PHARMACOLOGY

Drugs Acting on Cardiovascular System: Cardiac Glycosides and inotropic agents

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Introduction

Congestive heart failure (CHF) is a condition in which the cardiac output is inadequate to body demands and there is poor cardiac contractility and relaxation, resulting in symptoms of low cardiac out and congestion. It is a common heart disease that carries significant morbidity and mortality. CHF increases risk of death by 3 times and 60% of the patients die within 5 years of the diagnosis. Therefore it requires careful management by drugs and nondrug modalities.

Acute v/s chronic failure: Patients with acute failure present with breathlesness, pulmonary congestion and elevation of ventricular filling pressures. The objective of treatment is to provide immediate relief from dyspnoea and inotropic support to failing heart. In chronic heart failure symptoms of peripheral pooling of blood (oedema, hepatomegaly) and fatigue can be improved by long term use of drugs that provide functional and structural support to the failing heart and improve quality of life.

Systolic v/s diastolic failure: Systolic failure is a common abnormality characterized by low left ventricular ejection fraction (LVEF <40%, Normal 65±8%). It is due to a large but poorly contracting heart and the predominant symptoms are fatigue and low effort tolerance. In contrast to this, the diastolic failure is characterized by near normal sized heart and LVEF but there is stiffness of ventricles, which relax poorly. This is seen as a result of persistent hypertension, aortic stenosis, chronic myocardial ischemia and cardiomyopathy. It is seen in about 40%-60% of patients with CHF. The objective of therapy is to regress hypertrophic changes so that LV relaxation improves.

Other terms used are high v/s low output failure; forward v/s backward failure and right v/s left heart failure. The right-sided failure is characterized by pedal oedema, distended neck veins, congestive hepatomegaly and dyspnoea. The left heart failure manifests as orthopnoea, paroxysms of nocturnal dyspnoea and pulmonary oedema. In many cases of CHF there is involvement of both the ventricles.

Severity of Heart Failure: The New York Heart Association (NYHA) classification is commonly used to assess the functional severity of heart failure. In addition, CHF is classified in stages A-D depending on the extent of myocardial structural changes and severity of dysfunction. These stages determine the type of therapy needed (Table 1).

Table1: Classification and Drug treatment of Heart failure

Class*	**Functional status**	**Possible therapy**	**Stage****	**Symptoms/ severity**	**Possible therapy**
I	Symptoms at a level occurring in normal persons	ACE-Is, β-blockers	A	Increased risk of CHF, no symptoms	Risk reduction treat high BP, DM, IHD
II	Symptoms at moderate activity	Diuretics. ACE-Is, β-blockers	B	Structure/function abnormal but no symptoms	ACE-Is, ARBs
III	Symptoms at <normal level of activity	As above + digoxin & spironolactone	C	Symptomatic heart failure	As stage-3

IV	Symptoms at rest	Acute inotropes, Pre-afterload reduction. Assisted devices.	D	Advanced heart failure	Assisted-devices, Cardiac-resynchronization, ?transplant

.*The NYHA classification (classes-I, II,III and IV) denote patient's functional status.
**Stages A, B, C and D denote progressive development of severity of structural derangements in CHF.

Pathophysiology of Heart failure

In order to understand the role of pharmcotherapeutic agents in CHF, it is important to understand the haemodynamic and structural compensatory changes which occur in CHF. Normally cardiac output (4-6 lit/min) and stroke output (70 ml per beat) are determined by factors such as myocardial contractility, ventricular filling pressure, heart rate and peripheral vascular resistance. Diseases of heart muscle and adrenergic activity determine myocardial contractility. Two terms are commonly used:

Preload: It is left ventricular end diastolic pessure (LVEDP) and is determined by *venous return* and size of ventricular cavity (myocardial fiber length).

Afterload: It is the tension developed by ventricles during ejection and is determined by *peripheral vascular resistance*, ventricular wall thickness and compliance (or distensibility).

As is seen in the flow diagram-1, the key factor is poor myocardial contractility. This initiates a series of short and long-term compensatory neurohumoral responses in order to maintain cardiac output. However, these compensatory responses cannot sustain adequate cardiac output for a long period and thus a vicious cycle is maintained which further deteriorate cardiac performance(Flow diagram1).

