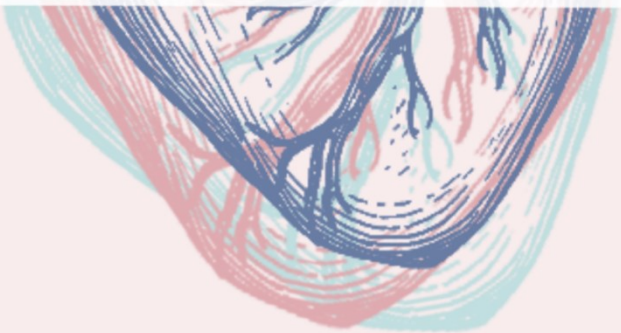
Cardio-Vascular System

6

Pharmacology



Writer: Mohannad AlDarras

S.corrector: Hadeel Abdullah

F.corrector: Dana Alnasra

Doctor: Munir Gharaibeh

Heart Failure (HF)

Definition: The heart is unable to provide adequate perfusion of peripheral organs to meet their metabolic requirements.

It is usually characterized by:

- Decreased CO
- Increased TPR (a compensatory mechanism)
  Progression to congestive heart failure (CHF) is accompanied by peripheral and pulmonary edema.

Causes of Congestive Heart Failure:

- Mechanical causes:

  Pressure overload causes, which include:

  - ✓ Hypertension
  - ✓ Aortic valve stenosis
  - ✓ Pulmonary hypertension

  Volume overload causes:

  - ✓ Valvular regurgitation
  - ✓ Shunts
  - ✓ Increased blood volume

- Impaired cardiac filling:
  - ✓ Pericardial disease (constriction or tamponade)
  - ✓ Restrictive heart disease (endo- or myocardial)
  - ✓ Ventricular hypertrophy
  - ✓ Ventricular aneurysm

- Myocardial failure:

  Primary causes include:
  - ✓ Loss of functioning muscle (due to infarction)
  - ✓ Cardiomyopathy
  - ✓ Myocarditis

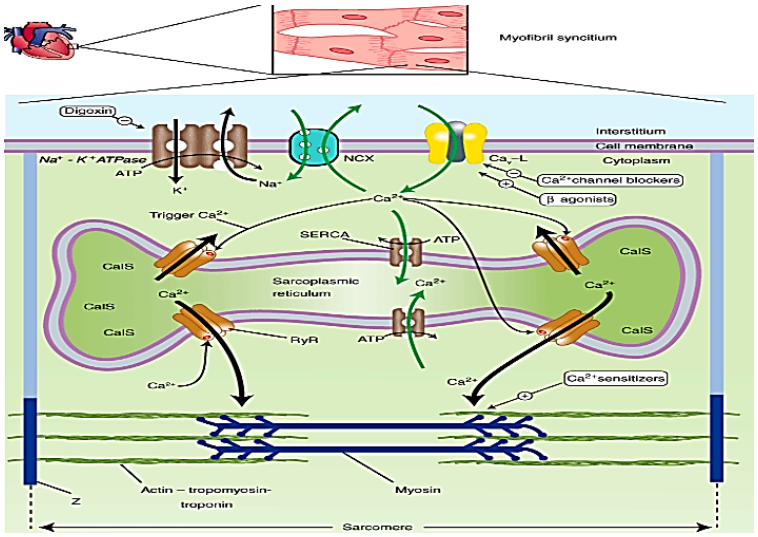
  Secondary:

  - ✓ Dysdynamic heart failure (response to chronic overload)
  - ✓ Drug-induced
  - ✓ Involvement in systemic disease, such as hypothyroidism (where we have overall slowing of metabolism and other body functions)

Cardiac output is the major factor contributing in the development of heart failure. It is determined by many factors including: (remember CO=SV x HR)

- Contractility
- Heart rate
- Afterload (ejection tension), it is the pressure that the heart must work against to eject the blood.
- Preload (end diastolic volume), increasing the venous return increases the preload which in turn increases CO.

This diagram shows the mechanism of myocardium contraction, contraction depends on the availability of extracellular calcium as well as intracellular calcium that is released from the sarcoplasmic reticulum (SR). Therefore, in treating HF we try to increase the availability of calcium for the cell.



