Pharmacology - CVS

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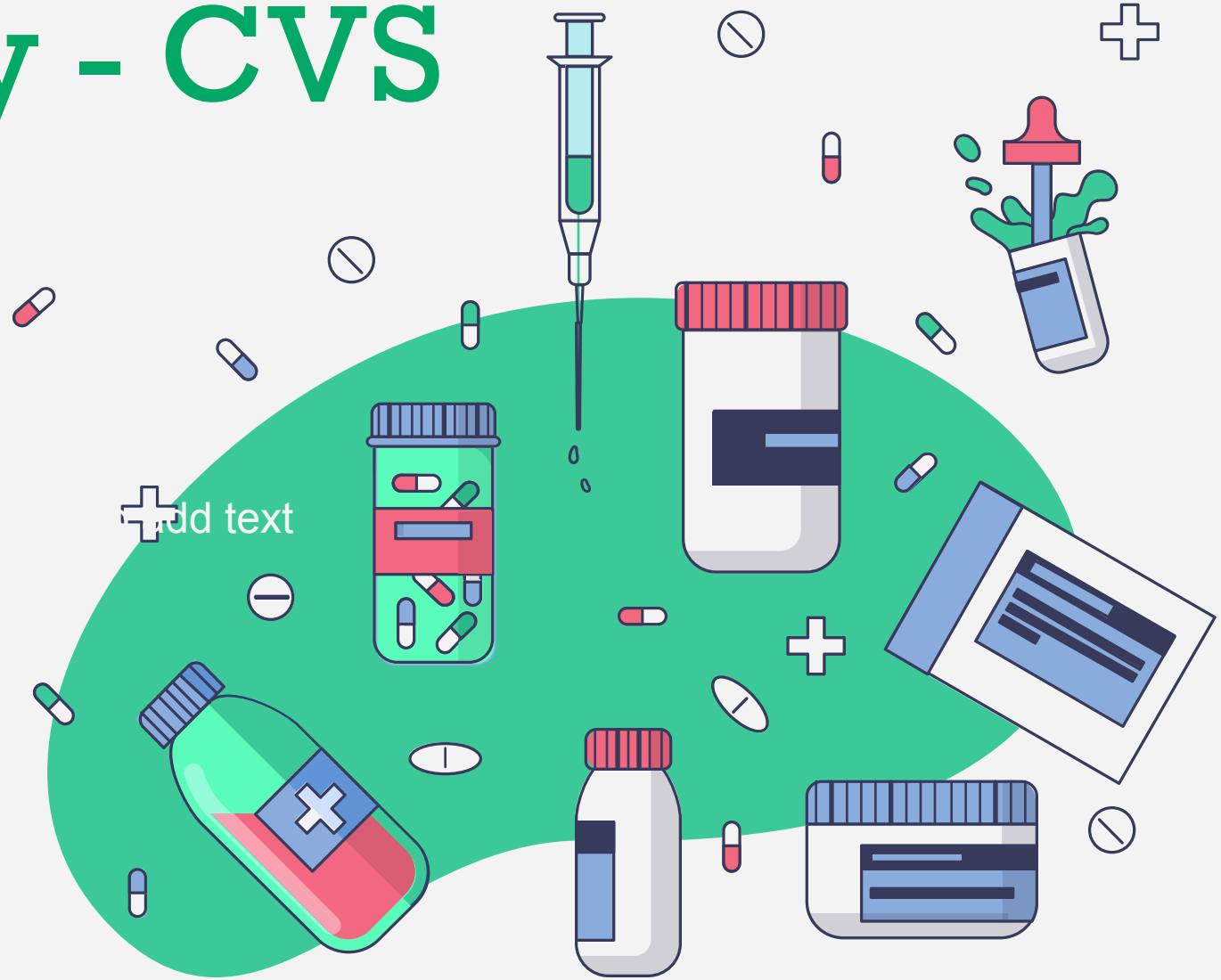

النادي الطلابي
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Drug Therapy of Heart Failure II

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Positive Inotropic Agents

Their use is contradictory to the use of β-blockers.

They stimulate cardiac contractility

- Logically will improve cardiac function.
- These drugs increase force of contraction by increasing intracellular cardiac Ca^{++} concentration.
- We have two types:
- **Cyclic AMP Independent Agent:**

  Digitalis

  They do not depend on cAMP to cause an inotropic activity of the heart muscle

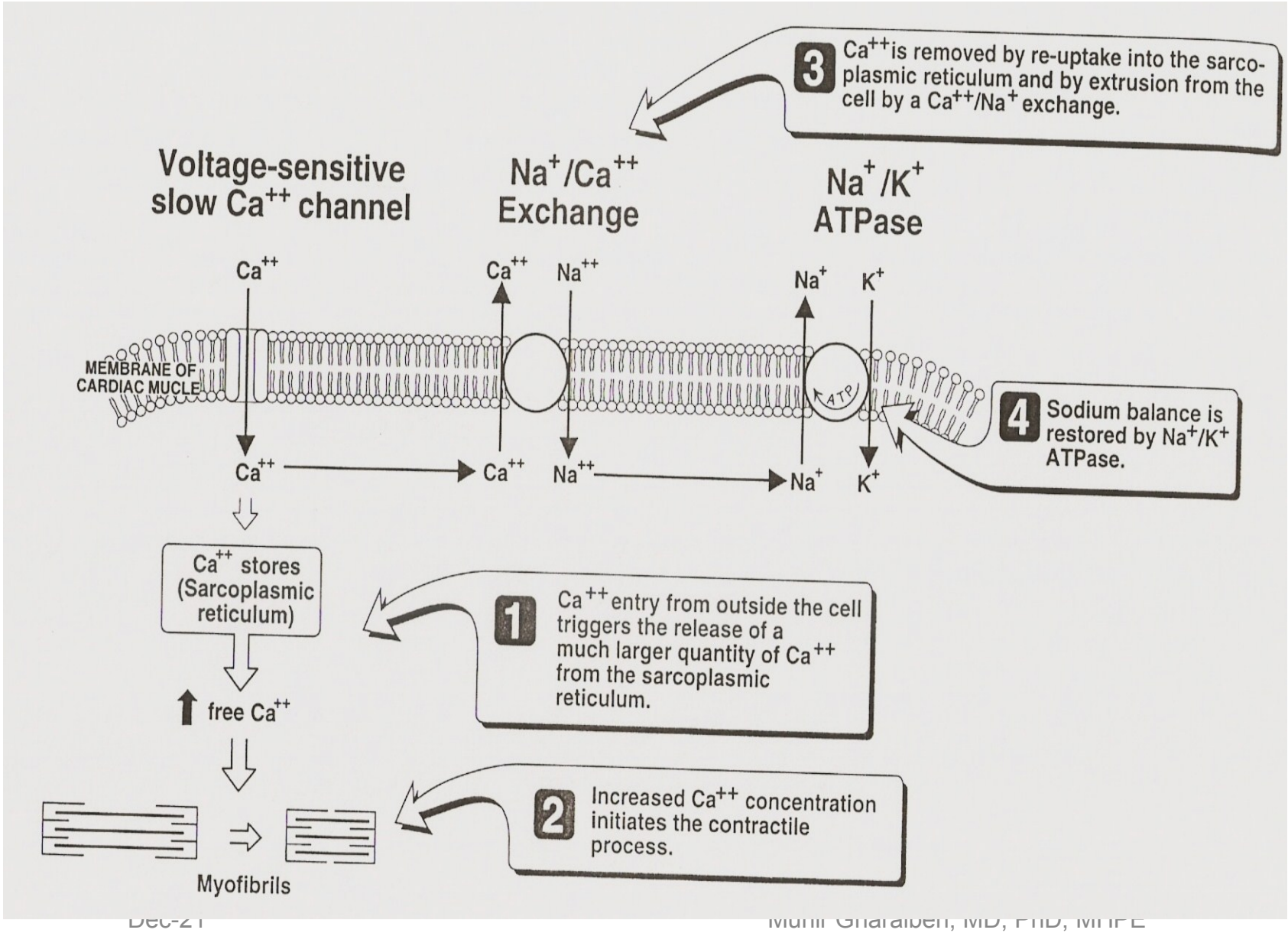
- **Cyclic AMP Dependent Agents:**

  β-adrenergic Agonists

  Phosphodiesterase Inhibitors

  These increase cAMP levels which is important for cardiac contractility

Role of Calcium and Sodium in Myocardial contraction



- Ca++ can enter through the calcium channels and it can also be exchanged with sodium through Na/Ca exchanger
- Na/K ATPase controls sodium entry
- The contraction of heart muscle depends on the interaction between myosin and actin filaments and calcium should be available for this interaction
- Calcium comes from outside as well as from internal stores, calcium from outside triggers the release of calcium from sacroplasmic reticulum
- And cAMP can release the calcium from internal stores

