Drugs Used in Heart Failure

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Heart Failure
Heart failure (HF), occurs when cardiac output is inadequate to provide the oxygen needed by the body.
Two Major Types of Failure:

Systolic Failure

- Occurs as a result of reduced mechanical pumping action (contractility) and reduced cardiac output and significantly reduced ejection fraction (< 45%; normal > 60%).
- (50% of younger patients).

Diastolic Failure

- Occurs as a result of hypertrophy and stiffening of the myocardium and loss of adequate relaxation playing a major role in reducing filling and cardiac output.
High-output Failure

- Is a rare form of heart failure.
- In this condition, the demands of the body are so great that even increased cardiac output is insufficient.
- High-output failure can result from hyperthyroidism, beriberi, anemia and arteriovenous shunts.
Signs and Symptoms of all Types of Heart Failure

- Tachycardia
- Decreased exercise tolerance
- Shortness of breath (dyspnea)
- Cardiomegaly
- Peripheral and pulmonary edema (the congestion of congestive heart failure)

Note: Decreased exercise tolerance with rapid muscular fatigue due to diminished cardiac output. The other manifestations result from the attempts by the body to compensate for the intrinsic cardiac defect.
Compensatory Physiological Responses in HF:

1) Increased sympathetic activity.
2) Activation of the renin-angiotensin system.
3) Myocardial hypertrophy compensations increase the work of the heart and lead to further decline in cardiac performance.

Decompensated HF:

If the adaptive mechanisms fail to maintain cardiac output, the HF is termed decompensated.
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).
In heart failure, output is reduced at all fiber lengths, the heart moves from point A to point B. Compensatory sympathetic discharge or effective treatment allows the heart to eject more blood, and the heart moves to point C on the middle curve.
# Drug groups used in heart failure

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<td>Beta blockers</td>
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Ace Inhibitors:

- Reduce peripheral resistance this lead to reduce afterload.
- Reduce salt and water retention (by reducing aldosterone secretion) and this lead to reduce preload.
- Reduction in tissue angiotensin levels also reduces sympathetic activity through diminution of angiotensin’s presynaptic effects on norepinephrine release.
- Reduce the long-term remodeling of the heart and vessels.
Angiotensin - Receptor Blockers

Antagonize all effect at angiotensin II type 1 receptor so lead to:

- Arteriolar and venous dilation
- Reduce aldosterone secretions
- Reduce cardiac remodeling
- Their use in HF is as a substitute for ACE inhibitors in those patients with severe cough or angioedema.
B-Blockers:

- Most patients with chronic heart failure respond favorably to certain β-blockers in spite of the fact that these drugs can precipitate acute decompensation of cardiac function.
- Studies with bisoprolol, carvedilol, long-acting metoprolol and nebivolol showed a reduction in mortality in patients with stable severe heart failure.
B-Blockers:

- Attenuation of the adverse effects of high concentrations of catecholamines (including apoptosis)
- Reduced remodeling through inhibition of the mitogenic activity of catecholamines.
- Decreased heart rate

Treatment should be started at low doses and gradually titrated to effective doses based on patient tolerance.
Diuretics

- Relieve pulmonary and peripheral edema.
- Reducing the symptoms of volume overload, including orthopnea and paroxysmal nocturnal dyspnea.
- Decrease plasma volume, decrease venous return to the heart (decrease preload).
- This leads to decreases the cardiac work and the oxygen demand.
- Decrease afterload by reducing plasma volume, thus decreasing blood pressure.
- Thiazide diuretics are relatively mild diuretics and lose efficacy if patient creatinine clearance is less than 50 mL/min.
- Loop diuretics are used for patients who require extensive diuresis and those with renal insufficiency.
# Summary of Diuretic Drugs used in Heart Failure

