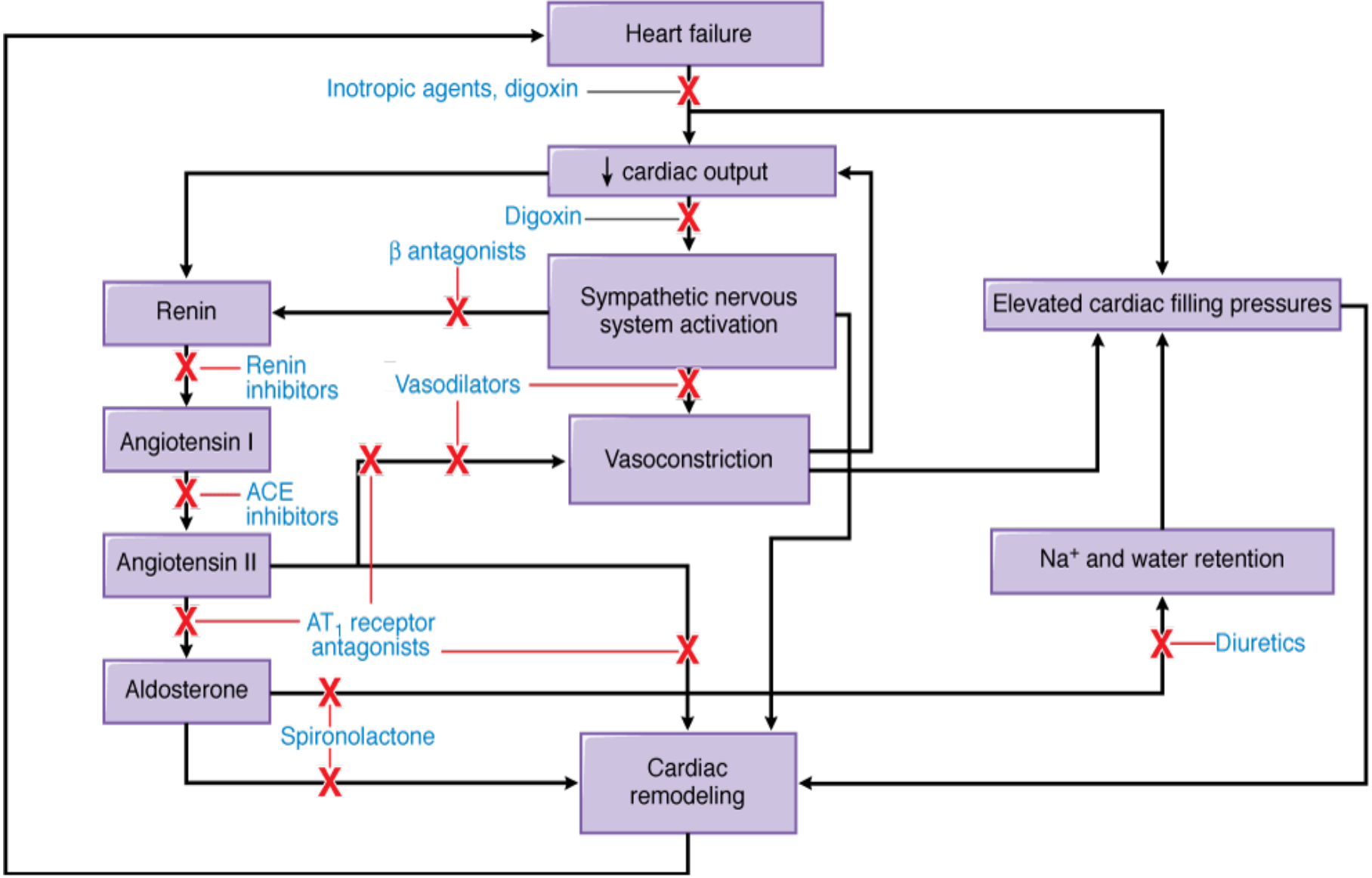
Drugs for Congestive cardiac (Heart) Failure (CCF or CHF)

Definition: Heart failure is a clinical syndrome caused by the inability of the heart to pump sufficient blood to meet the metabolic needs of the body.

Causes: Heart failure can result from any disorder that reduces

1. Ventricular filling (diastolic dysfunction)
2. Myocardial contractility (systolic dysfunction).
3. Coronary artery disease and hypertension.



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Pathophysiologic mechanisms of heart failure and major sites of drug action.

