DRUGS USED IN HEART FAILURE

Luke Lundau Biete
DipPharm, Bpharm, MclinPharm

Overview

- Congestive Cardiac failure (CCF) also known as Congestive Heart Failure is usually the end stage of a number of cardiovascular disorders

- It mostly presents with impaired ability of the ventricles to fill with blood or eject blood into circulation

Causes of Cardiac Failure

- Ischemic heart disease (most common cause)
- Hypertension
- Vulvular disorders
- Arrhythmias
- Viral and congenital cardiomyopathy
- Constrictive pericarditis
- Less commonly anemia, thiamine deficiencies or the use of some anticancer drugs like doxorubicin

Pathophysiology of Cardiac Failure

- The impaired ability of the ventricles to fill with or eject blood eventually produce molecular and cellular changes
- These changes occur at the level of cardiac myocytes and connective tissue thus leading to further structural and functional alterations in the ventricular function
- This process is called **cardiac** or **ventricular remodeling** which is characterized by cardiac dilation, ventricular wall thinning, interstitial fibrosis and wall stiffness
- These changes impair the ability of the heart to relax or contract

Pathophysiology of CCF Cont'd

- This cardiac remodeling is believed to result from the activation neuroendocrine by the ischemic, excessive stretch of muscles and other pathological stimuli

- The neuroendocrine systems involved include the

i. Renin angiotensin aldosterone axis

ii. The sympathetic nervous system

iii. Inflammatory cytokines like endothelin

- These mediators activate biochemical pathways that induce myocyte hypertrophy,apoptosis, collagen production and fibrosis

- ***All these lead to cardiac remodeling and loss of ventricular function***

- Chronic sympathetic nervous system stimulation of the injured myocardium will produce myocyte hypertrophy, increases production of myocardial cytokines like tumor necrosis factor α

- ***This ultimately leads to myocyte death due to activation of apoptotic pathway***

Pathophysiology of CCF Cont'd

- The hall mark of cardiac failure is a reduction in stroke volume and cardiac output at any diastolic muscle length which is measuring the ventricular end diastolic pressure (Pre-load)

- Reduction in stroke volume can be caused by diastolic and systolic dysfunction i.e. inability of the ventricles to fill or emptying respectively

- Systolic dysfunction can result from decreased cardiac contractility secondary to dilated or ischemic myocardium

- On the other hand, diastolic failure results from decreased compliance which is mostly presents as increased stiffness of ventricular tissue secondary to left ventricular hypertrophy and fibrosis

NB: ***Both systolic and diastolic heart failure can be caused or exacerbated by the process of cardiac remodeling***

Left ventricular Vs Right ventricular failure

Left ventricular heart failure

- Left ventricle inadequately causing increased blood pressure in pulmonary circulation
- Increased pressure forces fluid into the lung interstium therby causing pulmonary congestion and edema
- Pulmonary edema reduces diffusion of oxygen and carbon dioxide between alveoli and pulmonary capillaries and thus causing hypoxemia
- Hypoxemia can further lead to dysnea including exertional, orthopnea and paoxysmal nocturnal dysnea
- Patients often experience weakness and fatigue with reduced exercise tolerance due to generalized tissue hypoxia and organ dysfunction
- This comes about due to tissue hypoxia and organ dysfunction which come about to earlier stated combination of hypoxemia and heart's failure to pump adequate blood

Right ventricular heart failure

- Congestion in the peripheral veins leads to ankle edema to ambulatory patients
- In bedridden patients , congestion leads to sacral edema
- Also leads to hepatojugular reflux characterised by an increase in jugular vein distension when pressure is applied over the liver
- Right sided failure eventually leads to left sided failure because of the over working that is forced on the left ventricular activity due to the right ventricular failure

Aims of Treatment

- Relieve of symptoms
- Slow or reverse deterioration in myocardial function
- Improve quality of life
- Prolong survival

Approaches to CCF treatment

- Acute heart failure may require hospitalization and administration of intravenous medicines and oxygen
- Once stabilized patients can often be managed with oral medications, dietary restrictions and exercise guidelines
- Drugs can also be used to treat underlying conditions, control arrhythmia, prevent thrombosis and treat anemia