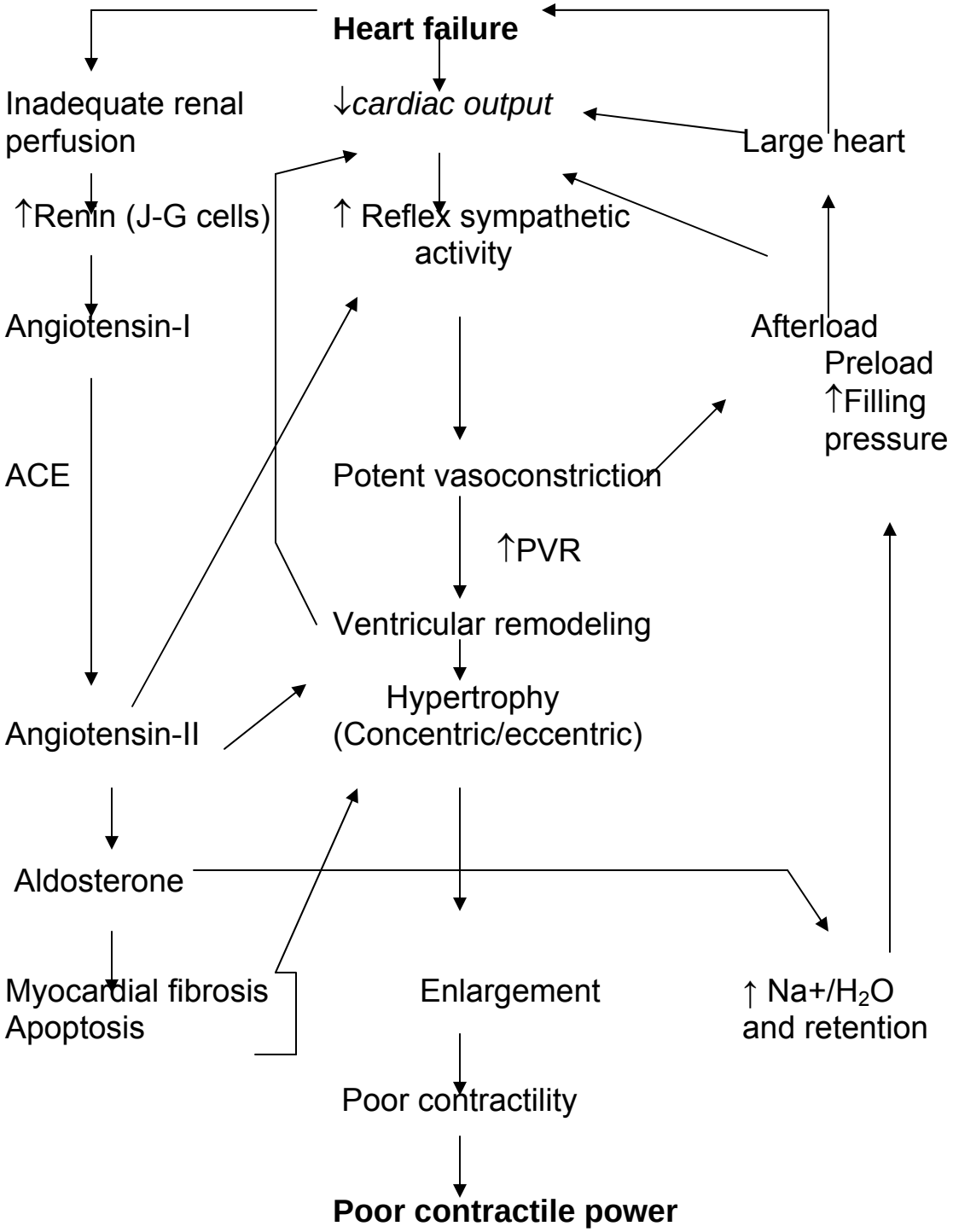
Structural changes in chronic CHF

Hypertrophy and remodeling: Remodeling includes slow structural changes, which occur in stressed myocardium and vascular tissues. These changes are due to growth of connective tissue, apoptosis, loss of normal myocytes and vascular intimal thickening with increased wall: lumen ratio. Normal cells are replaced by fibrous tissue, which cannot contract. A-II, aldosterone, TGF and IGF play role in inducing remodeling changes. Remodeling leads to concentric hypertrophy in diseases such as hypertensive heart failure (pressure overload) and eccentric hypertrophy in cases of aortic or mitral regurgitation with CHF (volume overload).

