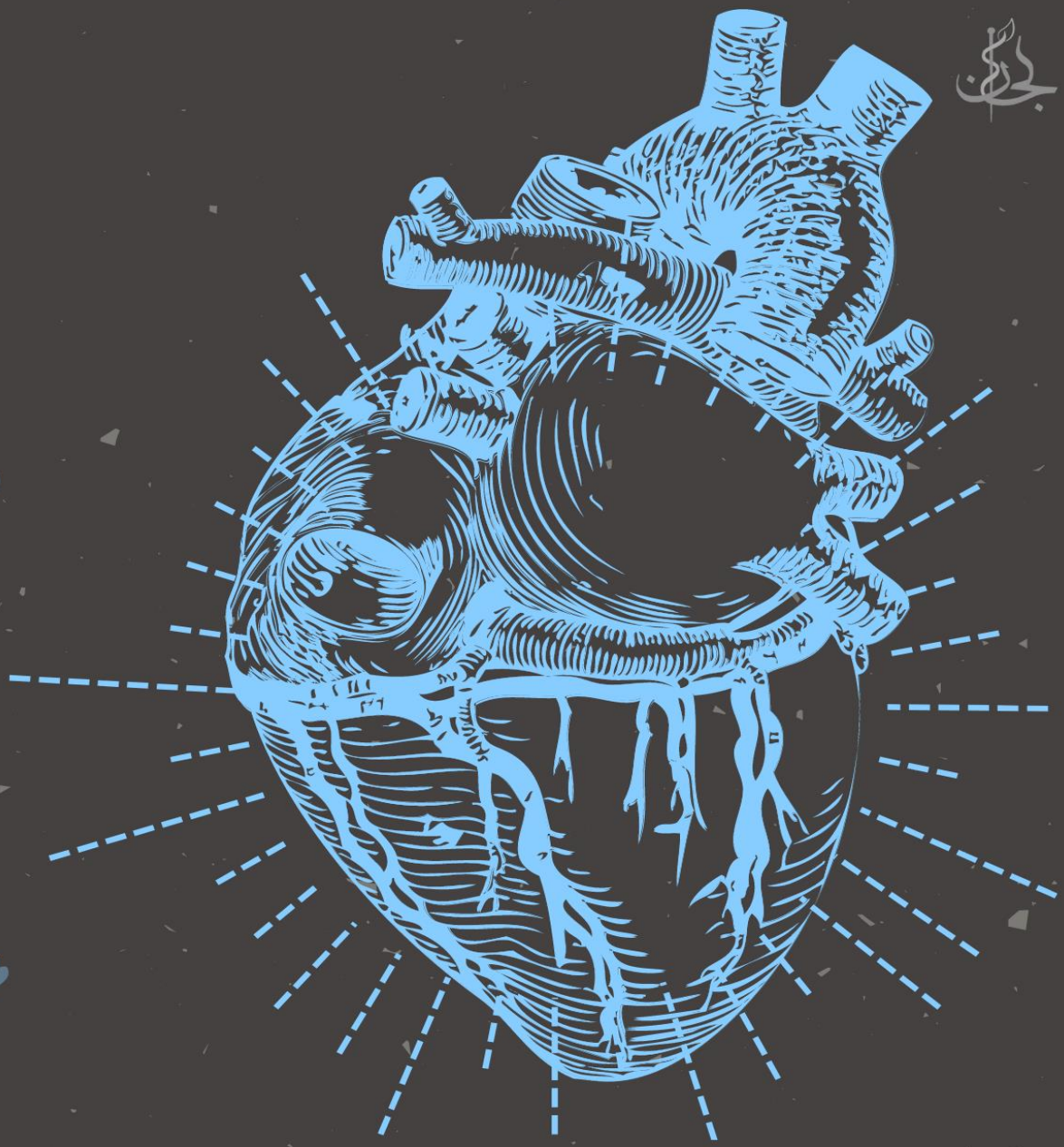
CVS



PHARMACOLOGY

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*Extra notes from new lectures are written by RED

