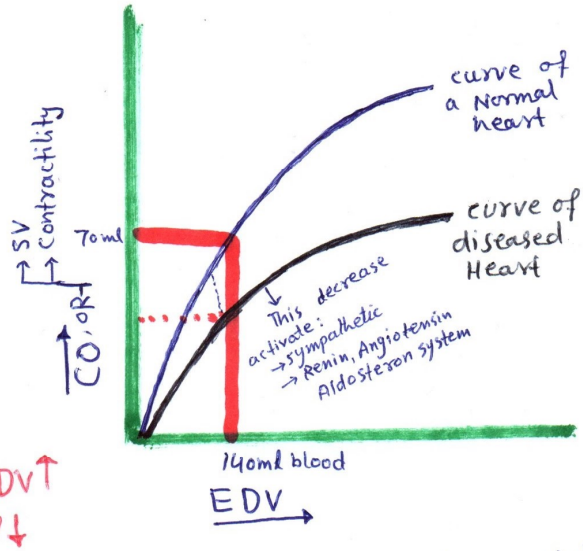
* more you strech the ventricles, more it contract within physiological limit.

Normal Heart

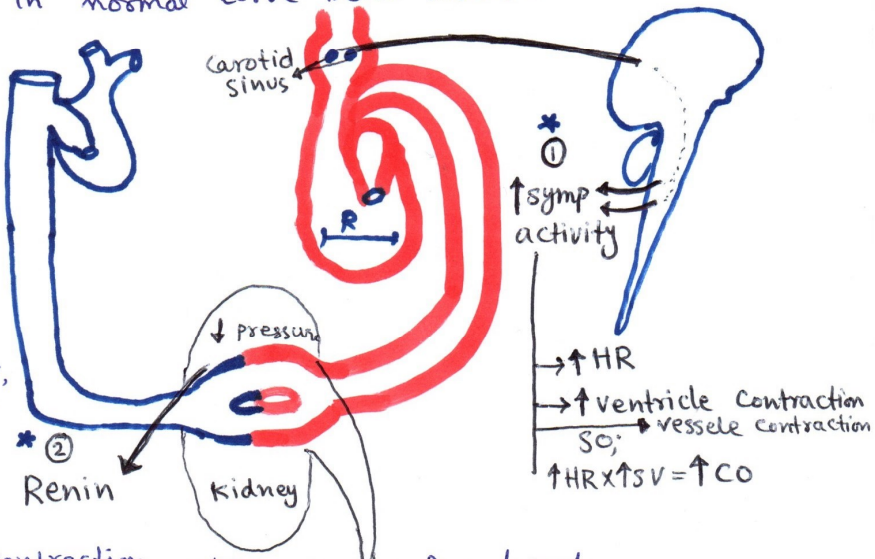
when EDV increase, the Cardiac output (co) increase progressively.

when left ventricle have 140ml of blood, & contracted, it eject 50% (70ml) of blood.

* if venoconstricted drugs are given, the EDV↑
* if venodilator drugs are given, EDV↓



* Compare both curve, by increasing by co (Contractility) the contractility in both curve increases, but more in normal curve than diseased curve.



This attempt is important for short time, & for long time it is dangereous.

If this attempt is for 1 or 2 hour, cause no problem, but occur for months/years, than ↑ sympathetic outflow cause pathology in heart

Because:

↑ symp cause arterio & veno contraction, which is bad for heart.

* ArterioContraction ⇒ it is difficult for left ventricle to push blood to right side.
* venocontraction ⟹ increase venous return is bad for heart.

Lamlos law $P = \frac{T}{R}$

$P = \frac{\text{Tention}}{\text{Radius}}$ ⇒ Power generated in myocardium

Diseased heart = $P = \frac{T\downarrow}{R}$ In diseased heart Tention is ↓es.

↑ sympathetic, ↑esed arteriocontraction, ↑ Resistance to blood flow, so more pressure is required to push the blood, while heart is already fail, & not able to generate enough tention.

If venoconstriction ↑, which ↑ venous return, so the diseased heart recieve more blood & push less blood, & blood remain within the ventricles, eventually ventricles dialated. (So Radius ↑).

$\downarrow P = \frac{T}{R\uparrow}$

Combine both equations: $\downarrow\downarrow P = \frac{\downarrow T}{\uparrow R}$

↓
B/C every time heart recieve more blood & push less blood.

Renin angiotensin system come with full intention but produce trouble for heart.

Heart fail ⟶ ↓ renal perfusion ⟶ ↑ renin production.

what are reasons of more Renin

① blood flow to kidney is less.

② ↓ Blood flow to kidney ⟶ ↓ Na to macula ⟶ ↑ Renin release.

③ CNS ⟶ ↑ sympathetic activity ⟶ Juxta glumerolar apparatus ⟶ ↑ Renin

Angiotensinogen $\xrightarrow{\text{Renin}}$ Angio-I $\xrightarrow{\text{ACE}}$ Ang. II + Aldosteron.

This high Ang II have advantages & disadvantages.

↑ Ang II ⟶ ↑ venocontriction ⟶ ↑ volume return ⟶ ↑ EDV ⟶ ↑ CO (for normal heart)

But ↑ EDV ⟶ ↑ Radius for diseased heart & further drop in Contraction

↑Ang II ⟶ ↑ arteriocontraction ⟶ ↑Resistance, so more pressure is required for diseased heart.

↑Aldosteron ⟶ ↑ Na^+ — H_2O retention ⟶ ↑Blood volume ⟶ ↑venous return ↓ ↑Radius of heart

chronic heart failure ⟶ chronic stimulation of sympathetic system ⟶ chronic stimulation of Renin-angiotensin system So, ↑arterio & veno constriction.

This neuro humeral compensatory mechanism are dangereous for heart in long term.

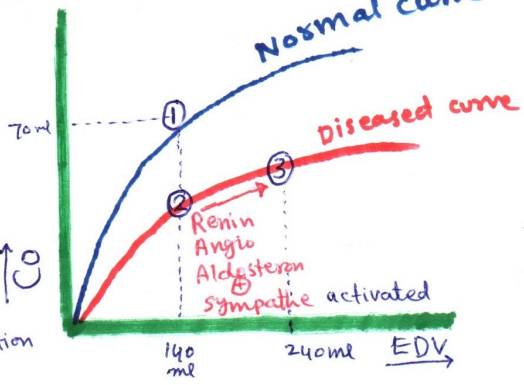
when Ang II is chronically high, it act as a growth factor, & stimulate the Myocardial cells and produce pathological hypertropy and cells produce alot of Connective Tissues.

when Aldosteron is high, It produce fibrosis of heart, such changes cause progressive failure of heart.

this Increase in Renin Angiotensin Aldosteron system cause pathological structure & morphological changes in the heart called HEART REMODELING.

Now apply these things in the graph

As curve drop sympathetic + Renin ang. Aldosteron system increses, they increase EDV but ejection not occur normaly. And a time occur when EDV increases but Cardiac output does not increases.



