Drugs for Congestive Heart Failure

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Congestive Heart Failure

Definition:

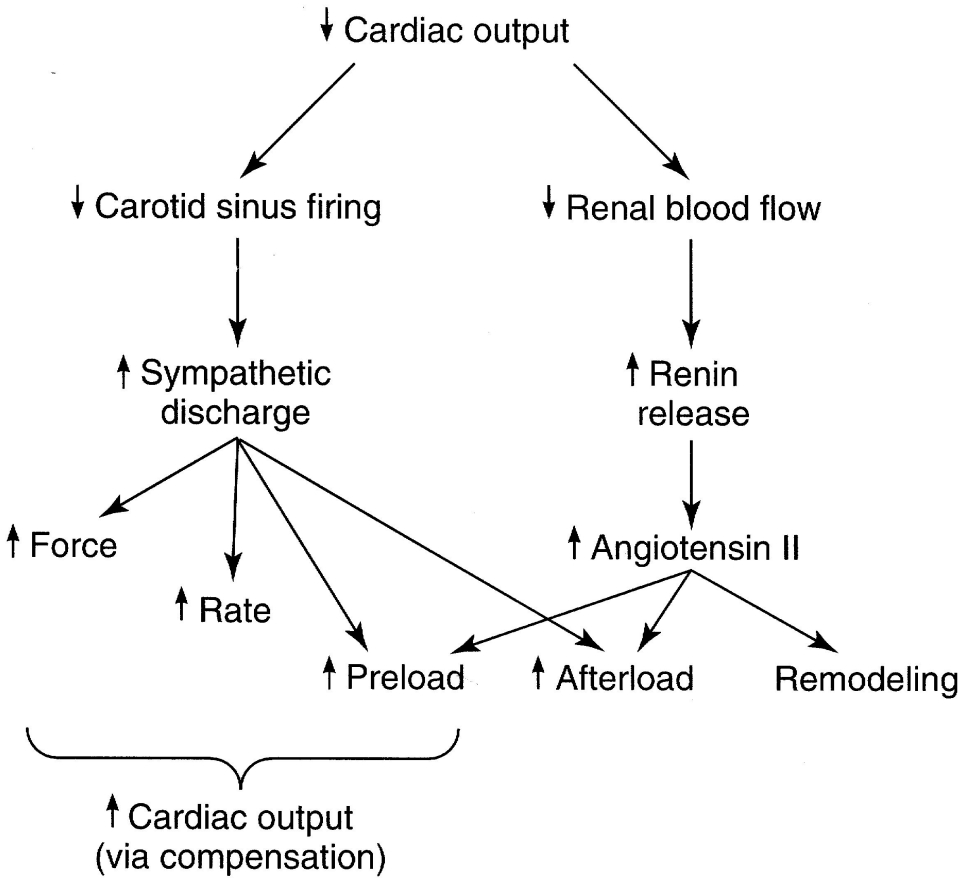
Failure of the heart to maintain a cardiac output sufficient to meet the metabolic demands of the body

Major Causes:

Ischemic Heart Disease, Chronic Hypertension, Valvular Heart Disease,Cardiomyopathies, COPD

Compensatory Mechanisms in Heart Failure

- **Mechanisms designed for acute loss in cardiac output**
- **Chronic activation of these mechanisms worsens heart failure**



Other Effects of CCF

1. Myocardial Hypertrophy –Increase in muscle mass to help maintain cardiac performance

2. However continued failure leads to Cardiac Remodeling which is dilatation and slow structural changes that occur in the stressed myocardium

Ultimately myocytes die through apoptosis causing even greater stress on the heart

Clinical Consequences

- Fatigue
- Peripheral Edema (Salt and Water Retention)
- Shortness of Breath due to Pulmonary Edema)

