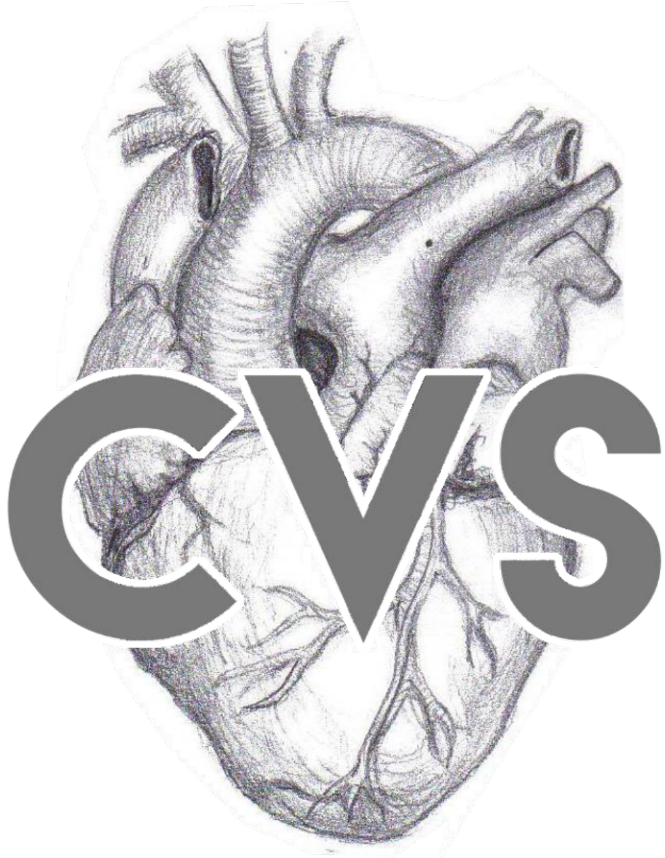

CVS

PHARMACOLOGY

☑ Sheet ○ Slide ○ Handout

Number

6

Subject

Heart failure Tx

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Price:

Heart Failure: definition & pathophysiology

When the heart becomes unable to provide the amount of O2 needed for the BODY >> we say that the heart has failed.
rem. In ischemic heart disease : the heart fails to provide enough O2 for itself (while in HF the failure is at the whole body level)
when we say HF , the first thing that comes to our minds is the reduction of SV and consequently the cardiac output , but actually>>

HF is irrespective (independent) from the cardiac output absolute value. As there's another variant in this situation which is (the Body needs of O2).
we can conclude that :
In HF the CO becomes unable to meet the metabolic needs of the body.

- ✓ **Now HF is not itself a disease but rather a complication of other diseases (like hypertension, ischemic heart diseases , valvular heart diseases, congenital heart diseases , arrhythmia …) so it's a syndrome rather than a disease. this implies that if u discover that the patient has HF >> u must investigate for the underlying cause and treat it.**

- ✓ **5-yr mortality rate ~ 50% , which means that 50% of those diagnosed with HF now will die after 5 years (this really dangerous >>similar to some kinds of cancer)**

Types of HF :

1) **Systolic HF:**
    a. **Reduced heart Contractility >> reduce pumping and ejection fraction (EF) .**

2) **Diastolic failure:**
    a. **Failure of relaxation**
    b. **Filling of heart will be impeded as the myocardium is stiff.**
    c. **Low CO.**

d. **Causes :**
    i. **Fibrosis of the myocytes after MI episode (fibrotic tissue unable to contract or relax)**
    ii. **Hypertrophy (as the myocardium will be stiff >> fail to relax)**
e. **Ejection fraction may be normal, even though stroke volume is significantly reduced.(explained in the 2nd note below)**

3) **High CO heart failure – will be discussed later**

Notes :