Positive Inotropic Agents

Cyclic AMP Independent Agent:

- **Digitalis: inhibits Na/KATPase.**

This pump is the mechanism which exchanges 3Na+ with 2K+ at the membrane of the cardiac muscle, it is not only present on the cardiac muscle , but it is available in most of the tissues in the body.
It takes sodium out.

Digitalis Glycosides

This drug was widely used throughout history to treat heart failure.

History:

- **Egyptians** got digitalis from **Squill(العنصل)**
- **Chinese** got digitalis from **Toad skin**
- **William Withering** ----- **Foxglove 1785**

And from this plant we extracted the active ingredient of digitalis which we use nowadays.

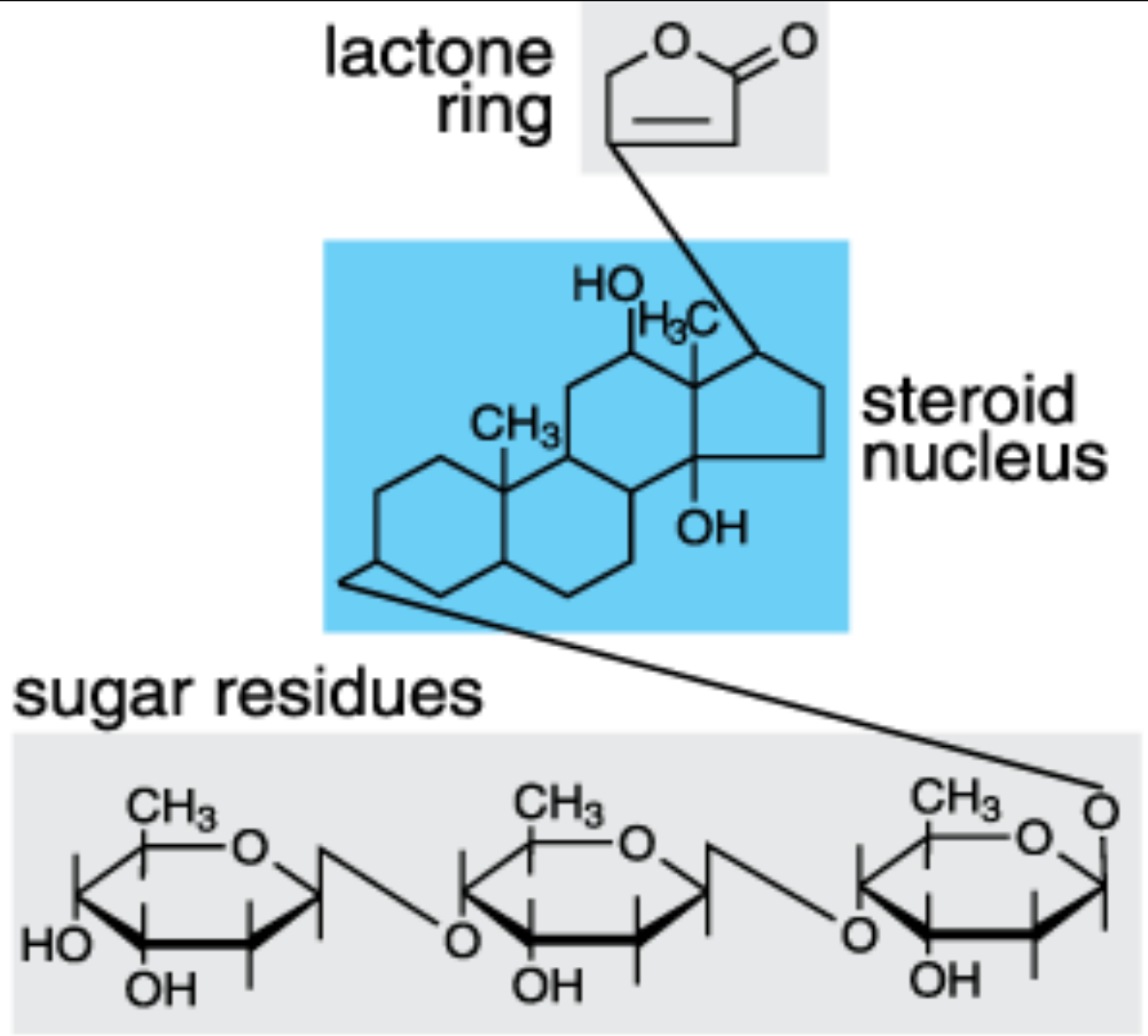
❖ We have different species of foxglove

- ***Digitalis purpura***
- ***Digitalis lanata***
- ***Strophanthus***

Digitalis doesn't work on the kidney tubules thus it doesn't have a real diuretic activity, but by enhancing the heart function, it leads to loss of fluids and relief of edema.

Foxglove

زهرة شبابنا



The active ingredient is a **glycoside**, meaning it's a group of sugar residues connected to a steroid nucleus that is connected to a lactone ring.

Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

Digitalis Glycosides

Mechanism:

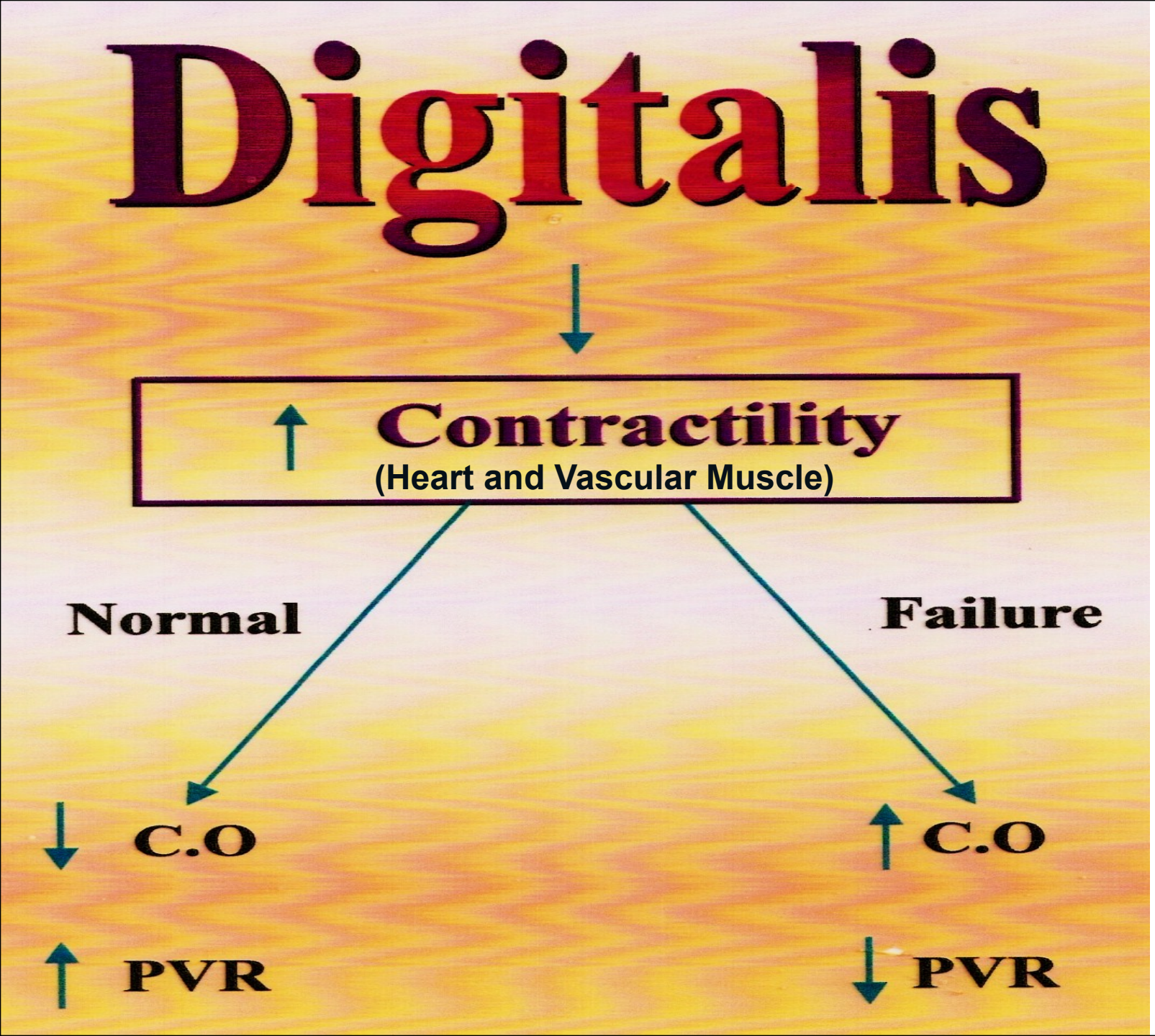
- **Inhibition of Na+/K+ ATPase**

Which will cause accumulation of Na+ inside the cell

Digitalis Glycosides

Actions:

- Positive Inotropic Effect
- Vascular Muscle Contraction — They cause contraction of all the muscles
- Vagal Stimulation — Which will cause suppression of the electrical activity of the heart
- Effects on Electrical Properties of Cardiac Tissues.



The main action is increasing the heart contractility (this occurs in all patients). But the effect of this drug differs according to the state of patients. In HF patients it causes an increase in CO and a decrease in PVR which is beneficial. However, in normal healthy people it was found to cause the opposite, decreasing CO and increasing PVR (not beneficial).

This is because, patients with HF have increased SNS activity which increases PVR to the maximum, where no further increase is possible. Giving **Digitalis** would increase the contractility and somehow upset the overactive SNS activity. Now, the inhibition of SNS will cause vasodilation, this will indirectly enhance the cardiac output, with increased contractility of the heart. Again, the blood vessels are dilated (PVR is reduced) therefore the CO (the flow) will be increased.

TABLE 13–2 Effects of digoxin on electrical properties of cardiac tissues.

Tissue or Variable	Effects at Therapeutic Dosage	Effects at Toxic Dosage
Sinus node	↓ Rate	↓ Rate
Atrial muscle	↓ Refractory period	↓ Refractory period, arrhythmias
Atrioventricular node	↓ Conduction velocity, ↑ refractory period	↓ Refractory period, arrhythmias
Purkinje system, ventricular muscle	Slight ↓ refractory period	Extrasystoles, tachycardia, fibrillation
Electrocardiogram	↑ PR interval, ↓ QT interval	Tachycardia, fibrillation, arrest at extremely high dosage

Very toxic

- It has direct and indirect effects:

- The indirect are mainly due to stimulation of the Vagus nerve which supplies mainly the atria and SA node only so cause suppression of the contraction of atria and the SA node electrical activity.

Direct effects occur with high (toxic) doses of Digitalis

- Increased PR is diagnostic of digitalis therapy

Digitalis Toxicity

The most important are the cardiac toxicities, but it can also cause other less serious ones :

- **G.I.T :**Anorexia, nausea, intestinal cramping, diarrhea.

Occur in most of patients 90%-100%, even with small doses.

- **Visual :**Xanthopsia, abnormalities in color vision.

a predominance of yellow in vision

As the doctor said نجوم الظهر

ما في نجوم ظهر الا اللي رح نشوفها بالفاينل ...هه يسعد مساكم

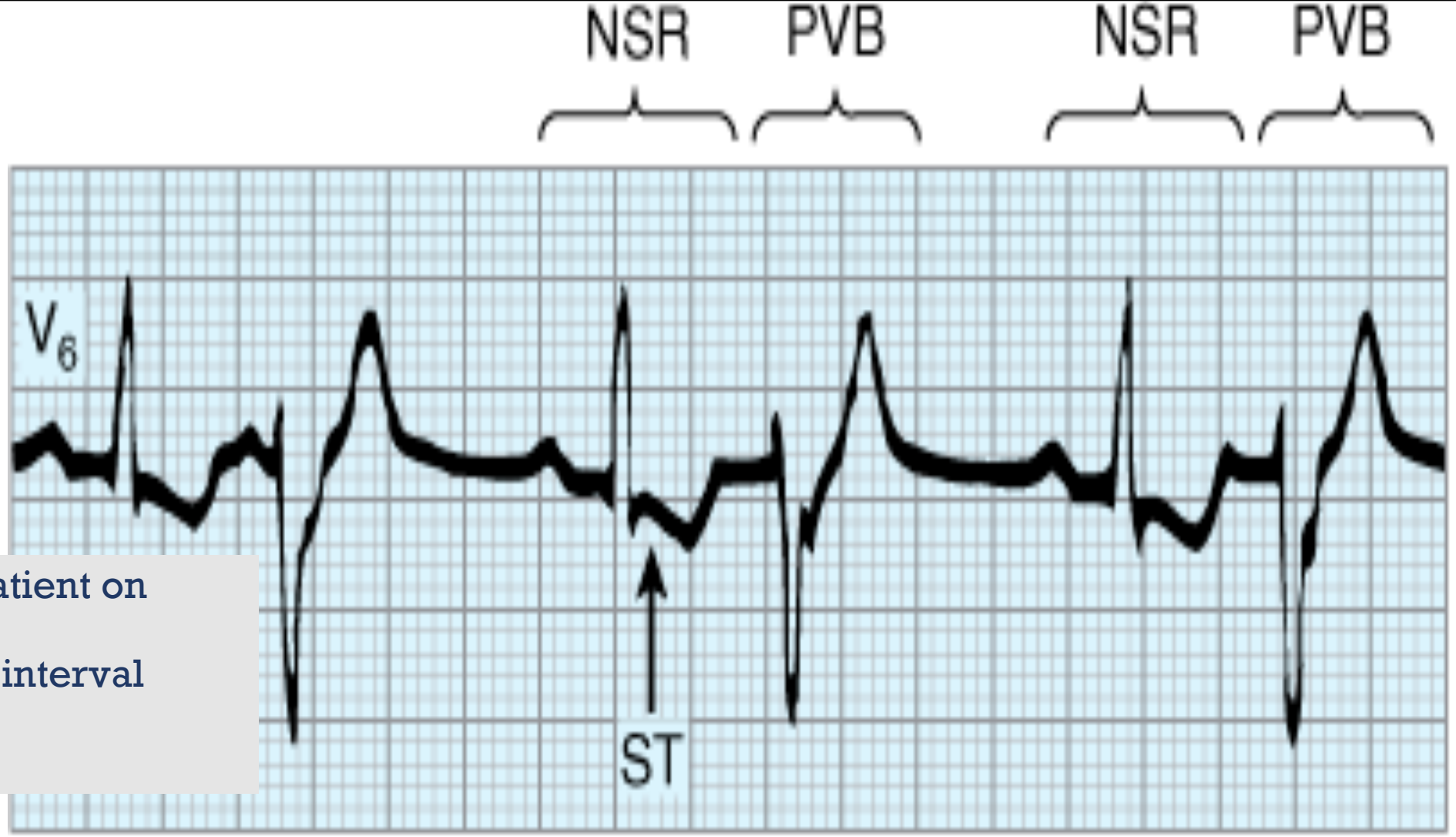
- **Neurologic:** Malaise, confusion, depression, vertigo
- **Cardiac:** severe bradycardia*, palpitations, syncope, arrhythmias, AV node block, ventricular tachycardia.