Classification of Drugs Used in CCF

A. Cardiac Targets

1. Cardiac Glycosides

Digoxin Digitoxin

2. Sympathomimetics

Dopamine Dobutamine

3. Phosphodiestrase Inhibitors

Amrinone Milrinone

4. Beta Blockers with ISA

Oxprenolol Pindolol

5. Sensitivity Contractile protein(levosimendan)

B. Non-Cardiac Targets

1. To Decrease Preload

a) Diuretics

i) Loop Diuretics

Frusemide

ii) Thiazide Diuretics

Chlorthiazide Indapamide

iii) Potassium Sparing Diuretics

Spironolactone

b) Nitrates

Nitroglycerin

c) ACE Inhibitors

Captopril

d) Angiotensin Receptor Blockers

Losartan

2. To Decrease Afterload

Vasodilators

a) Direct Vasodilators

Hydralazine

Na Nitroprusside

b) Indirect Vasodilators

i)ACE Inhibitors

Captopril,Enalapril

ii) Angiotensin Receptor Blockers

Losartan,Valsartan

iii) Alpha Blockers

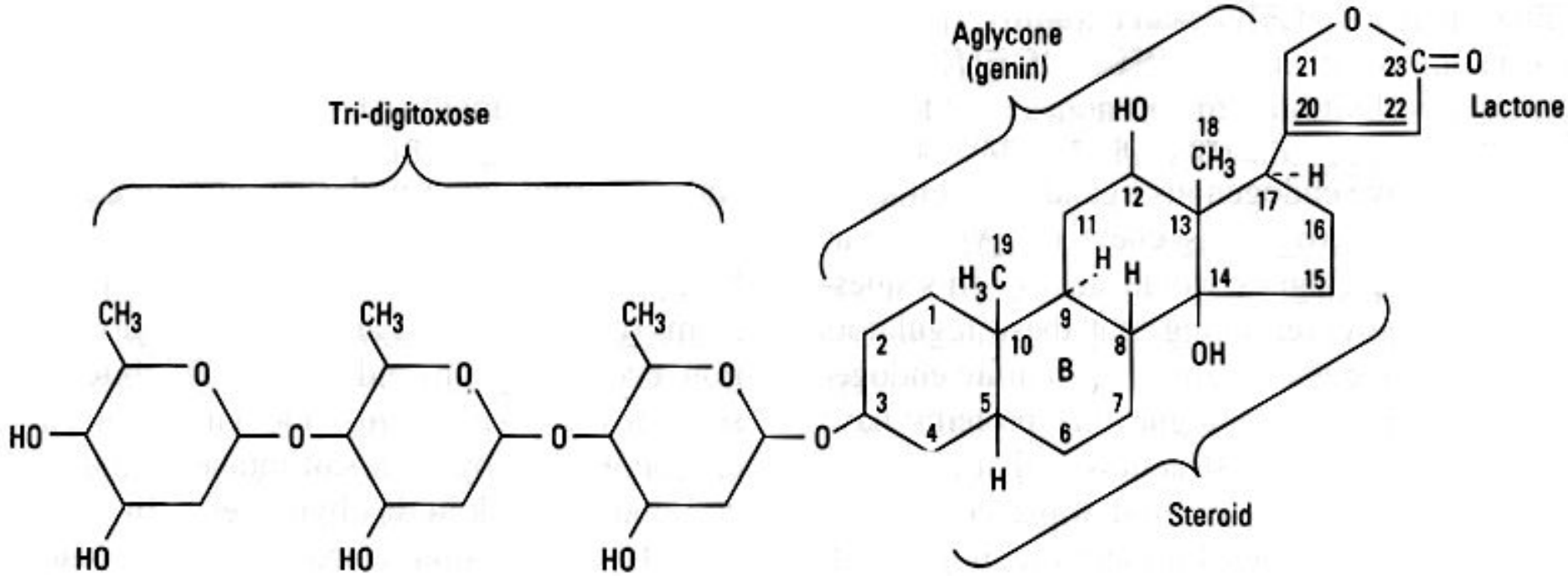
Prazosin

iv) Beta Blockers

Bisoprolol, Carvedilol, Metoprolol

Cardiac Glycosides

- **Digoxin**
- **Digitoxin**
- **Ouabain**



Mode of action

A. Inhibition of Na+/K+ ATPase in heart---positive inotropic effect

B. The consequences of inhibition of Na+/K+ ATPase also affect the Electrical function of the heart.

C. Cardiac glycosides also modify Autonomic Outflow & this affects electrical properties of heart

D. Inhibition of Na^+/K^+ ATPase in CNS & GIT--- produces adverse effects.

Mechanical Effects

1. Increased Contractility (Positive Ionotropic Effect)

↑ the stroke volume and thus Cardiac Output

- Duration of systole ↓
- more time for both ventricular filling and rest to the heart

O2 consumption → function of initial diastolic fibre length, such a reduction in size decreases the O2 consumption for a given work output.

digitalized heart can do the same work with less energy o

2. Heart Rate is decreased (Negative Chronotropic Effect) due to:

Vagal Action (Blocked by atropine)

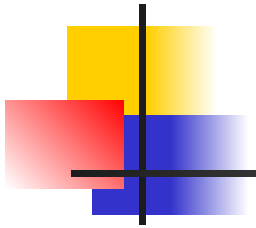
i) Direct stimulation of vagal nucleus
ii) Sensitization of the carotid baroreceptors
iii) Increased sensitivity of muscarinic receptors to Ach

- In CCF the sympathetic activity is increased due to compensatory mechanisms
