Diuretics

- **Among First-line therapy of heart failure**
- **Role in HF:**
- 1- Remove the signs and symptoms of volume overload (pulmonary congestion/ peripheral edema).
- 2- Reduce salt and water retention (Natriuresis)→↓ventricular preload and venous pressure.
- 3- Reduction of cardiac size →improve cardiac performance
- Loop diuretics – **furosemide:** most powerful and used for most patients
- Thiazide Diuretics- less effective but indicated in patients with hypertension and mild fluid retention: chlorthiazide, hydrochlorthiazide
- **Side effects of diuretics**: metabolic alkalosis, electrolyte imbalance (hypokalemia) and hypovolemia
- **N.B. Diuretics do not improve the mortality rate in patients**

K^+ Sparing Diuretics (aldosterone antagonists)

Mineralocorticosteroids

MRI

The most famous one

•Spironolactone, triamterene, amiloride are weak diuretics-for achieving volume reduction with minimal K^+ loss

•**Advantages of spironolactone**:

•1- Preserve K: prevents hypokalemia

Most precious intracellular ion is the potassium

•2- Decreases mortality in cases of sever HF

•3- Reverse aldosterone-induced remodeling

High reverse

Antagonise the aldosterone

•Dose: one tablet lasilactone 50 mg in the morning 5 days a week

Low diuritic so cant be used alone

Thats why we use this extra

2 days free due to the hypovolemia

Side effect= gynocomisine

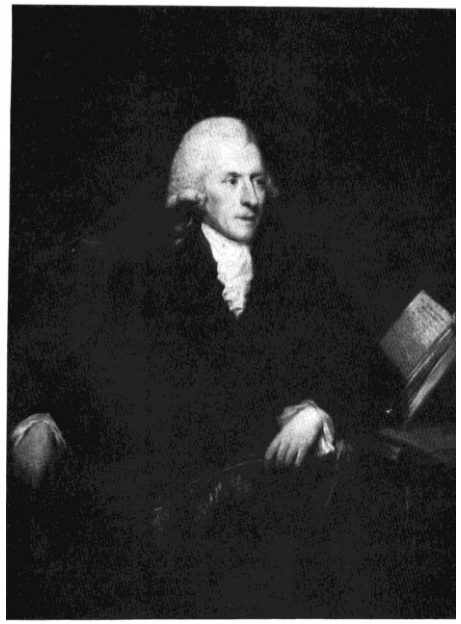
Drugs That Increase Contractility

Inotropic Drugs

- **Cardiac glycosides:**
- Digoxin, digitoxin Or digitalis
- **Phosphodiesterase inhibitors:**
- Amrinone , milrinone

Inotropic Drugs

- **Cardiac glycosides: Digoxin**



William Withering 1785

Foxglove plant

Not the first line

High toxicity

Theraputic dose

0.5 to 2 nanogram

2.1 toxicity ventricular arthymia that may cause death

Beneficial Effects Of Digoxin In HF

No adverse effect ether death or life

•**(Increasing the contractile force of the cardiac muscles)**

•**This effect is manifested in patients with heart failure, this results in:**

•1- **Increased C.O.P**: **increasing renal blood flow**

No renin or aldosterone

•(inhibition of RAAS): decreasing systemic & pulmonary congestion

present in the CNS & KIDNEY

•Diuresis: relief of edema

Best diuretic in the heart although its not a diuretic

•**Inhibition of central sympathetic stimulation**: normalization of BP

•**Improving tissue hypoxia**

•2- **Bradycardia:** diminishing tachycardia: increasing filling time: ↑COP

No permeant damage is the condition !!!!!!!!