Pharmacologic Drugs for CCF

- Pharmacological agents used to treat heart failure include drugs whose activities accomplish the following;

i. **Increase cardiac output**

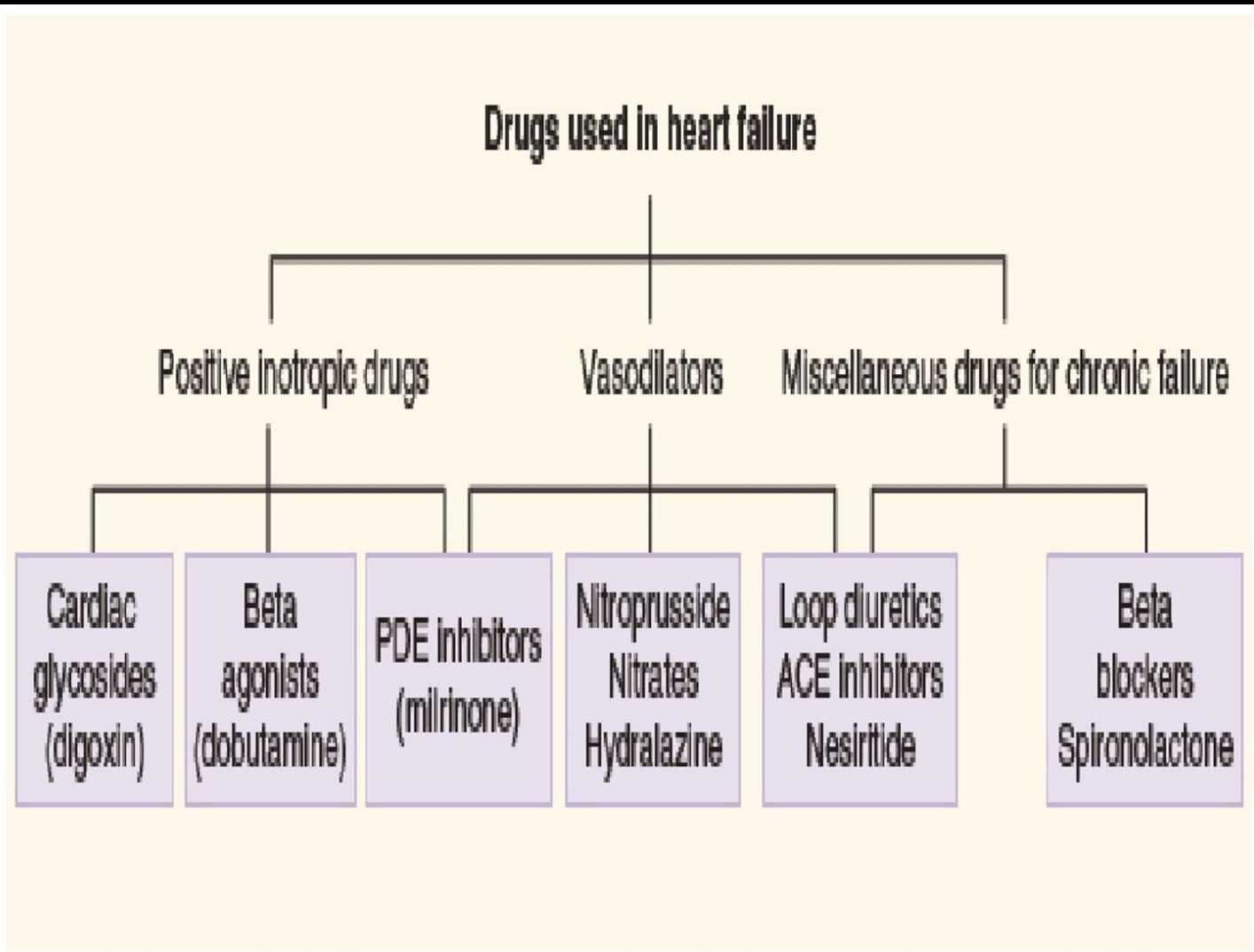
- Positive inotropics that increase cardiac contractility

- Vasodilators reduce cardiac afterload and impendance to left ventricular rejection

ii. Reduce pulmonary and systemic circulation

- Duretics which target edematous fluid and reduce plasma volume thereby decreasing circulatory congestion

iii. Slow or reverse cardiac remodeling - Angiotensin and sympathetic inhibitors works against cardiac remodeling


Drugs used in heart failure
Positive inotropic drugs
Vasodilators
Miscellaneous drugs for chronic failure
Cardiac glycosides (digoxin)
Beta agonists (dobutamine)
PDE inhibitors (milrinone)
Nitroprusside Nitrates Hydralazine
Loop diuretics ACE inhibitors Nesiritide
Beta blockers Spironolactone

Duretics

- Diuretics have been the mainstay for HF symptom management for many years
- Help to reduce plasma volume and edema
- This help relieve symptoms of volume overload such as shortness of breath (dyspnea)
- On the overall, diuretics are used for relief of acute symptoms of congestion and maintenance of volume (euvolemia)
- Diuretics interfere with sodium retention by increasing urinary sodium and free water excretion
- Recommended for all patients with clinical evidence of fluid overload retention

Duretics Cont'd

- Two types of diuretics are used for volume management in HF: thiazides and loop diuretics