- Digoxin, by improving the circulation decreases the sympathetic response and thus decreases the heart rate

Electrical Effects

1. Action Potential Duration (Direct Action)

- Shortened due to Increased K conductance caused by increased intracellular Calcium



2. RMP (Direct Action)

- This is made less negative.
- It is due to inhibition of Na Pump and causing decreased K in cells
- Delayed after depolarizations (DADs) after some time due to overloading with intracellular calcium and oscillations in Ca

Effects of Digoxin on electrical properties of cardiac tissues

Tissue or Variable	Effects at therapeutic Dosage	Effects at Toxic Dosage
Sinus node	↓ Rate	↓ Rate
Atrial muscle	↓ RP	↓ RP, arrhythmias
Atrioventricular Node	↓conduction velocity , ↑RP	↑RP, arrhythmias
Purkinje system, ventricular muscle	Slight ↓ RP	Extrasystoles, tachycardia, fibrillation
Electrocardiogram	↑ PR interval , ↓ QT interval	Tachycardia, fibrillation, arrest at extremely high dosage

RP = Refractory period

Overall Benefit of Digitalis to Myocardial Function

- ↑↑ **cardiac output**
- ↑ **cardiac efficiency**
- ↓ **heart rate**
- ↓ **cardiac size**

Uses of Digoxin

1. **CCF**
2. Atrial flutter
3. Atrial fibrillation
4. PSVT

Adverse Effects of Digoxin

- **Drug with a low Therapeutic Index**

1. Cardiac

- First sign of digoxin toxicity beside nausea and vomiting is BRADYCARDIA
- An afterdepolarization may reach threshold and elicit an action potential (ECTOPIC BEATS)
- BIGEMINY will be recorded on the ECG (PULSUS BIGEMINUS)

2. GIT

Anorexia, nausea and vomiting, abdominal pain and diarrhea

3. CNS Effects

Disorientation, hallucinations and visual disturbances
Agitation and convulsions rare

4. Endocrine

Gynaecomastia in men-structure resembles estrogens

Treatment of Digitalis Toxicity

- Reduce dose for 1st degree heart block, ectopic beats
- Atropine for advanced heart block
- KCl
- Antiarrythmics e.g. Lignocaine for ventricular arrhythmias and Propranolol for supraventricular arrythmias
- Fab antibodies for toxic serum concentration; acute toxicity

