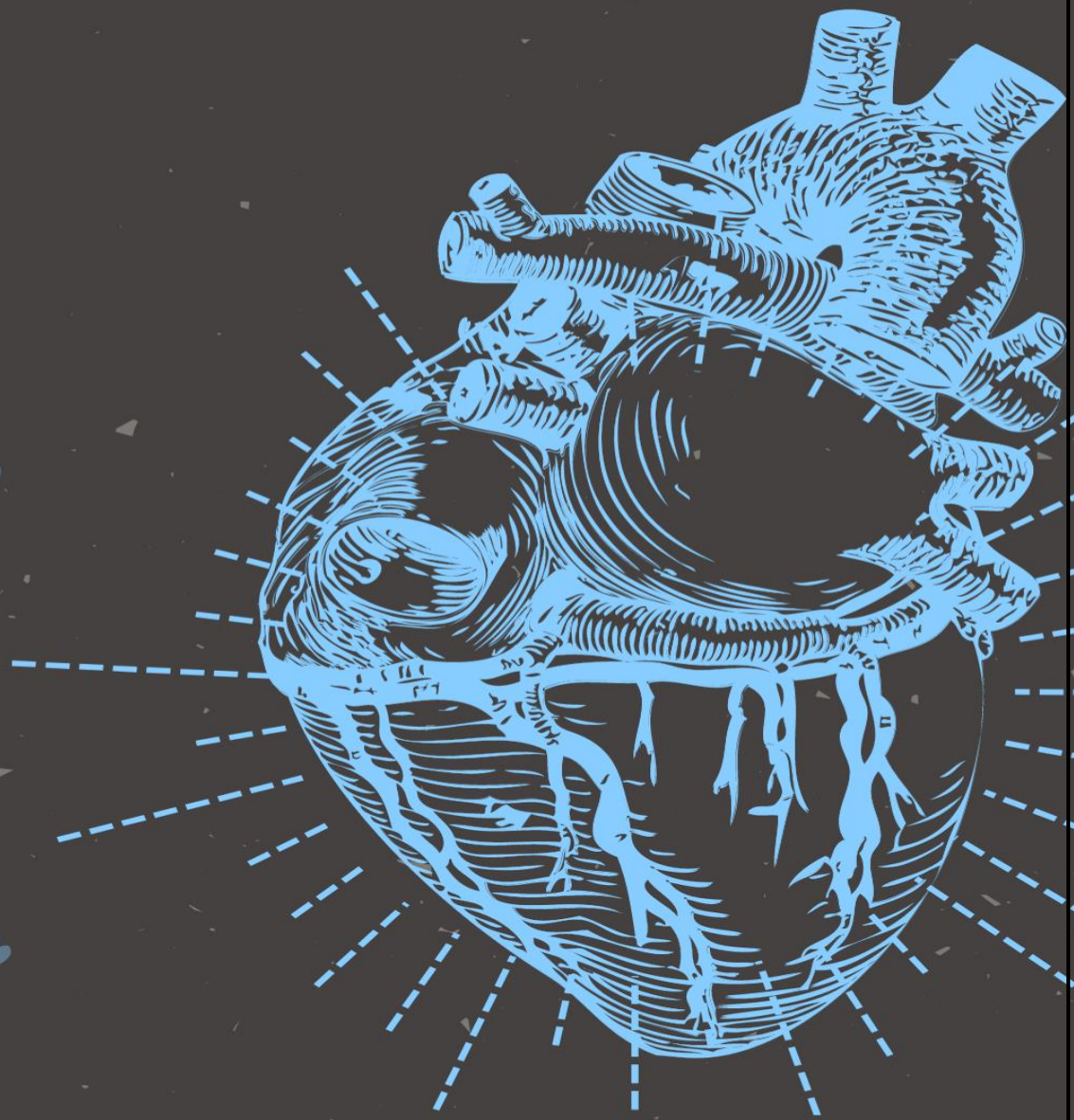
CVS



PHARMACOLOGY

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Positive Inotropic Agents

❖ Logically they will improve cardiac function.