- ✓ **Cardiac Tamponade (accumulation of fluid in the pericardial space, resulting in reduced ventricular filling) cause HF but it cannot be treated by drugs it rather needs surgical intervention.**
- ✓ **Ejection fraction is the amount of blood ejected from the ventricle from the volume of blood that was in the ventricles before contraction.(EF=SV/EDV) >> so EF is a "percentage" not an absolute value. normally EF= 60% (this means that some amount of blood (40%) remains at the ventricle after contraction >> ESV)>> this mean that the EF can be detected as normal even if the SV and EDV are reduced (like what happens in HF)**

Factors involved:

1. **Defects in excitation-contraction coupling machinery of the heart. This is believed to be the primary defect.**
2. **Baroreceptor reflex.**
3. **Sympathetic nervous system.**
4. **Kidney.**
5. **Renin-angiotensin-aldosterone system and other peptides.**
6. **Death of myocytes (apoptosis).**

Notes about involved factors:

Factor#1 : the defect here affects contractility and it is qualitative not quantitative>>meaning that the fibers aren't less in no but they are themselves defective in away that make them dysfunctional (unlike what happens in fibrosis>>less contractile myocytes).

Factor#2 the baroreceptors will work and activate the sympathetic system but at lower BP.

Factor#3 sympathetic stimulation, cause tachycardia , vasoconstriction & stimulation of renin

Factor#5 Renin-A-A system will increase BV >> increase venous retain to heart >> increase CO.

Factor#6 programmed myocyte death part of remodeling of the heart (not as response to ischemia)>> after the myocyte dies it turns into fibrous tissue>> not functioning.

Q : the effects of the sympathetic system and renin system seam to correct HF, so why are we talking about HF Tx.
these two reflexes serve the idea of correcting HF initially but after a while they become burden on the heart.
for example when sympathetic get activated:

- ✓ **tachycardia will induce hypertrophy of the heart >> failure to relax >> diastolic failure.**
- ✓ **also tachycardia > will reduce the duration of diastole >> reducing filling time >> reducing CO.**
- ✓ **vasoconstriction will increase afterload >> reducing CO.**
- ✓ **stimulation of renin : this will activate angiotensin II which induce vasoconstriction and Na retention and induce aldosterone secretion which increase Na and water retention >>increasing BV.**
- ✓ **Aldosterone is dangerous on the heart >> as it induce remodeling (= damage) of the heart "to be discussed later'.**
  note also angiotensin II and catecholamine excess (sympathetic stimulation) remodel the heart

So after all we conclude that "the body adaptations of the HF , will help just initially then they will make the heart fail even more"

General approach to treat HF

- **Clinical research has shown that therapy directed at non-cardiac targets may be more valuable for the long-term treatment of HF than traditional positive inotropic agents (cardiac glycosides, digitalis). (Prolong survival and reduce mortality).**

Generally speaking when Treating HF we are concerned with the non-cardiac contributors of HF "like blood vessels' >> so we will use things like vasodilators

and anti-hypertensive drugs. This strategy is very effective as it both prolong survival and reduce mortality

We never target the heart alone in HF , ie . we can never use +ve inotropic agents alone (to increase the contractility of the myocytes) >>> in fact these drugs are only used in acute (sometimes chronic) systolic HF (not diastolic: as the contractility is just right here)
what are these drugs (+ve inotropes) ?
-Digitalis (cardiac glycosides)

What is the 1st line of HF Tx? (will be discussed later)

- combination of ACE inhibitors OR ARBs ,certain β blockers , aldosterone receptor antagonists
OR in case of toxicity or allergy from the 1st combination
combination of hydralazine and nitrate can be used.

- **ACE inhibitors, ARBs, certain β blockers, aldosterone receptor antagonists, and combined hydralazine-nitrate therapy are the only agents in current use that prolong life in patients with chronic heart failure (both systolic and diastolic failure).**
- **Positive inotropic drugs are helpful mainly in acute systolic failure. Cardiac glycosides also reduce symptoms in chronic systolic heart failure.**

HF can be isolated Left HF (in this case it will show pulmonary congestion and edema as a backward effect) or isolated right HF (shows systemic edema at the limbs , veseral edema , ascites at the abdomen)or both Lt and Rt HF (congestive HF >> here we give the patient strong "high-sealing" diuretics IV.)
Note: high-sealed dirutics are so strong to the extant that if they were introduced to the urethra by a catheter >> urine will be excreted instantaneously.