The effects on cardiac function might complicate the heart failure

Ventricular tachycardia might lead to ventricular fibrillation and could be lethal if not treated immediately

- **Interactions.**
- *Pharmacological and toxic effects are greater in hypokalemic patients.*
- *K^+-depleting diuretics are a major contributing factor to digoxin toxicity.*

Most diuretics cause sodium, potassium and water excretion



This is an ECG of a patient on digitalis, notice:
1. The increase in PR interval
2. ST depression
3. Extrasystoles.

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Digitalis Toxicity

Treatment of Toxicity:

- **Reduce or stop the drug.** If possible
- **Cardiac pacemaker for heart block.**
- **Digitalis antibodies (Digoxin Immune Fab).**

This is used as an antidote for people who are trying to commit suicide by taking digoxin.

- **Arrhythmias may be converted to normal sinus rhythm by K^+ when the plasma K^+ conc. is low or within the normal range.** Even if the K+ levels were normal, we should also give K+
- **When the plasma K^+ conc is high, antiarrhythmic drugs, such as lidocaine, phenytoin*, procainamide, or propranolol, can be used.**

strongly indicated in digitalis toxicity

In this case, we do not give more K+ and to treat the arrythmia associated with high potassium levels we use antiarrythmic drugs.

Digitalis Glycosides

Therapeutic Benefits:

- **Was widely used in the treatment of heart failure.**
- **Nowadays, use is restricted *only to CCHF with supra-ventricular arrhythmia.***

Because it will be successful in suppressing the atrial activity and the SA node. Otherwise it should not be used.

- **Might decrease morbidity and improve quality of life.**
- **Withdrawal might be hazardous.**
- **Does not improve mortality**

Will not increase the life span of the patient, but it might improve the quality of the life of the patient

Basic Data of Three Cardiac Glycosides

	Digitoxin	Digoxin	Ouabain
GI absorption	100%	70 –85%	0
Polarity	Least	Somewhat	Highest
Protein binding	97%	< 30%	5 – 10%
Half-life	4 – 7 days	1.5-1.6 days	21 hr
Excretion route	Stool and kidneys; as hepatic metabolites*	Kidneys; largely unchanged	Kidneys; largely unchanged
Enterohepatic recycling	27%	6.8%	Unknown
Optimum serum levels	20-35 ng/ml	0.5-2.5 ng/ml	Unknown
V_d	0.6 L/kg	5-10 L/kg	Unknown

* About 8% of digitoxin is metabolized and excreted as digoxin in the urine. Digitoxin seems to be largely recycled to complete its metabolic degradation.

This enhances the chance of drug-drug interactions with drugs which can displace digitoxin leading to higher unbound free molecules which can be toxic.

Ouabain has to be given I.V.

different excretion route, digitoxin is eliminated through the intestines while digoxin is through the kidneys, so in cases of renal failure we can use digitoxin.

These drugs must be monitored regularly.

This table isn't for memorization, just know the details mentioned above and that digoxin has intermediate activity , and it's excreted from the kidneys.

Positive Inotropic Agents

Cyclic AMP Dependent Agents:

β-adrenergic Agonists:

NE

Dopamine

Dobutamine

Expected to be good in heart failure, but not the first-choice drugs to treat heart failure

Phosphodiesterase Inhibitors:

Amrinone(withdrawn)

Inamrinone

Milrinone

Which will prevent breaking down cAMP and consequently increase levels of cAMP and increase the contractility of the heart.

There are 5 Phosphodiesterase isozymes, inhibiting each one has a distinct effect

Sildenafil: (PDE-5 inhibitor), not an inotropic agent

Or viagra : causes vasodilation of penile veins which treats difficulty of erection in males

Positive Inotropic Agents

Cyclic AMP Dependent Agents:

β-adrenergic Agonists:

All increase myocardial oxygen consumption, so not helpful for chronic use, may be used (IV) for short term or in acute heart failure.

NE:

Used in acute heart failure(cardiogenic shock)

Cardiogenic shock : severe drop in blood pressure after MI

but can cause severe vasospasm and gangrene

Which may lead to Amputation

Ep:

Used in cardiac arrest, and it is first line in anaphylactic shock

as a final resort in CPR, intrathoracic injection.

زي المسلسلات
يحيى ما رح يموت

Works better in young people with better functioning hearts

Positive Inotropic Agents

Dopamine:

Was widely used in cardiogenic shock but caused cardiac arrhythmias.

Replaced NE, because it causes gangrene

Low doses: stimulate DA_1 receptors leading to renal vasodilation and improved renal perfusion.

DA1 are present in the CNS and renal arteries (**α and DA1**) as wel used in impending renal failure.

Intermediate doses: stimulate β_1 receptors leading to positive inotropic actions.

Increase BP

High doses: stimulate α receptors leading to vasoconstriction and elevation of blood pressure.

Can cause arrhythmias and ischemic changes.

because of the increase in myocardial oxygen consumption.

both intermediate and high doses are used to elevate BP, in treatment of shock we use intermediate dose >> increase renal flow and BP then higher doses >> stimulate **α >> increase BP**

Dobutamine:

Nonselective β and α1 agonist, used intermittently (IV) in CCHF. Produces mild vasodilation.

Has more inotropic than chronotropic actions.