❖ These drugs increase force of contraction by increasing intracellular cardiac

Ca++ concentration. We have two types:

1. **Cyclic AMP Independent Agents,** such as:

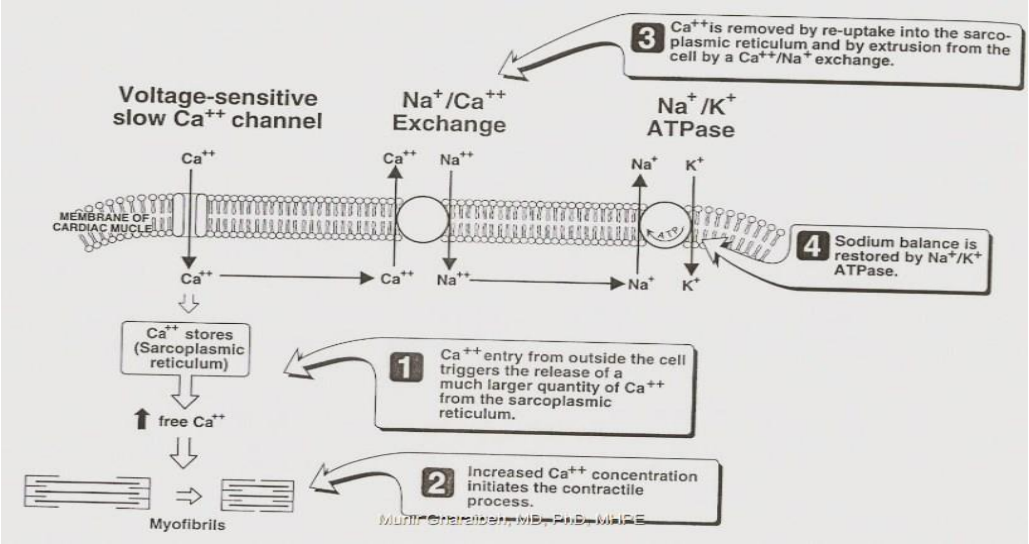
✓ **Digitalis**: inhibits Na/K ATPase , which causes accumulation of intracellular Na , that turns the Na/Ca channel all the way round , so Na goes out in exchange of Ca , this increases intracellular calcium , thus increases the contractility .

Remember that Na/K ATPase is found all over the body and not only in cardiac muscles , so toxicity is also expected .

2. **Cyclic AMP Dependent Agents**: (cAMP enhances MLCK)

Such as beta-adrenergic Agonists - sympathomimetics - , and Phosphodiesterase Inhibitors (which inhibits the breakdown of cAMP by PDE , thus increases the contraction).

We've taken this before in physio , please go over it



Digitalis Glycosides :

- ❖ Digitalis was a widely used drug in the treatment of HF.
- ❖ A History lesson:

✓ Egyptians got it from a plant called Squill (العنصل)

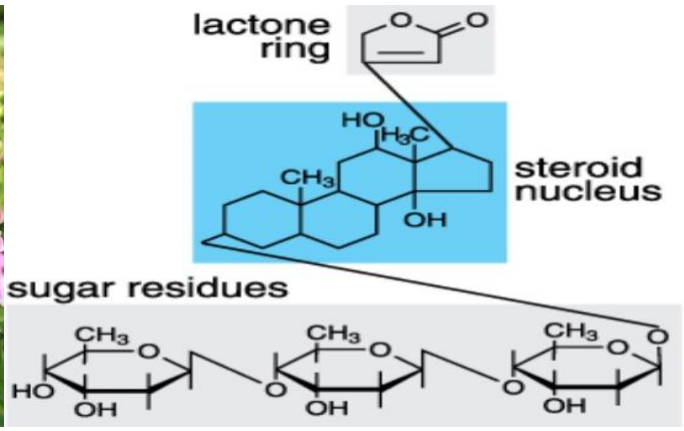
✓ Chinese got it from Toad skin

✓ In 1785, William Withering discovered a plant called Foxglove. And from this plant we extracted the active ingredient which we use nowadays.