PRE LOAD: load in the ventricle before contraction.
preload = EDV

AFTER LOAD: Resistance against which ventricle have to perform. → That is arteriolo contraction
post load = Resistance

↑ veno constriction = ↑ pre load

↑ arteriolo constriction = ↑ after load

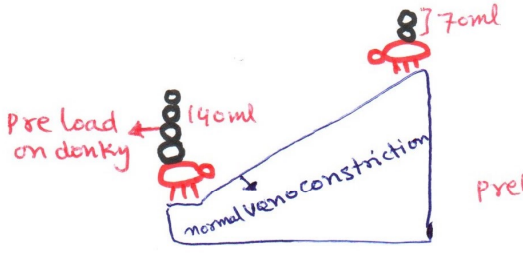
Diseased heart suffer from

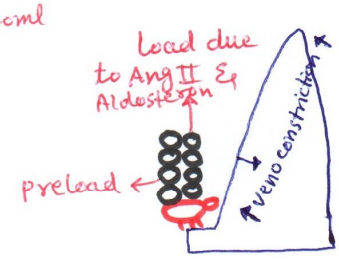
① Excessive pre load.
② Excessive after load.
③ decreased contractility
④ progressive failure of heart.

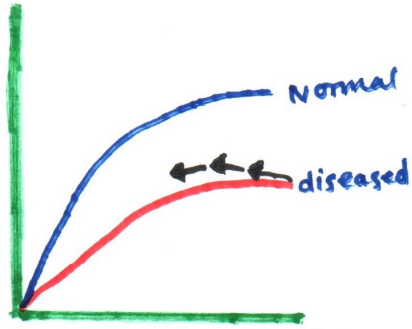
e.g: Heart is a weak donkey

we help this donkey by Reducing pre load & after load so, we give

Venodialator ⟶ ↓ pre load
Diuretics ⟶ cause → ↓ blood volume + pre load
→ Arterio + veno dialatation
→ ↓ End diastolic volume







For decreasing after load

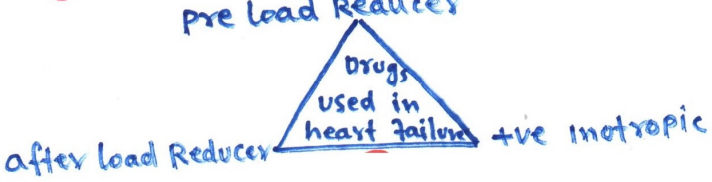
* Arteriodialators are given, so ↓ Resistance, ↓ pressure is required & CO↑

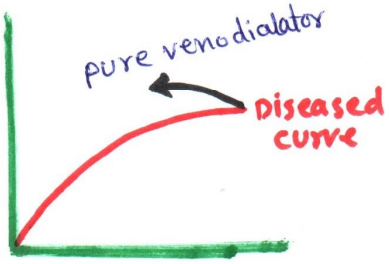
The diseased curve (↓) b/c of venodialators so;

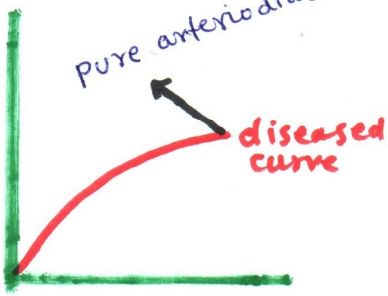
$\uparrow P = \frac{T\downarrow}{\downarrow R}$ so ↑CO

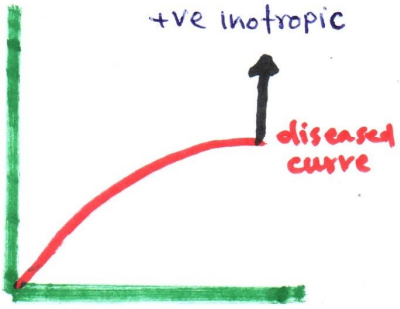
* Arterio/venodialator ⟶ ↑CO, so sympathetic Nervous system Relax (↓ sympathetic activity)

↑CO ⟶ ↑Renal perfusion ⟶ ↓Renin Angiotensin, so this is one way to treat failure heart patients.

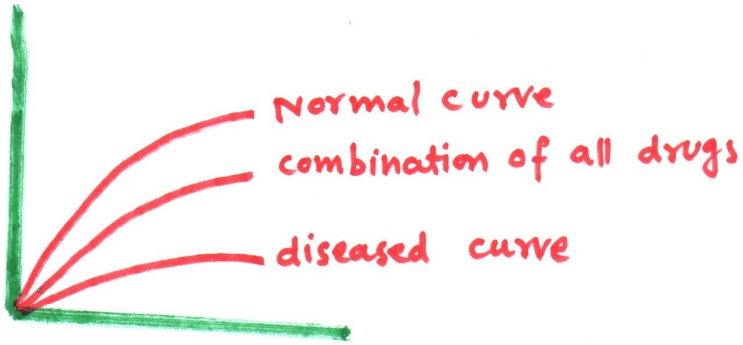








But if we combine all of them togather curve will move to better position.



Most better drugs for Congestive heart failure are Angiotensin converting Enzyme inhibitor (ACE-I).

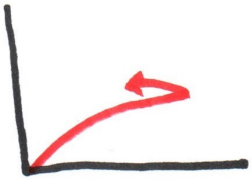
ACE-I e.g: Captopril & Enalapril ⊘ ACE → Angiotensin II

when given Angiotensin I

So ↓Angiotensim II + bradykinim b/c ACE also destroy bradykinin (a vasodialator).

↓Ag II → ↓EDV → ↓Radius so P↑ ⇒ $\uparrow P = \frac{T}{R\downarrow}$

↓Ang II → venodialation, so diseased curve move backward.



↓Ang II → ↓vasomotor tone → ↓ sympathetic activity → ↓preload → ↓Myocardial strech i.e (Diastolic stretch)

↓ preload → ↓ed Diastolic stress on ventricular wall.

↓ After load → ↓ed systolic stress on ventricular wall.

So ↓ hypertropy.

So Captopril or Analapril ↓ systolic & diastolic stress and ↓ growth factor for hypertropy so cause regression of progression Remodeling occur.

when Ang II inhibitors are given:

* Ang II mediated arterioloconstriction is loss plus
* Sympathetic stimulation by Ang II is loss so sympathetic mediated arterioconstriction loss.

↑ Ang II and Aldosteron cause heart myocardium to dialate & ↓ Contraction and pathological Extracellecular matrix formed.

* when heart radius ↑es it become globular heart.
* Normal shape of left ventricle is Elliptical.

ACE-I not only reduce morbidity but also reduce mortility in patient B/c:

1. It ↓ preload and after load on heart.
2. ↓ pathological Remodeling.
3. ↓ MI
4. ↓ Arrythmias
5. ↓ stroke

These drugs are given in all patient with congestive heart failure. Patients in which Ejection Fraction (EF) is ↓es than 35%. These drugs are effective.

Common ACE-I

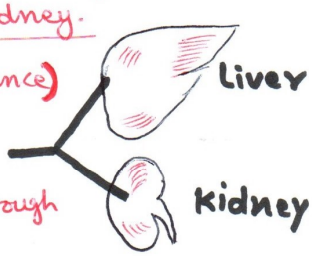
1. Captopril (active drug)
2. Enalapril
3. Ramipril
4. Lisinopril
5. Fosinopril

These are prodrugs, passes through liver become hydroxylated & Convert to active metabolite.