Thiazide duretics

- These drugs like hydrochlorothiazide, chlorthalidone, and metolazone block sodium and chloride reabsorption in the distal convoluted tubule

- Thiazide duretics are weaker than loop duretics in increasing urine output and are not utilised frequently as monotherapy in HF and thus mostly reserved for hypertension in patients with mild congestion

- Furthermore thiazides use is limited in patients with renal insufficiency except Metolazone which still returns its potency

- Metolazone is thus used in combination with loop duretics when patients develop duretic resistance (oedema unresponsive to loop duretics alone)

Loop duretics

- These agents, including furosemide, bumetanide, and torsemide, exert their action at the thick ascending loop of Henle
- Loop diuretics increase sodium and water excretion and induce a prostaglandin-mediated increase in renal blood flow which contributes to their natriuretic effect
- Unlike thiazides, they retain their diuretic ability in patients with poor renal function
- The choice of which loop diuretic to use and the route of administration depends on clinical factors, such as presence of intestinal edema and rapidity of desired effect

Loop diuretics Cont'd

- Oral diuretic efficacy may vary based on differing bioavailability, which is almost complete for torasemide and bumetanide, but averages only 50% for furosemide
- Patients with severe volume overload should be managed in an in-patient setting
- Once diuretic therapy is initiated, dosage adjustments are based on symptomatic improvement and daily body weight

Potassium Sparing Duretics

- Examples: Spironolactone, eplerenone
- These are Aldosterone antagonists competing for the mineralocorticoid receptors in the renal tubules and other tissues
- These drugs act on the kidney to increase sodium excretion, reduce potassium excretion while exerting a mild duretic effect
- Based on the effect on potassium, these drugs are referred to as potassium sparing duretics

Potassium sparing duretics Cont'd

- Spirolocatone has been found to reduce mortality in patients with severe heart failure
- This benefit has been attributed to the prevention of the adverse effects of aldosterone on the heart and the elevation of serum potassium level
- The survival benefits of these drugs are in addition to those provided by other drugs like angiotensin inhibitors and beta blockers
- Increased use of these drugs in elderly with renal insufficiency increases hospitalization and deaths because of the hyperkalaemic effect

Side effects of aldosterone antagonists

- Aldosterone antagonists produces endocrine side effects due to its binding on the androgen and progesterone receptors
- This leads to gynecomasticia and impotency in some male
- Eplerenon produces fewer endocrine side effects than spironolactone (1% to 10%)
- Due to eplerelone being expensive, it is recommended that treatment be commenced with spironolactone and only switch to eplerenone if endocrine side effects occur

Positive inotropics

- **Examples:** Digoxin (cardiac glycoosides), dobutamine (Beta adrenergic agonist) and milrinone which is an example of phosphodiesterase III inhibitor

- These drugs are called positive intropic drugs or agents because of their ability to increase cardiac contractility

Mechanism of action – Dobutamine and Milrinone

- Have the general effect of increasing calcium influx by increasing intracellular cAMP levels

- To achieve this Dobutamine enhances the secretion of adenyl cyclase to promote formation of cAMP while Milrinone cause accumulation of cAMP by inhibiting its phosphodiesterasse III from breaking it down

Digoxin

- Digoxin works by inhibiting the sodium pump (N^+,K^+ - Atpase)
- It has direct and indirect unique actions on the cardiac system
- These effects are positive inotropy, negative chronotropy and negative dromotropy
- This causes the increase in sodium which further increases the activity of Sodium – calcium exchanger
- This finally causes more calcium to enter the cardiac myocyte which brings about muscle contraction and the peak systolic muscle tension
- All these actions increase the stroke volume and the cardiac output

Side effects

- GIT reactions like anorexia, nausea and vomiting
- Cardiac reactions
- Neurological reactions e.g. blurred vision and yellow, green or blue chromatopsia (objects appearing unnaturally colored)
- Arrhythmias which are mostly precipitated by hypokalemia

Indications of Digoxin

- Systolic heart failure and not diastolic in that contractility is not affected in the later
- Cardiac failure with atrial fibrillation

Contraindications and cautions

- Anti-acids and cholestyramine reduce absorption of digoxin and so administration should be separated between 2 hours
- Diltiazem, quinidine and verapamil reduce digoxin clearance and hence leading to accumulation of digoxin (Dosing to be reduced up to 50% if concurrent use is to be unavoidable)
- Loop and thiazide duretics cause hypokalemia and hence predisposing to digoxin toxicity

NB:

- Digoxin does not prolong survival but simply reduces symptoms (reduces morbidity)
- This subsequently reduce the need for hospitalization and improves quality of life for patients with heart failure

VASODILATORS

Vasodilators used in treatment of cardiac failure include;

- Angiotensin inhibitors
- Combination of hydralazine and isorsobide dinitrate
- nesiritide