❖ We have different species of foxglove: Digitalis purpura, Digitalis lanata, Strophanthus

❖ 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.

❖ 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.



Actions: Na /K pumps aren't only found in cardiac muscles , so the expected outcome is both toxicity and effectiveness.

- ❖ Positive Inotropic Effect
- ❖ Vascular Muscle Contraction , one of the downsides is that this increases the afterload and decreases the CO.
- ❖ Vagal Stimulation, activating the PSNS which mainly affects the heart rate
- ❖ Effects on the Electrical Properties of Cardiac Tissues (predominately affects the atria) , an example would be the effect of PSNS stimulation that causes bradycardia and decreases the excitability .

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 good. However, in normal

healthy people it was found to cause the opposite, decreasing CO and increasing PVR.

This is because, patients with HF have an already increased SNS activity which increases PVR (peripheral vascular resistance) to the maximum, where no further increase is possible. So , Giving digitalis would increase the contractility and somehow disrupt the overactive SNS activity. Now, the inhibition of SNS will cause vasodilation. The blood vessels are dilated and ready to be filled with blood (PVR is reduced) therefore the CO (the flow) will be increased.

The effects of digitalis on electrical properties of cardiac tissue:

- ❖ It has direct and indirect effects, the indirect are mainly due to stimulation of the Vagus nerve which supplies the atria and SA node only
- ❖ Increased PR is diagnostic of digitalis therapy
- ❖ The direct effects occur at high toxic doses

The table below shows the exact effect on cardiac tissues. Please read it.

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

Ventricular

A commentary about the previous table :

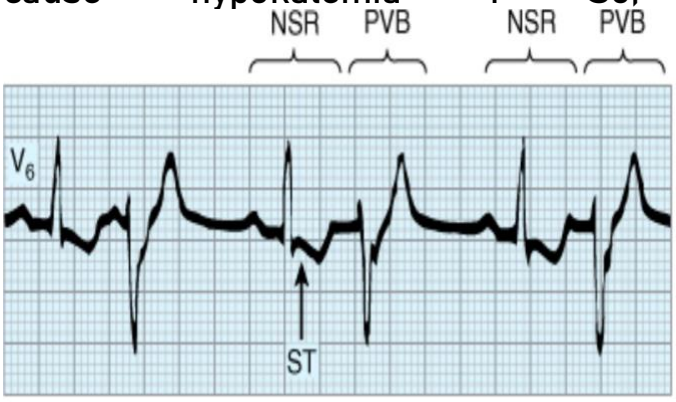
The effect of digitalis is very minimal passed the AV node , so the ventricles are very minimally affected , as opposed to the atria that is very highly affected by PNS stimulation .

Digitalis Toxicity:

1. The most important are the cardiac toxicities. But it can also cause other less serious ones.
2. GIT (occurs in almost all patients): Anorexia, nausea, intestinal cramping, diarrhea.
3. Visual effects: Xanthopsia, abnormalities in color vision.

> Xanthopsia على قولة الدكتور نجوم الظهر, scientifically it is a color vision deficiency in which there is a predominance of yellow in vision due to a yellowing of the optical media of the eye.

4. Neurologic: Malaise, confusion, depression, vertigo
5. Cardiac: severe bradycardia, palpitations, syncope, arrhythmias, AV node block, ventricular tachycardia which might lead to ventricular fibrillation and could be lethal.
6. Interactions with many drugs.
7. Pharmacological and toxic effects are greater in hypokalemic patients. K+-depleting diuretics are a major contributing factor to digoxin toxicity because they cause hypokalemia . So, they should be avoided



This is an ECG of a patient on digitalis, notice the increase in PR interval, ST depression and ventricular extrasystoles (that might convert into ventricular tachycardia that might also be converted to ventricular fibrillation and without rapid management this can be fatal)

Treatment of Toxicity:

1. Reduce the dose or stop the drug if possible.
2. Cardiac pacemaker for severe heart block.
3. Digitalis antibodies (Digoxin Immune Fab). This is used as an antidote for people who are trying to commit suicide by taking digoxin.

