Heart Failure:-

It is a condition where the heart does not have enough ability to pump blood to the vital organs of the body and this will causes problems.

Disease symptoms:

1) Shortness of breath

2) leg swelling (edema)

3) breathing worsens with lying flat (orthopnea)

4) Fatigue.

Types of heart failure:

1) Systolic heart failure: in one third of the cases, the cause of heart failure is a decrease in the strength of heart contraction and Reduction of ejection fraction during systole.
2) Diastolic heart failure: in one third of the cases, the cause of heart failure is ventricular stiffness and Disturbance in adequate filling during diastole.

Heart failure with too much output has not changed.

3) The remaining cases are a combination of systolic and diastolic disorders.

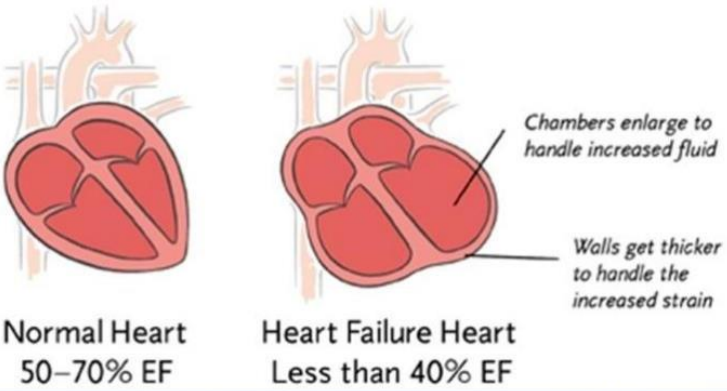
Grading of heart failure:-

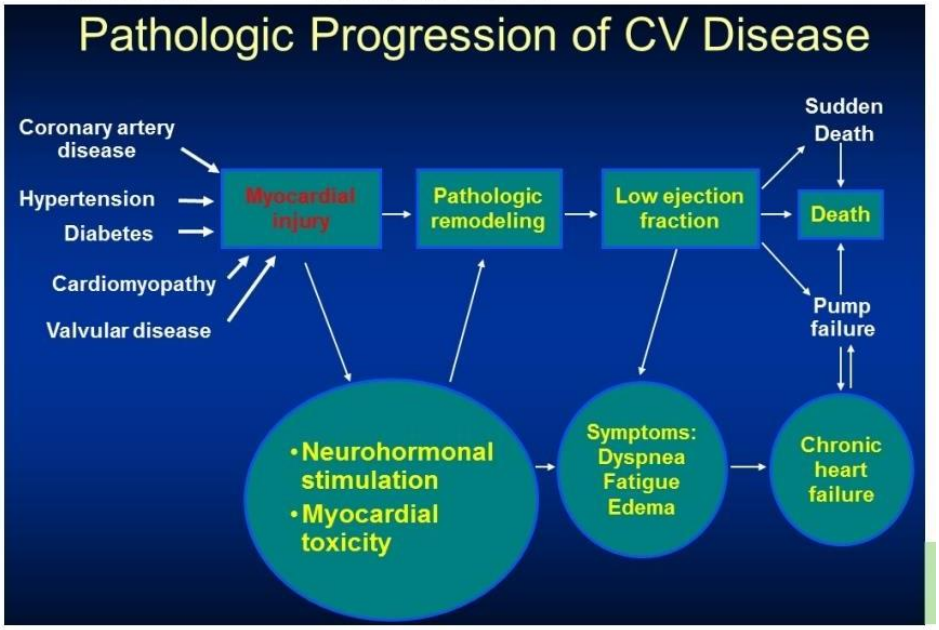
1) Asymptomatic
2) Symptomatic with moderate exertion
3) Symptomatic with minimal exertion
4) Symptomatic at rest.

There is another type of division which is done with the letters ABCD.

An important indicator in the diagnosis of heart failure:

EF (Fraction Ejection): cardiac output or the percentage of blood that is pumped by the heart in each beat decreases in failure (its value reaches from 62% to 42%, which is determined by the echo of the heart.)