•3- **Decreased heart size**

يعني ما لازم يكون القلب فيو أثر مرض مزمن واتوقع انه يرجع للحجم الطبيعي

Mechanism Of Action Of Digitalis

Although its also in the renal and CNS but more concentrated in the heart

Digitalis concentrated in myocardium 15 folds more than in other tissues

DIGITALIS ACTION

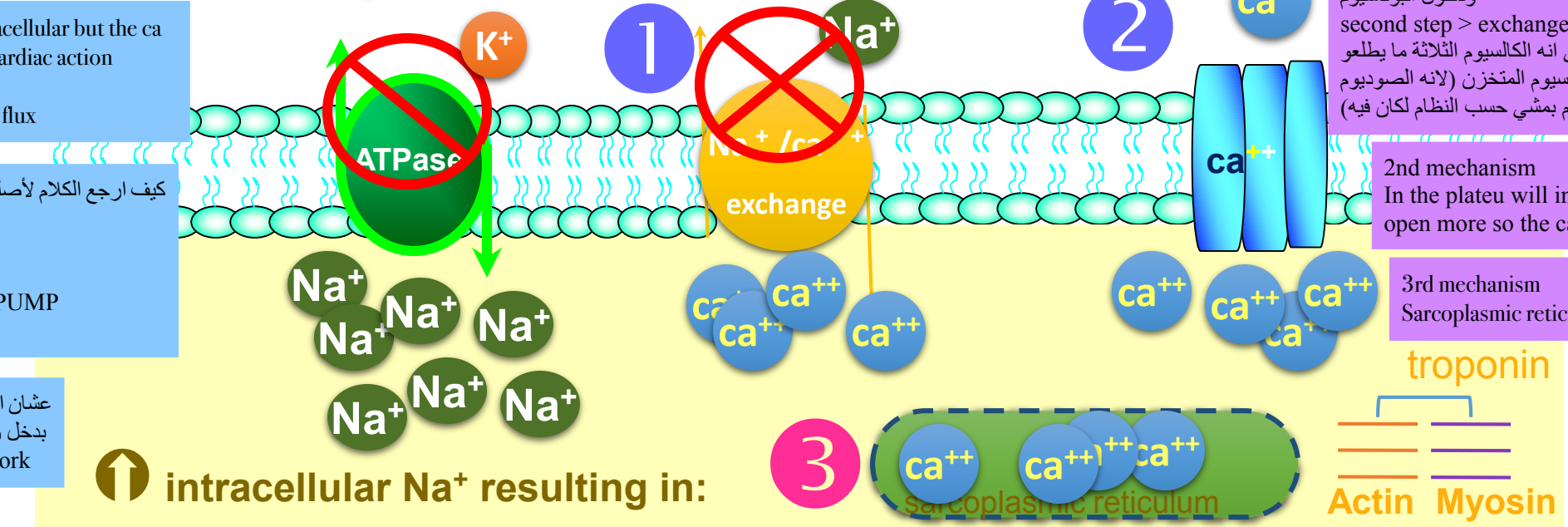
Digitalis Normally

Inc contractility by the ca intracellular but the ca is with na and k that work in cardiac action potential: normally in the AP
>> na influx - ca influx - k out flux

كيف ارجع الكلام لأصله بالوضع الطبيعي بدون digitalis
- na extracellular
- K intracellular
- Ca extracellular

BY THE NA-K ATPASE / PUMP
دخلت بالساهل بس الخروج اصعب

عشان اصلح الاوضاع كمان شو بسوي ؟
بدخل وحدة صوديوم وثلاثة كالسيوم برا
then the exchanger will work



The aim is to enter the largest amount of ca inside
First step > to block na-k atpase منعت خروج الصوديوم ودخول البوتاسيوم
second step > exchanger blocked
حافظت على انه الكالسيوم الثلاثة ما يطلعو بصير الصوديوم يخبط الكالسيوم المتخزن (لانه الصوديوم معصب انه ما عم بمشي حسب النظام لكان فيه)

2nd mechanism
In the plateu will increase the ca channels to open more so the ca will enter more

3rd mechanism
Sarcoplasmic reticulum to release calcium

intracellular Na^+ resulting in:

Force Of Contractility

Through the calcium increase

Ca intracellular
Is the net result in the digitalis

If toxicity happened we give the patient K supplement

Digitalis Mechanism Of Action

Its partial inhibition

If its complete will cause death

Who controls the partial?
- the potassium

VERY IMPORTANT TO BE CAREFUL IN CASES OF RENAL FAILURE OR HYPOKALEMIA

- **Digitalis increase intracellular free Ca+2 in CARDIAC CELL**, during systole .
- **Ca+2 inhibits troponin (relaxing protein):**
- Facilitates excitation -contraction coupling between actin and myosin leading to increased cardiac contractility.

Depolarising state without complete depolarisation
- so we fix it with the doses

By the k

- N.B. Digitalis inhibit Na+/K+ ATPase by competition **with K+** , So **hypokalemia increase Digitalis toxicity** , while K+ administration improve toxicity of digitalis.

Due to its action it will interrupt the heart ECG, automacity and contractility due to the intracellular na.

