Drug therapy for heart failure

Pharmacology Team 430

Done By:

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PHYSIOLOGY OF HEART FAILURE

Heart Failure:

Heart failure (HF) is a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body.

Results from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood to meet the body's needs at rest or during exercise.

There two types of heart failure :

1- Left heart failure (Pulmonary congestion)

2- right heart failure (peripheral edema)

Causes:

- Disorders of coronary arteries.
- High blood pressure
- Cardiomyopathy.
- Abnormal heart rhythm
- Heart valve disorder.

Role of physiologic compensatory mechanisms in the progression of HF:

Continuous activation of the sympathetic nervous system and the renin-angiotensin-aldosterone release

Remodeling of cardiac tissue (characterized by loss of myocytes, hypertrophy, and fibrosis). As a result, the structure of the heart becomes more spherical.

This will interfere with its ability to efficiently function as a pump. Creating an abnormal cycle that, if left untreated, leads to death.

Note: If the physiology of the cardiac muscle (Contraction & Action potential) is not fully understood, you can go back to the first 2 lectures of physiology.

Compensatory physiological responses in HF (Pathophysiology):

In HF the cardiac output is decreased, the failing heart undergoes three major compensatory mechanisms to enhance cardiac output .Although initially beneficial, these alterations ultimately result in further damaging of cardiac function:

1-Increased sympathetic activity:

Baroreceptors sense a decrease in blood pressure, so it will activate the sympathetic nervous system

Stimulates β adrenergic receptors in the heart(increased heart rate and force of contraction)	α1-mediated (vasoconstriction, which enhances venous return and increases cardiac preload).

These compensatory responses increase the work of the heart, therefore, can contribute to further decline in cardiac function.

2. Activation of the renin-angiotensin system:

Fall in cardiac output decreases blood flow to the kidney, and renin is released

increase in the formation of angiotensin II , which is a potent vasconstrictor. Venoconstriction (Increased pre-load) & Arterioconstriction(Increase of afterload or resistance).

Increased release of aldosterone, which causes water and salt retention

Blood volume and pressure increases, and more blood is returned to the heart.

the heart is unable to pump this extra volume, venous pressure increases and peripheral edema and pulmonary edema occur.

increase the work of the heart and, therefore, can contribute to further decline in cardiac function.

3. Myocardial Hypertrophy:

The heart increases in size

Excessive elongation of the muscle fibers results in weaker contractions of the heart

structure of the heart changes and so lose the ability to eject blood. (systolic failure)