Pathophysiology of the disease:

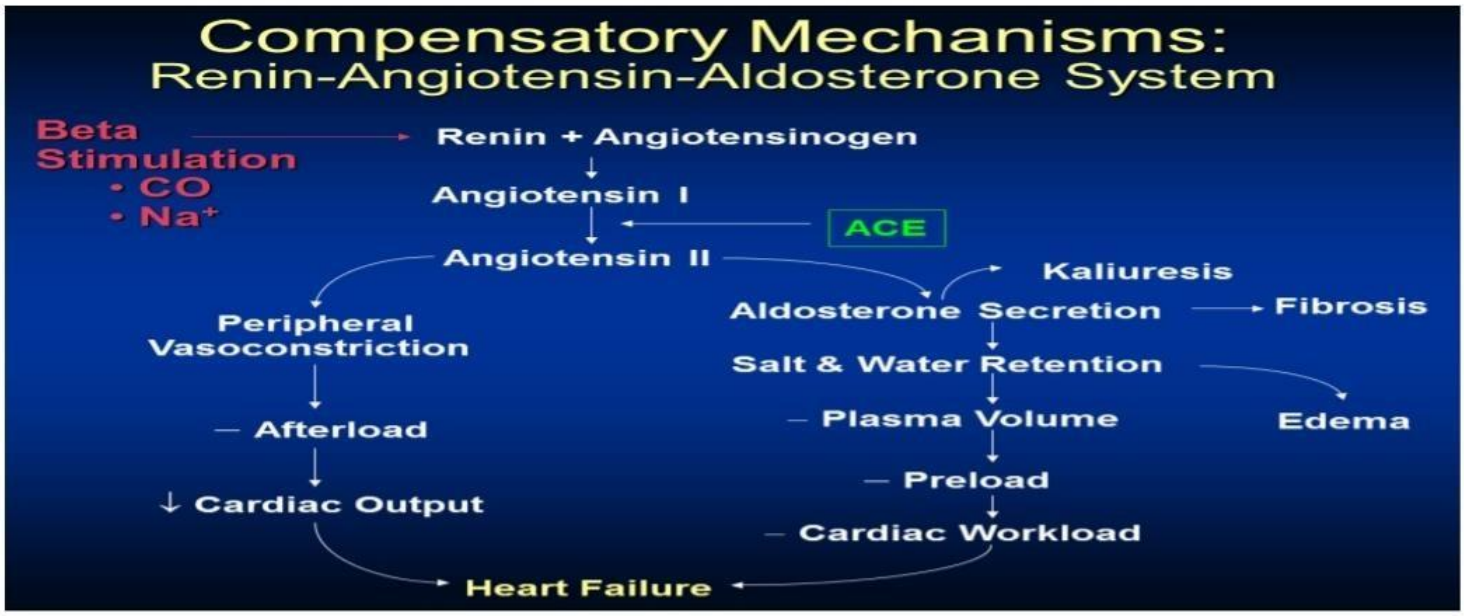
Coronary artery disease, hypertension, diabetes, cardiomyopathy and heart valve diseases can cause myocardial damage. These changes cause pathological changes, due to which we have a decrease in cardiac output. A decrease in cardiac output causes dyspnea, fatigue, and can lead to chronic heart failure. Sometimes it also causes acute heart failure and sudden death occurs.

Compensatory Mechanism:

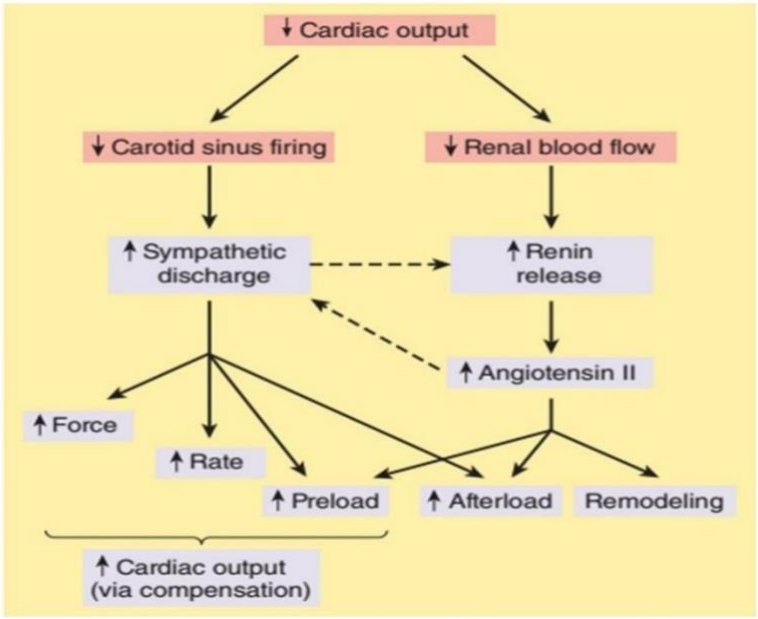
In heart failure, the cardiac output is reduced and as a result the renal blood circulation is reduced and as a result the renin-angiotensin system is activated. Renin secretion is increased and then we have increase in angiotensin 1 and 2.Increase in angiotensin 2 causes:

1) vasoconstriction: followed by an increase. We have the load and then the reduction of the output of the heart. In fact, a heart that does not have enough power to pump blood faces a higher vascular resistance, and the so-called defective cycle occurs.
2) Aldosterone is secreted. Aldosterone causes fibrosis of blood vessels and myocardium and causes water and salt retention, increases plasma volume and cardiac preload, which worsens the condition and we have swelling in this condition.

The main defect in congestive heart failure is the reduction of contractile strength. The main responses in heart failure are tachycardia, which is an early manifestation, 2- increased peripheral vascular resistance, 3- water and salt retention, 4- heart size increases, 5- apoptosis.



According to the picture opposite, in heart failure, with a decrease in cardiac output, we have an increase in the preload and afterload, heart rate, and finally the contraction strength.



The heart is not enough to produce the proper output.

Drugs used:

Treatment of chronic heart failure:

1) Diuretics: excretion of water and salt
2) Aldosterone antagonists: such as spironolactone and eplerenone
3) ACEinhibitors: reducing afterload and water and salt retention Such as captopril and enalapril.
4) Beta blockers; Decreased sympathetic overstimulation. Metoprolol, isoprolol, carvedilol.
5) Positive inotropic drugs: direct stimulation of heart contraction – such as cardiac glycosides (digoxin).
6) Vasodilator drugs: reduction of preload or afterload – such as hydraluzine.
7) Angiotensin receptor blockers: such as losartan and valsartan.

According to the professor, catecholamines actually whip the heart and increase apoptosis in cardiac cells.

The best way to treat acute heart failure is a diuretic, the loop of Henle, and in Very severe cases, a

TABLE 13–1 Therapies used in heart failure.

Chronic Systolic Heart Failure	Acute Heart Failure
Diuretics	Diuretics
Aldosterone receptor antagonists	Vasodilators
Angiotensin-converting enzyme inhibitors	Beta agonists
Angiotensin receptor blockers	Bipyridines
Beta blockers	Natriuretic peptide
Cardiac glycosides	Left ventricular assist device
Vasodilators	
Resynchronization therapy	

positive inotropic drug eg Beta agonist (dobutamine) and phosphodiesterase inhibitor or vasodilator. Note: Nesiriptide is a recombinant form of peptide ,It is a cerebral natriuretic, has vasodilatory and diuretic effects and recentlyrecently, It has been strongly emphasized in the treatment of acute heart failure.

Classification and treatment of chronic heart failure patients:

Depending on the severity of the disease, the type of medicine used for patients is listed in the table.

1) In people who are in the NYHA division in the pre failure section the Blood pressure, obesity, diabetes and hyperlipidemia should be controlled.
   They have their own medicine.
2) In its 1st form, ACEinhibitor or ARB such as captopril, enalapril, isinopril or elozartan and valsartan are used, and diuretics, due to the fact that there is edema are being used. Beta blocker is also used.
3) In type 2 and 3, the doctor adds a drug such as spironolactone and may use digoxin or vasodilator drugs such as nitrate or hydralazine depending on the condition.
4) in type 4, when the person is uncomfortable even at rest, other drugs do not help much. In these cases, we use devices (devise assist).Or even in the a heart transplant.