ACE inhibitors

ACE inhibitors modify neurohormonal activity in HF by:

- Prevention of conversion of Angiotensin 1 to Angiotensin 2
- They also diminish the inactivation of bradykinin Vasodilation occurs as a result of decreased levels of the vasoconstrictor angiotensin II and increased levels of bradykinin (a potent vasodilator)
- By reducing angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone
- This leads to;

- Peripheral vasodilation - Decreased afterload -Decreased BP

- This then causes down regulation of sympathetic nervous system while improving the baro receptor function
- Patients who received most benefit had greatest neurohormonal activation

Action of ACE Inhibitors on the heart

- ACE inhibitors decrease vascular resistance (afterload) and venous tone (preload), resulting in increased cardiac output
- ACE inhibitors also blunt the usual angiotensin II–mediated increase in epinephrine and aldosterone seen in HF
- ACE inhibitors improve clinical signs and symptoms of HF and have been shown to significantly improve patient survival in HF

Indications of ACE Inhibitors

- ACE inhibitors may be considered for patients with asymptomatic and symptomatic HF
- Importantly, ACE inhibitors are indicated for patients with all stages of left ventricular failure
- Patients with the lowest ejection fraction show the greatest benefit from use of ACE inhibitors
- Depending on the severity of HF, ACE inhibitors may be used in combination with diuretics, β-blockers, digoxin, aldosterone antagonists, and hydralazine/isosorbide dinitrate fixed-dose combination
- Patients who have had a recent myocardial infarction or are at high risk for a cardiovascular event also benefit from long-term ACE inhibitor therapy

Angiotensin receptor blockers (ARBs)

- These are competitive antagonists of the angiotensin II type 1 receptor
- ARBs have the advantage of more complete blockade of angiotensin II action, because ACE inhibitors inhibit only one enzyme responsible for the production of angiotensin II
- Further, ARBs do not affect bradykinin levels
- ARBs are a substitute for ACE inhibitors in those patients who cannot tolerate the latter

Beta blockers

- Examples: Carvedilol, Bisoprolol, Metoprolol
- Although it may seem contradictory or counterintuitive to administer drugs with negative inotropic activity in HF, evidence clearly demonstrates improved systolic functioning and reverse cardiac remodeling in patients receiving β-blockers
- These benefits arise in spite of an occasional, initial exacerbation of symptoms and so it is recommended that the drugs be given only in patients who have been stabilized
- The benefit of β-blockers is attributed, in part, to their ability to prevent the changes that occur because of chronic activation of the sympathetic nervous system
- These agents decrease heart rate and inhibit release of renin in the kidneys
- Additionally, β-blockers prevent the deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy, and cell death.

Indications for Beta blockers

- β-Blockade is recommended for all patients with chronic, stable HF
- Treatment should be started at low doses and gradually titrated to target doses based on patient tolerance and vital signs
- Both carvedilol and metoprolol are metabolized by the cytochrome P450 2D6 isoenzyme, and inhibitors of this metabolic pathway may increase levels of these drugs and increase the risk of adverse effects
- β-Blockers should also be used with caution with other drugs that slow AV conduction, such as amiodarone, verapamil, and diltiazem

NB:

- ***Beta blocke reduce morbidity and mortality associated with HF***

Nitrates and Hydralazine

- Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing venous capacitance
- Nitrates are commonly used venous dilators to reduce preload for patients with chronic HF
- Arterial dilators, such as hydralazine reduce systemic arteriolar resistance and decrease afterload
- If the patient is intolerant of ACE inhibitors or β-blockers, or if additional vasodilator response is required, a combination of hydralazine and isosorbide dinitrate may be used. A fixed-dose combination of these agents has been shown to improve symptoms and survival in black patients with HFrEF on standard HF treatment (β-blocker plus ACE inhibitor or ARB)
- Headache, hypotension, and tachycardia are common adverse effects with this combination
- Rarely, hydralazine has been associated with drug-induced lupus

Order of therapy

- Experts have classified HF into four stages, from least severe to most severe.
- Note that as the disease progresses, polytherapy is initiated
- In patients with overt HF, loop diuretics are often introduced first for relief of signs or symptoms of volume overload, such as dyspnea and peripheral edema
- ACE inhibitors or ARBs (if ACE inhibitors are not tolerated) are added after the optimization of diuretic therapy
- The dosage is gradually titrated to that which is maximally tolerated and/or produces optimal cardiac output
- β-blockers were added after optimization of ACE inhibitor or ARB therapy
- Digoxin, aldosterone antagonists, and fixed-dose hydralazine and isosor□bide dinitrate are initiated in patients who continue to have HF symptoms despite optimal doses of an ACE inhibitor and β-blocker

END