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

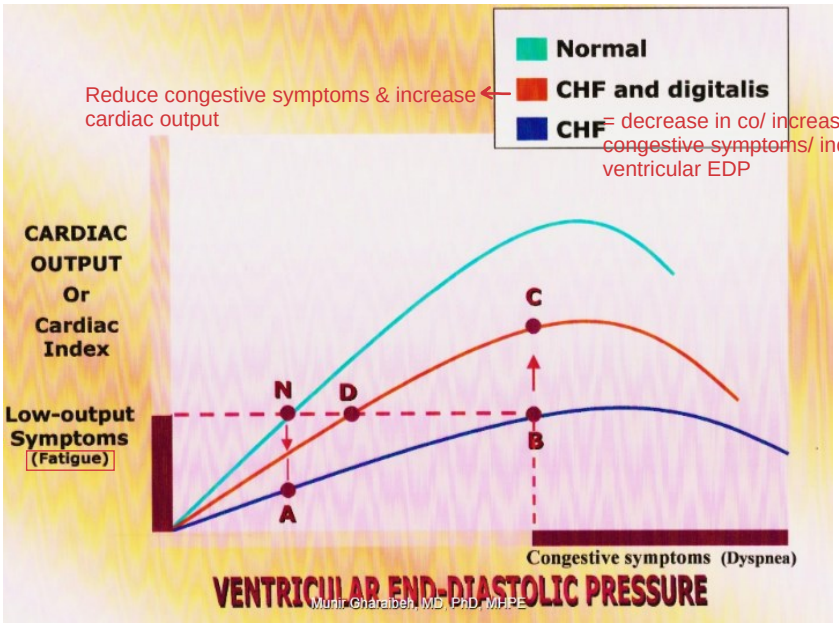
II. Frank starling mechanism:

Venous return

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.

*Works for a while then cardiac output will start going down

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.



NOTE :Poor blood supply => fatigue
Congestive symptoms => dyspnea in the lung(due to fluid congestion in lung tissue)

III. Increased activity of sympathetic nervous system

This mechanism isn't effective for long time (we will know more in the beta blockers part)

↳ Redistribution of blood to important viscera (kidneys, heart and brain)
Reduce blood supply to less important organs , like skeletal muscles (this explains the fatigue)

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:

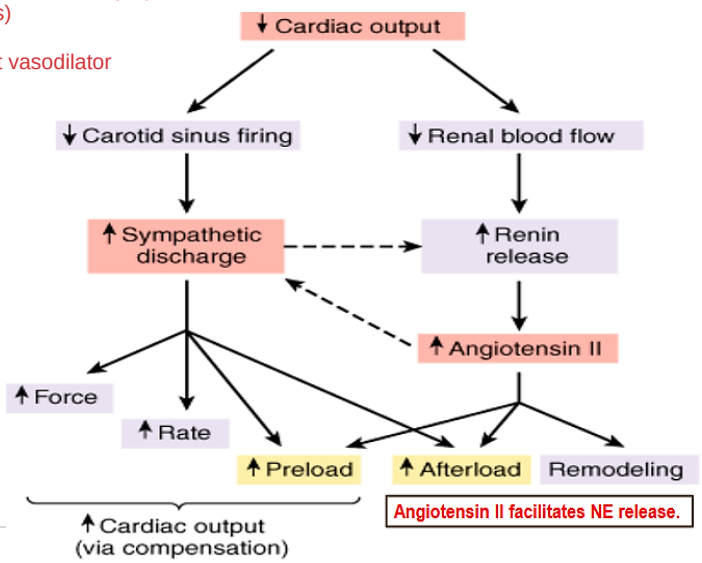
*Drop in CO => drop in blood pressure => stimulate baroreceptor reflex => tachycardia & increase the contractility => increase CO

- 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).

*Coronary circulation is under the control of metabolic state of cardiac muscle, not the sympathetic.
*blood flow to the brain is controlled by co2 (vasodilator leads to headaches)
*stimulation of dopamine receptors in renal artery cause renal dilation
*The more the heart is metabolising (form adenosine) whichever is a potent vasodilator

Consequences of hyperadrenergic state:

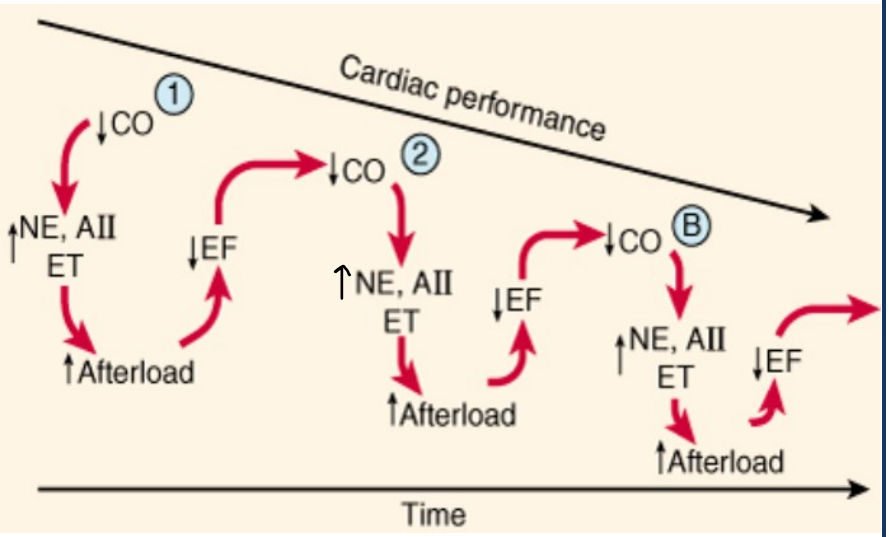
- Enhancement of renin-angiotensin-aldosterone-system (RAAS) leading to increased aldosterone and Angiotensin II levels.
- Irreversible myocyte damage, cell death, and fibrosis.



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. Not related directly to the reduction in CO
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). Can be checked by Ecocardiogram or radiologically

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. Like leg or pulmonary edema
- Improve myocardial efficiency (without increasing oxygen consumption). we use drugs that preserve cardiac efficiency
  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. Like vasodilators, sum apathetic against, etc.
- CHF should be viewed as a complex, interrelated sequence of events involving hemodynamic, and neurohormonal events.

The Problems facing HF patients

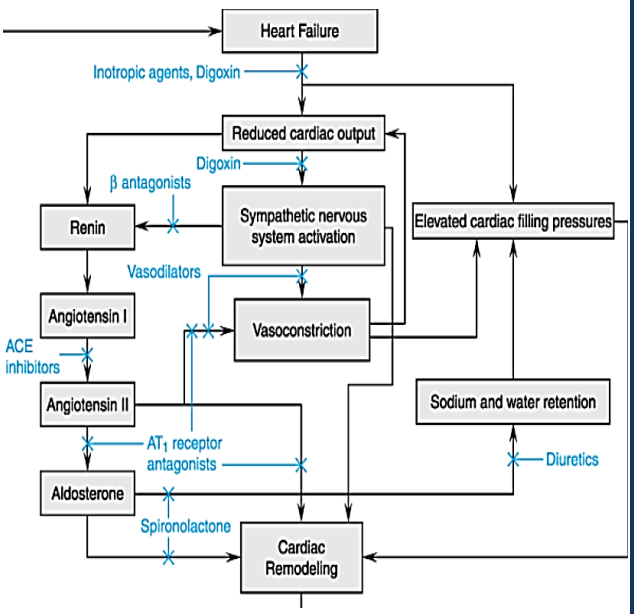
- Reduced force of contraction
- Decreased cardiac output
- Increased total peripheral resistance
- Inadequate organ perfusion
- Edema
- Decreased exercise tolerance
- Ischemic heart disease
- Sudden death (5-year survival rate is low)
- Histopathologic changes such as ventricular remodeling and decreased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

Diuretic: drugs which increase salt & water excretion throw the kidney , preferably not to excrete potassium

- 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. Like Frank starling mechanism
- Can be used alone initially, and this might be sufficient in mild cases. (Prefailure condition)
- Given IV, producing rapid relief of symptoms.
- Maybe used in combination with digitalis or other drugs. Compatible with almost all the drug used in treatment of hypertension
- Causes metabolic side effects; hypokalemia (low K+ can increase the toxicity of drugs like digoxin), decrease in BP. Hyperlipidemia, hyperglycaemia,hyperuricemia
- Cheap drugs, and can be reduced or withdrawn easily. → In the treatment in hypertension & heart failure
- They may not work in treating HF in many cases, we call this, Diuretic Resistance in Heart Failure.

In sever edema, the edema might engulf the gut wall =>impair the absobtion of all drugs =>this problem is fixed by IV diuretics (then edema will be relieved & we can start oral treatment)

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. (Consuming Salty food),This way, diuretic will increase salt excretion by 20% only
- 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.