Except **FOSINOPRIL** all drugs go out of the body through kidney.

(balance clearance)

↳ Fosinopril go out of the body through



Uses of ACE-I

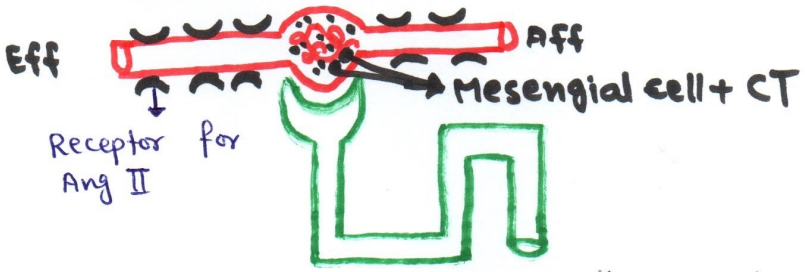
1. CHF
2. HTN
3. patient with recent MI
4. Diabetic Nephropathy
5. Diabetic Retinopathy

All of ACE-I taken orally preferably on Empty stomach b/c food retard its absorption.

In diabetic patients:

Basment membrane is damaged, and proteneous substances oozes out of glomeruli into mesengial cells and mesangeal cells are destroyed.

patient develop arteriosclerosis in afferent and efferent arterioles, so blood flow to glomeruli is reduce.



Ang II mostly acts on Affevent arteriole than Efferent.

In such patients when Ang II acts on its receptor on efferent arteriole, cause its further constriction, so in glumeroli pressure increases further, so substances enter to mesengium & further destroy the mesengium

Benifits of ACE-I in Diabetic Nephropathic Patient.

- ↓ systolic BP
- ↓ glomerular hypertention (↓ systemic BP) → ↓ damage of mesangium.
- ↓ Ang II (↓ stimulation of growth Factor on mesengial cells so ↓ spread of Diabetic Nephropathy).

Adverse Effects of ACE-I (CAPTOPRIL)

Cough (dry cough) b/c bradykinin not destroyed b/c ACE are inhibited, the bradykinin in lungs cause cough.

Angio edema

Protein urea

Taste change

O → Hyp**O**tention

Pregnancy (contraindicated) 

Rashes

Increase → K^+ b/c ↓ Aldosteron, (Aldosteron absorb → Salt, H_2O & Expell K^+)

Renin b/c AngI —✗→ AngII, the deficiency of AngII stimulate the Release of renin.

(can't convert to)

Low → AngII, Aldosteron

Angioedema occur due to → Bradykinin precifitate Angioedema; C_1 esterase inhibitors are inhibited

Unknown but some of these drugs activate immune system & produce Ab against basement membrane, so protein urea occur.

why hypotention occur?

Hypotention occur mostly in first dose, & seen in patient with increased plasma Renin Angiotensin e.g → CHF, salt depleted

These drugs should not be given in pregnancy because cross the placental blood barier.

Comparision of ACE-I with ARB's (angiotensin receptor blockers)

1. Losartan
2. VAlsartan
3. Candesartan

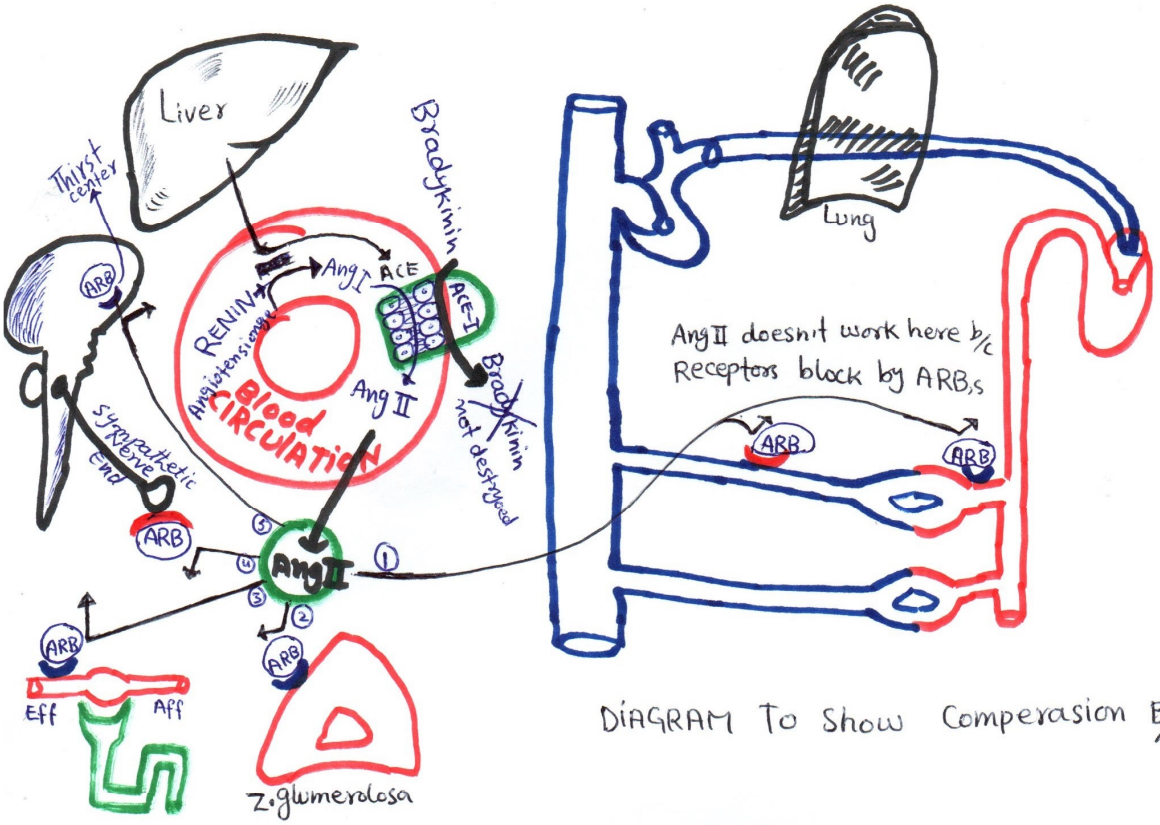


DIAGRAM To Show Comperasion B/w ACE-I & ARB

Angiotensin II acts on veins, Arteries, hypothalamus (thirst center), zona glamerulosa, sympathetic nerve endings, & cause → venocontriction, ARteriocontriction, ↑ Aldosteron, To drink H_2O

The ARB's block these receptors from Ang II.

ARB's Cause

① Cause arteriolodialation] ↓ systolic BP.
② Cause venodialation] ↓ Diastolic BP.
③ ↓ Aldosteron ⟶ ↓ Na^+, H_2O retention → ↓ blood volume.
④ ↓ efferent arteriole constriction
⑤ ↓ sympathetic outflow
⑥ ↓ Ang II work on synapse.

ARB's Canit prevent the Conversion of Ang I ⟶ into Ang II, so angiotensin II increases but its receptor are blocked, so it is not able ~~do~~ to do work.

ARB's Canit block ACE so, bradykinine are destroyed by ACE, so Cough & Angioedema not produced.