Phosphodiesterase Inhibitors

- **amrinone**
- **milrinone**

Mechanism of Action

- **inhibition of type III phosphodiesterase**
- **(Enzyme that breaks down cAMP)**
  - **↑ intracellular cAMP**
  - **↑ activation of protein kinase A**
    - **Ca^{2+} entry through L type Ca channels**
    - **inhibition of Ca^{2+} sequestration by SR**

- **↑ cardiac output**
- **↓ peripheral vascular resistance**

Adverse Effects of Phosphodiesterase Inhibitors

- **Cardiac arrhythmias**
- **GI: Nausea and vomiting**
- **Hepatotoxicity**
- **Bone Marrow depression**
- **Sudden death**

Mechanism of Action: Dopamine

- **Stimulation of cardiac β_1–adrenoceptors: ↑ inotropy > ↑ chronotropy**
- **Increase in CO**
- **peripheral vasodilatation**
- **↑ myocardial oxygen demand**
- **Dobutamine also used**

Adverse Effects

- **Dobutamine**
  - **Tolerance**
  - **Tachycardia**
- **Dopamine**
  - **tachycardia**
  - **arrhythmias**
  - **peripheral vasoconstriction in higher doses**

ACE Inhibitors & Angiotensin Receptor Blockers in CCF

Mechanism of Action

- **Afterload reduction**
- **Preload reduction**

- **Reduction of facilitation of sympathetic nervous system**
- **Reduction of cardiac hypertrophy and decreased cardiac remodeling**

Diuretics: Mechanism of Action in Heart Failure

- **Preload reduction: reduction of excess plasma volume and edema fluid**
- **Afterload reduction: lowered blood pressure**
- **Reduction of facilitation of sympathetic nervous system**

Spironolactone

- **Aldosterone antagonist, K-sparing diuretic**
- **Prevention of aldosterone effects on:**
  - **Kidney**
- **Aldosterone elevated in CHF**
- **Mobilizes edema fluid in heart failure**
- **Prevention of hypokalemia induced by loop diuretics (protection against digitalis toxicity)**
- **Prolongs life in CHF patients**

Vasodilators

- **Mechanism of action: reduce preload and afterload**
- **Drugs used**
  - **Sodium nitroprusside**
  - **Hydralazine**
  - **Ca^{2+} channel blocker (Only Amlodipine)**
  - **Prazosin**

β-Blockers in Heart Failure: Mechanism of Action

Beta Blockers with ISA

Beta Blockers with ISA e.g. oxprenolol have an advantage of maintaining a degree of Beta 1 receptor activation, while at the same time blunt the cardiac response to increased sympathetic nerve activity or to circulating adrenaline