- In therapeutic dose leads to **partial inhibition** of Na^+/K^+ ATPase enzyme

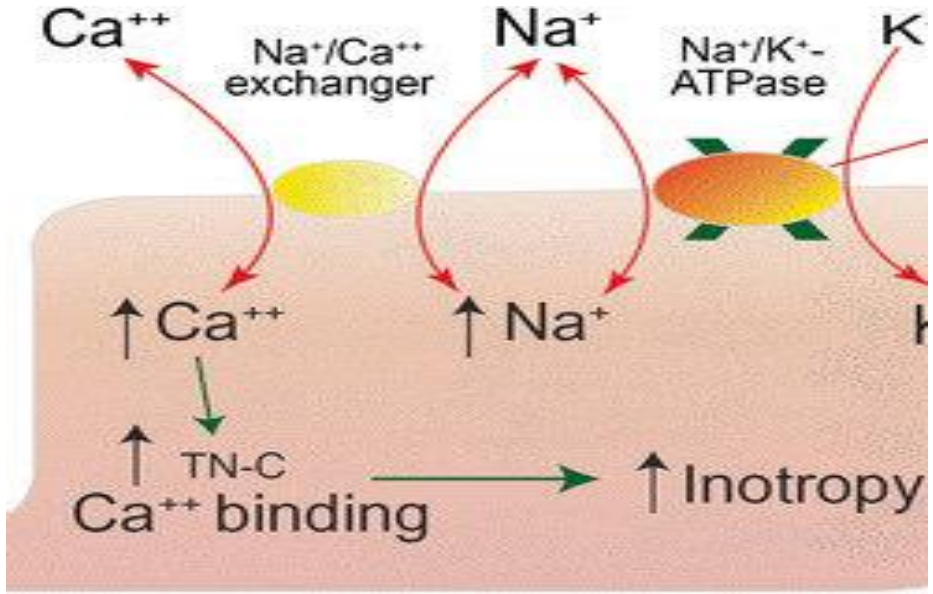
Should take with the digitalis high food with potassium like :
- banana
- Tomato juice
- Spinach

Pump :
بنعاكس اشي طبيعي
gradient عكس ال

The antagonise of the digitalis IS THE K ION

Digitalis increase intracellular free Ca+2 in cardiac cells by :

- **1- Inhibition of membrane bound Na+ K+ Atpase enzyme**: ↑ increasing intracellular Na+ → ↑ increasing free intracellular Ca+2
- **2- Digitalis may directly facilitate the entry of Ca+2 into cardiac cells during the plateau of the action potential.**
- **3- Digitalis may increase the release of stored Ca +2 from the sarcoplasmic reticulum.**



Pharmacological actions

CARDIAC

- Contractility: ↑force of contraction & Cardiac Output: +ve inotropic
- ↓ Heart rate : - ve chronotropic: vagal stimulation: by direct and indirect mechanisms

Bradycardia

- Conductivity: - ve dromotropic↓ CV in AV node

Spontaneous depolaraisation

- Increased automaticity: ectopic foci
- Increased excitability: arrhythmia
- Rhythmicity: disturbed

More than one base-makers

بؤر غريبة بالقلب بس هي طبيعية مو اشي سام للدوا

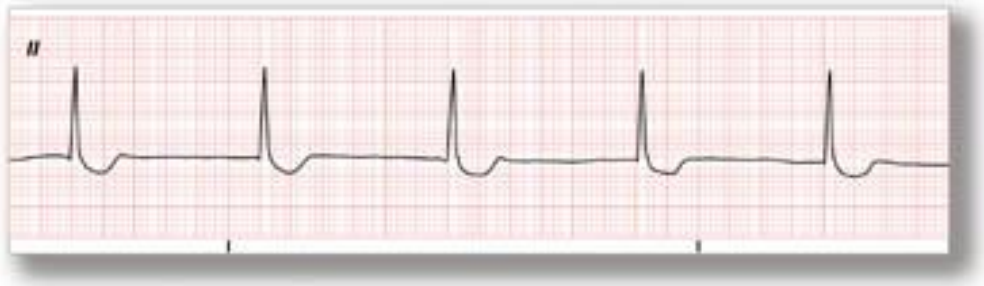
EXTRA CARDIAC

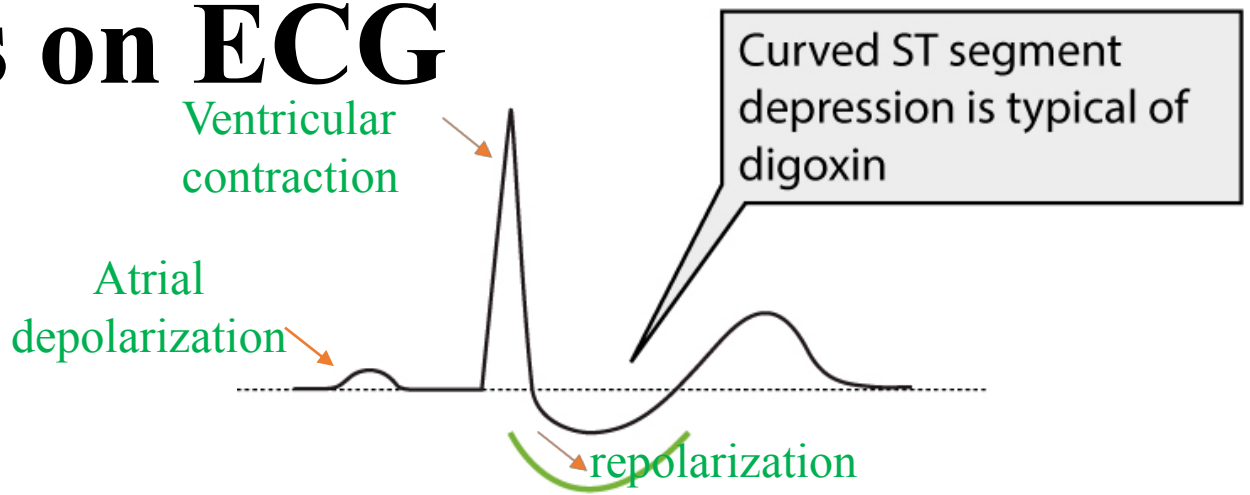
- Kidney:
- Due to improvement in circulation and renal perfusion
- Retained salt and water is gradually excreted
- CNS:
- Nausea, vomiting