Drug therapy for CHF or CCF

A) Relief of congestive/low output symptoms and restoration of cardiac performance

Inotropic drugs: Digoxin, Dobutamine/ Dopamine, Amrinone/Milirinone

Diuretics: Furosemide, Thiazides

Vasodilators: Hydralazine, Nitrate, Nitroprusside

ACE inhibitors (Captopril, Enalapril)*/AT1 antagonists* (Losartan)

β- blockers: Metoprolol, Bisoprolol, Carvedilol, Nabivolol

B) Arrest/reversal of disease progression and prolongation of survival

ACE inhibitors (Captopril, Enalapril)*/AT1 antagonists (ARBs)*(Losartan)

β- blockers: Metoprolol, Bisoprolol, Carvedilol

Aldostreone antagonist: Spiranolactone, Eplerenone

Pharmacology of Digoxin

Pharmacokinetics

Absorption: Food delays absorption of digoxin tablet.

Distribution: Volume of distribution is 6- 8 L/kg. Digoxin is concentrated in heart, Skeletal muscle, liver and kidney.

Metabolism: Metabolized in liver. Cumulative drug plasma $t_{1/2}$ is 40 hrs.

Excretion: It kidney through glomerular filtration.

Dose: Digitalization 1- 1.5mg, oral

Maintenance dose 0.25-0.75 mg, oral

Pharmacology of Digoxin

1. Heart

a) Force of contraction

i) Digoxin gives positive inotropic action in failing heart

ii) Increases velocity of tension development.

iii) Increases capacity to contract more forcefully when subjected to increased resistance to ejection.

b) Tone

Maximum length of the fiber at a given filling pressure. Decrease end diastolic size of a failing heart.

c) Heart rate

i) HR is decreased , bradycardia in CCF.

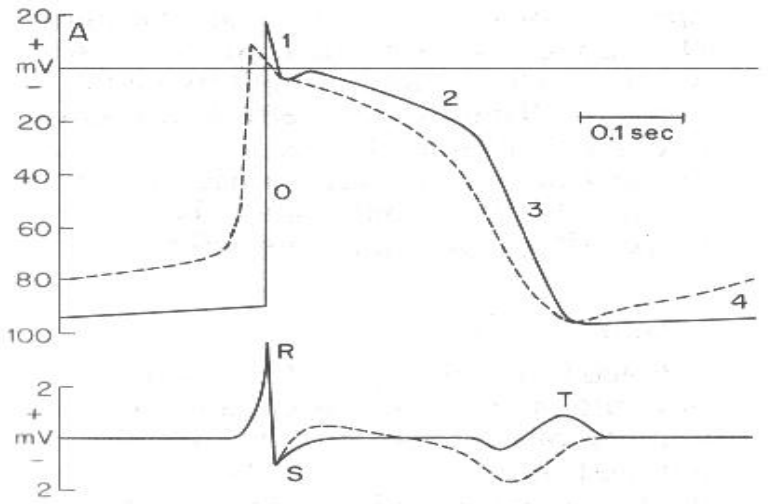
ii) Improved circulation

iii) Restores diminished vagal tone and abolish sympathetic over activity.

iv) Slows down the heart

d) Electrophysiological properties

1) Action potential (AP)



i) The rate of 0 phase depolarization is reduced at AV node and bundle of His

ii) The slope of phase 4 depolarization increases in the purkenji fibers

iii) The SA and AV node automaticity is reduced at the therapeutic concentration by vagal action by hyperpolarization to reduce their phase-4 slope

iv) Toxic dose markedly reduce resting membrane potential of SA nodal cells

v) Action potential is reduced

2) Effective refractory period (ERP)

i) In atrium ERP is decreased by vagal action and increased by indirect action.

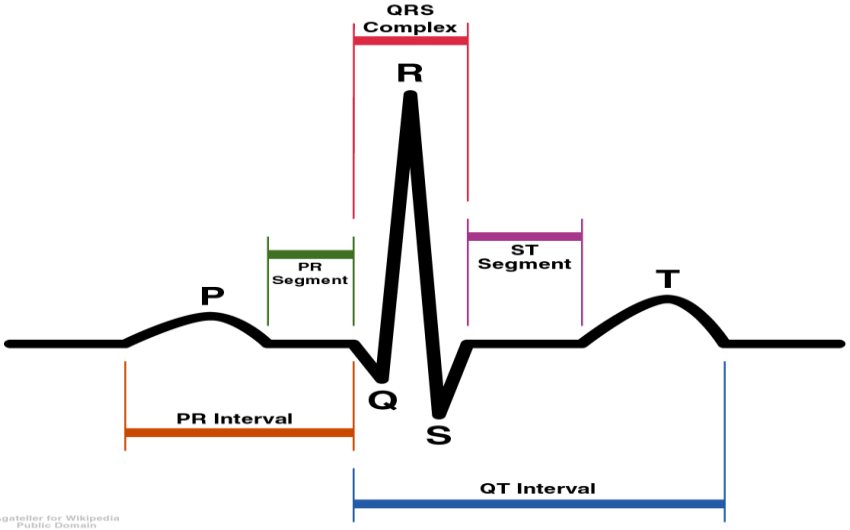
ii) In AV node and bundle of His ERP is increased by vagomimetic and antiadrenergic actions.