Mechanisms of HF

In general, we have reduction in the intrinsic myocardial contractility. It could be due to:

- Depletion of NE norepinephrine in heart muscle
- Decreased myosin ATPase activity
- Decreased ATP and other high energy phosphate compounds
- Decreased beta receptors density (due to downregulation after chronic exposure to high levels of catecholamines)
- Abnormal calcium binding (the major contributing factor) could be due to:
  - ✓ Less calcium stored in the SR
  - ✓ More calcium is stored in mitochondria
  - ✓ Lesser amounts of calcium are released from the SR upon excitation
  - ✓ Lesser reuptake of calcium back into the SR after the end of contraction
  - ✓ Slow and abnormal reuptake of calcium into the mitochondria leading to slow relaxation, instead of being reuptaken into SR.

Compensatory Mechanisms in Heart failure

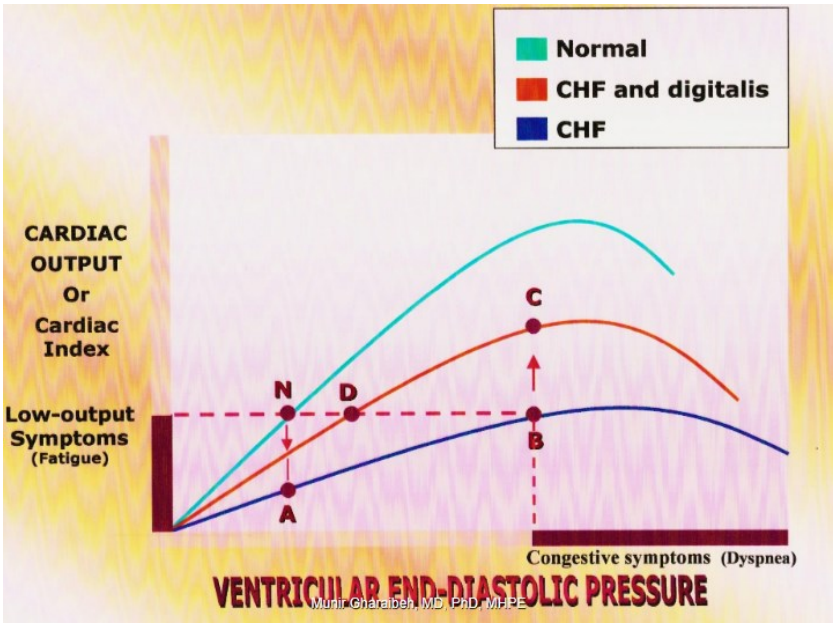
There are three compensatory mechanism that take place in patients with HF:

I. Myocardial hypertrophy, leading to increased wall tension and voltage

II. Frank starling mechanism:

Simply put, Increase in EDV (within physiologic limits) leads to increase in CO, but in HF patients, with the same increase in EDV, the cardiac output doesn't increase as much.

The orange curve shows a CHF patient with ongoing treatment, we notice that the curve doesn't go up to the normal level, meaning these patients can never achieve the normal cardiac output again.



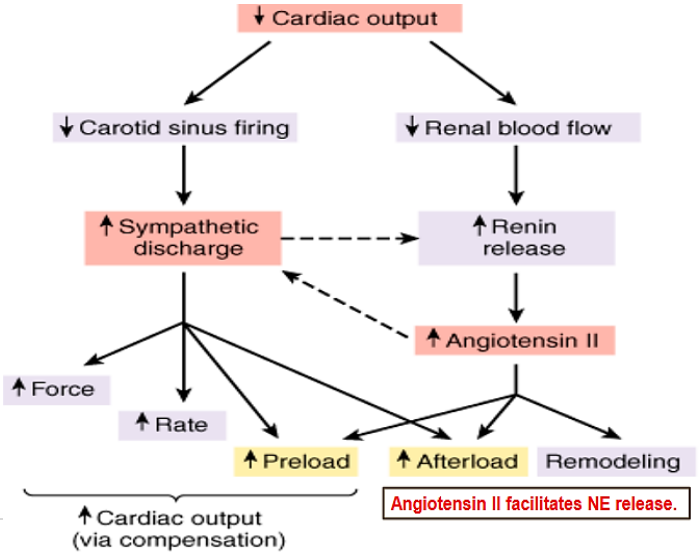
III. Increased activity of sympathetic nervous system

In a failing heart, the loss of contractile function leads to a decline in CO and a decrease in BP. Now baroreceptors sense the hemodynamic changes and initiate countermeasures to maintain support of the circulatory system. This is achieved by activation of the SNS and suppression of PSNS through central pathways. This helps maintain adequate cardiac output by:

- Increasing myocardial contractility and heart rate (β1-adrenergic receptors)
- Increasing peripheral vasomotor tone (α1-adrenergic receptors) to maintain systemic blood pressure. (constricting peripheral blood vessels).