ve inotropic+ كيف هو
And -ve chronotropic
؟؟

By the direct and indirect action of SA nodes by the vagal tone

Digitalis effects on ECG





- ECG: not indicator of toxicity but indicates treatment with digitalis.
- 1- Prolongation of P-R interval
- 2- High R wave
- 3- Depressed S-T segment
- 4- Inverted T- wave
- 5- Bradycardia
- 6- Any type of ahrrythmia: pulsus bigemini or trigemini

slower conduction

Ion distributoion is not well organised

+inotropic and high contraction

Inc oxygen consumption by the ventricles

The mens mostach

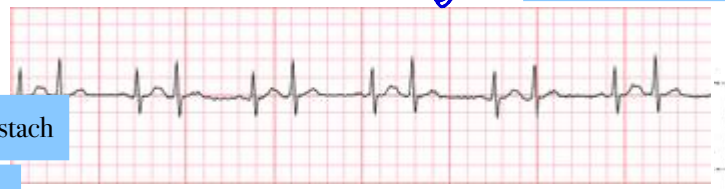
Incomplete repolaraisation

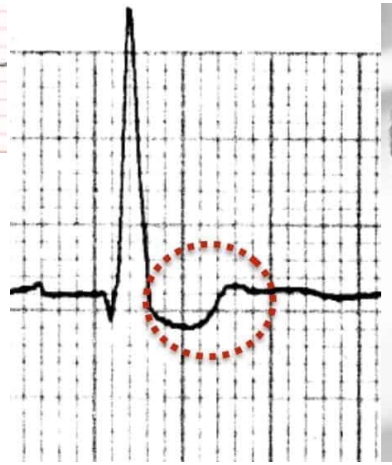
Far away peaks from each other

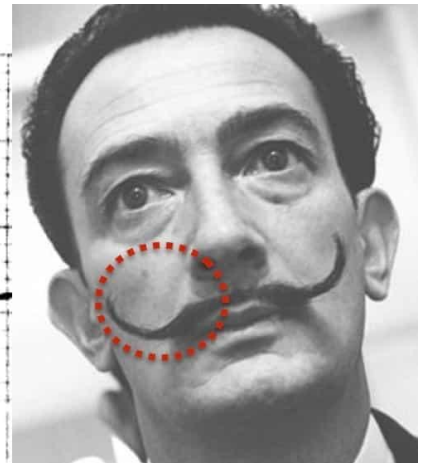
ثنائي الضربات

Due to ectopic foci

Down to up







Clinical Uses Of Digoxin

Dec preload
Dec afterload
!!! before giving the digitalis factors اصلح ال

•**1- Congestive heart failure: mild to moderated cases of HFrEF (less than 40%) who do not respond to other medications.**

•**2-CHF associated with Cardiac arrhythmias:**

- Atrial fibrillation

بحاول اخلي ال rate العالي لفوق ما يوصل لل ventricle

Differ in their rate

- Atrial flutter
- Paroxysmal supraventricular tachycardia

•**DOSE**: Lanoxin tablet 0.25 mg once in the morning after breakfast 5 days/ week

•**Sever HF**:

•**Loading dose**: **2 tab. Twice daily for 2 days** or **2 tab, thrice daily for 1 day**

Half life of digoxin 48h

•**Then maintenance dose**

Contraindications

Absolute

- 1- Heart block
- 2- WPW syndrome
- 3- Hypertrophic obstructive cardiomyopathy
- 4- Ventricular arrythmia

Atrial and ventricle linking is blocked

Extra bundle in the ventricles
In the accessory of the bundle has conductivity highest than the normal so it will dec the normal conductivity

congenital anomly of the heart that enlarge in the heart walls (hypertrophy) > more contraction > pressure on the aorta > faint > no enough blood reached to the brain
When the child do sports might faint