USES OF ARB,s

① ARB,s are given to patient in which ACE-I are not tolerated due to cough & angioedema.

② These are Antihypertensive drugs.

side effects of ARB,s

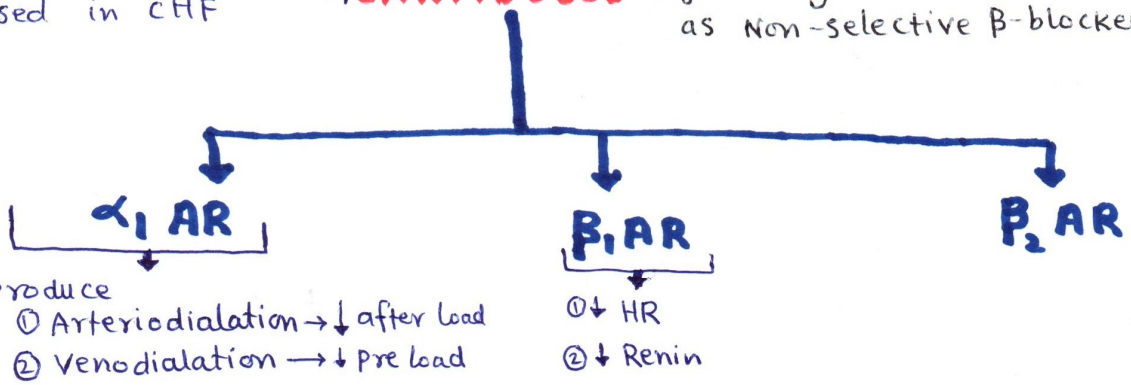
side effects of ACE-I & ARB,s are same except ARB,s produce no cough & angioedema.

* CHF and β-blockers

In CHF → ↓ CO → ↑ sympathetic stimulation.

β-blockers not only reduce HR but also decrease the abnormal function of the heart (ie: cardiac remodeling)

Common β-blockers used in CHF
- METOPROLOL → it is longer acting
- CARVIDOLOL → generally it is α-blocker as well as Non-selective β-blocker



NOTE: In many Acute serious CHF β-blockers should not be given because they are -ve inotropic.

* CHF & DIURETICS:

- **THIAZIDE** (mild diuretic)
- **LOOP DIURETICS** (strong diuretic)

* Thiazide lose its efficiency when GFR drop.
* Loop diuretics keeps on working even when GFR reduced.

Diuretics Produce

① Loss of salt & water (nitreuresis + Diuresis) so → ↓ Blood volume & ↓ BP
② venodialation ⟶ ↓ Preload
③ Arteriodialation ⟶ ↓ after load.

Diuretics acts as a vasodialator.

Spirinolacton used in advanced stage of heart failure

Spirinolactone bind with Aldosteron receptor & block its action.
& K^+ loss by Aldosteron is also not there, so spirinolacton prevent hypokalemia.
Spirinolacton decrease retention of salt & water.

* ↑ Aldosteron cause stimulation of myocardial cells & lead to hypertropy.
* spirinolacton also prevent Aldosteron mediated remodiling.

* CHF & Direct Vasodialator → Venodialator (Isosorbid dinitrat) / Arteriodialator (Hydralazine)

Combination of Isosorbid dinitrate & hydralazine derease preload & after load, are used in CHF, produce best result.

NOTE: This combination are used in patients who are intolerated to → ACE-I & ✗ / ARB,s ✗

+ve Inotropic Drugs used in heart Failure.

heart failure is a clinical pathological condition due to structural & functional dysfunction of heart, due to which heart is unable to produce enough cardiac output to perform the needs of perephral body.

classification of **Heart failure** according to CO of failing heart

Normal CO = 5 Liter

High output H·F

ie
① Hyperthyroidism
② Anemia (↓ common)

In These cases the body ↑ its demond, So heart inspite of ↑CO is not able to sustain the body needs.

Low output Failure

e.g
① MI &
② Ischemia (more comun)

in this case heart is unable to produce enough cardiac output.

Forward Failure

if left ventricle fail, thain either is ↓CO. or ↑ pulmonary edema

This decrease CO is called forward failure & patient feel:
* fatigue so patient
① ↓ Excercise tolerance
② Low Pulse

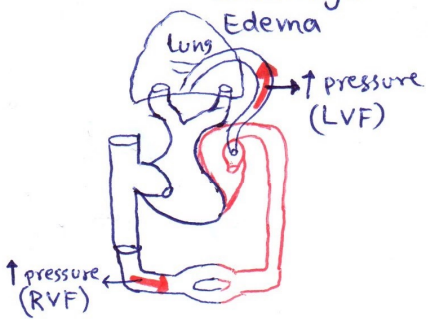
backward Failure

in backward failure there is
① → Pulmonary edema (basal crepitation)
② → dyspnea
③ → cough
④ → orthopnea
⑤ → Paroxysmal dyspnea.

Bi ventricular Failure

Right ventrile Failure

↓
Generalized Edema



left ventricle Failure

↓
Pulmonary Edema

Diastolic Failure

During diastaly normal heart relax & fill from blood properly.

* The hypertropic ventricles does not relax during diastaly, so not fill properly,

its sign & symptoms are same like backward faiture

Systolic Failure

If there is problem of Contractility of heart Than SV↓, & there is a problem of systolic BP In this case main problem is forward failure, but eventually develop backward failure.

If there is left ventricular hypertropy, so blood move in backward direction, pressure in the left ventricle + pulmonary pressure increases. pulmonary capillary pressure increases, and pulmonary arterial pressure increases., so Pulmonary edema occurs.

If there is right ventricle failure, back pressure in the right ventricle increase, this increase pressure in Rt ventricle increase pressure in Right atrium, & the blood move back and oozes out of systemic capillary so produce Generalized edema.

Drug used in low cardiac out put failure doesn't used in high output failure.

These Drugs also used in Left ventricular failure & Biventricular failure.

+ve inotropic drugs cause contraction of heart, so only used in forward failure.

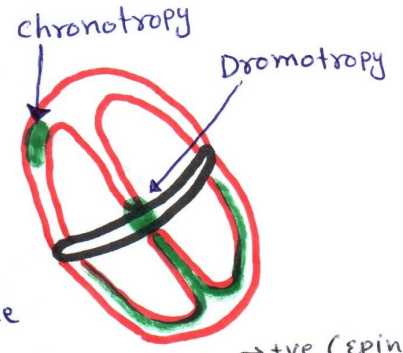
Drugs used in systolic failure, doesn't used in Diastolic failure.

What are +ve inotropes?

Inotropy: chang in the contraction of myocardium → +ve / -ve

Chronotropy: any thing which change the HR → +ve (Epinephrine) / -ve (CCB, β-blocker)

chronotropic Drugs work on SA-node



Dromotropy: chang in the Conductivity of Av-node → +ve (Epinephrine) / -ve (CCB, β-B....)