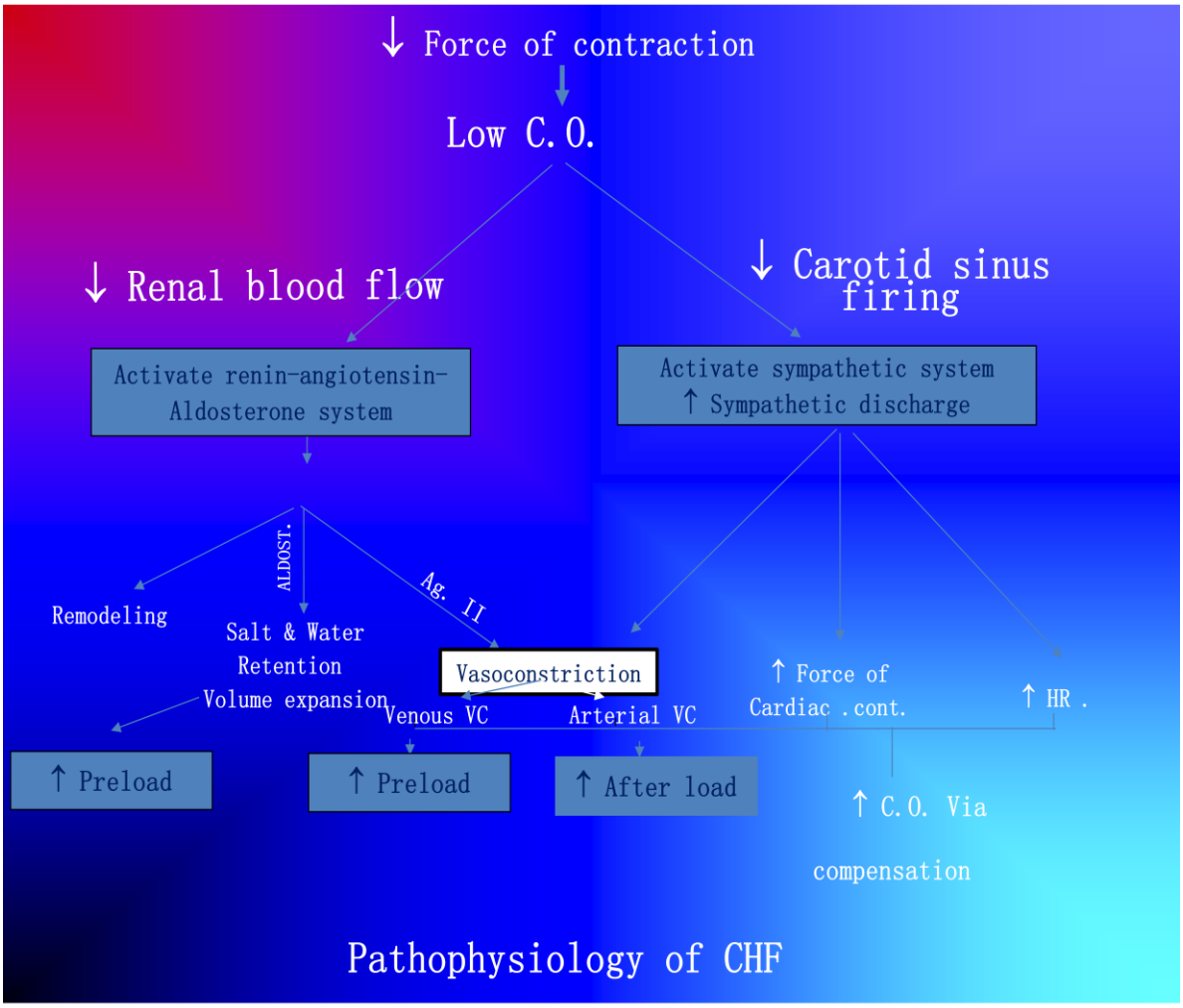
OR

the ability of the heart to relax and accept blood is impaired by structural changes (diastolic failure) , which is less common.

However, both systolic and diastolic dysfunctions commonly coexist in HF

- If the mechanisms listed above adequately restore cardiac output, the HF is said to be compensated. However, If the adaptive mechanisms fail to maintain cardiac output, the HF is termed decompensated.

Summary of pathophysiology:



Heart failure symptoms

- Tachycardia
- Decreased exercise tolerance (rapid fatigue)
- Dyspnea (pulmonary congestion)
- Peripheral edema.
- Cardiomegaly. (cardiac enlargement)

Factors affecting cardiac output and Heart Failure

- Cardiac contractility
- Preload
- Afterload
- Heart rate.

Drugs used in the treatment of heart failure

1- Drugs that increase contractility

- **Cardiac glycosides**
- **Phosphodiesterase inhibitors**
- **β- adrenoceptor agonists**

A-Cardiac glycosides (Digoxin)

- From the plant digitalis Lanta (A sugar- steroid like)

PHARMACOLOGICAL ACTIONS:

CARDIAC:

1-Direct increase: in force of contraction of the myocardium (+ve inotropic effect accompanied by reduction of the size of the failing heart leading to increased cardiac output.

2-Increase of heart excitability and automaticity:

- This effect is not therapeutically useful(digitalis-induced arrhythmia
- Digitalis toxicity increases the automaticity of Purkinji fibers and they take over as the heart pacemaker (arrhythmia).

3- Effects on conduction & refractory period:

- Slowing of conduction and prolongation of atrial & A.V. node refractory period. (In ECG : prolongation of the PR interval)
- Shortening of ventricular refractory period (In ECG : reduced QT interval)

EXTRACARDIAC EFFECTS: increases vagal activity on the heart:

1-Decrease of atrial refractory period leading to conversion of atrial flutter to fibrillation

2- Slowing of A.V. conduction

3- Bradycardia

MECHANISM OF ACTION:

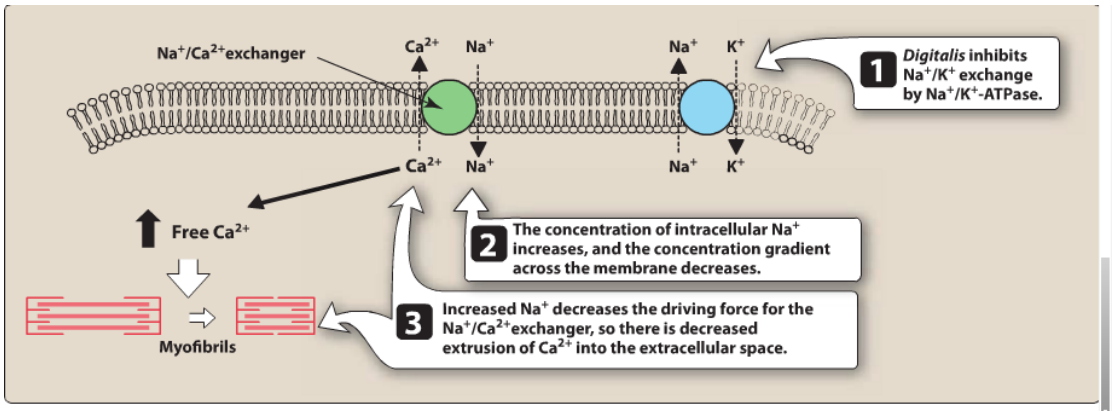


Figure 16.8
Mechanism of action of cardiac glycosides, or *digitalis*. ATPase = adenosine triphosphatase.

Thearupatic Uses

- Congestive heart failure
- Atrial arrhythmias
- Atrial flutter
- Atrial fibrillation
- Supraventricular tachycardia

pharmacokinetics

- Drug has narrow therapeutic index
- Absorption: orally : 40-80% leading to variable bioavailability I.V. acts within 15 min-3hrs
- Distribution & Metabolism: 25% protein bound, cumulative, metabolized in liver to cardioactive metabolite
- Elimination; Slow, mainly renal , t1/2 40 hrs

Adverse Effects

Cardiac adverse effects

- digitalis-induced arrhythmias can cause any type of arrhythmia
- especially:
  1-extrasystoles, coupled beats
  2-ventricular tachycardia or fibrillation
  3-A.V.block, cardiac arrest.

C.N.S

- Headache
- visual disturbances
- drowsiness

GIT

- Anorexia
- Nausea
- Vomiting
- diarrhea

Treatment of the adverse effects:

1- Stop the use of digitalis If only GIT & Visual Disturbances appears.
2- If there is a Bradycardiac arrhythmia. (Atropine)
3- If it's mild extrasystole (K+ supplements are used)
4- If these supplements fail to treat these adverse effect, we use antiarrythmic drugs (mexiletine & Beta blockers)
5- FAB fragment (Digitalis anti-bodies) : They bind with digitalis in the blood and prevent it from affecting the heart. Used in severe accidental poisoning.

Note: GIT & Visual disturbances are the first adverse effects that appear s in the patient.

FACTORS INCREASE DIGITALIS TOXICITY

- Small Lean body mass
- Renal diseases
- Hypothyroidism
- Hypokalemia
- Hypomagnesemia
- Hypercalemia

DRUG INTERACTIONS

- Diuretics→ hypokalemia (arrhythmia)
- Quinidine : ↑plasma level of digitalis

CONTRAINDICATIONS

- **Toxic myocarditis**
- **Constrictive pericarditis**
- **DC cardioversion**

B- β-Adrenoceptor agonist

- Dopamine: Acts on: α, β1 and dopamine receptors.
- Used in: acute L.H.F. mainly in patients with impaired renal blood flow.
- Dobutamine: Selective β1 agonist
- Used: in the treatment of acute heart failure (cardiogenic shock)
- They are not used in chronic cases for they might lead to arrhythmia & Angina.

C- Phosphodiesterase Inhibitors:

- **Bipyridines :(Amrinone ,Milrinone)**
- **Only available in parenteral (injection) form.**
- **Half-life 3-6hrs.**
- **Excreted in urine**

Mechanism of action:

- **Inhibit phosphodiesterase isozyme 3 in cardiac & smooth muscles → :↑ cAMP**
  This results in an increase of intracellular calcium and, therefore, cardiac contractility increases.
- In the heart : Increase myocardial contraction
- In the peripheral vasculature: Dilatation of both arteries & veins → ↓ afterload & preload.