TABLE 13–3 Classification and treatment of chronic heart failure.

ACC/AHA Stage[1]	NYHA Class[2]	Description	Management
A	Prefailure	No symptoms but risk factors present[3]	Treat obesity, hypertension, diabetes, hyper…
B	I	Symptoms with severe exercise	ACEI/ARB, β blocker, diuretic
C	II/III	Symptoms with marked (class II) or mild (class III) exercise	Add aldosterone antagonist, digoxin; Ch…
D	IV	Severe symptoms at rest	Transplant, LVAD

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1) **cardiac glycosides (digoxin):**

digitalis lanava - digitalis purpurea is the scientific name of the foxglove plant, it is also called fox glove. This plant has been used since ancient times.It has been used for heart failure. It is available in white and pink colors, which has various cardiac glycosides, the most famous of which is digoxin. The drug digoxin produced, of course, this chemical substance has been found in various plants, such as oleander, which has the property of trying. In the history of medicine, a group of soldiers in the World War died due to the use of oleander wood as skewers.

In plants, we have substances with a chemical structure that cannot be chemically synthesized for us, and digoxin is one of those things that is extracted from the plant itself, but nowadays no one uses digitalis to treat heart failure, because digoxin is present in digitalis. Depending on the circumstances.

Geographical and cultivation environment, the height of the cultivation place, the time of collection, the method of cultivation of the plant and other factors are variable. Digoxin is one of the Low Therapeutic Index drugs and is toxic. In fact, the separation of the active substance helped us to standardize them, so that the digoxin powder contains 0.25 mg of the active substance, and we also have ampoules and digoxin syrup. It requires special technology and its bio availability can be different from factory to home work. (Warfarin tablets are imported in the same way).

Pharmacokinetics of the drug:

✔ Digoxin has about 80 to 65% oral bioavailability, which can be distributed or distributed in different parts of the body, including the CNS.

✔ It does not have much metabolism in the body, so two-thirds of this drug is excreted intact through the urine.

✔ Any place where the drug was excreted intact through the urine, dose adjustment is required in renal failure, that is, we must adjust the dose of the drug and Reduce the distance according to the severity of the insufficiency.

✔ The half-life is about 36 to 40 hours, and it is used day and night.

✔ After starting the treatment, after about 5 days, we reach the peak effect of this drug. In many countries of the world, we have a term called TEM, which is trapeutic drug monitoring. It determines in the blood and adjusts the distance based on the concentration. This is not done in our country, and based on this, some doctors tell the patient not to take the medicine for example 1 day a week because the medicine does not accumulate in the body.

✔ In the old days, ampoules of digoxin were used for acute heart failure, which is not effective today, and if the patient responds to a different set (say, ACE inhibitor, diuretic, etc.), digoxin will not enter the scene. Despite the fact that medicine has been leading the way in failure for more than 100 years.

Mechanism

It is considered in the form of a heart muscle cell.

Digoxin is a partial inhibitor of the sodium pump called ATPase. The function of this pump is to return the sodium that has entered the cell in the Depolarization phase to the outside and bring potassium in. By inhibiting the sodium pump, it accumulates inside the cell.

In the other part (Na-Ca exchange) we have NCX, because the concentration of sodium inside increases, calcium does not leave the cell and remains inside the cell, and as a result, the concentration.

In muscle, both calcium channels and sarcoplasmic reticulum play a role in the entry of calcium into the sarcoplasm, the increase of calcium in the cell acts like a trigger and causes a lot of calcium to flow out of the sarcoplasmic reticulum and actin and myosin fibers of the muscle. It collapses and contracts the muscle.

✔ Digoxin, by acting on calcium channels, causes more calcium to enter the cell. So,

we have two mechanisms of action for Digoxin.