Relative

Sick sinus : Fainting to the least external pressure

- 1- Bradycardia: beta blockers, verapamil, myxedema, sick sinus syndrome
- 2- Systemic or pulmonary hypertension
- 3- Renal and hepatic impairment
- 4- DC cardioversion
- 5- MI
- 6- Acute myocarditis of rheumatic fever

Hypo function in the thyroid

Disorganise the ions

Necrosis
With the drug may rapture due to high contractility

Drug interactions of digitalis

The patient will have Dyspepsia
Gastric distress
With congestion

To lower the blood lipid

- **1- Antacids, cholystramine**: decrease digitalis absorption
- **2- Atropine**: increases digitalis absorption while metoclopramide decrease

Antispasmodic by the parasympathetic effect

Dec mortality of GIT

Opposite to atropine
Prokinetic drugs
Increase motality
For nausea and vomiting

- **3- Quinidine**: decreases digitalis clearance

Anti arrthymitic

- **4- K- losing diuretics**: increase digitalis toxicity

Toxicity of digoxin

لما بوقت الرسام "فان دوخ" كانو بستخدموا الـdigitalis لعلاج الـepilepsy فبصير عندو مشاكل بالرؤية و colour vision.

ألوان الطيف الشمس الطبيعي هي green.
- دوا الفياجرا بكون Blue vision.

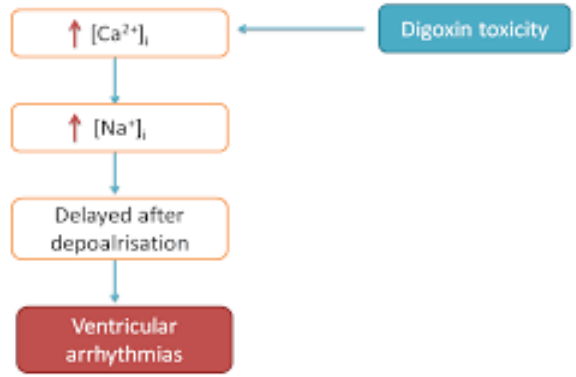
Extra-Cardiac

اذا شكى المريض منهم بوقف الجرعة تبعتله وبلبله يراجعني.

- **GIT**: Nausea & vomiting, anorexia (**first to appear**) Earliest.
- **CNS**: convulsions
- **Vision**: visual disturbances: halos, scotoma (رؤية من أنبوب), sudden loss of vision, yellow vision
- **Endocrine:** Gynaecomastia
  - steroids similar to androgens so will affect the androgens receptors.

Cardiac

- Bradycardia (first cardiac toxic sign)
- Pulsus bigemini
- Atrial flutter → fibrillation
- Ventricular extra-systole → tachycardia → fibrillation
- Partial heart block → complete block



Factors Increase Digitalis Toxicity

- Small (Lean) body mass
- Old age
- Renal diseases
- Hypokalemia
- Hypercalemia
- Drug interactions:
- Diuretics→ hypokalemia (arrhythmia)

- Quinidine : ↑plasma level of digitalis

Treatment Of Digitalis Toxicity

- **1- Stop digitalis**
- **2- Oral or parenteral potassium supplements**
- **3- For ventricular arrhythmias:**
  - Lidocaine IV drug of choice
- **4- For supraventricular arrhythmia:**
  - Propranolol may be given IV or orally
- **5- For AV block and bradycardia**
  - Atropine IM
- **6- Digoxin antibodies**: (digibind) **FAB fragment life saving: most spesific**

fractenated Anti bodies.

أحدث اشي لعلاج ال heart failure.

Ivabredine

لما يعمل congestion ولا volume over load.