- **Beta Blockers without ISA**

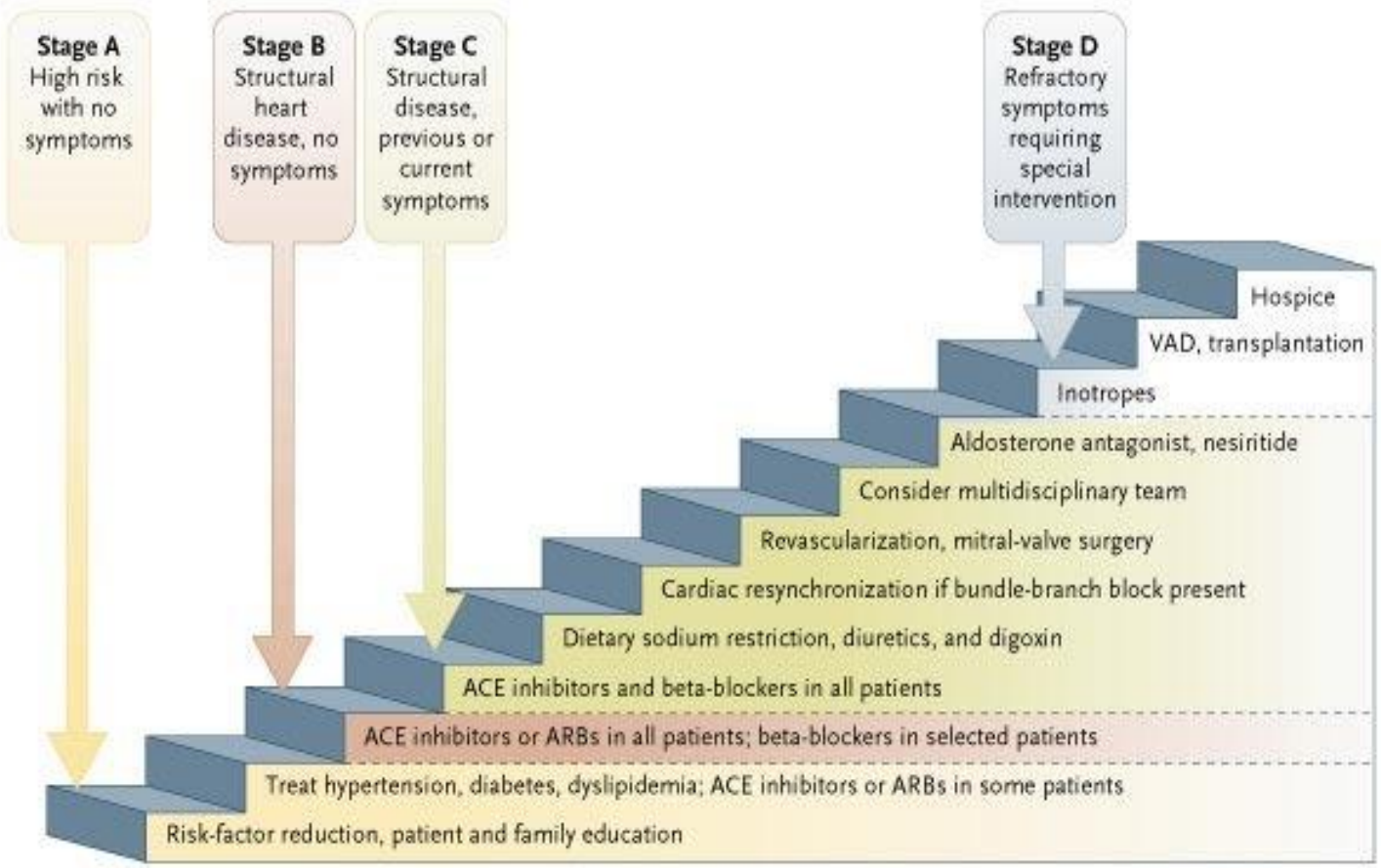
For example Bisoprolol, Metoprolol and Carvedilol act by:

- **Reduction in damaging sympathetic influences in the heart :**

1. Tachycardia, arrhythmias

2. Remodeling through inhibition of mitogenic activity of catecholamines)

3. Decrease in adverse effects of high concentrations of catecholamines including apoptosis
   - inhibition of renin release
- **Carvedilol:**
   - Beta blockade effects
   - peripheral vasodilatation via α_1-adrenoceptor blockade


Stage A
High risk with no symptoms
Stage B
Structural heart disease, no symptoms
Stage C
Structural disease, previous or current symptoms
Stage D
Refractory symptoms requiring special intervention
Hospice
VAD, transplantation
Inotropes
Aldosterone antagonist, nesiritide
Consider multidisciplinary team
Revascularization, mitral-valve surgery
Cardiac resynchronization if bundle-branch block present
Dietary sodium restriction, diuretics, and digoxin
ACE inhibitors and beta-blockers in all patients
ACE inhibitors or ARBs in all patients; beta-blockers in selected patients
Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or ARBs in some patients
Risk-factor reduction, patient and family education