**Not used in cardiogenic shock

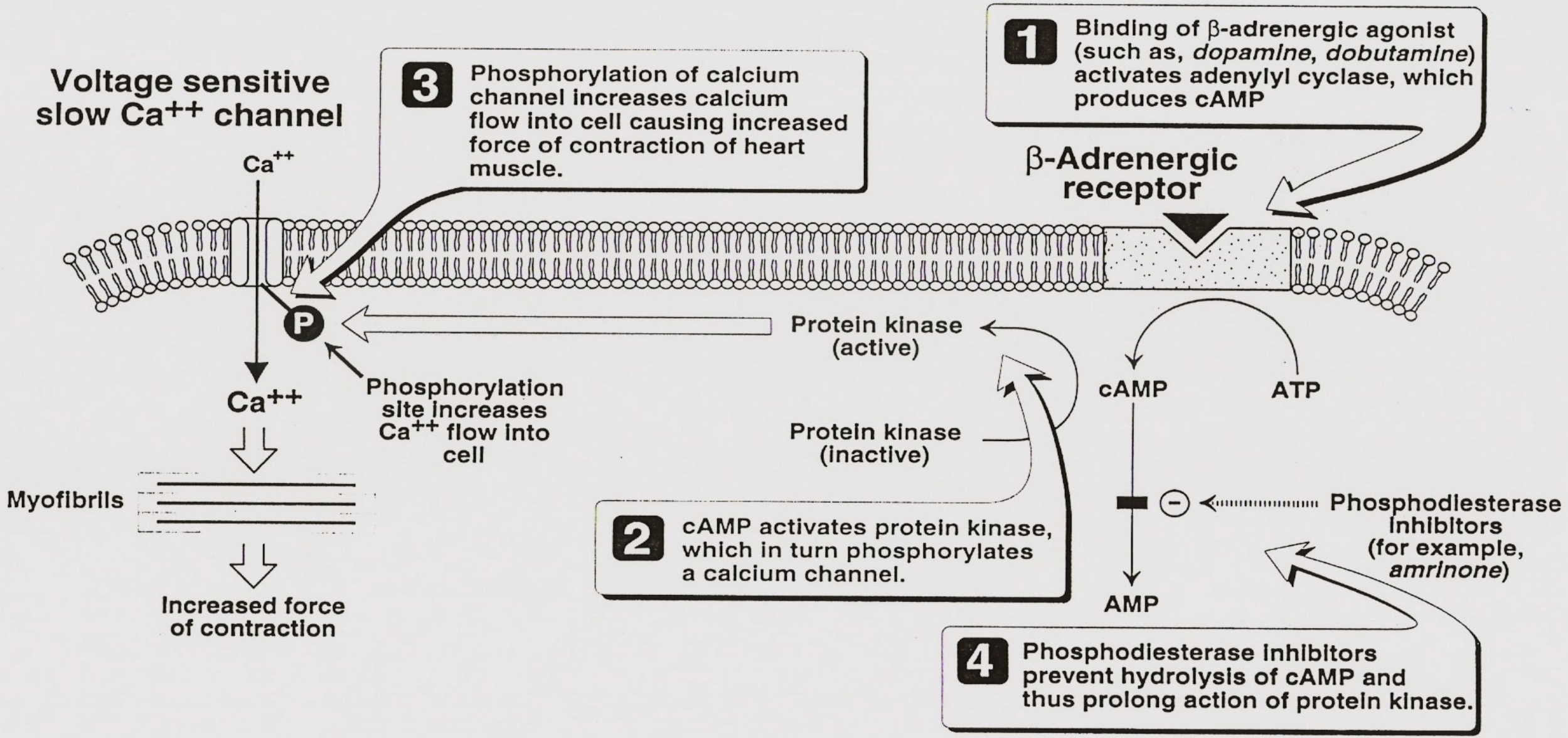


Figure 16.11

Sites of action of β-adrenergic agonists on heart muscle.

Positive Inotropic Agents

Phosphodiesterase Inhibitors:

PDE inhibition leads to accumulation of cAMP and cGMP leading to positive inotropic activity and peripheral vasodilation. Respectively

Toxic: arrhythmias, and thrombocytopenia.

Short acting, so reserved for parenteral therapy of acute heart failure.

Inamrinone (PDE-3)

Milrinone (PDE-3)

Vesanirone (PDE-3)

Vasodilators

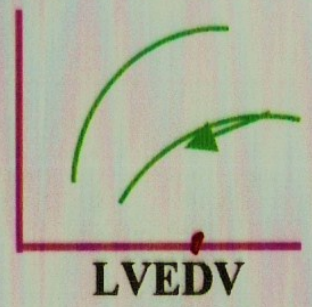
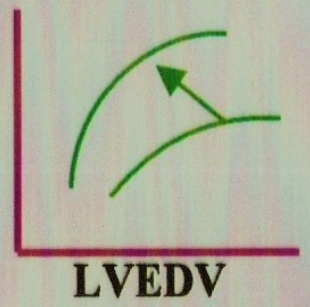
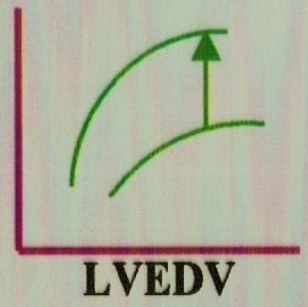
- **Affect preload and/or afterload without directly affecting contractility.**

We have 3 types, arterial, venous and mixed dilator

- **Consequently, can decrease myocardial ischemia, enhance coronary blood flow and decrease MVO2.**
- **Can be used in acute heart failure and for short periods in CCHF.**
- **Hydralazine** (an arterial dilator) **–Isosorbide dinitrate** (venous dilator) **combination was documented to decrease mortality in African americans, maybe by reducing remodeling of the heart.**
- **Can be combined with ACEI, diuretics and digitalis.**

they are not good for chronic use.

About the figure, The upper curves are healthy people, the lower curves are HF patients, and the arrow indicates the shift that occurs after taking the corresponding drug.

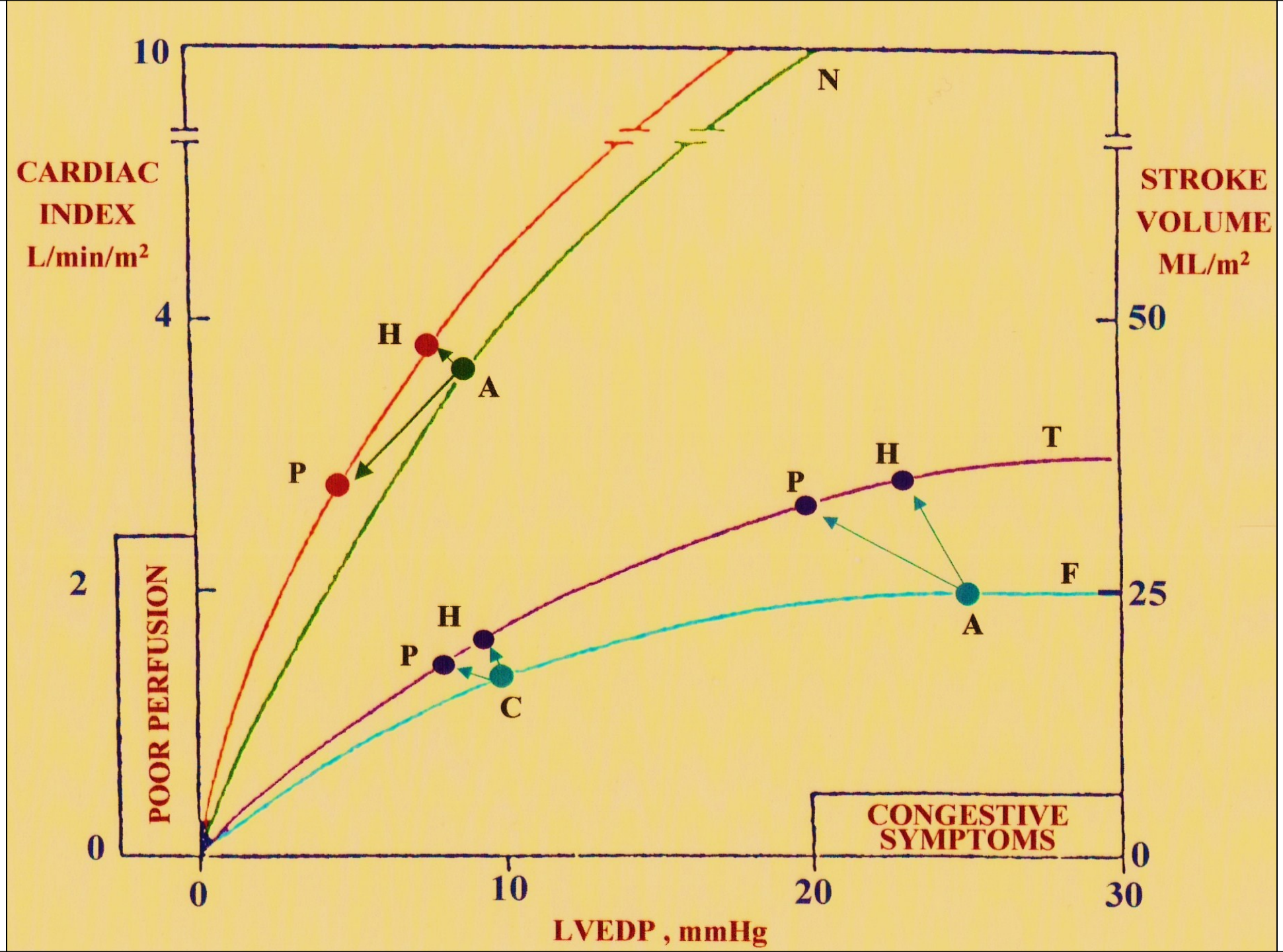
Venous Dilators	Mixed Action	Arterial Dilators
Nitroglycerin Isosorbide dinitrate	Nitroprusside Captopril Enalapril Hydralazine + Nitrate	Hydralazine Minoxidil
		
↓ LVEDV ↓ MVO2 — CO	↓ LVEDV ↓ MVO2 ↑ CO	— LVEDV ↓ MVO2 ↑ CO

Explanation of the previous diagram

Venous dilators will cause pooling of blood in veins which will reduce the burden on the right side of the heart. Causing decrease in left ventricular end-diastolic volume LVEDV and decrease in MVO2 but will not affect cardiac output. Unlike in healthy people, decreasing the venous return in HF patients will not affect the CO, because it decreases the congestive symptoms of heart failure (There is already an increased volume of blood [congestion])

Arterial dilators, don't affect the LVEDV, but they will reduce PVR and thus increasing the cardiac output CO, reducing the stress on the left side of the heart and improving organs' blood perfusion like brain , kidney , muscles

Mixed action drugs, will produce the two effects together reducing LVEDV, MVO2 and increasing CO.