Consequences of hyperadrenergic state:

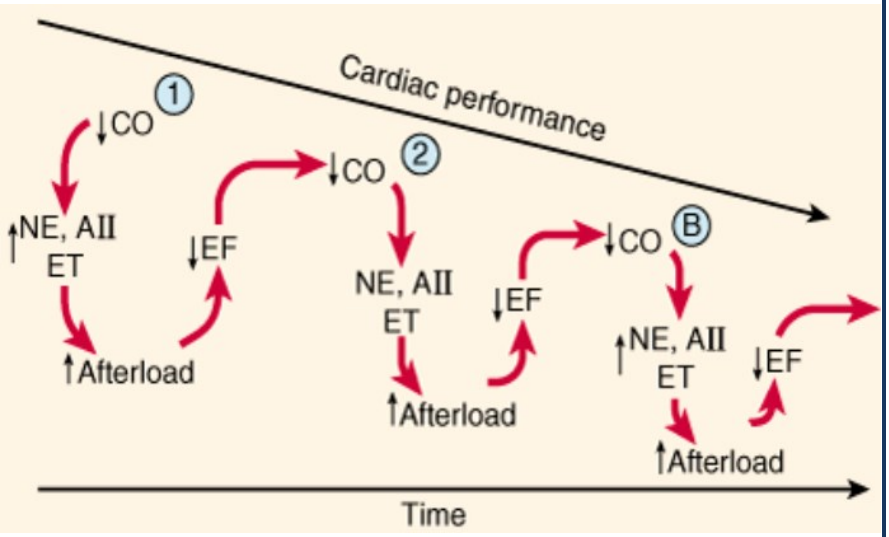
- Enhancement of renin-angiotensin-aldosterone-system (RAAS) leading to increased aldosterone and Angiotensin II levels.
- Irreversible myocyte damage, cell death, and fibrosis.



Angiotensin II contributes to cells apoptosis and damage, thus, it promotes HF expansion.

- Increased peripheral vasomotor tone leading to increased left ventricular (LV) afterload.
- This places an added stress upon the left ventricle, increase in myocardial O2 demand and ventricular remodeling (it may be beneficial in early stages but not in later stages).
- The frequency and severity of cardiac arrhythmias are enhanced in the failing heart.

Heart failure is a progressive disease meaning the cardiac performance worsens as time passes, especially if it isn't treated. Patients enter a vicious cycle of compensatory mechanisms trying to correct the problem but also worsens the case even more. (notice how the increased afterload leads to decreased ejection fraction which leads to lower CO over time.)



Signs and Symptoms of HF

- Symptoms of HF are either due to decreased cardiac output or congestive symptoms. They include:

1. Tachycardia & sweating, due to increased SNS activity.
2. Decreased exercise tolerance & shortness of breath (SOB), due to decreased blood flow to the muscles.
3. Peripheral and pulmonary edema, due to congestion.
4. Cardiomegaly (cardio-dilation with or without hypertrophy).

Classification of chronic heart failure:

ACC/AHA stage	NYHA class	Description	management
A	Pre-failure	No symptoms but risk factors present	Treat obesity, hypertension, diabetes, and hyperlipidemia.
B	I	Symptoms with sever exercise	ACEI / ARBs, Beta blockers, and diuretics.
C	II / III	Symptoms with marked class II or mild class III exercise	Add aldosterone antagonist, digoxin; CRT, hydralazine / nitrate.
D	IV	Sever symptoms at **rest**	Transplant, LVAD

Objectives of Long-Term Management of Chronic Cardiac Failure

- Improve cardiac performance (hemodynamics) at rest and during exercise. (some patients are free of symptoms during rest)
- Relieve symptoms.
- Improve myocardial efficiency (without increasing oxygen consumption).
  Myocardial efficiency measures the heart pumping and contractility in relation to its oxygen consumption; in treating HF, we don't want to increase the heart mechanical work while increasing its oxygen demand (e.g. sympathomimetic drugs).
- Improve quality of life, particularly symptom-free and effort tolerance, as much as we can depending on the age of the patient and stage of the disease, ranging from just relieving the dyspnea and orthopnea at night to being fully mobile and able to climb stairs for example.
- Improve patient survival, bear in mind that survival is the most important, we have many drugs which can almost relieve the symptoms and improve quality of life but shorten the survival causing early death.