Some of the diuretics reach

This percentage is enough to treat hypertension & heart failure, but taking more salt will make the treatment harder

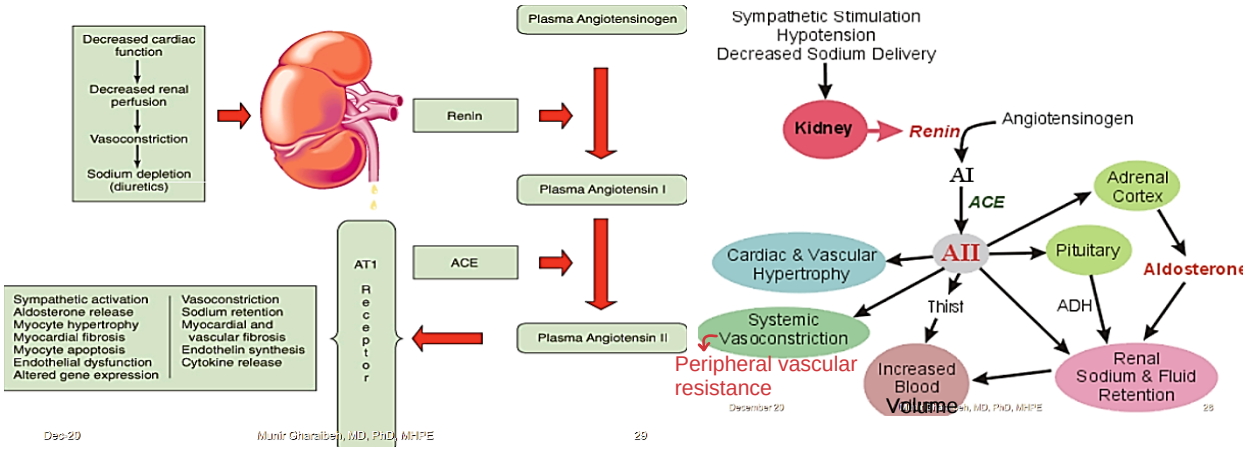
*Cause salt & water retention(edema)
* Analgesic use (Like in osteoarthritis)

*note : Some of the diuretics reach the site of action by glomerular filtration but other reach from the kidney interstitium
In case of heart failure,some drugs won't reach the site of action (like thiazide) but others may reach from interstitium

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

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

-Doctor didn't add any new information, just read the figures-



Potential Roles of Aldosterone in the Pathophysiology of Heart Failure

This table wasn't mentioned by the doctor (this doesn't mean it's not required)

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)

The standard treatment

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. Controlled by SNS
- Decrease aldosterone causing decreased fluid retention, decreased K+ loss, and consequently reduced arrhythmias. Hyperkalemia causes cardiac arrhythmia
- Reduce myocyte & fibroblast growth factors causing reduced cardiac remodeling. Angiotensin 2 share in the process of hypertrophy

With sympathetic over stimulation there will be reduced number/down regulation of beta1 receptors due to increased concentration of catecholamines
Decrease catecholamines will decrease the contractility & increase the number of beta 1 receptors
** increase no. Of receptors + little amount of catecholamines = better cardiacs output (the opposite isn't true)

Therapeutic Values of ACEI:

- Nowadays drugs of choice in treatment of HF.
- No tolerance. The effect is consistent & you can increase the dose
- Retard the progression of HF. By stopping the process of remodeling
- 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. Start with a small doses then increase it until the patient can't tolerate that hight doses

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.

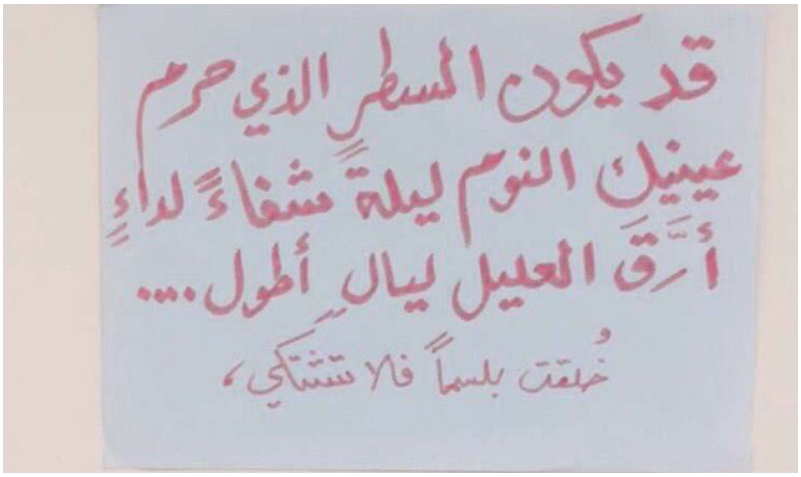
Toxicity of ACEI:

- Hypotension (first dose phenomenon)
- Renal Impairment (proteinuria)
- K+ retention Depends on other factors
- 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).

