Pharmacology - Final CVS

Lecture 1

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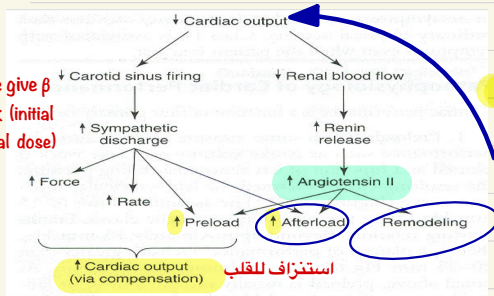
NOTES FOR REVISION

Edema !!
If there is fluids we start using diuretics
For African Americans : start with hydralazenie & Nitrates
Decrease the afterload
Decrease the preload

Heart Failure Drugs (lecture 1)



Here give β block (initial partial dose)

Degenerative disease
The body considers it as a hypotension!

In treatment we need to stop this mechanism

Figure 13–2. Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, angiotensin II increases sympathetic effects by facilitating norepinephrine release.

Every single patient with HF you start with ACEI (except for African American)

The efficacy of ACEI is more than ARBs (We can use ARBs) but also it depends on the symptoms (if the patient has cough give ARBs)

Physiological responses in HF

- Myocardial hypertrophy, here the heart increases in size and its chamber dilate, initially this will lead to a stronger contraction.

- However, excessive elongation of fibers will result in weaker contraction, and the ejection of the blood will be diminished, producing systolic failure.

Treating HF

- The main aims being
  - (1) decrease the symptoms.
  - (2) slow disease progression
  - (3) improve survival

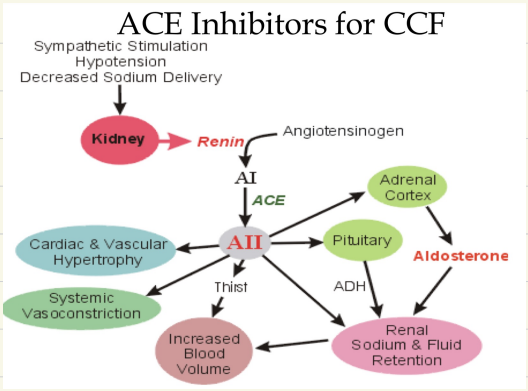
Six Classes of drugs have been shown to be effective :

(1) ACE inhibitors — With or without symptoms (dyspnea & fluid retention)
(2) β-adrenergic blocking agents, — Always ON
(3)diuretics, — Loop diuretics usually (Fursamide)
(4) inotropic agents, — The only new drug in this lecture
(5) direct vasodilators, and
(6) aldesterone antagonist — We add them to increase the efficiency of ACEIs

- Depending on the severity of HF and individual patient factors, one or more of these classes of drugs are administrated

ACE Inhibitors

- Decreases vascular resistance and so blood pressure, resulting in an increase in the cardiac output.
- They also blunt the usual angiogensin II-mediated increase in adrenaline and aldesterone seen in HF.
- These agents show a significant decrease in the mortality and morbidity.
- May be considered as a single-agent therapy in patients who have mild dyspnea on excursion, and do not have signs of volume overload.
- Early use of these ACE Inhibitors Indicated in patient with all stages of left ventricular failure, with or without symptoms



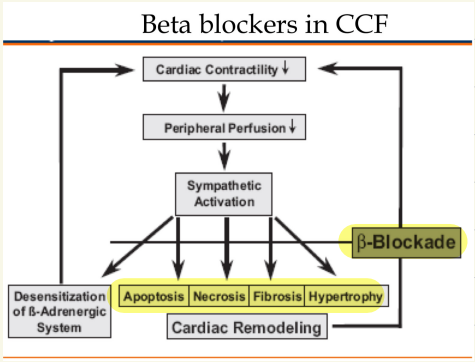
Adverse effects :

- Dry irritating persistent cough
- Hyperkalemia
- Angioedema
- Fetal toxicity

Patients with heart failure due to left ventricular systolic dysfunction who are still symptomatic despite therapy with an angiotensin converting enzyme inhibitor and a beta blocker may benefit from the addition of candesartan, following specialist advice

β-adrenergic blocking agents

- Although it may seem in logical to administer drugs with negative inotropic activity to patient with HF.
- Several clinical studies have clearly demonstrated improve systolic functioning and reverse cardiac remodeling in patients receiving β blocker
- The benefit is attributed in part to their ability to prevent changes of the sympathetic system, include decreasing the heart rate and inhibiting renin secretion.
- Bisoprolol, carvedilol or nebivolol should be the beta blocker of first choice for the treatment of patients with chronic heart failure due to left ventricular systolic dysfunction



- produce benefit in the medium to long term.
- In the short term they can produce decompensation with worsening of heart failure and hypotension. So a patient with decompensated heart failure is not given β blocker
- They should be initiated at low dose and only gradually increased with monitoring up to the target dose.
- contraindicated in patients with asthma, second or third degree atrioventricular heart block or symptomatic hypotension and should be used with caution in those with low initial blood pressure (ie systolic BP <90 mm Hg)

Diuretics

These are useful in reducing the symptoms of volume overload by :

- decreasing the extra cellular volume
- decreasing the venous return

• Diuretic therapy should be considered for heart failure patients with dyspnoea or Oedema
• Loop diuretics like furosemide and bumetanide are the most effective and commonly used.
• Thiazides are effective in mild cases only.