The following graph summarizes the mechanism of Action of - β-Adrenoceptor agonists & Phosphodiesterase inhibitors.

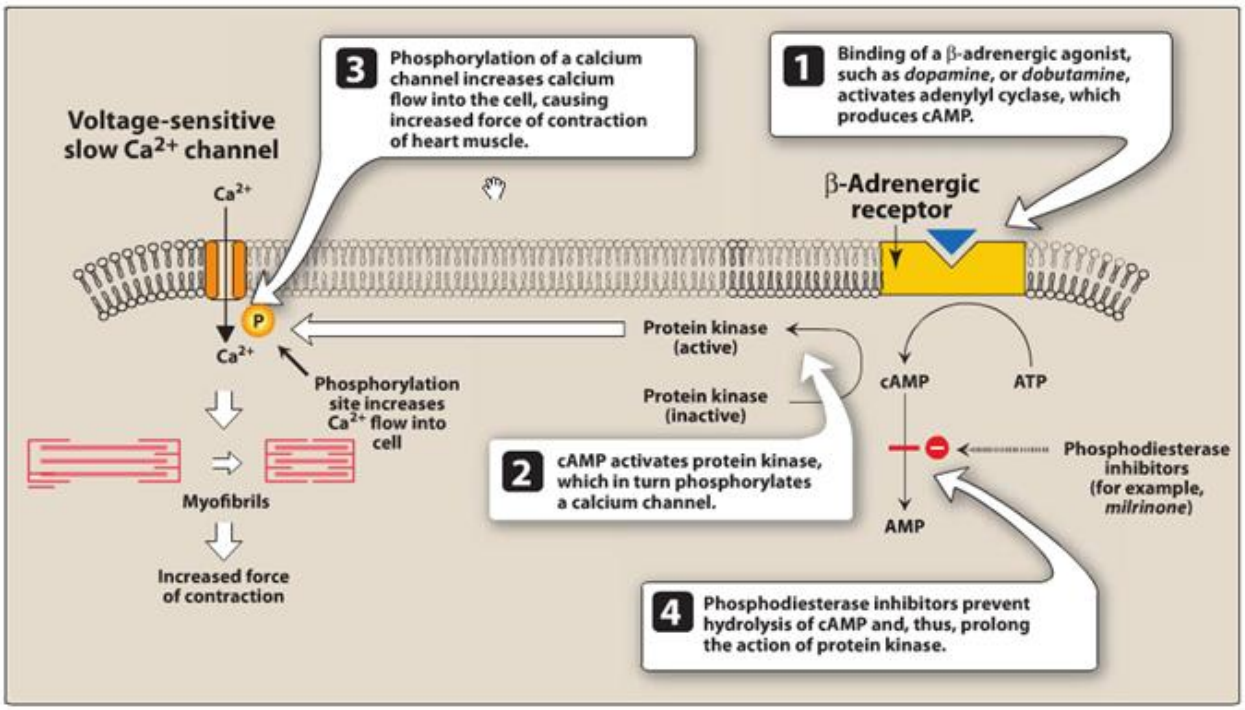


Figure 16.12
Sites of action by β-adrenergic agonists on heart muscle. AMP = adenosine monophosphate; ATP = adenosine triphospha
cAMP = cyclic adenosine monophosphate; P = phosphate.

Therapeutic uses

- **<u>Used only intravenously for management of</u> acute heart failure**

Adverse effects:

- Nausea ,vomiting
- Arrhythmias (less than digitalis)
- Thrombocytopenia
- Liver toxicity
- Milrinone less hepatotoxic and less bone marrow depression than amrinone.

2- Drugs that leads to reduction of preload

A) Diuretics (hydrochlorothiazide)

Action:

- Reduce salt and water retention→↓ventricular preload and venous pressure.
- Reduction of edema and its symptoms
- Reduction of cardiac size →improve cardiac performance

B) Venodilators (Nitroglycerine)

- Selective venodilators as nitroglycerine is used when the main symptom is dyspnea due to pulmonary congestion.
- Dilate venous capacitance vessels and reduce ventricular filling pressure (reduce preload).

3- Drugs that reduce afterload (resistance):

- Arteriolodilators (e.g. Selective hydralazine) are used when the main symptom is rapid fatigue due to low cardiac output.
- Reduce peripheral vascular resistance.