Cardiac enlargement: Compensatory hypertrophy and dilatation of heart to normalize cardiac output, puts stress on myocardium because it has to generate extra wall tension.

$$\text{Laplace law indicates that Wall tension} = \frac{\text{Intraventricular pressure} \times \text{Ventricular radius}}{\text{Wall thickness}}$$

That means a dilated heart (radius more) with normal wall thickness has to generate greater wall tension and the afterload on hypertrophied heart is less.

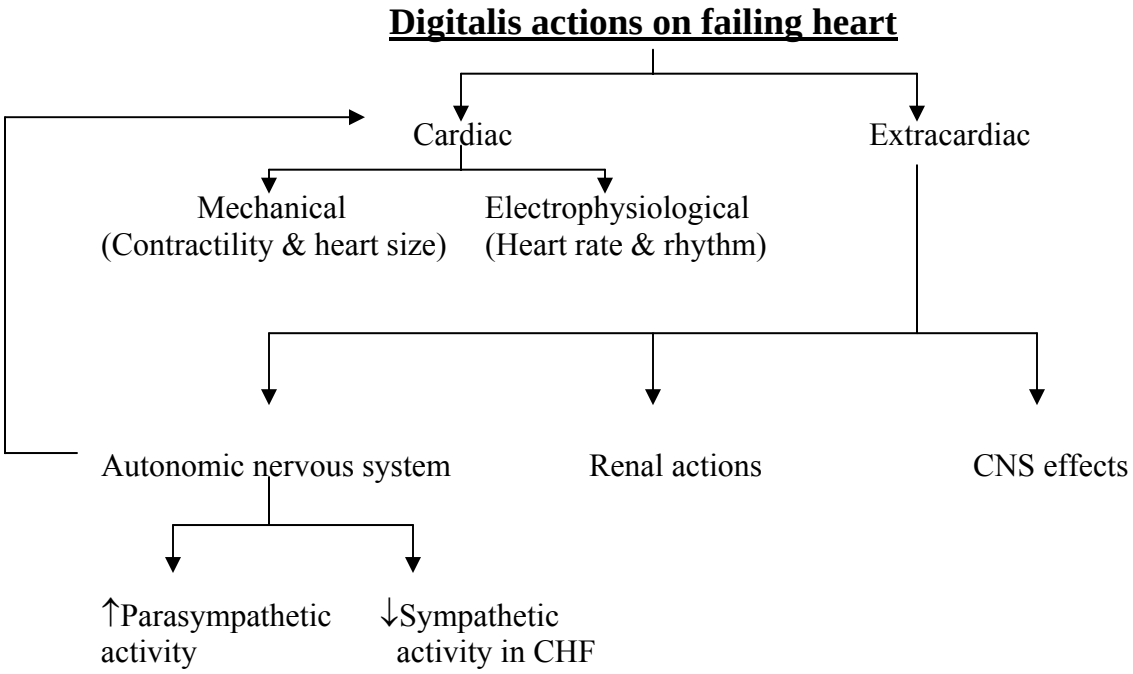


Flow diagram 1: Pathophysiology of Heart Failure

Contractile dysfunction: There is abnormality of contraction and relaxation, which is caused by

a. Reduced Ca++ sequestration in sarcoplasmic reticulum and greater Na+Ca++ exchange leading to accumulation of Ca++ inside cells. Sarcoplasmic calcium channel dysfunction is found in CHF.
b. Production of poorly contractile proteins by altered gene transcription, which is further contributed by activation of metalloproteinases. These result in a marked derangement of alignment of sarcomeres with matrix.
c. Disturbed Ca++ delivery to the contractile proteins

Adrenergic receptor dysfunction: β_1-receptors are down regulated in heart failure. Therefore, reduced c'AMP production and subnormal Ca++ release and sequestration with each cardiac cycle leads to poor contractions (Flow diagram 2).