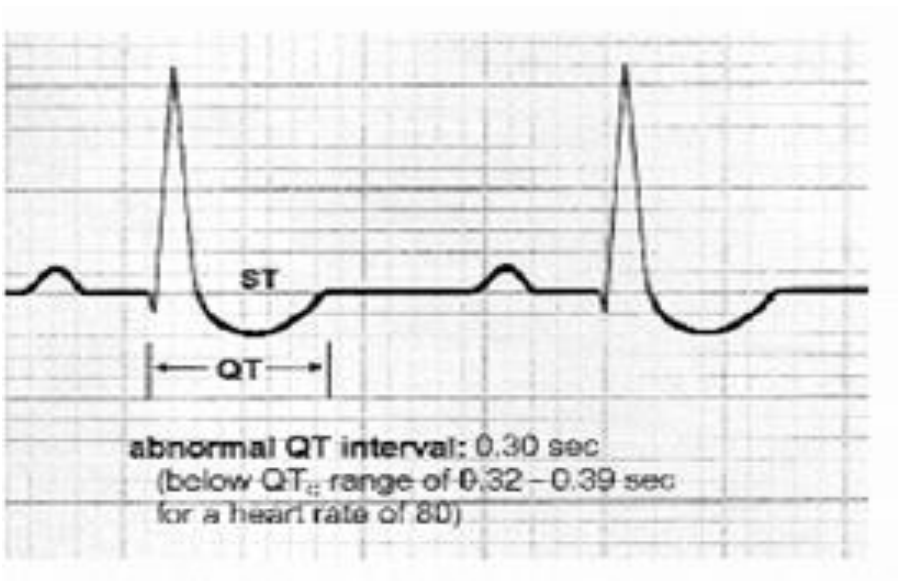
iii) In ventricle ERP is increased by direct action.

c) Excitability: It increased by low dose and decreased by high dose

d) Conduction: AV conduction is slowed at therapeutic dose by decrease in rate of phase 0 depolarization.

e) ECG: At therapeutic doses





Normal ECG **ECG after Digitalis**

i) Decreases amplitude or inversion of T wave.

ii) Increases P-R interval.

iii) Shortening of Q-T interval

iv) Depression of ST segment due to interference with repolarization.