4- Drugs that Reduce after load & preload (Venodilators & Arteriolodilators)

A) Angiotensin converting enzyme inhibitors:

MOA:

Block the enzyme that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II &Stop the rate of bradykinin inactivation. (Decrease Sympatehtic activity)

ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention (decreas Blood pressure)

reduce the rate of bradykinin inactivation. (leads to Vasodilation)

Reduction of preload & Afterload

Increase in cardiac output

The next figure summarizes the MOA

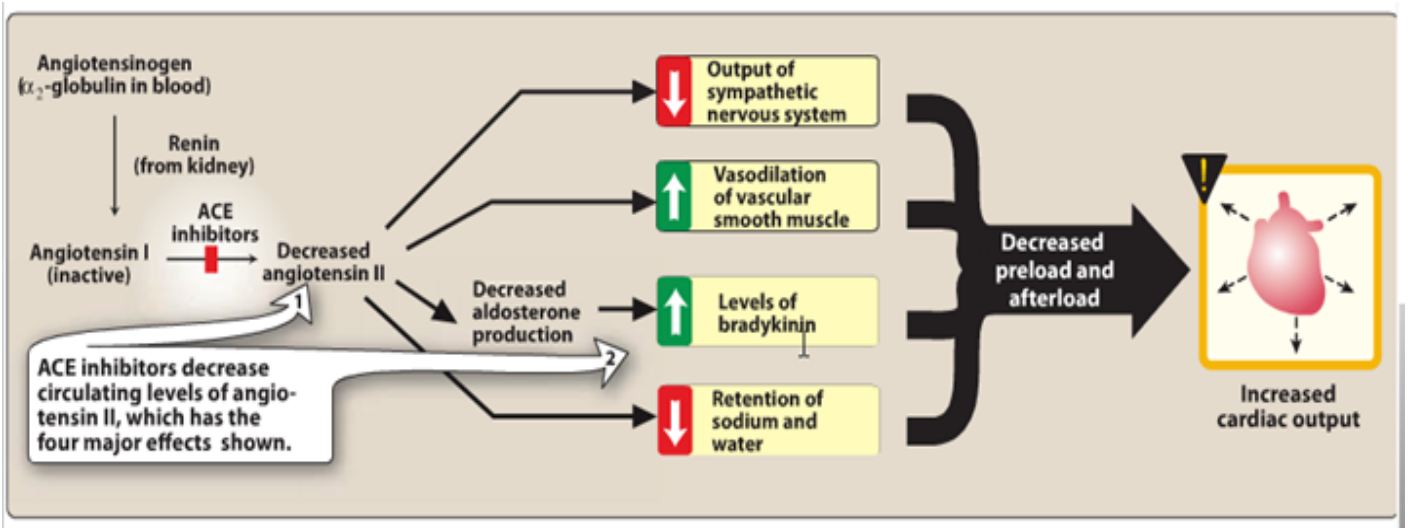


Figure 16.5
Effects of angiotensin-converting enzyme (ACE) inhibitors.

B) Angiotensin receptor blockers

MOA:

Extremely potent competitive blockers of the AT 1 receptor.

Leads to a block of action of angiotensin II

Note:

"Angiotensin receptor blockers have the advantage of more complete blockade of angiotensin action, because ACE inhibitors inhibit only one enzyme responsible for the production of angiotensin II. Further, the ARBs do not affect bradykinin levels. Although ARBs have actions similar to those of ACE inhibitors, they are not therapeutically identical."

Source Lippincott Illustrated reviews p.g 189

Uses of converting enzyme inhibitors & angiotensin receptor blockers in heart failure

- **↓Peripheral resistance (Afterload)**
- **↓Venous return (Preload)**
- **↓sympathetic activity**
- **↓remodeling (cardiac & vascular) →↓mortality rate**

C) Direct acting vasodilators:

- **(Sodium nitropruside)** The most potent vasodilator.
- **Given I.V. in refractory heart failure, acts immediately and effects lasts for 1-5 minutes.**

Note:

Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing the venous capacitance; arterial dilation reduces systemic arteriolar resistance and decrease afterload.