1 Digoxin increases the entry of calcium into the cell during the plato phase.

2 By inhibiting the sodium potassium ATPase pump, some calcium can be released from the network of ER.

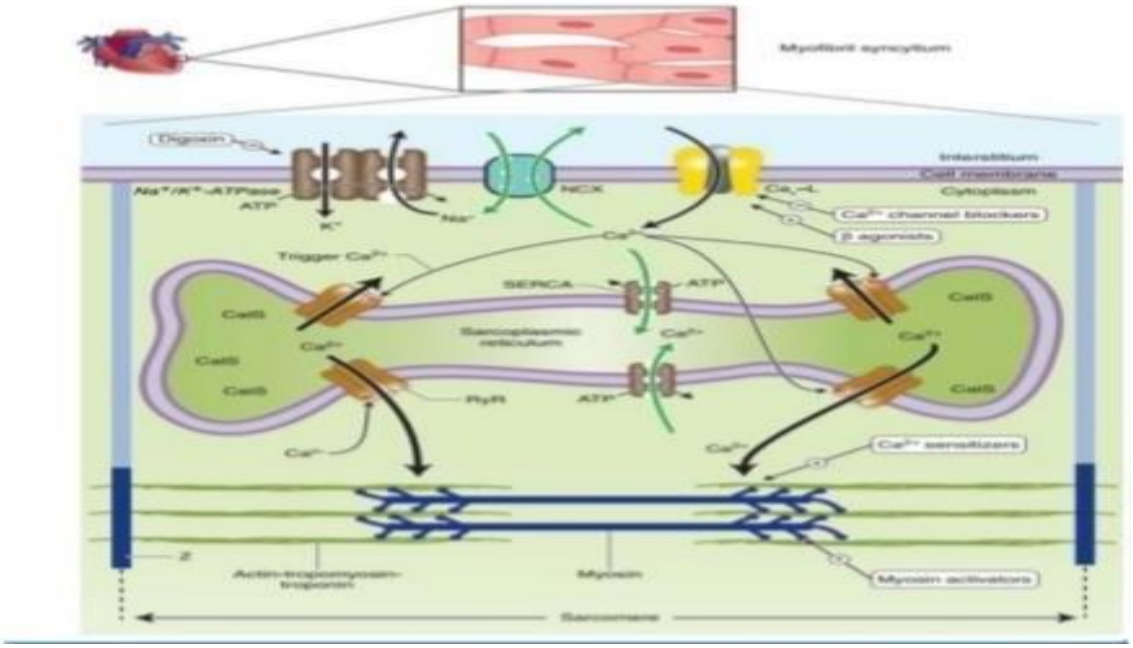

Fig ---------We don't intend to stop the operation of this pump completely (one of the reasons). The toxicity of the drug is the failure of the pump (the inhibition of the inotropic effect of the pump). It creates a positive effect on the drug and increases the contraction power of the heart)))

mechanism

In the past decade, it has been shown that there is a receptor on the sodium potassium ATPase pump for digoxin, and it has been suggested that there may be endogenous compounds of this substance in the body. This issue is also relevant for drugs and opioids. Compounds such as beta-endorphin and meth-enkephalin have been proposed even today as cannabinoid endogenus (internal cannabis). For this reason, verapamil (one of the non-dihydropyridine CCBs) is a negative inotrope in the treatment of heart failure, which causes a decrease in the contraction force of the heart (due to the presence of zinc calcium channels). These are the cells. The yellow form is the type of calcium channel that is inhibited by drugs such as verapamil and valitazem.

It has a series of vagomimetic effects and lowers the heart rate and increases the contractile force of the heart.)))

The duration of the treatment is short.

Electrical and mechanical effects of digoxin:

Digoxin has a series of electrical effects and a series of mechanical effects, for example, it lowers the heart rate and increases the contraction power of the heart.

Mechanical effects: by increasing the contractile strength of the heart, these drugs cause an increase in the ventricular ejection fraction (decrease in end-systolic and end-systolic size)

Diastole, increased cardiac output, decreased compensatory response of the sympathetic system and increased renal blood supply.