Your mental health is more important than anything in the whole world, stay safe!!

4. Arrhythmias may be converted to normal sinus rhythm by K+, so we give K+ when the plasma K+ concentration is low or within the normal range.
   (it treats atrial fibrillation by causing bradycardia and AV block , so atrial contractions will not be transmitted to the ventricles , which reduces the risks of ventricular tachycardia , now atrial fibrillation is merely treated by giving anticoagulants) .
5. If arrythmias develop when the plasma K+ concentration is high, antiarrhythmic drugs, such as lidocaine (IV), phenytoin (strongly indicated in digitalis toxicity), procainamide (orally) , or propranolol, can be used.

Therapeutic Benefits:

- ❖ Was widely used in the treatment of heart failure.
- ❖ Nowadays, its use is and should be only restricted to chronic congestive heart failure CCHF with supraventricular arrhythmia.
- ❖ Might decrease morbidity and improve quality of life.
- ❖ Does NOT improve mortality.
- ❖ Withdrawal might be hazardous.

Different cardiac glycosides (Digitalis Glycosides) :

- ❖ Nowadays only digoxin is available.
- ❖ Different oral absorption, ouabain has to be given I.V.
- ❖ Different protein binding ability, for example digitoxin has 97%, this enhances the chance of drug-drug interactions with drugs which can displace digitoxin leading to higher unbound free molecules which can be toxic.

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.

❖ Different half-life, 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 , and in cases of hepatic failure we use digoxin.

❖ These drugs have to be monitored regularly.

This table isn't for memorization, just know the details mentioned above and that digoxin is somewhat in the middle between these two, and its excreted from the kidneys.

Cyclic AMP Dependent Agents

Beta-adrenergic Agonists:

❖ They increase in the activity in Beta receptors and increase cAMP , thus they all increase myocardial oxygen consumption, so they are not helpful for chronic use, because they might affect the efficiency of the heart and cause ischemic heart disease.

❖ They may be used (IV) for short term or in acute heart failure.

❖ Norepinephrine (NE): Was used in acute heart failure or cardiogenic shock – when the blood pressure becomes almost zero (severe drop in blood pressure post-MI) and in emergencies but it caused severe vasospasm and gangrene, which could lead to amputation. So, it's no longer used.

They used to use norepinephrine, but because of the vasospasm and gangrene they shifted to the usage of Dopamine .

Unfortunately , patients which took Dopamine had higher mortality rates because of arrhythmias , so they went back to norepinephrine again .

❖ Epinephrine: Still used in cardiac arrest, as a final resort in CPR, by intracardiac injection. Works better in young people with better functioning hearts

Dopamine:

- ❖ Widely used in cardiogenic shock.
- ❖ It has three distinct effects depending on the given dose:

- ✓ Low doses: stimulate DA1 receptors leading to renal vasodilation and improved renal perfusion , used in renal failure , and in cardiogenic shock to solve the decrease in renal perfusion .

  Extra : (normally in shock there is a decrease in kidney perfusion, coronary perfusion , and cerebral perfusion).

- ✓ Intermediate doses: work on β1 receptors leading to positive inotropic actions on the heart. Also used in renal failure.
- ✓ 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.

Dobutamine:

- ❖ Nonselective β and α1 agonist, used intermittently (IV) in CCHF.
- ❖ Produces mild vasodilation.
- ❖ Has more inotropic than chronotropic actions.

Phosphodiesterase Inhibitors:

❖ PDE inhibition leads to accumulation of cAMP and cGMP leading to positive inotropic activity and peripheral vasodilation respectively (because cGMP is found in the wall of blood vessels).

❖ Toxic side effects: arrhythmias, and thrombocytopenia.
❖ Short acting, so they are reserved for parenteral therapy of acute heart failure.

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

Examples include: Inamrinone (PDE-3), Milrinone (PDE-3), Vesanirone (PDE-3), Sildenafil is a vasodilator but doesn't have ionotropic effects because the heart doesn't have PDE-5 receptors (Viagra, inhibits PDE-5, causes vasodilation of penile veins which treats erectile dysfunction)

Vasodilators :

These are vasodilators that work directly on blood vessels.