10
4
2
0
CARDIAC INDEX L/min/m²
STROKE VOLUME ML/m²
50
25
0
N
H
A
P
T
H
P
F
A
H
P
C
POOR PERFUSION
CONGESTIVE SYMPTOMS
0
10
20
30
LVEDP , mmHg

Vasodilator Drugs Used to Treat Heart Failure

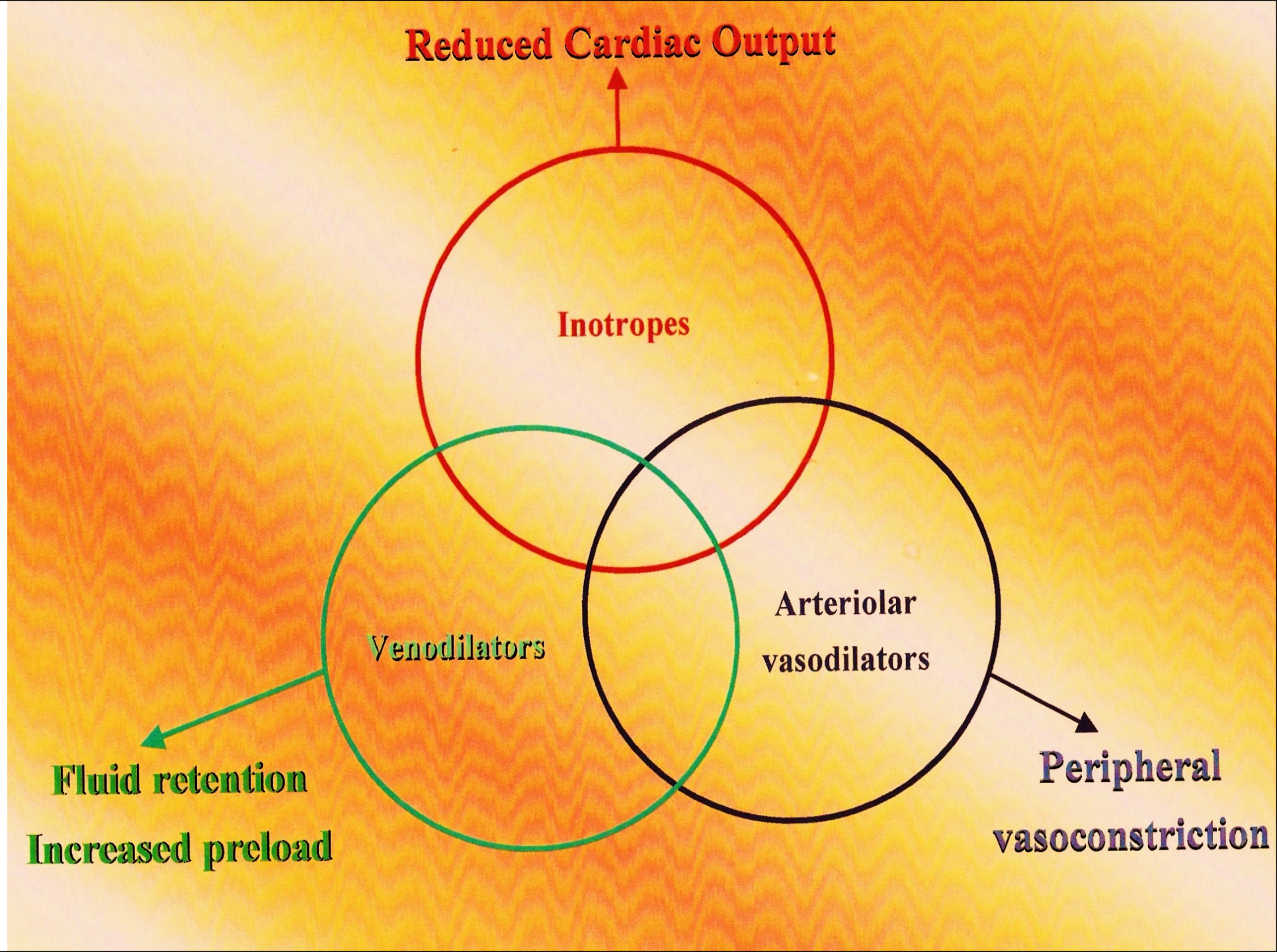
Venous dilating activity

Venous & arterial dilating activity

DRUG CLASS	EXAMPLES	MECHANISM OF VASODILATING ACTION	PRELOAD REDUCTION	AFTERLOAD REDUCTION
Organic nitrates	Nitroglycerin, isosorbide dinitrate	NO-mediated vasodilation	+++	+
Nitric oxide donors	Nitroprusside	NO-mediated vasodilation	+++	+++
Angiotensin-converting enzyme inhibitors	Captopril, enalapril, lisinopril	Inhibition of Ang II generation, decreased bradykinin degradation	++	++
Angiotensin receptor blockers	Losartan, candesartan	Blockade of AT_1 receptors	++	++
Phosphodiesterase inhibitors	Milrinone, inamrinone	Inhibition of cyclic AMP degradation	++	++
Direct-acting K^+-channel agonist	Hydralazine	Unknown	+	+++
	Minoxidil	Hyperpolarization of vascular smooth muscle cells	+	+++
α_1 Adrenergic antagonists	Doxazosin, prazosin	Selective $_1$ adrenergic receptor blockade	+++	++
Nonselective α adrenergic antagonists	Phentolamine	Nonselective α adrenergic receptor blockade	+++	+++
Vasodilating β / $_1$ adrenergic antagonists	Carvedilol, labetalol	Selective $_1$ adrenergic receptor blockade	++	++
Ca^{2+} channel blockers	Amlodipine, nifedipine, felodipine	Inhibition of L-type Ca^{2+} channels	+	+++
adrenergic agonists	Isoproterenol	Stimulation of vascular $_2$ adrenergic receptors	+	++

These are the major problems in HF , depending on the case of the patient the drug is prescribed

For example, if the patient has increased preload, reduced CO we give drugs that treat both (inotropes, venodilators).