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<th>Subclass</th>
<th>Mechanism of Action</th>
<th>Effects</th>
<th>Clinical Applications</th>
<th>Pharmacokinetics, Toxicities, Interactions</th>
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<tr>
<td><strong>DIURETICS</strong></td>
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<tr>
<td>• Furosemide</td>
<td>Loop diuretic: Decreases NaCl and KCl reabsorption in thick ascending limb of the loop</td>
<td>Increased excretion of salt and water • reduces cardiac preload and afterload • reduces pulmonary and peripheral edema</td>
<td>Acute and chronic heart failure • severe hypertension • edematous conditions</td>
<td>Oral and IV • duration 2-4 h • Toxicity: Hypovolemia, hypokalemia, orthostatic hypotension, ototoxicity, sulfonamide allergy</td>
</tr>
<tr>
<td>• Hydrochlorothiazide</td>
<td>Decreases NaCl reabsorption in the distal convoluted tubule</td>
<td>Same as furosemide, but less efficacious</td>
<td>Mild chronic failure • mild-moderate hypertension • hypercalciuria • has not been shown to reduce mortality</td>
<td>Oral only • duration 10-12 h • Toxicity: Hyponatremia, hypokalemia, hyperglycemia, hyperuricemia, hyperlipidemia, sulfonamide allergy</td>
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- Three other loop diuretics: Bumetanide and torsemide similar to furosemide; ethacrynic acid not a sulfonamide
- Many other thiazides: All basically similar to hydrochlorothiazide, differing only in pharmacokinetics
Vasodilators

- Vasodilators are effective in acute heart failure
- Venodilators (isosorbide dinitrate) they provide a reduction in preload, uses in acute and chronic heart failure
- Arteriolar Vasodilators (hydralazine), they provide a reduction in afterload. Hydralazine and isosorbide dinitrate can reduce damaging remodeling of the heart
- Combined arteriolar and venous (Nitroprusside) uses in acute decompensated heart failure

**Note:** Calcium-channel blockers should be avoided in patients with HF
Inotropic Drugs:

- Positive inotropic agents enhance cardiac muscle contractility and thus, increase cardiac output.
- Although these drugs act by different mechanisms, in each case the inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle.
Inotropic Drugs:

1. Digitalis
   - Is the name for the family of plants (foxglove)
   - Digitalis purpurea, a major source of these agents.
   - Most of the medically useful cardiac glycosides, eg, digoxin

2. Adrenergic agonists

3. Phosphodiesterase inhibitors
1. Digitalis

- They can increase the contractility of the heart muscle are widely used in treating HF
- The cardiac glycosides influence the sodium and calcium ion flows in the cardiac muscle, thereby increasing contraction of the atrial and ventricular myocardium (positive inotropic action).
- Have a low therapeutic index.
Mechanism of Action Digitalis:

- Increase force of contraction, by inhibiting Na+/K+ ATPase in the cardiac cells causing increase of the entrance of Na+ and Ca+2 inside cardiac cells, increasing contractility of the heart muscles
Schematic diagram of a cardiac muscle sarcomere, with sites of action of several drugs that alter contractility. Na⁺/K⁺-ATPase, the sodium pump, is the site of action of cardiac glycosides.
Mechanism of action of cardiac glycosides, or digitalis. ATPase = adenosine triphosphatase
Cardiac Effects of Digitalis

- **Mechanical Effects**

  The increase in contractility by digitalis results in increased ventricular ejection, decreased end-systolic and end-diastolic size, increased cardiac output, and increased renal perfusion. These beneficial effects permit a decrease in the compensatory sympathetic and renal responses. The decrease in sympathetic tone is especially beneficial: reduced heart rate, preload and afterload permit the heart to function more efficiently.
Electrical Effects
Include early cardiac parasympathomimetic responses and later arrhythmogenic actions
Effects of digoxin on electrical properties of cardiac tissues.