- ❖ They affect preload and/or afterload without directly affecting contractility.
- ❖ Consequently, they can decrease myocardial ischemia, and enhance coronary blood flow and decrease myocardial oxygen consumption (MVO2).
- ❖ Can be used in acute heart failure and for short periods in CCHF under direct supervision , they are not good for chronic use.
- ❖ We have 3 types, atrial, venous and mixed dilators.
- ❖ Hydralazine (an arterial dilator)-Isosorbide dinitrate (a 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.

Venous dilators will cause pooling of blood in veins which will reduce theburden on the right heart , beneficial in right-sided heart failure .

Causing decrease in left ventricular end diastolic volume LVEDV , thus decreases load on the heart , intraventricular tension and MVO2 and enhances cardiac efficiency , and increase the cardiac output .

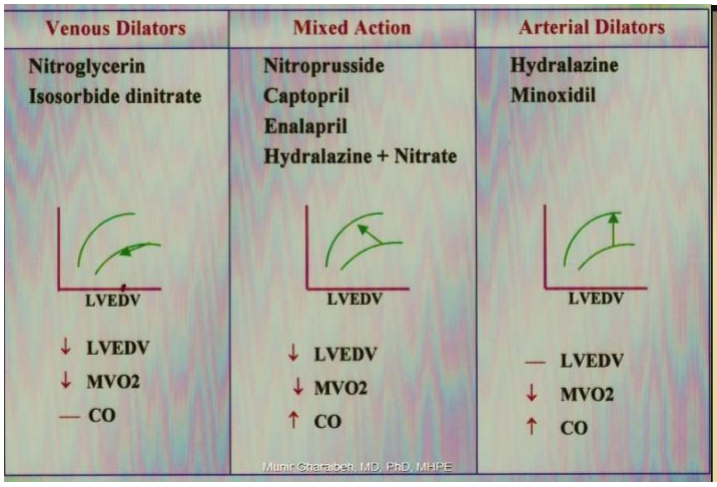
Unlike in healthy people, decreasing the venous return in HF patients will not affect the CO, because it decreases the congestive symptoms of heart failure (There is already an increased volume of blood [congestion]) .

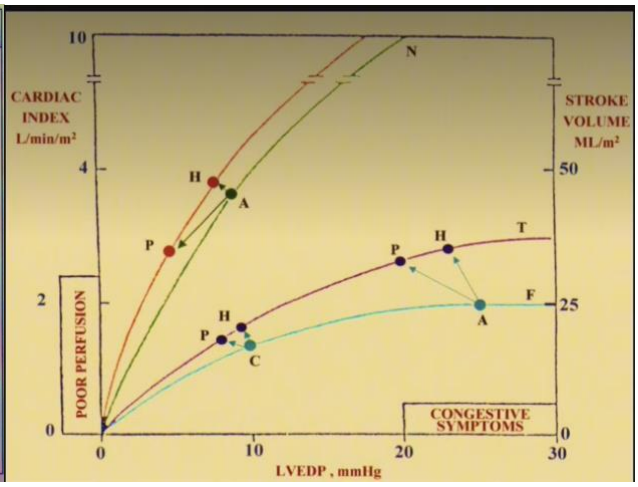
* extra : heart failure can be right sided , left sided , or chronic congestive heart failure -both sided , end stage- .

Arterial dilators, these don't affect the LVEDV, but by causing arterial dilation they will reduce PVR and thus decreasing the afterload ,increasing the cardiac output CO, reducing the stress on the left heart and improving organs' blood perfusion , beneficial in left-sided heart failure .

But in severe arterial dilation , there will be a decrease in organic perfusion .