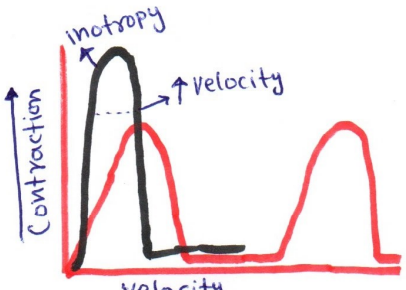
Bathmotropy: some tissues in myocardium have automatism.

cleinotropy: increase of velocisty & contraction

Ca^+ loadey in Heart

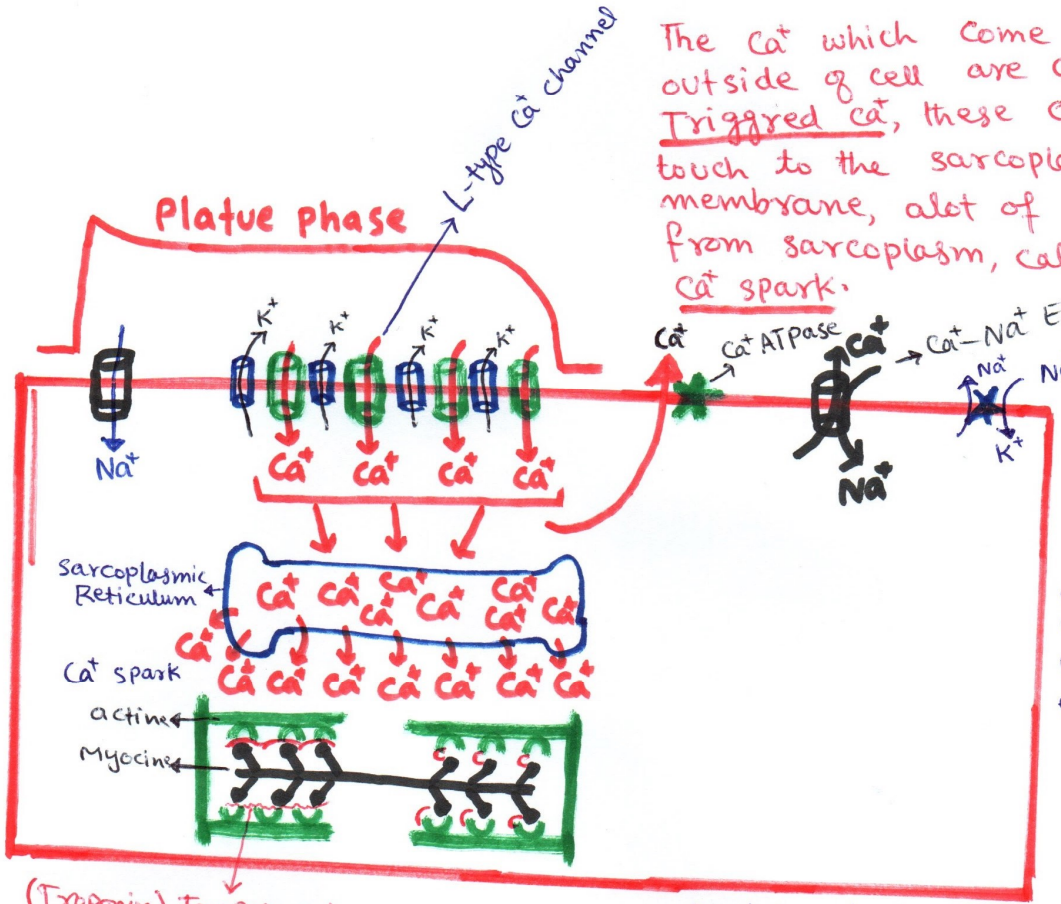
These 3 things ↑Ca^+ in heart cells

1. Ischemia
2. Digitalis
3. ↑ sympathetic activity



clinotropic action

action of SA-node AV-node, Atria & ventricles depends on Ca^+.



The Ca^+ which come from outside of cell are called Triggred ca^+, these Ca^+ when touch to the sarcoplasmic reticulum membrane, alot of Ca^+ released from sarcoplasm, called Ca^+ spark.

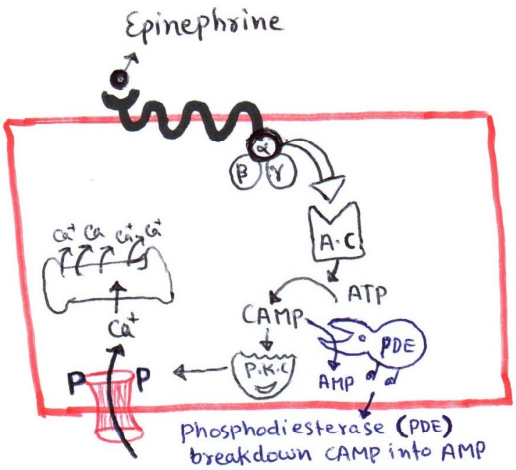
for any cell which undergo contraction 1st it will undergo electrical stimulation.

(Troponin) Tropomycine
The troponin prevent actin & myocine to donit attach with one anothere, But when Ca^+ spark occur, it pull the troponine & Actine-myocine attach & cause contraction of the cell.

During diastolic Relaxation the Ca^+ back absorb by sarcoplasmic reticulum.
& the triggered ca^+ also go out from the cell.

How the cell undergo Electrical stimulation?

+ve inotropic action of sympatomemitic Drugs ⟹



Detail of previous Diagram

* when i.e Epinephrine bind to its receptor, the α-unit of the receptor activate Adeny cyclase which convert ATP into CAMP. the CAMP stimulate protein kinase-C, which phosphorelate the L-type Ca^+ Chanel, & Ca^+ come into cell which release Ca^+ from Sarcoplasmic reticulum, which pull the troponine, & Actine & Myocine bind to one another & Contraction occur.

Caffine & Digoxin inhibit PDE So the level of CAMP↑, as a result HR↑ e.g

How Depolarization Caus Myocardial contraction

① Na^+ move & depolarization occur

② Depolarization Sensitive K^+ & Ca^+ channel opens they produce plautue phase.

③ than Ca^+ channel block & K^+-channel remain open, & K^+ goes out so repolarization occur.

④ These Ca^+ acts on Sarcoplasmic reticulum & Cause Ca^+ spark.

⑤ These spark Ca^+ bind with troponin-C & Expose Ca^+ binding sites to Actin & Myocine fillaments start contraction.

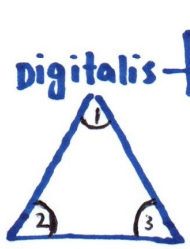
⑥ Sarcomere become shorter & Cause Contraction.

⑦ Tension produce in the wall ⟶ that is translate into pressure & SV is ejected.

How Repolarization Cause Myocardial Relaxation.

As membrane become repolarize many repolarization sensitive Mechanism occur to cause ventricular relaxation, we need to decrease Ca^+ level by two mechanisms ① Ca^+ is pumped back to sarcoplasmic reticulum. → Ca^+ ATPase
② Ca^+ is pumped out of the cell by → Ca^+-Na^+ antiport.
So Actin-Myocine interaction loss & Diastolic relaxation occurs.
AT the end of mechanism Na^+-K^+ ATPase move Na^+ out & K^+ in, on this way contraction is followed by relaxation.