- Heart failure is a syndrome of different causes.
- It can involve the right ventricle, left ventricle or both.
- Cardiac output usually below normal.
- Systolic dysfunction associated with low cardiac output, low ejection fraction (< 45%; normal > 60%) is typical of acute failure (MI).

- Diastolic dysfunction often occurs as a result of hypertrophy and stiffening of the myocardium. Cardiac output is low, but ejection fraction may be normal. This type of heart failure does not usually respond well to positive inotropes.

Now , let's discuss the third type of Heart failure

High CO heart failure

- ✓ Occur in
  - Hyperthyroidism (also called thyrotoxicosis) as it's accompanied with high metabolic rate >> needs of O2 increase >> as a result of that tachycardia occur >> by upregulation of B adrenergic receptor (no. of receptors increase)
  - Anemia >> as compensation for the O2 reduction in anemia (due to lower RBC count) tachycardia will occur.(this compensatory effect helps just initially then it will fail , and the failure will manifest)
  - Beriberi disease (vit. B1 deficiency) : rare , cause microscopic AV shunts (cause less oxygenated blood to reach the systemic circulation), however these shunts are reversible >> will disappear as soon as giving B1 supplements.
  - AV shunts (major /congenital) : here less oxygenated blood reach tissues.

Note : here the real meaning of HF must get clear to u by now, as in the previous situations the heart Did provide organs with blood , but it is the amount of O2 in this delivered blood that is NOT enough.(deoxygenated blood delivered) .
another note: to treat HF in these situations we treat the underlying cause (not with HF drugs that we will talk about in this lecture)

- ✓ In hyperthyroidism : do a surgery or radiation or give antithyroid drugs
- ✓ Correct the anemia
- ✓ Give B1 supplement for beriberi
- ✓ Surgically correct major AV shunts

"High output" failure also occurs:

- **The demands are so great that even increased cardiac output is insufficient.**

1. **Hyperthyroidism**
2. **Anemia**
3. **Beriberi (vitamin B_1) deficiency**
4. **AV-shunts**

- **Responds poorly to drugs and should be treated by correcting the underlying cause.**

Signs and symptoms of all Types of HF:

1. **Tachycardia.**
2. **Shortness of breath.**
3. **Decreased exercise tolerance.**
4. **Cardiomegally.**
5. **Peripheral and/or pulmonary edema**
6. **Rapid muscular fatigue**

Notes about S&S of HF :

1: Tachycardia, due to sympathatic stimulation

2: shortness of breathe due to hyperventilation that try to provide the body with more O2.

3: decrease exercise tolerance as a result of increased O2 demand during exercise.

4: cardiomegaly , due to congestion of the heart and fluid overload in the body >> these all dilate the heart. Or in case of HTN or stenosis of any type can also cause cardiomegaly but due to hypertrophy of myocytes.

5:muscle fatigue , due to failure to satisfy their O2 demand.

Compensatory effects in HF

- ✓ **Could be extrinsic or intrinsic**

Extrinsic-s:

I. Neurohumoral (extrinsic) compensation:

1. The sympathetic nervous system:

The baroreceptor reflex appears to be reset with a lower sensitivity to arterial pressure in patients with heart failure→ reduced sensory input to the vasomotor center even at normal pressure →

→ increased sympathetic and reduced parasympathetic outflow → tachycardia, increased cardiac contractility and increased vascular tone.