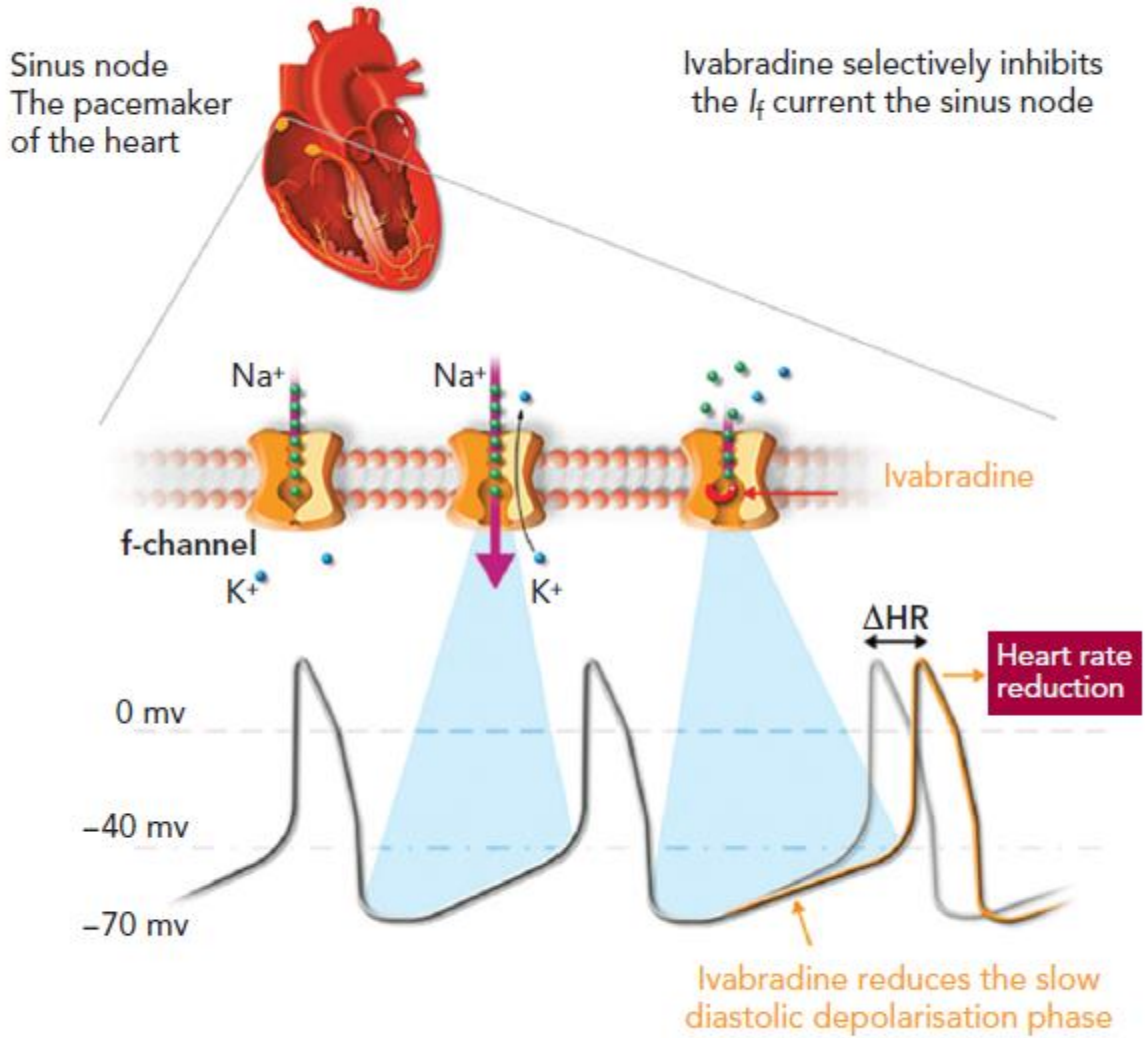
- **The First Selective and Specific I_f Inhibitor**
- Blocks the channel responsible for the cardiac pacemaker spontaneous firing (funny channel), I(f), which regulates heart rate.

بتخلي ال SA node تعمل spontaneous depolarisation ↓HR.

- Without affecting any other cardiac ionic channels (including calcium or potassium).
- This results in reduced heart rate.
- Indicated in patients of CHF not responding or intolerant to B blockers
- **Adverse effects:**
- Bradycardia, atrial fibrillation and phosphenes (vision disorder).

أضغط على ال eye pupil
واذا شفت ألوان بتصير
هالحالة.