+ve Inotropic drugs 3 groups



Digitalis → Digoxin
Digitalis → Digitoxin

(PDE-I) Phosphodiesterase Inhibitors → Dopamin & Dobutamine

- Amrinone
- Milrinone

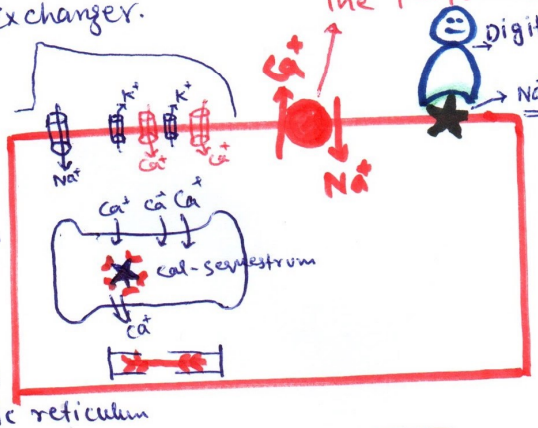
] Inhibit phosphodiesterase enzyme, so CAM not distryoed, & the level of CAMP ↑, which ↑ Ca^+.

Digitalis bind with Na^+-K pump & slows dowen it. so decrease Efflux of Na^+, & ↑ Na^+ intracellecularly, so further influx of Na^+ Extracellecular Na^+ decreased, Than Na^+ – Ca^+ exchanger canit work & Ca^+ start accomudation, & the depolarization will not come out so Ca^+ level in sarcoplasmic reticulum increases, so with each Action potential extra Ca^+ will release & Extra contraction will occur, so on this way digitalis produce +ve inotropy.

Direct Action

Action 1

NOTE: Digitalis has primary action on Na^+–K pump & 2ndary action on Na^+ – Ca^+ Exchanger.



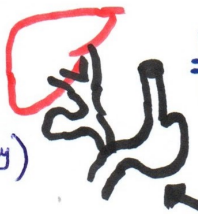
This is called ↳ cal-sequestrum, the Ca^+ which come in set on the cal-sequestrum protein

so as during each depolarization Ca^+ goes in, ↑ Ca^+ in sarcoplasmic reticulum so ↑ intracellecular Ca^+.

So the Na^+-K^+ pump is blocked by digitalis, further Na^+ will not go in, So the Na^+-Ca^+ Exchanger will not work properly, & the Ca^+ accomudate within the cell

Digoxin

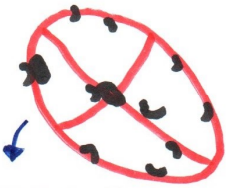
1. commonly used
2. have shorter halflife (36 hr or 1.5 day)
3. start action after 20 minutes.
4. plasma protein binding 30%
5. clearance by glomeruli →



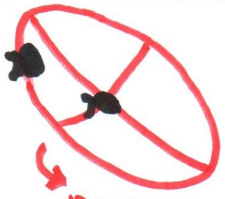
Digitoxin

1. half life 5 days (longer action)
2. start action after 60 minutes
3. plasma protein binding = 90%.
4. clearance by hepatobillary syste
5. **it is more toxic only used in Renal failure patients.**

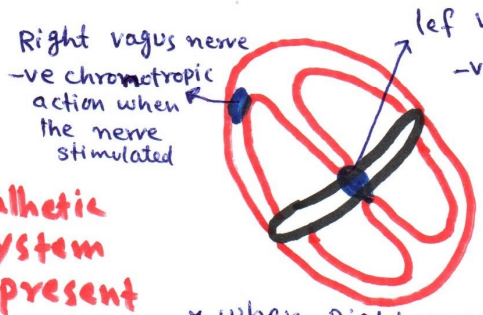
② Indirect action of Digitalis



Sympathetic Nervous system present all over the heart.



Parasympathetic Nervous system are only present in SA, AV-node Less in Atria & No in ventricles



* when Right vagus fires the SA-node activity ↓.
* when left vagus fires the AV-node activity ↓.

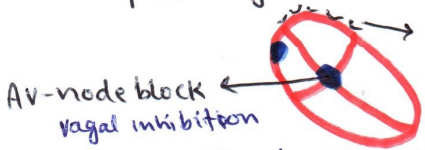
Ca^+ have +ve chronotropic action on SA-node, while Right vagus have -ve chronotropic action. if both are present the right vagus is dominant over Ca^+, so SA-node is inhibited.

Ca^+ have +ve dromotropic action on AV-node, while left vagus have -ve dromotropic action, if both are present the left vagus is dominant over Ca^+, so inhibition of AV-node occur.

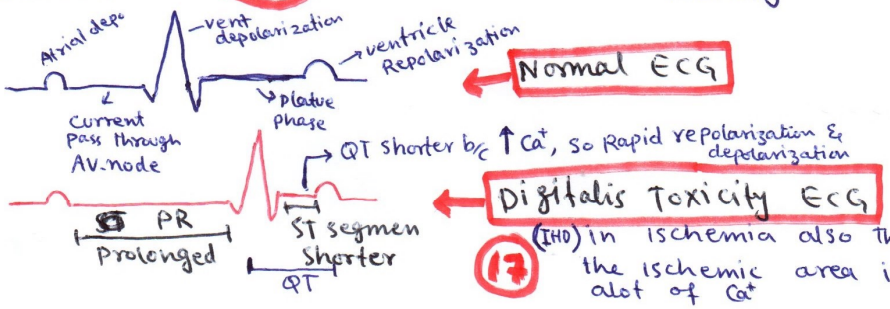
Digitalis → **Direct action** ($\uparrow Ca^+$) stimulate atria & ventricles
Digitalis → **Indirect action** (vagotonic effect) inhibit SA-node & AV-node.

Toxicity of Digitalis → Sinus (SA) bradycardia, AV bradycardia
Toxicity of Digitalis → Atrial & ventricular Tachycardia

If too much toxicity occur, it cause AV-node block so no impulse goes dow, cause Atrial tachycardia & AV-node block.



if such condition seen in ECG its means ~~Digitalis~~ Digitalis toxicity.

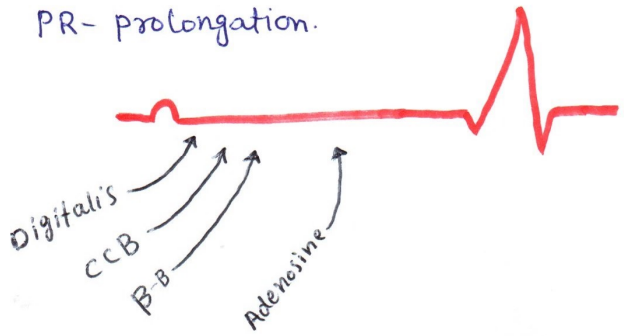


NOTE

in Digoxin toxicity the current very slowely passes from AV-node to ventricles

(IHD) in ischemia also the QT shortened b/c the ischemic area is loaded with alot of Ca^+

all those drugs which inhibit AV-node lead to PR- prolongation.