• The dose of diuretic should be individualised to reduce fluid retention without overtreating, which may produce dehydration or renal dysfunction.
• Loop diuretics and thiazides cause hypokalemia.
• Potassium sparing diuretics help in reducing the hypokalemia due to these diuretics.

Spironolactone

Inhibition of Na-Ka pump

• Generally Patient with advanced heart disease have elevated levels of aldosterone due to angiotension II stimulation and decrease hepatic clearance of this hormone.
• Spironolactone is a direct antagonist of aldesterone, and so prevent sodium retention, myocardial hypertrophy, and hypokalemia. It is a potassium sparing diuretics
• Spironolactone should be preserved for the most advanced cases of HF. We added it either to potentiate or for its activity by preventing the myocardial hypertrophy
Tissue dependent activity
• The dose of spironolactone should be no more than 25-50 mg/day and it is only recommended in those with moderate to severe heart failure due to LVSD.
• Main side effects include CNS effects, such as confusion, endocrine abnormalities, and gastric disturbances like peptic ulcer .
• Eplerenone can be substituted for spironolactone in patients who develop gynaecomastia

Stage C Therapy
(Reduced LVEF with Symptoms)

- Aldosterone Antagonists :

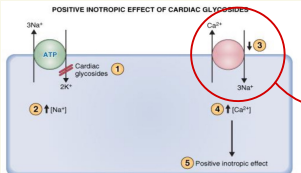
Addition of an aldosterone antagonist is recommended in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration.

- Creatinine should be less than or equal to 2.5 mg/dL in men or less than or equal to 2.0 mg/dL in women and potassium should be less than 5.0 mEq/L. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists.

- Routine combined use of an ACEI, ARB, and aldosterone antagonist is not recommended for patients with current or prior symptoms of HF and reduced LVEF.

Inotropic drugs (Digitalis)

- Increase the contractibility of heart muscles, and therefore are widely used in treatments of HF, causing the cardiac output to more closely resemble that of the normal heart.
- The most widely used is digoxin).
- Influence the sodium and calcium ions flows in cardiac muscle, thereby increasing contraction of the atrial and ventricular myocardium (positive inotropic action).
- The digitalis glycoside show only a small difference between a therapeutically effective dose and doses that are toxic or fetal. So these agents have a low therapeutic index or window



Inhibiting the Na-K ATP pump (Na still intracellular , K extracelluar)

This exchanger is gradient dependent so increasing the Na concentration in the cell will stop it
Which decreases Ca concentration (you return the heart to its normal EF and normal pumping) by making the heart cell easier to be depolarized

Digoxin

+ve inotopic activity
-ve chronotropic activity

- Digoxin is indicated with severe left-ventricular systolic failure after initiation of ACE inhibitors, diuretics, and β-Blocker.
- Patient with mild to moderate HF will usually respond to ACE inhibitors and diuretics, and do not need digoxin.
- No good oral inotropic agents exist other than digoxin.
- Digoxin also has a rapid onset of action, making it useful in emergency condition, in which the drug in given intravenously, and the onset of action will be within 5-30 minutes.

• Adverse effects:

The lowest!

- digoxin have a low margin of safety (narrow therapeutic index) and intoxication from excess of both drug is common.
- intoxication is frequently precipitated by depletion of serum K+ due to diuretic therapy.
- It also may happened because of the accumulation over a long period of time. as the signs of systemic intoxication appear, the therapy must be discontinued.

these signs includes:

Yellow holes (this side effect is for digoxin specifically)

1. Anorexia, nausea and vomiting and diarrhea.
2. Vision changes (xanthopsia), fatigue and headache.
3. cardiac effects that include: premature ventricular contraction, and ventricular tachycardia and fibrillation. Arrhythmia and atrial tachycardia.

The Antidote: DIGIFab ⚠

Digoxin interaction:

Kinetic point of view

Quinidine, varapamil, and amiodarone can cause digoxin intoxication, both by replacing digoxin from tissue protein binding sites, and by competing with digoxin for renal secretion.

These are Anti-Arrhythmic drugs

Macrolide and tetracycline antibiotics should be avoided because they elevate digoxin serum concentration and enhance the risk for digoxin toxicit

β-adrenergic agonist and Amrinone

- Dobutamine is a BI adrenergic agonist that has positive inotropic effect and is the most used inotrope agent after digoxin. It still has a vasodilation activity so more hypotension (for this we give presser (noreadrenaline)
- As mentioned, must be given by intravenous infusion and is used in the treatment of acute HF in a hospital setting.
- Amrinone Have a positive inotropic effect and increase systemic vasodilation.
- Amrinone used in short term therapy of HF that is refractory to other agents.

Stage C Therapy
(Reduced LVEF with Symptoms)

- Hydralazine and Isosorbide Dinitrate:

The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACEI and beta- blocker for symptomatic HF and who have persistent symptoms. A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency. But in patients with bilateral renal stenosis we can't give ACEI so we give this combination

- African-American patients with advanced heart failure due to left ventricular systolic dysfunction should be considered for treatment with hydralazine and isosorbide dinitrate in addition to standard therapy.

Charles Cullen

- admitted in 2003 to killing as many as 40 hospital patients with overdoses of heart medication—usually digoxin—at hospitals in New Jersey and Pennsylvania over his 16-year career as a nurse.
- On March 10, 2006 he was sentenced to 18 consecutive life sentences and is not eligible for parole

غَفر الله لكاتِبها وقارئها
ودارسِها ومُدرسها
وللمسلمين والمسلمات
جميعًا