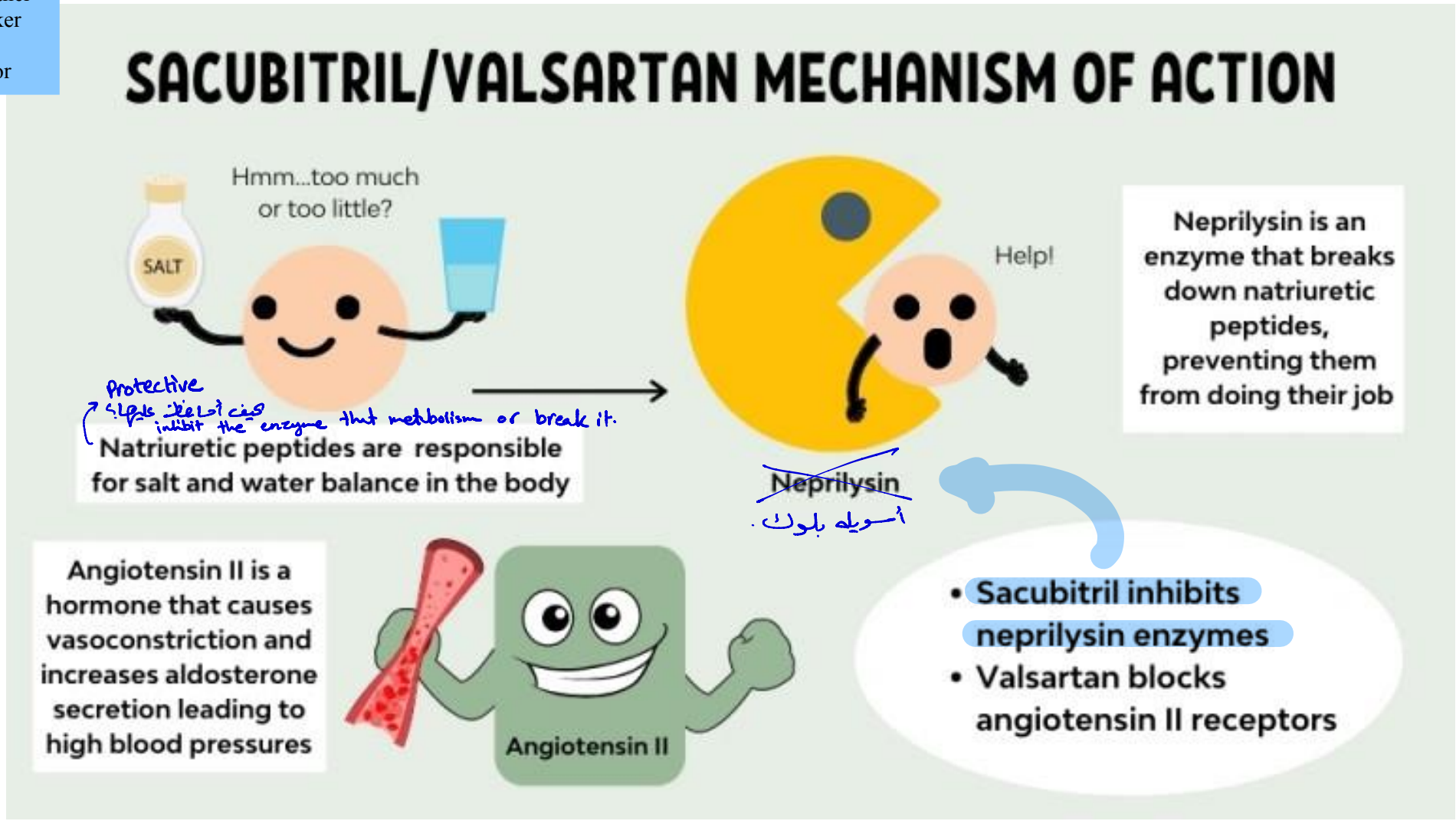
Figure 1: Mechanism of Action of Ivabradine



Source: http://www.shift-study.com/ivrabradine/mode-of-action/ Reproduced with the permission of Servier © 2016.

ARNI (angiotensin receptor/neprilysin inhibitor)

giving two drugs together
- angiotension blocker fmily of sartain.
- Neprilysin inhibitor