- **Initially this is beneficial, it increases cardiac output and renal perfusion.**
- **After a short time, down regulation of β_1-adrenoceptor – G protein effecter system → reduced stimulatory effect.**

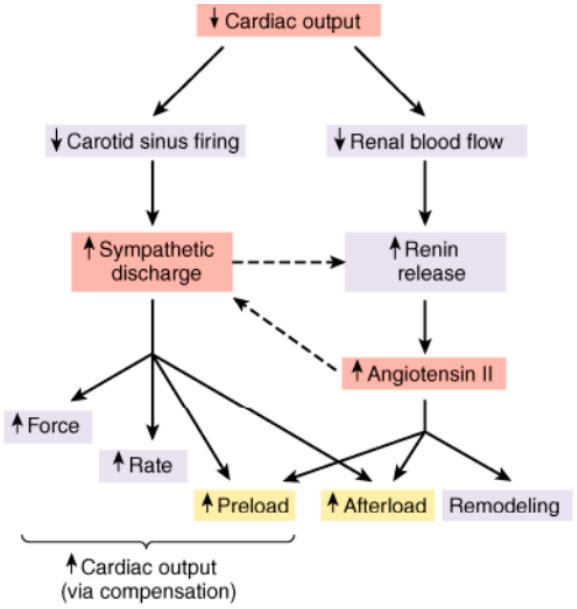
2. Increased angiotensin II production:

a. vasoconstriction and increased after load.

b. sodium and water retention and increased preload.

c. remodeling of both the heart and the vessels.

3. ANP, ADH, and endothelin production.



Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, sympathetic discharge facilitates renin release, and angiotensin II increases norepinephrine release by sympathetic nerve endings (*dashed arrows*).

Notce tachycardia will always induce hypertrophy of mayocytes (it's like any other muscle >> when used a lot it will hypertrophies)

Intrinsic-s :

1) Hypertrophy of the heart (as a result of tachycardia maybe) this effect is good at the beginning but then when the heart atrophies without good O2 supply to the heart itself >> it will become ischemic and this worsen the heart failure.

2) Remodeling of the heart : the heart here is dilated but because of fluid overload (passive stretch , high EDV) but rather because structural changes at the level of myocardium, two major things happen (along with other things):

- ✓ Fibrosis : proliferation of CT cells without damaging the myocytes (it is not healing response but rather a 1ry fibrosis process) >> this is due to catecholamine & angiotensin
- ✓ Some myocardial cells acquired fetal properties , these cells love to apoptose when do >>they are replaced by fibrotic tissue.

To sum up : hypertrophy and fibrosis induced by compensatory effects worsen HF by putting another load on normal myocytes and interfering with their function (which was not enough from the beginning)

Notes: *normal (original) fetal myocytes are replaced by adult's ones (when it's the right time) . * tissue angiotensin system is the one responsible for tissue remodeling and it's also blocked by ACE-I.

II. Intrinsic compensatory mechanisms:

1. **Myocardial hypertrophy improves cardiac performance initially. Later on, it can lead to ischemia, impairment of diastolic filling and changes ventricular geometry.**
2. **Remodeling is a term applied to dilation of the heart (other than passive stretch) and the slow structural changes that occur in stressed myocardium:**
   a. Proliferation of connective tissue cells.
   b. Abnormal myocardial cells with some biochemical characteristics of fetal myocytes.. myocytes die at an accelerated rate through apoptosis, leaving the remaining myocytes subject to even greater stress.

Some terms that are related to principle of HF Tx:

(1) **Preload** and venous retain : increased by veno-constriction (venous tone) >> when the preload is increased >> more load on heart >> worsening of HF

i. Can be corrected by venodilators and strong diuretics (to reduce the BV)
   note : salt restriction can also reduce the BV but initially (then this method fail)