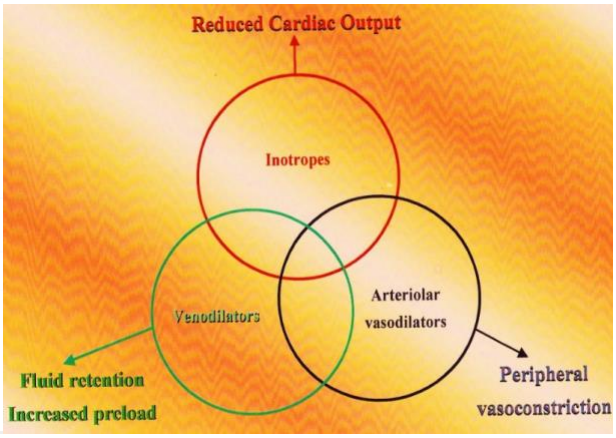
Mixed action drugs, will produce the two effects together reducing LVEDV, MVO2 and increasing CO.





Depending on the specific case of the patient we choose the appropriate drug. For example, if the patient has increased preload & reduced CO we give drugs that treat both. Look at the Venn diagram.

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	+	+++
$_1$ Adrenergic antagonists	Doxazosin, prazosin	Selective $_1$ adrenergic receptor blockade	+++	++
Nonselective $^{\alpha}$ adren ergic antagonists	Phentolamine	Nonselective adrenergic receptor blockade	+++	+++
Vasodilating $^{\beta}$ $_1$ adrenergic antagonists	Carvedilol, labetalol	Selective $_1$ adrenergic receptor blockade	++	++
Ca^{2+} channel blockers	Amlodipine, nifedipine, felodipine	Inhibition of L-type Ca^{2+} channels	+	+++
adrenergic	Isoproterenol	Stimulation of vascular	+	++

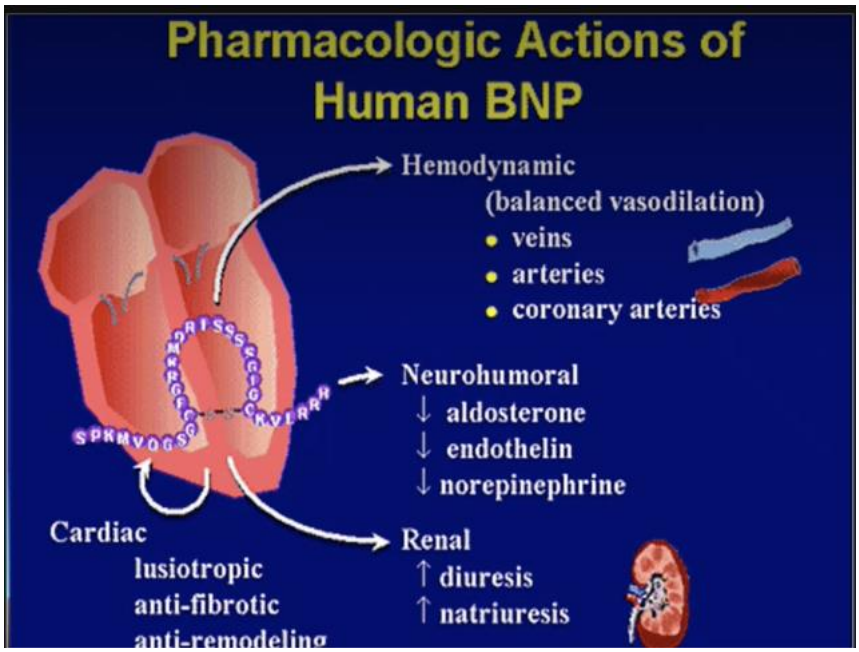


BNP- Niseritide

- ❖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 and diuresis.

- ❖BNP is cleaved by Neprilysin , which is inhibited by Sacubitril , and this is what we use .
- ❖Niseritide is a recombinant human

BNP approved for treatment of acute decompensated CHF.