<table>
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<tr>
<th>Tissue or Variable</th>
<th>Effects at Therapeutic Dosage</th>
<th>Effects at Toxic Dosage</th>
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<tbody>
<tr>
<td>Sinus node</td>
<td>↓ Rate</td>
<td>↓ Rate</td>
</tr>
<tr>
<td>Atrial muscle</td>
<td>↓ Refractory period</td>
<td>↓ Refractory period, arrhythmias</td>
</tr>
<tr>
<td>Atrioventricular node</td>
<td>↓ Conduction velocity, ↑ refractory period</td>
<td>↓ Refractory period, arrhythmias</td>
</tr>
<tr>
<td>Purkinje system, ventricular muscle</td>
<td>Slight ↓ refractory period</td>
<td>Extrasystoles, tachycardia, fibrillation</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>↑ PR interval, ↓ QT interval</td>
<td>Tachycardia, fibrillation, arrest at extremely high dosage</td>
</tr>
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</table>
Early Responses

- The effects on the atria and AV node are largely parasympathetic (mediated by the vagus nerve) and can be partially blocked by atropine.
- Increase in the AV nodal refractory period.
- Increased PR interval
- Shortened QT
Toxic Responses

- Increased automaticity, caused by intracellular calcium overload, is the most important manifestation of digitalis toxicity.
- Intracellular calcium overload results in delayed afterdepolarizations, which may evoke extrasystoles, tachycardia, or fibrillation in any part of the heart. In the ventricles, the extrasystoles are recognized as premature ventricular beats (PVBs).
Therapeutic Uses Digitalis:

1. HF with Atrial fibrillation

- Digitalis
  - Reduce the conduction velocity
    - Or
  - Increase the refractory period of the AV node so that ventricular rate is controlled within a range compatible with efficient filling and ejection.
  - This therapeutic objective due to the parasympathomimetic action of digitalis (high doses may be required).
Therapeutic Uses Digitalis:

2. Congestive Heart Failure

Digitalis may improve functional status (reducing symptoms), it does not prolong life.

**Note:** Other agents (diuretics, ACE inhibitors and vasodilators) may be equally effective and less toxic.
Pharmacokinetics of Digitalis:

- Oral, paraentral
- Digoxin, is 65–80% absorbed after oral administration.
- The half-life of Digoxin is 36–40 hours in patients with normal renal function.
- Digoxin is not extensively metabolized in humans; almost two thirds is excreted unchanged by the kidneys.
- Requiring dose adjustment in patient with renal dysfunction.
- Digoxin has a large volume of distribution.
- A loading dose regimen is employed when acute digitalization is needed.
- Digitoxin has a much longer half-life and is extensively metabolized by the liver before excretion in the feces.
Side Effects of Digitalis Glycosides

1. Cardiac arrhythmia, characterized by slowing of atrioventricular conduction associated with atrial arrhythmias
2. Gastrointestinal effects: Anorexia, nausea, and vomiting
3. Central nervous system effects: These include headache, fatigue, confusion, visual changes, blurred vision, alteration of color perception.
4. Hyperkalemia, serum potassium will already be elevated at the time of diagnosis (because of potassium loss from the intracellular compartment of skeletal muscle and other tissues)

5. Gynecomastia (a rare effect)
Factors Predisposing to Digitalis Toxicity:

- Electrolytic disturbances:
  - Hypokalemia
  - Hypercalcemia
  - Hypomagnesemia

- Drugs: Quinidine, verapamil, and amiodarone, can cause digoxin intoxication, both by displacing digoxin from tissue protein-binding sites and by competing with digoxin for renal excretion.

- Hypothyroidism, hypoxia, renal failure, and myocarditis are also predisposing factors to digoxin toxicity
  - Digitalis-induced vomiting may deplete serum magnesium and similarly facilitate toxicity.
Digitalis toxicity with electrolytic disturbances:

- Potassium and digitalis interact in two ways.
  1. They inhibit each other’s binding to Na⁺/K⁺-ATPase
    - Hyperkalemia reduces the enzyme-inhibiting actions of cardiac glycosides
    - Hypokalemia facilitates these actions.
  2. Abnormal cardiac automaticity is inhibited by hyperkalemia.
- Calcium ion facilitates the toxic actions of cardiac glycosides by increasing intracellular calcium stores and may cause digitalis-induced abnormal automaticity. Hypercalcemia therefore increases the risk of a digitalis-induced arrhythmia.