Electrical effects: early electrical effects include: increasing the PR interval due to the decrease in the atrioventricular conduction speed, flattening of the wave, parasympathetic effect on the atria and AV node, increasing the duration of AV inexcitability, slowing down the ventricular rate, shortening the QT, and reversing the wave T and lowering of the ST segment are late electrical effects: they occur due to an increase in intracellular calcium and cause an increase in automatism, tachycardia, atrial and ventricular fibrillation.

Poisoning:

1) The most and the first side effects of this drug are its gastrointestinal side effects which lead to anorexia, nausea and vomiting and diarrhea. This medicine stimulates the digestive system both directly and centrally. By stimulating the CNS, digoxin sends a message to the vomiting center and induces nausea and vomiting through a center called CTZ.

2) Sometimes, if a person consumes a lot of salt, he experiences hallucinations and balance disorders.

3) Vision and color recognition disorders may be seen on objects with yellow and yellowish-green colors.

4) Gynecomastia occurs in men.

5) Most importantly, digoxin may cause fatal cardiac arrhythmia. Sometimes 4 to 5 tablets of this drug lead to cardiac arrest and death of a person, the dosage of this drug is from half a tablet to 2 tablets.

(((*1-Chronic poisoning occurs due to the accumulation of calcium in the heart cell and causes automaticity of the arrhythmia.*

2- If serum potassium or magnesium decreases or serum calcium increases. Arrhythmia is more likely.

3-Acute poisoning causes a drop in heart function and leads to cardiac arrest.)))

Predisposing factors for digoxin poisoning:

Electrolytes can affect digoxin poisoning. Several factors that increase poisoning:

1) Hypokalemia for any reason can increase digoxin toxicity, so with weak digoxin poisoning, potassium can be given to the person because potassium can displace digoxin from its binding site.
2) Hypomagnesemia
3) Hypercalcemia

Treatment of digoxin poisoning:

1) The first remedy for potassium or magnesium deficiency and hypercalcemia:

Mild poisoning can be treated by removing one or two digitalis doses and administering oral or parenteral potassium supplements. Potassium should not exceed 3.5-5 milliequivalents be more per liter. Hypomagnesemia should also be treated. In severe acute poisoning (for example in suicide), severe hyperkalemia occurs and potassium supplements should not be prescribed.))

2) Antiarrhythmic drugs: If automaticity is significant and does not respond to potassium, antiarrhythmic drugs are effective. Drugs that do not impair the heart's contractility (such as lidocaine or phenytoin) are desirable. Propranolol is also effective.

((*In acute poisoning, all the pacemaker cells of the heart are inhibited, and in these patients, antiarrhythmic drugs are dangerous, and the use of a pacemaker may be necessary*.))

3) Anti-digoxin antibodies: To treat digoxin poisoning, designed monoclonal antibodies called fragment fab, which are digoxin antidotes. Which are specifically attached to digoxin and excreted through urine.

Drug interactions of digoxin:

1) Diarrhea and vomiting: these substances themselves reduce the concentration of potassium, which leads to the worsening of the patient's condition, so if digestive complications begin after taking this medicine, the person should avoid taking the next pill.
2) Medicines that lead to hypokalemia: such as hydrochlorothiazide and forsamide.

((*3) Quinidine: It reduces the clearance of digoxin and thus increases the level of digoxin and increases the possibility of poisoning.*

4) digoxin + cholestyramine: reduction of digoxin absorption

5) digoxin + aspirin: increase in poisoning with digoxin.))

Today, due to less consumption of this drug, the cases of poisoning with it have also decreased. ARBs and ACEIs have replaced them.

The therapeutic and toxic effects of digoxin on the heart are listed in the table below.

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

2) Betablockers:-

Propranolol worsens the patient's condition. But nebivolol and, metoprolol, carvedilol, bisoprolol are used to reduce the mortality of patients,

Mechanism:

According to the definition, we know that beta-blockers reduce the contraction force of the heart, but there are other properties in this collection that help in the treatment of heart failure, some of these properties are common with propranol, but there are certain differences among them.