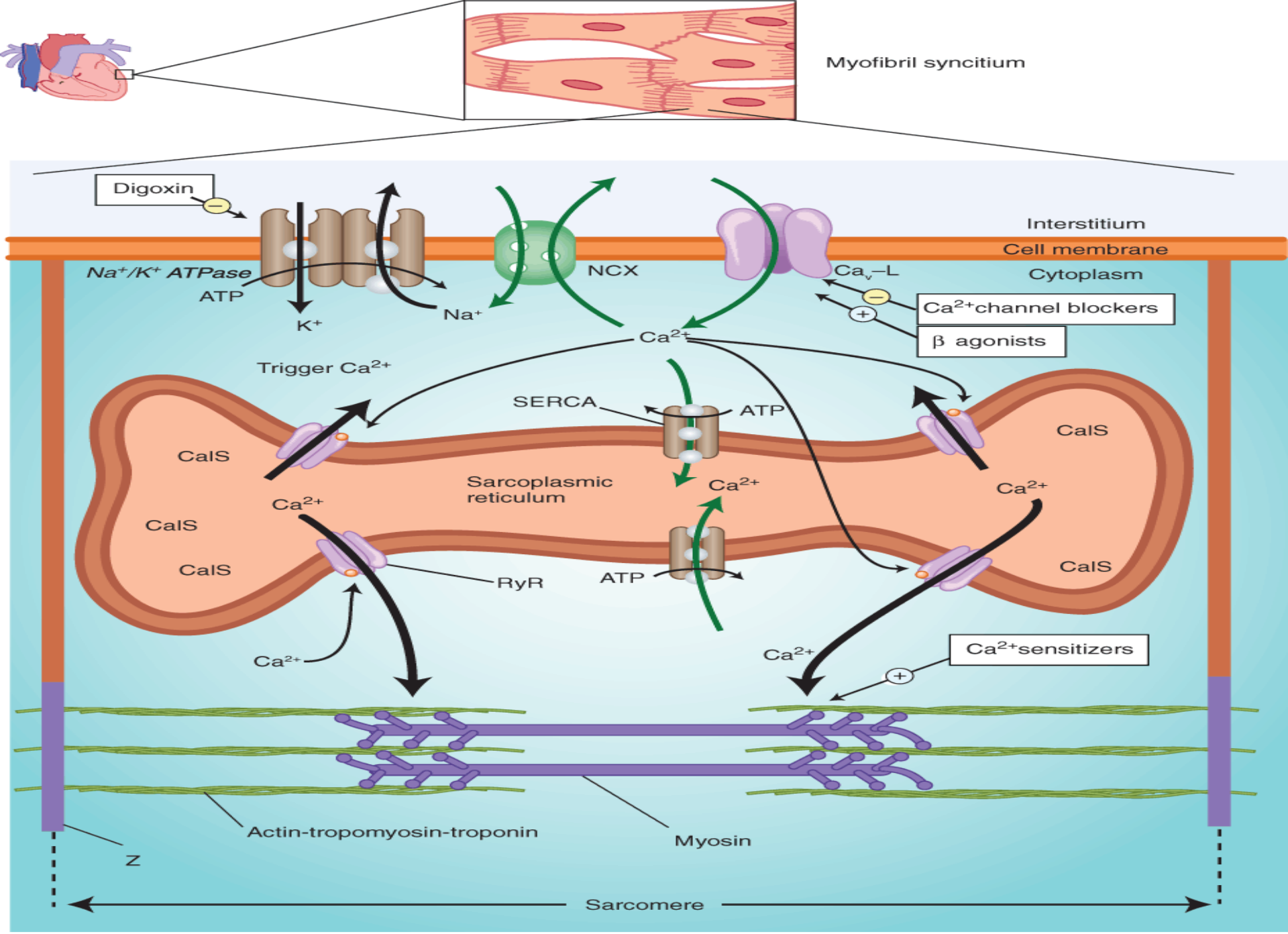
Mechanism of action

1. Inhibition of Na^+/K^+ ATPase results in a small increase in intracellular sodium. The increased sodium alters the driving force for sodium-calcium exchange by the exchanger, NCX, so that less calcium is removed from the cell.

2. The increased intracellular calcium is stored in the sarcoplasmic reticulum and upon release increases contractile force.

3. The consequences of Na^+/K^+ ATPase inhibition are seen in both the mechanical and the electrical function of the heart.

4. Digitalis also modifies autonomic outflow, and this action has effects on the electrical properties of the heart.



Source: Trevor AJ, Katzung BG, Masters SB: *Pharmacology Examination & Board Review, 9th Edition:* www.accesspharmacy.com

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Adverse effects

1. Increased automaticity, caused by intracellular calcium overload, is the most important manifestation of digitalis toxicity.

2. Intracellular calcium overload results in delayed after depolarizations, which may evoke extrasystoles, tachycardia, or fibrillation in any part of the heart.

3. In the ventricles, the extrasystoles are recognized as premature ventricular beats (PVBs). When PVBs are coupled to normal beats in a 1:1 fashion, the rhythm is called bigeminy.

Digitalis toxicity

1. The major signs of digitalis toxicity are arrhythmias, nausea, vomiting, and diarrhea. Rarely, confusion or hallucinations and visual aberrations may occur.
2. The treatment of arrhythmias is important because this manifestation of digitalis toxicity is common and dangerous.
3. Chronic intoxication is an extension of the therapeutic effect of the drug and is caused by excessive calcium accumulation in cardiac cells (calcium overload). This overload triggers abnormal automaticity and the arrhythmias.
4. Severe, acute intoxication caused by suicidal or accidental extreme overdose results in cardiac depression leading to cardiac arrest rather than tachycardia or fibrillation.

Treatment of digitalis toxicity includes several steps, as follows.

1.Further dose must be stopped

2. For tachyarrhythmias: Correction of Potassium or Magnesium Deficiency

3. For ventricular arrhythmias: Antiarrhythmic Drugs eg, lidocaine or phenytoin.

4. For supraventricular arrhythmias: Propranolol i.v may me given

5. For A-V block and bradycardia: Atropine 0.6-1.2mg i.m; otherwise cardiac pacing is recommended.

6. Digoxin Antibodies: Digoxin antibodies (Fab fragments; Digibind) are extremely effective and should always be used if other therapies appear to be failing.