Uses of β-adrenoceptor blockers in heart failure:

- **Reduce catecholamine myocyte toxicity (remodeling)**
- **Decrease mortality rate**
- **Decrease heart rate**
- **Inhibit renin release**
- **e.g. Metoprolol**

Note:

The benefit of β blockers their ability to prevent the changes that occur because of the chronic activation of the sympathetic nervous system, including decreasing the heart rate and inhibiting the release of renin. These actions decrease remodeling, hypertrophy and cell death.

Management of Heart Failure

Management of chronic heart failure	Management of acute heart failure
Reduce work load of the heart: ● Limits patient activity ● Reduce weight ● Control hypertension	Volume replacement (If there is loss of blood)
Restrict sodium	Diuretics
Diuretics	Positive iontropic drugs
Angiotensin Converting enzyme inhibitors & Angiotenisin receptor blockers	Vasodilators
Digitalis	Antiarrhythmic drugs
β- blockers	Treatment of myocardial infarction (By catheterization)
Direct vasodilators	

[Note:

Calcium-channel blockers should be avoided in patients with HF. By blocking the Calcium channels, causing a decrease in the slow inward current of ECF calcium that triggers cardiac contraction. This will reduce contraction leading to a failing heart that is filled with blood (Congestive heart Failure).

Drugs That increase contractility

	Cardiac Glycosides(DIGOXIN / DIGITOXIN / OUABAIN)	Phosphodiesterase Inhibitors(BIPYRIDINES: (AMRINONE ,MILRINONE)
Pharmacological Actions	**Cardiac:** **1-Direct increase:** in force of contraction of the myocardium (+ve inotropic effect accompanied by reduction of the size of the failing heart leading to increased cardiac output. **2-Increase of heart excitability and automaticity:** -This effect is not therapeutically useful(digitalis-induced arrhythmia -Digitalis toxicity increases the automaticity of Purkinji fibers and they take over as the heart pacemaker (arrhythmia). 3- Effects on conduction & refractory period: -Slowing of conduction and prolongation of atrial & A.V. node refractory period. (In ECG : **prolongation of the PR interval)** - Shortening of ventricular refractory period **(In ECG : reduced QT interval)** **Extracardiac Effects:** **-** ↑ vagal activity on the heart : 1- ↓ of atrial RP → conversion of atrial flutter to fibrillation 2- Slowing of A.V. conduction 3- Bradycardia	• Inhibit phosphodiesterase isozyme 3 in cardiac & smooth muscles → :↑ cAMP • In the heart : ↑myocardial contraction • In the peripheral vasculature: Dilatation of both arteries & veins → ↓ afterload & preload.
Clinical Uses	• Congestive heart failure • Atrial arrhythmias: (Atr. flutter, Atr. fibrillation) • Supraventricular tachycardia	• Used only intravenously for management of acute heart failure
Pharmacokinetics	• Drug has narrow therapeutic index • **Absorption**: orally: 40-80% → variable bioavailability I.V. acts within 15 min-3hrs • **Distribution & Metabolism:** 25% protein bound, cumulative, metabolized in liver to cardioactive metabolite • **Elimination**; Slow, mainly renal , $t_{1/2}$ 40 hrs	• Only available in parenteral form. • Half-life 3-6hrs. • Excreted in urine.
Adverse Effects	**Cardiac:** digitalis-induced arrhythmias can cause any type of arrhythmia especially: • extrasystoles, coupled beats • ventricular tachycardia or fibrillation • A.V.block, cardiac arrest. **Extra cardiac**: **GIT :**Anorexia, nausea, vomiting, diarrhea **C.N.S. :** Headache, visual disturbances, drowsiness **Treatment of adverse effects:** • Atropine • Antiarrythmics • K supplements FAB	• Nausea ,vomiting • Arrhythmias (↓than digitalis) • Thrombocytopenia • Liver toxicity • Milrinone less hepatotoxic and less bone marrow depression than amrinone.
Toxicity	**Factors increase digitalis toxicity**: -Small Lean body mass - Hypokalemia - Hypomagnesemia -Hypercalemia -Renal diseases -Hypothyroidism	

contraindications	• Toxic myocarditis • Constrictive pericarditis Cardioversion
Drug Interactions.	• Diuretics→ hypokalemia (arrhythmia) Quinidine : ↑plasma level of digitalis

β-Adrenoceptor agonists:

DOPAMINE:

Acts on: α ,β_1 and dopamine receptors.