(2) **Afterload** and total peripheral resistance (arterio-resistance exactly),

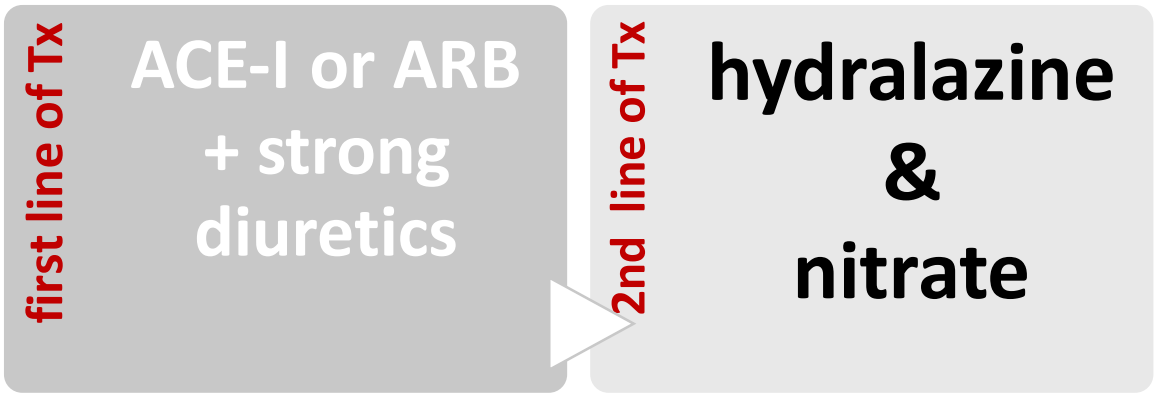
i. Corrected by vasodilators

And that's it , vasodilators and diuretics are first line of therapy for HF.
notes:
we use ACE-inhibitors for vasodilation as they dilate both veins and arteries (reducing both pre- and afterloads)
also Angiotensin receptor blockers (ARB) is also a vasodilators.

ACE inhibitors VS ARB, what to use:
using ARB is more specific as they antagonize angiotensin coming from any pathway not just angiotensin converting enzyme pathway >> this makes ARB more specific. And more importantly we use ARB when we have S&S of angioedema and cough as ACE inhibitors interfere with bradykinin degradation (inactivation) which worsening these signs.
but generally speaking we give all the patient ACE-inhibitors first , then if he develop cough or angioedema we give him >> ARB.

what to do when the patient cannot be given ACE-inhibitors nor ARB because of his renal artery stenosis (notice these info. Are highly dependent on med-term material لذا إن كنتَ ممن أوتوها فقد تكون معلومات غريبة ☺)
also if we have a pregnant we don't give ACE-I or ARB

We give him hydralazine-nitrate , which are considered as 2nd line of Tx.



Notes:

- ✓ hydralazine reduce afterload while nitrate work more on venous side and thus reduce preload.
- ✓ When we say strong diuretic we mean Furosemide loop diuretic (given IV) or any loop diuretic will be great >> to get rid of the fluid.

Left ventricular Function Curve

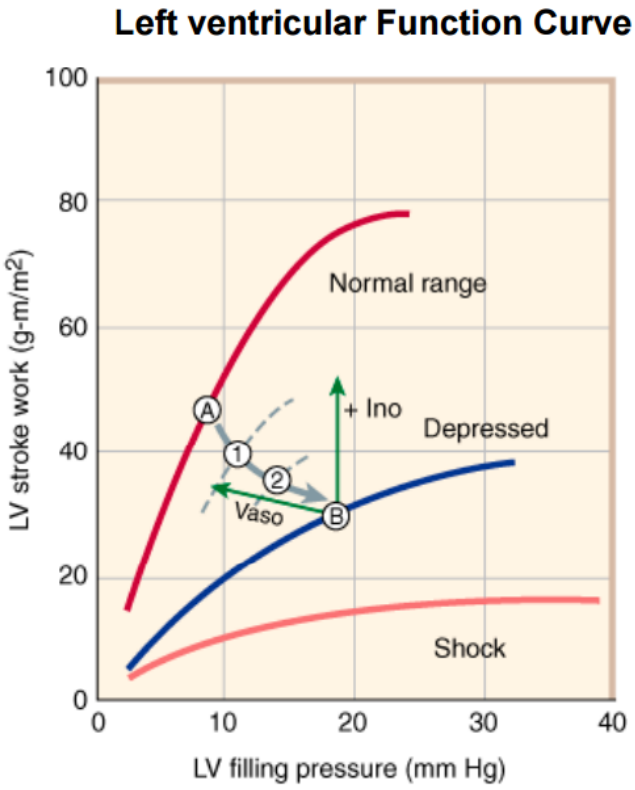
in this curve we observe the ventricular filling on (x axis) vs SV (y axis).
as u know from physiology that up to physiological limits the cardiac filling (EDV) increase the SV and sequencely the CO.