(BNP)-Niseritide

- **Brain natriuretic peptide (BNP) is secreted constitutively by ventricular myocytes in response to stretch.**

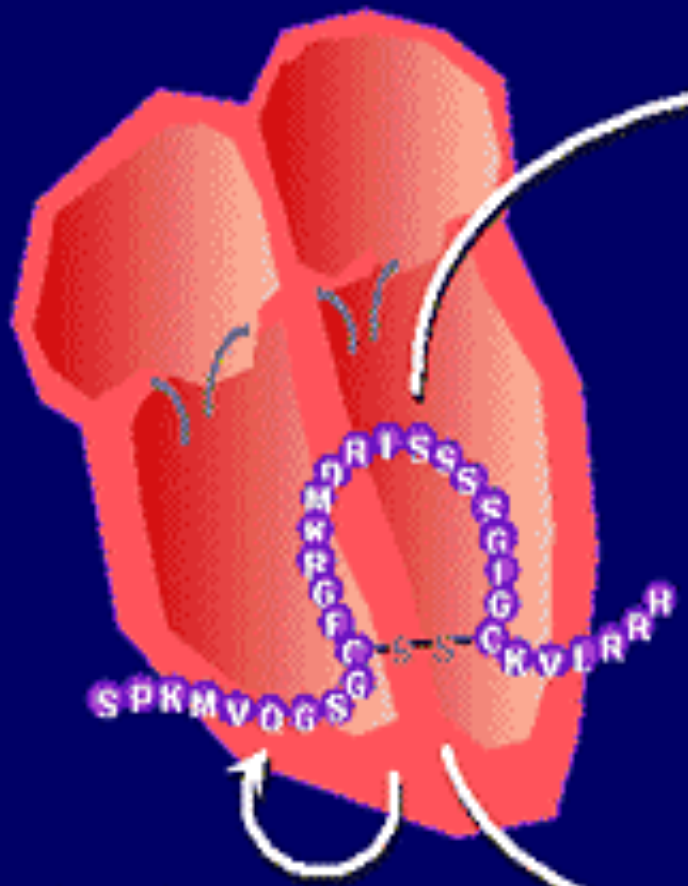
- **BNP increases levels of cGMP.**

- **BNP is released under atrial and ventricular stress leading to vasodilation, natriuresis (loss of sodium) and diuresis.**

- **Niseritide: a recombinant human BNP was used for treatment of acute decompensated CHF.**