Drug interaction

1.Quinidine causes a well-documented reduction in digoxin clearance and can increase the serum digoxin level if digoxin dosage is not adjusted

2.Digitalis toxicity, especially arrhythmogenesis, is increased by hypokalemia, hypomagnesaemia, and hypocalcaemia.

3. Loop diuretics and thiazides, which are always included in the treatment of heart failure, may significantly reduce serum potassium and thus precipitate digitalis toxicity.

4. Digitalis-induced vomiting may deplete serum magnesium and similarly facilitate toxicity. These ion interactions are important in treating digitalis toxicity.

Brands

DIGOXIN 0.25 mg tab., 0.5mg/2ml inj.

Digitoxin: DIGITOXIN 0.1mg tab

Other Drugs Used in Congestive Cardiac Failure

The other major agents used in heart failure include

I) Diuretics

1. Diuretics are the first-line therapy for both systolic and diastolic failure and are used in heart failure before digitalis and other drugs are considered.
2. Furosemide is a very useful agent for immediate reduction of the pulmonary congestion and severe edema associated with acute heart failure and for moderate or severe chronic failure.
3. Thiazides such as hydrochlorothiazide are sometimes sufficient for mild chronic failure.
4. Clinical studies suggest that spironolactone and eplerenone (aldosterone antagonist diuretics) have significant long-term benefits and can reduce mortality in chronic failure.

II)Angiotensin Antagonists

1. These agents have been shown to reduce morbidity and mortality in chronic heart failure.
2. Angiotensin antagonists reduce aldosterone secretion, salt and water retention, and vascular resistance. They are now considered, along with diuretics, to be first-line drugs for chronic heart failure.
3. The angiotensin receptor blockers (ARBs, eg. losartan) appear to have the same benefits as ACE inhibitors (eg. captopril**)**

III) Beta$_1$-Adrenoceptor Agonists

1. Dobutamine ($\beta_1$selective) and dopamine are often useful in acute failure in which systolic function is markedly depressed.

2. However, they are not appropriate for chronic failure because of tolerance, lack of oral efficacy, and significant arrhythmogenic effects.

IV) Beta-Adrenoceptor Antagonists

1. Several β- blockers (carvedilol**,** labetalol, metoprolol) have been shown in long-term studies to reduce progression of *chronic* heart failure.

2. This benefit of β-blockers had long been recognized in patients with hypertrophic cardiomyopathy but has now been shown to occur also in patients without cardiomyopathy.

3. Nebivolol, a newer β-blocker with vasodilator effects, is investigational in heart failure. Beta blockers are not of value in acute failure and may be detrimental if systolic dysfunction is marked.

V) Phosphodiesterase Inhibitors

1. **Amrinone and milrinone** are the major representatives of this infrequently used group.

2. These drugs **increase cyclic adenosine monophosphate (cAMP) by inhibiting its breakdown by phosphodiesterase** and cause an increase in cardiac intracellular calcium similar to that produced by α-adrenoceptor agonists.

3. Phosphodiesterase inhibitors also cause vasodilation, which may be responsible for a major part of their beneficial effect.

4. At sufficiently high concentrations, these agents may increase the sensitivity of the contractile protein system to calcium.

5. These agents should not be used in chronic failure because they have been shown to increase morbidity and mortality.

Vasodilators

1. Vasodilator therapy with nitroprusside or nitroglycerin is often used for acute severe failure with congestion.
2. The use of these vasodilator drugs is based on the reduction in cardiac size and improved efficiency that can be realized with proper adjustment of venous return (preload) and reduction of resistance to ventricular ejection (afterload).
3. Vasodilator therapy can be dramatically effective, especially in cases in which increased afterload is a major factor in causing the failure. The natriuretic peptide nesiritide acts chiefly by causing vasodilation, although it does have natriuretic effects as well. It is given by IV infusion for acute failure only.
4. Chronic heart failure sometimes responds favorably to oral vasodilators such as hydralazine or isosorbide dinitrate (or both), and the combination has been shown to reduce mortality in African Americans.

Nonpharmacologic Therapy

1. A variety of surgical procedures to remove nonfunctional regions of damaged myocardium have been attempted with mixed results.

2. Resynchronization of right and left ventricular contraction by means of a pacemaker has been beneficial in patients with long QRS (indicating conduction abnormalities).

3. Patients with coronary artery disease and heart failure may have improved systolic function after coronary revascularization.