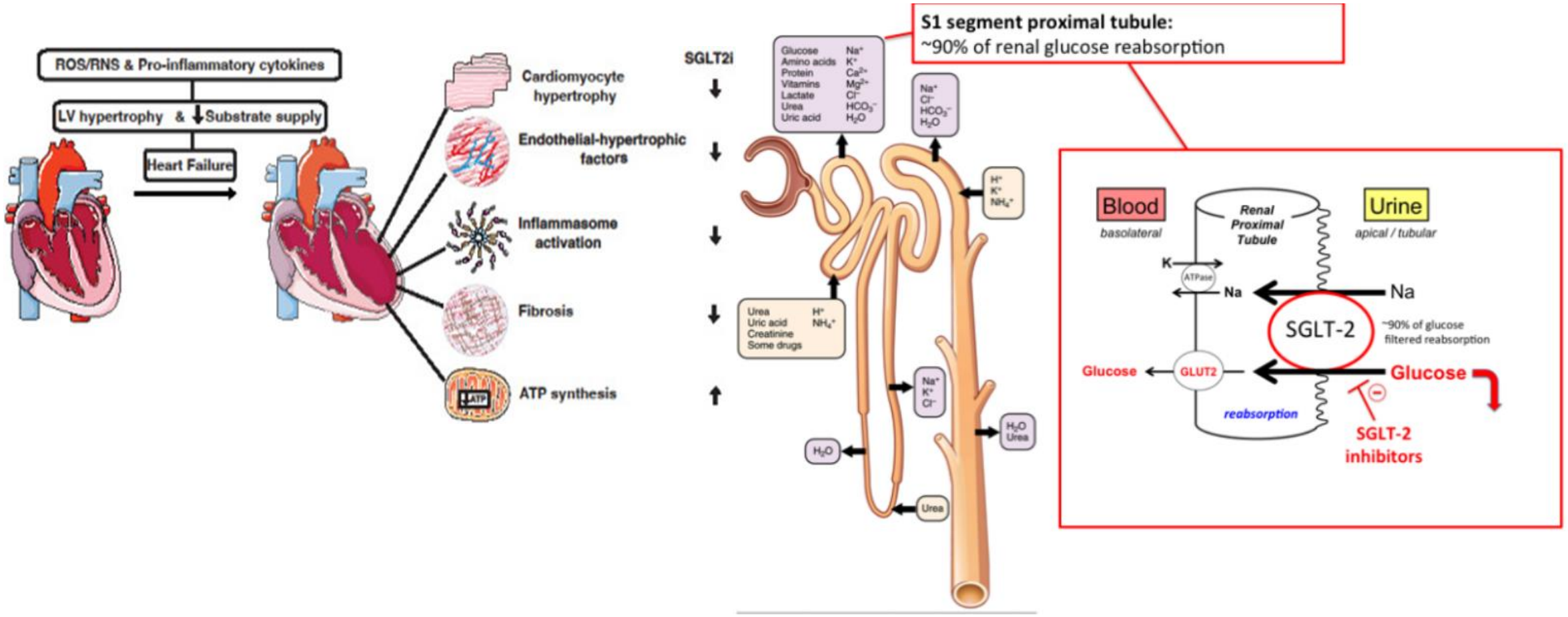


- **Adverse effects of Sacubitril-valsartan:**
- Hypotension, hyperkalemia and renal failure
- **Indications**:
- ARNI new class of drugs indicated in patients not responding to ACEIs or B blockers

SGLT-2 Inhibitors
Canagliflozin

- **Mechanism of Action:**
- **Inhibits the Na-glucose co-transporter 2 (SGLT-2)** in the kidney to reduce glucose reabsorption, resulting in increased urinary glucose excretion, and lower plasma glucose.
- **SGLT-2** is expressed in the proximal tubule and **mediates reabsorption of ~90% of filtered glucose**.
- **SGLT2 inhibition appears to underlie the ability of "gliflozins" to produce additional effects in the reduction of mortality and CV events in patients with heart failure.**

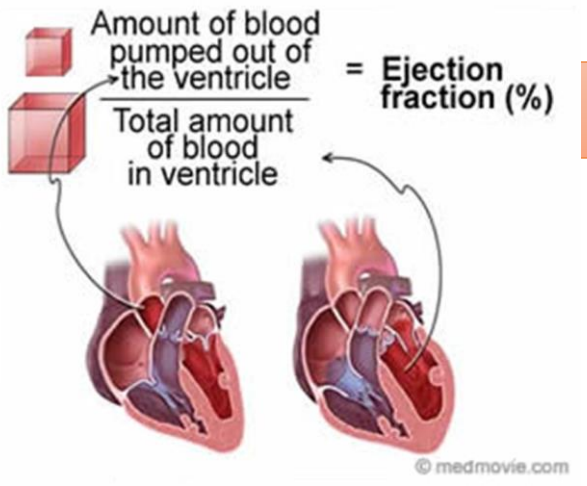
Mechanism of action& bebecicial effects of gliflozins in HF



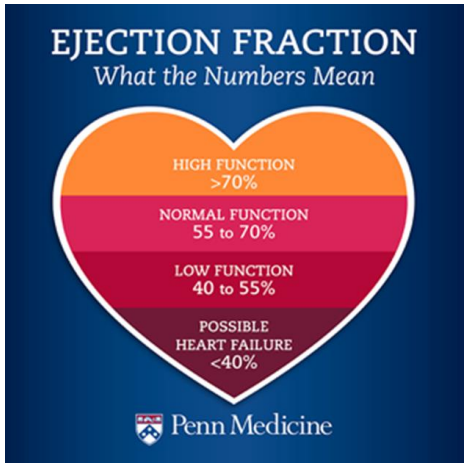
Management Of Chronic Heart Failure

- Lifestyle changes
- Drug therapy
- Surgery for correctable problems
- Implantable devices
- Heart transplant
- **Diet and lifestyle measures**
- Moderate physical activity, when symptoms are mild or moderate; or bed rest when symptoms are severe.
- Weight reduction
- Sodium restriction – excessive sodium intake may precipitate or exacerbate heart failure, thus a "no added salt" diet (60–100 mmol total daily intake) is recommended for patients with CHF.
- Stop smoking

Approach to the Patient with HFrEF



Assessment of LV function (echocardiogram)



reduced ejection fraction

EF < 40%

Volume overload + symptoms with reduced ejection fraction.
= first line → Duritics.

Assessment of volume status

Signs and symptoms of fluid retention

No signs and symptoms of fluid retention

no volume overload.

First Line

Diuretic

± digoxin → لو احتجت

ACE Inhibitor

β-blocker

Digoxin