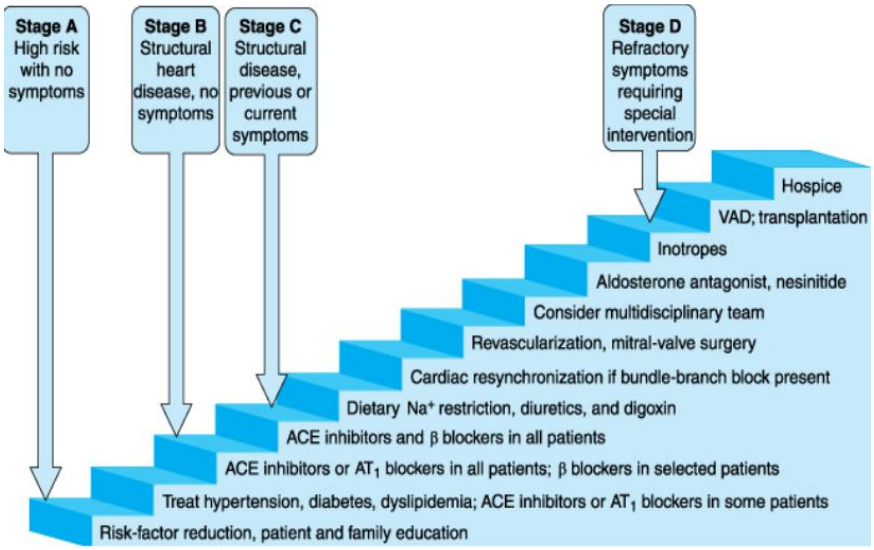
The actions of BNP:

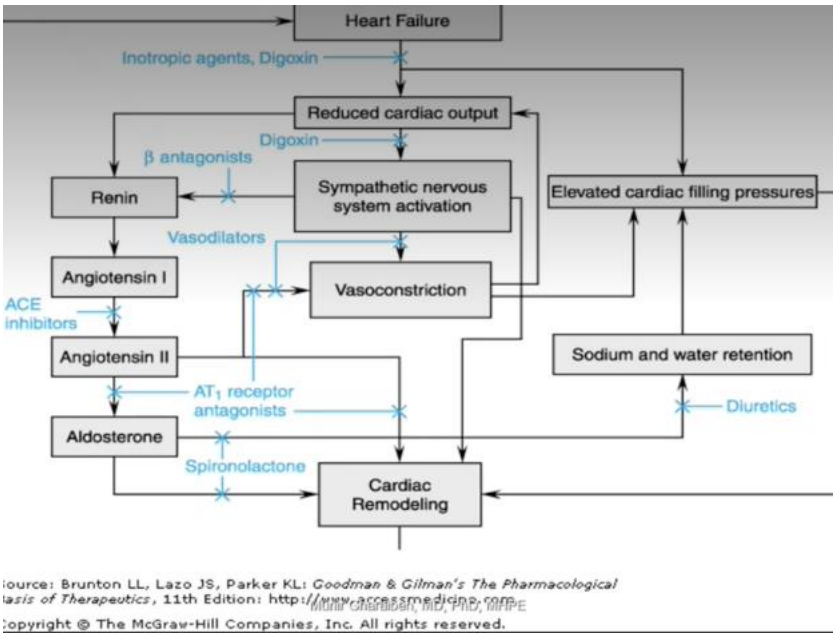
- ❖ Reduces systemic and pulmonary vascular resistances, causing an indirect increase in cardiac output and diuresis.
- ❖ Effective in HF and pulmonary hypertension because of reduction in preload and afterload.
- ❖ Hypotension is the main side effect .
- ❖ has positive lusiotropic effect , which is an increase in the relaxation (the decrease in intracellular calcium)

Sacubitril:

- ❖ Is a Neprilysin inhibitor used in combination with valsartan (an ARB) to reduce the risk of cardiovascular events in patients with chronic heart failure.
- ❖ Neprilysin also breaks down angiotensin I and II, endothelin-1 and peptide amyloid beta- protein.
- ❖ Inhibition of Neprilysin therefore leads to reduced breakdown of endogenous natriuretic peptides in addition to increased levels of vasoconstricting hormones such as angiotensin II.

Management of HF starting from high risk to end stages of the disease:





Errors in Management of HF:

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

Good luck