Take a short break, you did a great job



Let's continue talking about drugs used in heart failures

Beta blockers

Traditionally, we know that beta 1 receptors' activation via the sympathetic nervous system stimulates the heart function with both chronotropic and inotropic effects, by that sense beta blockers should have negative inotropic effects. The patient has heart failure so do we further depress his heart????

Sympathetic system activation => + heart rate / +contractility

-They are depressing the heart muscle & heart rate leadings to increase the CO
-(when used in small doses & with increased number of beta receptors => increase the CO

- Nowadays there is overwhelming evidence to support the use of β-blockers in CHF.
- Not useful in refractory or severe HF. So, we limit their use for early stages of HF.
- Mechanism involved remains unclear.
- Part of their beneficial effects may derive from slowing of heart rate, decreased cardiac work and consequently decreased myocardial O2 consumption (a major factor) which leads to enhanced efficiency. This would lessen the frequency of ischemic events and arrhythmias that can complicate HF.
- Suggested mechanisms also include reduced remodeling of the heart muscle.

*Note: Heart remodelling contributes to the progression of the disease

- β-Blockers may be beneficial through re-sensitization of the down-regulated beta receptors, thus improving myocardial contractility, this might be the most important effect.

At the early stage of heart failure, there's is a Sympathetic stimulation Leads to down regulation of beta receptors because of the high amount of norepinephrine

- Should be started with low doses and gradually increased. To cope with the already down-regulated receptors.

takes long time (up/down regulation process need a few weeks to resensitise new receptors

- Recent studies with metoprolol, carvedilol, bucindolol, and bisoprolol showed a reduction in mortality in patients treated with these drugs.
- This does not mean that other older beta blockers (for example propranolol) are not effective.
- Contraindicated in severe, refractory, unstable cases.

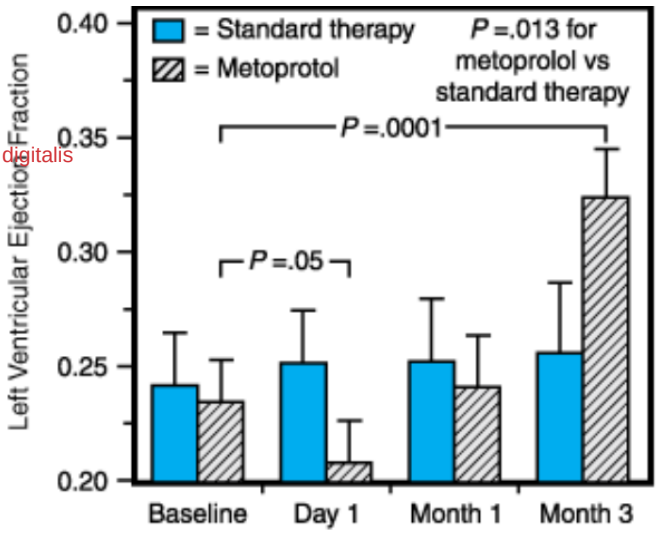
beta-blocker will suppress the cardiac function when given in high doses & Add to the problem of heart failure

-Blocking the receptors will increase the sensitisation and increase no/ Up regulation of the receptors
-This might contribute to enhance the activity of catecholamine

The figure to the right shows the effect of using beta blockers in HF.

The blue columns refer to standard therapy ACEI or digitalis without the use of beta blockers, while cross-hatched bars refer to the treatment using metoprolol which is a beta 1 selective blocker.

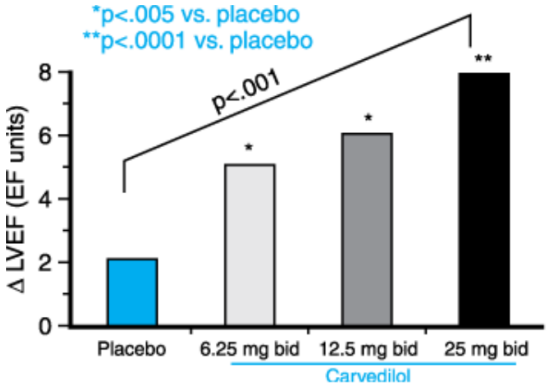
In the beginning, we started with patients having heart failure, with a low left ventricular ejection fraction (the y-axis). After one day, we notice the patients on metoprolol have even



more depressed heart, but after one month, the standard therapy improved the heart just a little bit, while the metoprolol patients have significant improvement, after 3 months, the beneficial effect of metoprolol has exceeded the effect of standard therapy.

Bottom line is that on the long run beta blockers are more effective.

- This figure shows treatment with increasing doses of carvedilol
  - You will increase left ventricular ejection fraction



Thank you