In heart failure the whole curve will be depressed (both filling and contractility are affected), looking at the curve will make u recognize that the depression is down and to the Right.
to correct this depression the curve must re-shifted up and to the left.
the correction is accomblished by drugs:

- ✓ +ve inotropes will increase the contractility of the heart >> thus increasing the SV >> the curve is re-shifted upward
- ✓ Vasodilators >> reduce BP and venous retain >> re-shift the curve to the left.
  by this the curve get back to normal.

Look at the curve

note : here we are not specific about the HF type. In diastolic HF we don't use +ve inotropes.



Relation of left ventricular (LV) performance to filling pressure in patients with acute myocardial infarction, an important cause of heart failure. The upper line indicates the range for normal, healthy individuals. At a given level of exercise, the heart operates at a stable point, eg, point A. In heart failure, function is shifted down and to the right, through points 1 and 2, finally reaching point B. A "pure" positive inotropic drug (+Ino) would move the operating point upward by increasing cardiac stroke work. A vasodilator (Vaso) would move the point leftward by reducing filling pressure. Successful therapy usually results in both effects.

Now read these slides:

Pathophysiology of Cardiac Performance

1. **Preload:**
   - Preloads > 20-25 mmHg (because of ↑ blood volume, ↑ venous tone) → pulmonary congestion.
   - Reduced by salt restriction, diuretics & venodilators.
2. **Afterload:**
   - The resistance against which the heart pumps.
   - It is represented by aortic impedance and systemic vascular resistance.
   - In chronic failure, as cardiac output declines, systemic resistance increases as a result of sympathetic stimulation and activation of renin-angiotensin-aldosterone system & endothelin.
   - Reduced by arterial dilators.
3. **Contractility:**
   - Intrinsic contractility is reduced in chronic heart failure (low output) → decreased velocity of muscle shortening and rate of intraventricular pressure development and stroke output.
   - Heart is still capable of responding to positive inotropes.
4. **Heart rate:**
   - Major determinant of cardiac output
   - Increase as a compensatory mechanism to reduced cardiac output (β_1)
   - First mechanism that comes into play to maintain cardiac output.

Diuretics

- **They reduce salt and water retention, edema, and symptoms.**
- **Reduce venous pressure and ventricular preload.**
- **Reduction of heart size → improve pump efficiency (major importance in systolic failure).**

Loop diuretics (furosemide) are the drugs of choice in congestive heart failure.

Loop diuretics= strong diuretics = high sealed diuretics , these are used in HF first given at the hospital (IV) then at home (oral).

Another diuretic to mention here is spironolactone

this diuretic is K sparing (we always want to keep K level normal at the heart >> as both hypo+hyper K are arrhythmogenic , some kinds of arrhythmias cause

direct death , others cause HF while others are mild may induce stasis /thrombosis /emboli)

What's important about spiro. Is that it can reduce the mortality of HF patient by reducing the remodeling.

Spironolactone (and eplerenone):

1.Is an aldosterone antagonist, prevents sodium and water retention.

2.Decreases morbidity and mortality in patients with severe heart failure.

3.Prevents myocardial and vascular fibrosis and barorecepyor dysfunction induced by aldosterone.

Notice that dirutics have two roles in HF mangemet

[1] loop diuretic >> given first to reduce fluid overload

[2] spironolactone >> given after a while to reduce mortality by reducing cardiac remodeling

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