- **BNP is cleaved by Neprilysin which is inhibited by Sacubitril**

Pharmacologic Actions of Human BNP

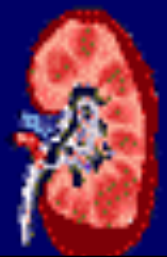


Hemodynamic
(balanced vasodilation)
- veins
- arteries
- coronary arteries

Neurohumoral
- ↓ aldosterone
- ↓ endothelin
- ↓ norepinephrine

Cardiac
- lusiotropic
- anti-fibrotic
- anti-remodeling

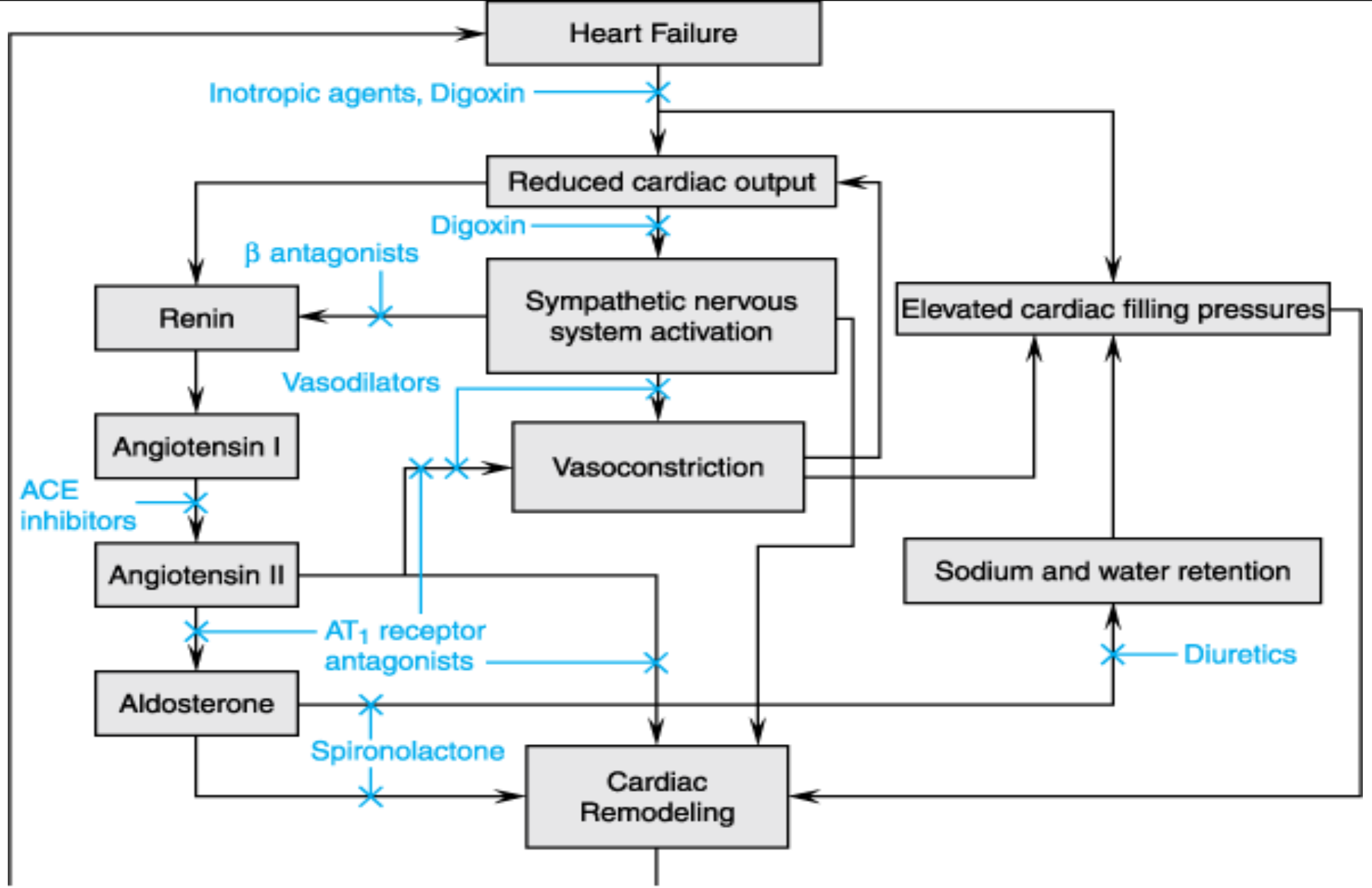
Renal
- ↑ diuresis
- ↑ natriuresis



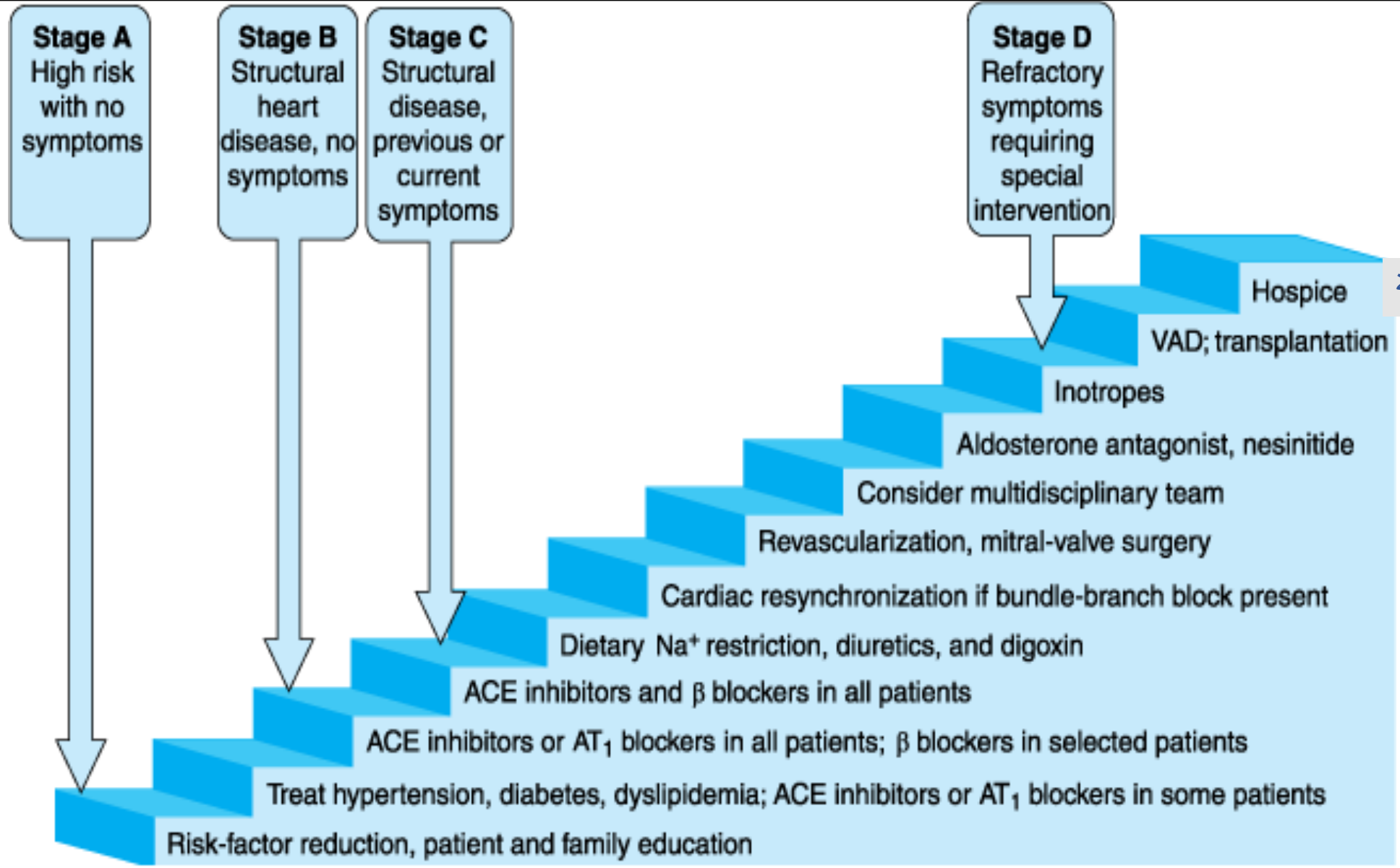
Sacubitril

- **Neprilysin inhibitor used in combination with valsartan *(Entresto)* to reduce the risk of cardiovascular events in patients with chronic heart failure.**
- **Also breaks down angiotensin I and II, endothelin-1 and peptide amyloid beta-protein.**

One of angiotensin receptor blockers



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com



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Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

Management of HF

Steps in the Prevention and Treatment of Chronic Heart Failure.

ACC/AHA Stage	Step[1]	Intervention
A, B	1	Control hypertension, hyperlipidemia, glucose metabolism (diabetes), obesity
C	2	Reduce workload of the heart (limit activity, put on temporary bed rest)
	3	Restrict sodium intake, give diuretics
	4	Restrict water (rarely required)
C, D	5	Give angiotensin-converting enzyme inhibitor or angiotensin receptor blocker
	6	Give digitalis if systolic dysfunction with third heart sound or atrial fibrillation is present
	7	Give beta blockers to patients with stable class II–IV heart failure
	8	Give aldosterone antagonist
	9	Give vasodilators
D	10	Cardiac resynchronization if wide QRS interval is present in normal sinus rhythm
	11	Cardiac transplant

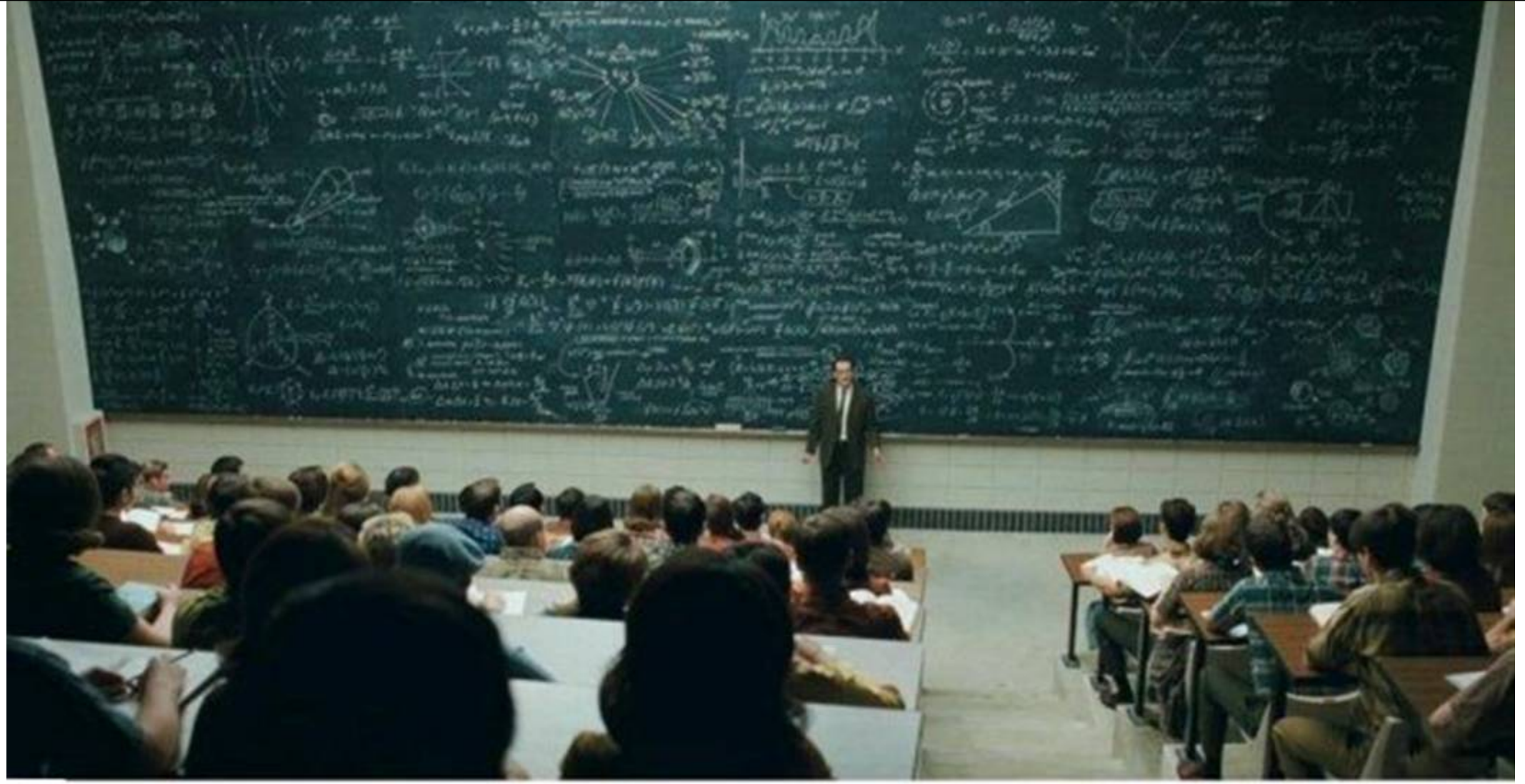
Not imp

Errors in Management of HF

- **Missed diagnosis.**
- **Improper dosage of diuretics.**
- **Failure to assess quality of life.**
- **Failure to consider long term therapeutic goals.**
- **Underprescribing of ACEI.**
- **Use of potentially harmful drugs.**
- **Failure to use hydralazine-isosorbide combination which has proved evidence of benefit.**

We need diuretics to reduce plasma volume and reduce the burden on the right side of the heart or reduce the preload.

We should prescribe ACEI to the highest tolerable doses, until the patient starts to complain of side effects (cough)



This slide is from the dr
عيدكم مبارك

مفهوم لو اعيدلكم الدرس ....