Cardiac vs Noncardiac Therapeutic Targets

- By Conventional belief, everybody thinks that the primary defect in HF is in the heart. Reality is that HF involves many other processes and organs (kidneys and peripheral blood vessels).
- Research has shown that therapy directed at noncardiac targets is more valuable than cardiac targets.
- CHF should be viewed as a complex, interrelated sequence of events involving hemodynamic, and neurohormonal events.

The Problems facing HF patients

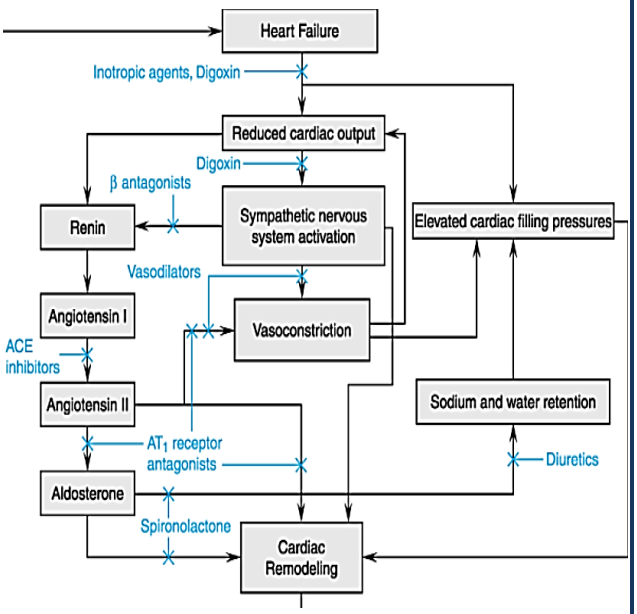
- Reduced force of contraction
- Decreased cardiac output
- Increased total peripheral resistance
- Inadequate organ perfusion
- Edema
- Decreased exercise tolerance
- Ischemic heart disease
- Sudden death (5-year survival rate is low)
- Histopathologic changes such as ventricular remodeling and decreased function

Non-pharmacologic treatment

- Salt restriction
- Treat the underlying cause *(e.g. hypertension)*
- To moderate exercise, patients should no longer perform exercises requiring great effort such as certain sports, climbing the stairs. etc.
- Heart transplantation, as a final solution.

Drugs groups used in heart failure

Chronic 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	
Vasodilators	



Diuretics

We talked about these drugs in the treatment of hypertension, they are also used for treating heart failure.

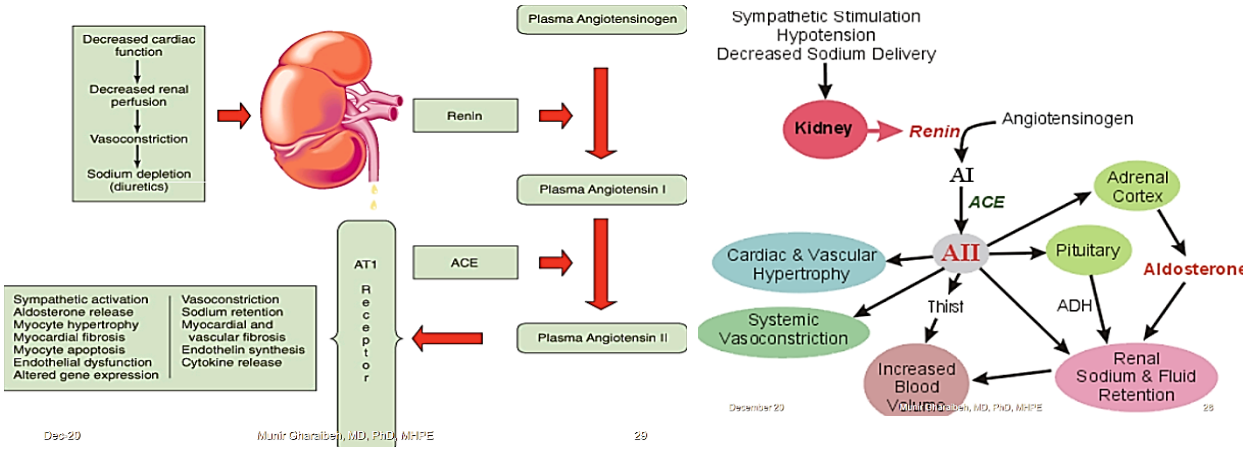
- Only indicated for HF with congestive symptoms, as they don't affect the heart muscle itself.
- Do not increase the CO, and maybe even decreases CO when used in high doses, since they decrease blood volume which decreases venous return.
- Can be used alone initially, and this might be sufficient in mild cases.
- Given IV, producing rapid relief of symptoms.
- Maybe used in combination with digitalis or other drugs.
- Causes metabolic side effects; hypokalemia (low K+ can increase the toxicity of drugs like digoxin), decrease in BP.
- Cheap drugs, and can be reduced or withdrawn easily.
- They may not work in treating HF in many cases, we call this, Diuretic Resistance in Heart Failure.