- The effects of magnesium ion are opposite to those of calcium.
Drugs interacting with digoxin and other digitalis glycosides

Increased digitalis concentration may occur during concurrent therapy

Enhanced potential for cardiotoxicity

Decreased levels of blood potassium

Corticosteroids
Thiazide diuretics
Loop diuretics

Amiodarone
Erythromycin
Quinidine
Tetracycline
Verapamil
Management of Digitalis Toxicity:

- Discontinuing cardiac glycoside therapy
- Determining serum potassium levels, and if indicated, giving potassium supplements.
- Digoxin levels must be monitored in the presence of renal insufficiency, and dosage adjustment may be necessary.
- Severe toxicity resulting in ventricular tachycardia may require administration of antiarrhythmic drugs and the use of antibodies to digoxin (digoxin immune Fab), which bind and inactivate the drug.
2. Beta Adrenergic Agonists:
- Adrenergic stimulation causing positive inotropic effects and vasodilation.
- Dobutamine is the most commonly used inotropic agent other than digitalis.
- Dobutamine leads to an increase in intracellular cyclic adenosine monophosphate (cAMP), which results in the activation of protein kinase. Protein kinase phosphorylate slow calcium channels and increases entry of calcium ion into the myocardial cells, thus enhancing contraction.
- Dobutamine must be given by intravenous infusion.
3. Phosphodiesterase inhibitors (Bipyridines)
Inamrinone (previously called amrinone) and milrinone
Selective inhibitors of PDE3 (heart-specific subtype (type III) of phosphodiesterase, that inactivate cGMP and cAMP
- Increase the intracellular concentration of cAMP. This results in an increase of intracellular calcium and cardiac contractility and accelerate myocardial relaxation
- Cause balanced arterial and venous dilation with a consequent decrease in systemic and pulmonary vascular resistances and left and right-heart filling pressure
Pharmacokinetic

- Available For Iv form only
- Half-lives 3-6 hours
- 10-40% being excreted in the urine
Side Effect of Bipyridines

- Inamrinone may cause nausea and vomiting, arrhythmias, thrombocytopenia and liver enzyme changes (withdrawn in some countries)
- Bone marrow and liver toxicity (Inamrinone more than Milrinone)
- Arrhythmias (Milrinone)
- Long-term therapy may increase mortality
Natriuretic Peptide: Nesiritide

- Is a synthetic form of the endogenous peptide brain natriuretic peptide (BNP)

Clinical Uses

- In acute (not chronic) cardiac failure

Mechanism of Action

- Activate BNP receptors
- Increases cGMP in smooth muscle cells
- Vasodilation
- Diuresis
Pharmacokinetic of Nesiritide

- Short half-life of about 18 minutes
- Administered as a bolus intravenous dose followed by continuous infusion.

Adverse Effect of Nesiritide

- Excessive hypotension
- Renal damage
- May increase mortality
Pharmacologic Therapies for Heart Failure

- The removal of retained salt and water with diuretics
- Reduction of afterload and salt and water retention by means of angiotensin-converting enzyme (ACE) inhibitors
- Reduction of excessive sympathetic stimulation by means of β blockers
- Reduction of preload or afterload with vasodilators
- In systolic failure, direct augmentation of depressed cardiac contractility with positive inotropic drugs such as digitalis glycosides
- Considerable evidence indicates that angiotensin antagonists, certain β-adrenoceptor blockers, Adosterone antagonists spironolactone and eplerenone also have long-term beneficial effects.
**Acute heart failure**

- Should be treated with a loop diuretic; if very severe, a promptacting positive inotropic agent such as a B agonist or phosphodiesterase inhibitor, and vasodilators should be used as required to optimize filling pressures and blood pressure. Nesiritide, heavily promoted for use in acute failure.

**Chronic Heart Failure**

- Best treated with diuretics (often a loop agent + spironolactone) + ACE inhibitor and, if tolerated, a B blocker. Digitalis may be helpful if systolic dysfunction is prominent.