The concentration of catecholamines (norepinephrine and epinephrine) in heart failure increases in a compensatory way and intensifies the induction of apoptosis in the heart muscle cells, and with the passage of time, the damage in the tissue increases. Beta-blockers can prevent these effects. So that:

1) It suppresses the mitogenic effects of catecholamines and reduces remodeling.
2) They also cause the heart rate to decrease.
3) Upregulation of beta receptors happens by inhibiting beta receptors.

In general, it has been seen in clinical activities that Morbidity and Mortality have decreased due to the use of beta-blockers, which is more important than the mentioned scientific justifications. Of course, in the case of drugs such as carvedilol, these effects add to its alpha blocker effect and decrease vascular resistance and afterload.

((*Many drugs are in salt form, such as morphine sulfate and diclofenac sodium, which sulfate and sodium do not play a role in the treatment of these drugs. About Metaprolol, be careful that this medicine has two salts, one is tartrate and one is succinate; that Metoprolol Tartrate, named Metoral, exists in the Iranian market It has anti-anginal and anti-blood pressure properties, but clinical studies have been conducted on metoprolol succinate in heart failure. Methohexal in The principle of metoprolol is succinate, which has a special place in heart failure.*)))

3) Diuretics:

Especially agent loop such as Forsmid is the drug of choice in heart failure.

These drugs lead to the reduction of water and salt retention in the body and control the symptoms of heart failure; But they have no direct effect on the contractile power of the heart. In fact, they can reduce Preload plasma volume and venous pressure.

In long-term use of these drugs, it has been seen that cardiac size can also change.

In total, many positive effects have been proposed for these drugs, which have made them used as the drug of choice for years; But we must be careful
which, if combined with digoxin, lead to severe hypokalemia, but if a diuretic is combined with a drug such as spironolactone, we are no longer worried about the patient's hypokalemia.

As mentioned, spironolactone and eplerenone, in addition to their diuretic effects, are aldosterone receptor antagonists, which inhibit the hydrotic effects of high aldosterone on vascular smooth muscles and heart tissue, prevent vascular edema and fibrosis, and prevent the progression of the disease.

4) Beta agonists:

They are useful in acute failure shock.

They are positive inotropes and increase CAMP, such as dobutamine and dopamine.

5) **Vasodilator**:

Hydralazine and isosorbide dinitrate reduce mortality.

Nitroprusside and nitroglycerin are effective in the treatment of acute heart failure and improve the efficiency of the heart and its size. They are especially effective when the increase in afterload is one of the main causes of heart failure.(such as persistent high blood pressure in a person who recently has MI)

6) ACEI

They reduce mortality and morbidity and are used together with diuretics in the first line of heart failure treatment.

7) Phosphodiesterase inhibitors:

These drugs inhibit the degradation of cAMP by phosphodiesterase and increase intracellular calcium, which increases the contractile strength of the heart. They are used in acute heart failure, such as Amrinone and Milrinone.

Note: In general, the drugs used in this field fall into two general categories.

1) Some improve the symptoms, such as diuretics and digoxin

2) Some of them are survival and make a person live longer, such as beta blockers, ACE inhibitors, ARBs, and aldosterone blockers.

Summary of heart failure drugs:

- ACE inhibitor: They reduce angiotensin 2 and aldosterone and reduce afterload and preload.

- Beta-blockers: they reduce the rate of vasodilation.

- Digoxin: causes a decrease in heart rate and increases the contraction strength of the heart. It is used in patients with a high degree of insufficiency.

- Diuretic: it increases fluid excretion and reduces edema and reduces the preload of the heart.

- Aldosterone antagonist: increases the volume of urine and removes the adverse effects of aldosterone.

Heart Failure Treatments: Medication Types

Type	What it does
•ACE inhibitor (angiotensin-converting enzyme)	•Expands blood vessels which lowers blood pressure, neurohormonal blockade
•ARB (angiotensin receptor blockers)	•Similar to ACE inhibitor—lowers blood pressure
•Beta-blocker	•Reduces the action of stress hormones and slows the heart rate
•Digoxin	•Slows the heart rate and improves the heart's pumping function (EF)
•Diuretic	•Filters sodium and excess fluid from the blood to reduce the heart's workload
•Aldosterone blockade	•Blocks neurohormal activation and controls volume