Causes of Diuretic Resistance in Heart Failure:

- Noncompliance with medical regimen, because they cause diuresis which isn't favorable by patients especially when going out. Also, excess dietary Na+ intake is also a sort of noncompliance because it opposes the activity of diuretics.
- Decreased renal perfusion and glomerular filtration rate (drugs won't be able to reach the site of action).
- Selective reduction in glomerular perfusion pressure following initiation (or dose increase) of ACE inhibitor therapy.
- Nonsteroidal anti-inflammatory drugs, they can cause salt and water retention.
- Primary renal pathology.
- Reduced or impaired diuretic absorption due to gut wall edema and reduced splanchnic blood flow; edema in the intestinal villi would affect oral drugs. (diuretics or antibiotics for example). In this case we give IV drugs.

Relationship between Renin-Angiotensin-Aldosterone System and Heart Failure:

Bottom line is, Angiotensin II is very hazardous in HF.



Potential Roles of Aldosterone in the Pathophysiology of Heart Failure

Mechanism	Pathophysiologic effects
Increased Na+ and water retention	Edema, elevated cardiac filling pressures
K+ and Mg2+ loss	Arrhythmogenesis and risk of sudden cardiac death
Reduced myocardial norepinephrine uptake. *EXTRA: the impairment of the NE uptake contributes to the -already- enhanced cardiac NE release in HF. In other words, aldosterone promotes sympathetic overstimulation in failing hearts.*	Potentiation of norepinephrine effects, myocardial remodeling, and arrhythmogenesis
Reduced baroreceptor sensitivity	Reduced parasympathetic activity (risk of sudden cardiac death).
Myocardial fibrosis, and fibroblast proliferation	Remodeling and ventricular dysfunction
Alterations in Na+ channel expression	Increased excitability and contractility of cardiac myocytes

Angiotensin Converting Enzyme Inhibitors (ACEI)

Pharmacological Actions:

- Blockade of ACE
- Reduce angiotensin II levels
- Increase bradykinin levels
- Inhibit SNS, leading to decreased NE release and upregulation of beta1 receptors.
- Balanced (indirect) vasodilators causing reduction of both afterload and preload.
- Decrease aldosterone causing decreased fluid retention, decreased K+ loss, and consequently reduced arrhythmias.
- Reduce myocyte & fibroblast growth factors causing reduced cardiac remodeling.

Therapeutic Values of ACEI:

- Nowadays drugs of choice in treatment of HF.
- No tolerance.
- Retard the progression of HF.
- Decrease arrhythmias.
- Proved to decrease mortality, but only when the highest tolerated doses are used. Meaning, we have to give the maximum tolerable doses to the patients, without causing excessive side effects such as cough.

Preparations of ACEI:

- Captopril, Enalapril, Lisinopril, Quinapril, Fosinopril.
- They all have same efficacy, but differ in potency, meaning each of these drugs is given in different concentration to reach the same effect. For example, a 50 mg dose of a certain drug could have the same effect as a 600 mg of another drug.
- Might differ in toxicity

Efficacy is the maximum effect which the drug can exert.

Potency is the concentration required to produce 50% of that drug's maximal effect.

Toxicity of ACEI:

- Hypotension (first dose phenomenon)
- Renal Impairment (proteinuria)
- K+ retention
- Cough (occurs in 10% of patients)

Angiotensin II Receptor Blockers (AT-1)

- Result in more complete inhibition of angiotensin II actions with no effects on bradykinins.
- May be only indicated when ACEIs are intolerable.
- Most expensive, but fastest growing class of antihypertensive drugs.
- Free of side effects, especially cough.
- Examples include: Losartan, Valsartan, Candesartan, Irbesartan, Eprosartan, Telmisartan (also increases peroxisome proliferator-activated receptor "PPR"-γ activity).

Good Luck