① Digitalis → ↑ vagotonic activity of AV-node so inhibition occur

② CCB → Block the Ca^+ channel of AV-node

③ B-B → inhibit sympathetic activity of AV-node

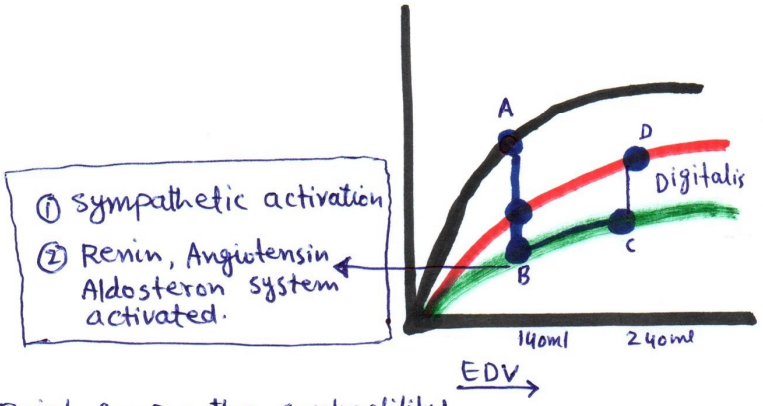
④ Adenosine → it is a short acting AV-nodal inhibitor, it opens K^+ channel of AV-node, cell loss alot of K^+, & lead to inhibition

Massage on baroreceptor of Neck, stimulate Vagus nerve so AV-node inhibition occur.

QT interval → Duration b/w start of depolarization to the end of repolarization

Ca^+ loading Makes the myocardium more efficient.

Digitalis	Ischemic heart disease
load Myocardium with Ca^+	Load Myocardium with Ca^+
effect ST-segment & T-wave	Effect ST-segment & ~~&~~ T-wave



① sympathetic activation
② Renin, Angiotensin Aldosteron system activated.

Point A—B = the contractility↓ (cardiac output drop)

here digoxin increase tention (contraction)
→ ↑ CO
→ veins become dialated
→ Renal perfusion become good so Renin angiotensin aldosteron system are inhibited
↳ ↓ salt
↳ ↓ water

So ventricle radius become smaller, artery become relax, so resistance ↓.

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

Point B = Cardiac failure without compensatory mechanisms
Point C = Cardiac failure with compensatory mechanisms
Point D = The CO↑ after digoxine.
↓ contractility

Good effect of Renin Angiotensin Aldosteron + symp

① Cause retention of salt and water so ↑ EDV.

② sympathetic activation ↑ CO by venoconstriction

Bad effects of Renin Angiotensin Aldosteron + Sympathetic.

① ↑ sympathetic activity cause to ↑ Arteriolconstriction, so more blood come to heart → ↑ stress on heart → ↑ Extracellecular matrix.

② Due to chronic Neuro Humoral Compensatory Genomic activation Myocardium become very very poor type of Myocardium.

Laplace's law for Digoxin

$$P \propto \frac{\uparrow T \text{ (Digoxin)}}{R}$$

Digitalis ↑ tention so ↑ pressure, ↑ CO **(Direct Action)**

Perfusion to kidney become good → Renin angiotensin Aldosteron system activated

↓ venous return

↓ EDV → so curve move backward

(Indirect action) ←

↑ CO, so ↓ sympathetic activation + ↓ Renin angiotensin aldosteron system, so mechanisms relaxes.

① At D-point the salt & H_2O retention is less **so venous return ↓**

② sympathetic relaxation → **↓ venous Return**

③ Renin, Angiotensin Aldosteron inhibition → **↓ venous return**

So, Radius ↓

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

As sympathetic + Renin Ang. Aldosteron Relaxe → Arteriodialation occur so not only resistance ↓ but pressure required also ↓

So, heart now become smarter again.

In cardiac failure we initially use

Diuretics + **ACE-I**

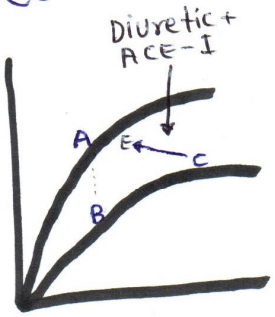
Diuretics → ↓ venous return → ↓ EDV → ↓ Radius → So $P = \frac{T}{R\downarrow}$

ACE-I → ↓ Angi-II → ↓ venous return → venodialation → ↓ Radius So, $P = \frac{T}{R\downarrow}$

ACE-I → ↓ Aldosterone → ↓ salt + H_2O retention → ↓ EDV → ↓ Radius → So $P = \frac{T}{R\downarrow}$

with the same tention when we reducing the radius, Pressure ↑es so it start increasing CO.

So it is better to move from C ⟶ E



Aldosterone in high concentration will cause changes in genetic expression of Myocardium.

↑Ang II alter the genetic expression of myocardium, if patient come with heart failure it is better to give 1st ACE-I & Diuretis & β-blockers & Than Digitalis.

ACE-I, Diuretics, β-blocker → cause reversal of Neuro Humoral → ↑ long term survival.

Clinical uses of Digoxin

in First Line of HF we give Diuretics, ACE-I, β-blockers, these drugs inhibit reverse Neuro Humoral inhibitory strech.
if these Drugs are not effective than Digitalis are given.

① Left ventricle systolic failure
② Heart failure + Atrial fibrilation

Digoxin not used in
- Rt-ventricle failure
- Diastolic failure

Heart Failure + Atrial fibrilation Detail

atrial fibrilation is not dangerous as ventricles only fills 20% by atria

in atrial fibrilation the electrical activity in atria is ↑350/min, many depolarizing wave hitting AV-node at high frequency and irregularly.

all this increase electrical activity from atria should not pass to ventricle, so the ventricular Tachyarrythmia not occur.

In fibrilation atrial electrical activity increases but mechanically atria fail to contract cardiac output is still maintained by ventricles.

1st we need to ~~[illegible]~~ relive atrial fibrilation
If we doesnit do this than we need to inhibit AV-node
So that ventricles are protected from atrial activity.
So that atrial fibrilation doesnit participate ventricular Tachyarrythmia

* in this case digitalis is best drug, As digitalis increase vagal tone to AV-node, & inhibit AV-node to donit allow it to pass much impulses.

* Heart failure compensated by its +ve inotropic action. and for atrial fibrilation it cause inhibition of AV-node through vagus & desed passage of impulses.

Atrial Flutter + ventricular Tachycardia

250—350 b/min

Digoxin → Atrial fibrilation (>350 b/m)

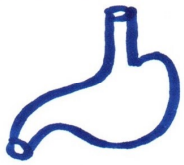
When we give Digoxin the atrial flutter change to Atrial fibrilation while ↓ ventricle Tachycardia so it is good to controle ventricle rate

180 b/min

Digoxin → b/c inhibit AV-node

↓ Responce rate in ventricle decrease 80 b/min

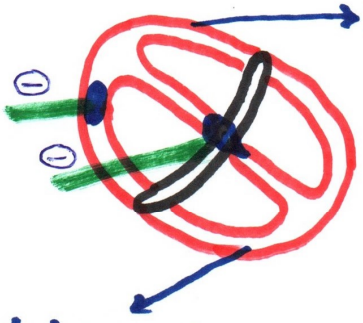
side effects of Digoxin

① GIT  ANV (Anorexia, Nausea, vomiting)

② Cardiac

Vagus inhibit SA & AV node

Indirect effect of Digoxin



→ Stimulate atrial myocardium
- electrically
- Mechanically

} & Cause
- → Atrial premature beat
- → Tachycardia Atrial
- → Atrial flutter → Fibrilation

Stimulate vent. Myocardium
- → electrically
- → Mechanically

} & Cause
- → ↑ ventricle premature beat
- → ventricular Tachycardia
- → ventricular flutter
- → ventricular fibrilation

Atrial premature beat

* too much inhibition of SA-node produce →
  - → sinus bradycardia
  - → sinus arrest
* too much inhibition of AV-node produce → Nodal block or junctional block or Heart block.