Used in: acute L.H.F. mainly in patients with impaired renal blood flow.

DOBUTAMINE :

Selective β_1 agonist

Use : in the treatment of acute heart failure (cardiogenic shock)

Uses of β-adrenoceptor blockers in heart failure:(not included in drugs ↑ contractility)

- ↓ catecholamine myocyte toxicity (remodeling)
- ↓ mortality rate
- ↓ heart rate
- Inhibit renin release

e.g. METOPROLOL

Effect	**↓ Preload**		**↓ Afterload**
Classification	**Diuretics**	**Venodilators**	**Arteriolodilators**
Drug	**HYDROCHLOROTHIAZIDE**	**NITROGLYCERINE**	**HYDRALAZINE**
Mechanism of Action	• ↓ salt and water retention→ ↓ ventricular preload and venous pressure. • ↓ of edema and its symptoms • Reduction of cardiac size → improve cardiac performance	• Dilate venous capacitance vessels and ↓ ventricular filling pressure.	↓ peripheral vascular resistance (Afterload)
Clinical Uses		Selective venodilators as it is used when the main symptom is **dyspnea** due to pulmonary congestion.	Selective arteriolodilators as it is used when the main symptome is **rapid fatigue** due to a decreased cardiac output.

Drugs that decrease preload & Afterload

Drug	**Angiotensin Converting Enzyme Inhibitors**	**Angiotensin Receptor Blockers**	**Direct Acting Vasodilators (SODIUM NITROPRUSIDE)**
Mechanism of Action	• Block the enzyme that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II • Stop the rate of bradykinin inactivation. • These actions decrase preload & afterload	• block angiotensin $_1$ receptors • ↓ action of angiotensin 11	
Clinical Uses	↓ Peripheral resistance ○ (Afterload) ↓ ↓Venous return ○ (Preload) ↓ sympathetic activity ↓ remodeling ○ (cardiac & vascular) → ↓ mortality rate		
Pharmaco kinetics			given I.V. in refractory heart failure, acts immediately and effects lasts for 1-5 minutes

Review Questions

1- Digitalis has a profound effect on myocyte intracellular concentrations of Na+, K+, and Ca2+.These effects are caused by digitalis inhibiting:

A) Ca2+- adenosine triphosphatose (ATPase) of the sarcoplasmic reticulum.
B) Na+/K+-ATPase of the myocyte membrane.
C) Cardiac phosphodiesterase.
D) Cardiac β1 receptors.
E) Juxtaglomerular renin release.

Correct answer = B. The cardiac glycosides bind to and block the action of the Na+/K+-ATPase. This leads to increased intracellular sodium. The diminished sodium gradient results in less Ca2+ being extruded from the cell via the Na+/Ca2+-exchanger. Cardiac glycosides do not bind to the Ca2+-ATPase. They have no direct effect on phosphodiesterase, β1 receptors, or rennin release.

2- Compensatory increases in heart rate and renin release that occur in heart failure may be alleviated by which of the following drugs?

A. Milrinone.
B. Digoxin.
C. Dobutamine.
D. Enalapril.
E. Metoprolol.

Correct answer = E. Metoprolol, a B1-selective antagonist prevents the increased heart rate and renin release that result from sympathetic stimulation, which occurs as compensation for reduced cardiac output of heart failure. Enalapril is an ACE inhibitor that actually increases renin release. Dobutamine increases cardiac contractility but does not slow the heart rate or interfere with renin release. Digoxin decreases the heart rate because of its vagomimetic efects, but it does not decrease renin release.

3- A 46-year-old man is admitted to the emergency department. He has taken more than 90 digoxin tab-lets (0.25 mg each), ingesting them about 3 hours before admission. His pulse is 50 to 60 beats per minute, and the electrocardiogram shows third-degree heart block. Which one of the following is the most important therapy to initiate in this patient?

A. Digoxin immune Fab.
B. Potassium salts.
C. Lidocaine.
D. Phenytoin.
E. DC cardioversion.

Correct answer = A. In the severely poisoned patient, reduction of digoxin plasma concentrations is paramount and can be accomplished with administration of antidigoxin antibodies. Potassium concentrations, if low, can be increased, but not much greater than 4 mM. Antiarrhythmics are useful if there is need, but not in this case. DC cardioversion is used only if ventricular fibrillation occurs.