NOTE

normally impulse moving from atria to ventricle is delayed only for 0.1 second

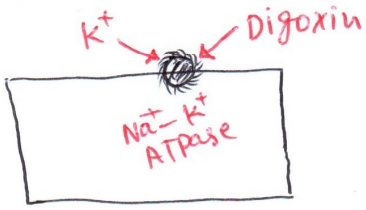
- 1° heart block → every impulse from atria pass to ventricles but with undue delay
- 2° heart block → Some impulses from atria pass to ventricles but some are aborted (failed).
- 3° heart block → No impulse pass from atria to ventricles.

In III° heart block we need artificial pacemaker (pacing of heart)

③ CNS side effect

(i) Fatigue
(ii) headach
(iii) Confusion (person is disoriented in time, person & place).
(iv) Delirium (Acute hyperactive confusion)
(v) Blurred vision (due to cilliaris muscle ANS disturbance)
(vi) Yellow vision
(vii) Micropsia (things are seen very small).
(viii) Macropsia (" " " " large).

Conditions which predispose to Digoxin Toxicity



K^+ & Digitalis compete at K^+–Na^+ ATPase

Normal level of K^+ = 3·5 – 5·5 meq/L

① Hypokalemia: As both compete for receptor if $\downarrow K^+$ so even this normal amount of Digoxin will cause over stimulation of cell by loading with Ca^+, so Digitalis Toxicity will occur & ventricular Tachycardia occur.

Why hypokalemia occurs?

Because as these patients are already heart patient & taking Diuretics (specially loop diuretics), so these are K^+ wasting, so more K^+ loss in urine & if at same time Digitalis are given, Digitalis toxicity occur.

K^+ Level is maintained by giving K^+ sparing Diuretics specially → spirinolactone, & by giving K^+ we must have to maintain K^+ level b/c it is so dangerous.

② Hypomagnisium: alot of Mg^+ are lost in vomiting & Digoxin Toxicity occur

③ Hypercalcemia: ↑ Ca^+, ↑ loading of cell with Ca^+ by Digitalis, so digitalis toxicity occur.

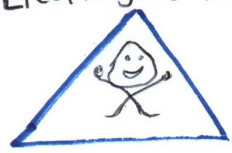
④ β1 Adrenergic receptor Stimulants: (Sympathomimetic activity)

e.g: ⓐ Dopamin ⓑ Dobutamine ⓒ Epinephrine ⓓ Nor-Epinephrine.

these drugs also cause Ca^+ loading in cell, so these along with Digoxine increase its toxicity.

⑤ Myocardial Ischemia: myocardial cell membrane is when destryed, alot of Ca^+ move into it + Digoxin so its toxicity occur.

Digoxin Should not be given in these Conditions



other drugs which should not be used with digoxine e.g
- → Quinidine (↓ renal clearance of Digoxin)
- → Amidarone
- → verapamil

These drugs displace digoxin from plasma protein, so Digoxin level become higher & Digoxin Toxicity occur.

NOTE

before giving Digoxin we must have to check the above electrolytes

How patient with Digoxin Toxicity is Managed?

① Stop Digoxin

② Check Serum electrolytes → K^+, Mg^+, Ca^+

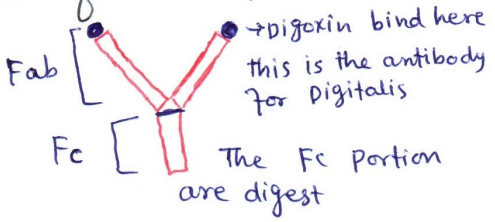
③ Antarrythmic drugs → Phenytoin, Lidocain

They reduce generation as well propagation of action potential.

④ Pacing or Atropine for III° heart block.

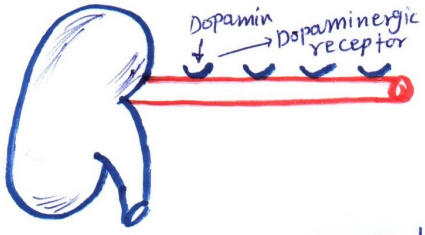
⑤ Digibind (Antidote of digoxin):

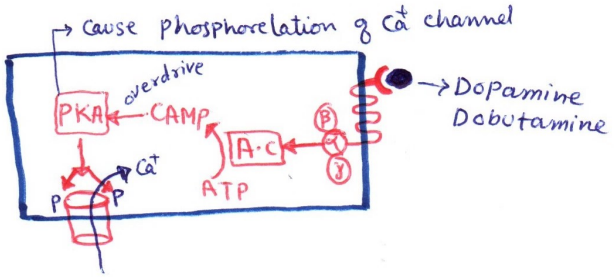
Digoxin have long half life than Digibind, so we have to use it again & again upto toxicity disappear.



Other Inotropic Agents → BA-agonist, PDE-I (Parentrally)

① β-Adrenergic Agonist → Dobutamine (β_1), Dopamine (D, β_1, α_1)

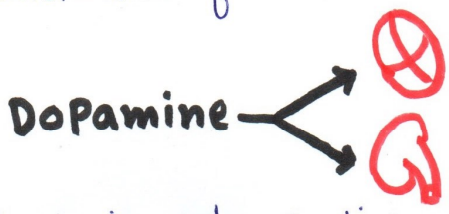




Dopamine cause renovascular dialation, & ↑ renal blood flow.

→ Dopamine is best in patient with cardiac failure + Hypertention.

→ Patient with hypotention have more chance of renal failure b/c of venoconstriction of renal vesseles.



If there is only cardiac failure we use Dubotamine.

β-adrenergic agonist are given in:

① Post cardiac surgery (b/c after heart surgery heart contract poorly)

② Post. MI → Shock (Patient leading to shock after MI)

③ Interactable heart failure (ie: refractory heart failure)
↳ e.g: patient have to transplant heart after 2week, we maintain heart in these 2weeks by β-A agonist.

② Phosphodiesterase Inhibitors (PDE-I) → Amrinone, Milrinone

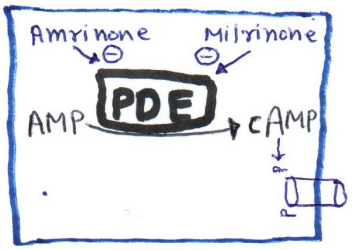
The drugs are not used for long term, b/c ↑ the mortality.

These drugs inhibit PDE enzyme & its associated action.

* These drugs are only given when Dopamin & Dobutamin fail.

→ Digoxin (orally)

→ other Inotropic are (Parentrally)



END OF CHF Drugs

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