Flow diagram 2: Actions of Digitalis on Heart

Classification of Drugs used in CHF

A. Drugs acting on Renin angiotensin aldosterone axis

1.Angiotensin converting Enzyme-inhibitors (ACE-Is)
Active agents- Captopril, Lisinopril
Prodrugs - Alacepril, benazepril, enalapril,fosinopril, quinapril, perindopril, ramipril

2. Angiotensin receptor blockers(ARBs) or sartans
Losartan, valsartan, telmisartan, candesartan

3. Aldosterone antagonists- Spironolactone. Eplerenone.

B. **β-receptor antagonists-** Bisoprolol, carvedilol, metoprolol,

C. **Diuretics-** Loop acting agents* and thiazides
D. **Cardiac glycosides**
E. **Other inotropes*-** Dobutamine, dopamine, dopexamine, ibopamine
F. **Vasodilators-**
    a. Venodilators- Nitroglycerine*, isosorbide dinitrate, isosorbide mononitrate.
    b. Arteriolar dilators- Hydralazine, CCBs, minoxidil.
    c. Mixed dilators- ACE-Is, nesiritide*, nitroprusside*, prazosin.
G. **Inodilators*-** Inamrinone, milrinone, enoximone
H. **Calcium sensitizers-** Pimobendan, levosimendan
I. **Newer agents-** Combined ACE and NEP inhibitors-Omapatrilat, sampatrilat, fosidotrilat
J. **Supportive drugs-** Antiarrhythmics, antiplatelet drugs & anticoagulants, lipid lowering agents.

*** indicates that these drugs are used in acute heart failure**

Another way of classifying drugs is according to their impact on long-term survival.

Group-1: Agents that provide relief from fluid retention but overall survival Unaffected-Diuretics

Group-2: Agents which regress structural changes and reduce mortality on long term use-ACE-Is, ARBs, β-blockers.

Group-3: Agents which provide acute inotropic support but increase mortality on prolonged use-Inamrinone, milrinone

Group-4: Agents that increase cardiac output on long term use but mortality is not reduced-cardiac glycosides, vasodilators

Group-5: those agents that have uncertain value-Calcium channel blockers (dihydropyridines).

Cardiac Glycosides

Sir William Withering described the powerful effects of the decoction of foxglove in dropsy in 1775-76. The leaves of the foxglove-herb are long digit like (hence the name‘digitalis’) and are rich source of glycosides. Glycosides are sugar containing organic compounds. There are several species of digitalis that yield different glycosides. The digitoxin is obtained from the leaves of Digitalis purpurea and digoxin from the leaves of D.lanata. There are other glycosides of pharmacological importance such as ouabain or strophanthin-G (obtained from seeds of strophanthus gratus), gitoxin and deacetylated lanatoside. Some toads (Bufo vulgaris) secrete bufotoxins (glycosides) from their cutaneous glands. Recently, endogenous ouabain like substances is in found in mammals also.

Clinically, digoxin is the most commonly used cardiac glycoside now days. Digitoxin is used sometimes. All cardiac glycosides have similar cardiovascular actions and therefore, a generic term digitalis, is used in this chapter. Most of the details pertain to digoxin and wherever necessary, differences between digoxin and digitoxin are also described.

Structure of Cardiac Glycosides

A glycoside is composed of two parts;aglycone or genin and a sugar.

Glycoside = Aglycone or Genin + Sugar moiety
1-4 linked monosaccharide
at C3

Steroid nucleus (CPPP ring)

Unsaturated Lactone at C17

Digoxin = Digitoxigenin (Steroid nucleus + unsaturated lactone at C17) + Tridigitoxose (sugar) at C3 and two OH groups at C14 and C18 of steroid ring.
Digitoxin = As above but with only one OH group.

The structure of digoxin is depicted in Fig.1. The pharmacological activity resides in genin and the sugar moiety modifies permeability. Presence of an extra OH group in digoxin makes it more water soluble as compared to digitoxin, which is a more lipophilic drug.

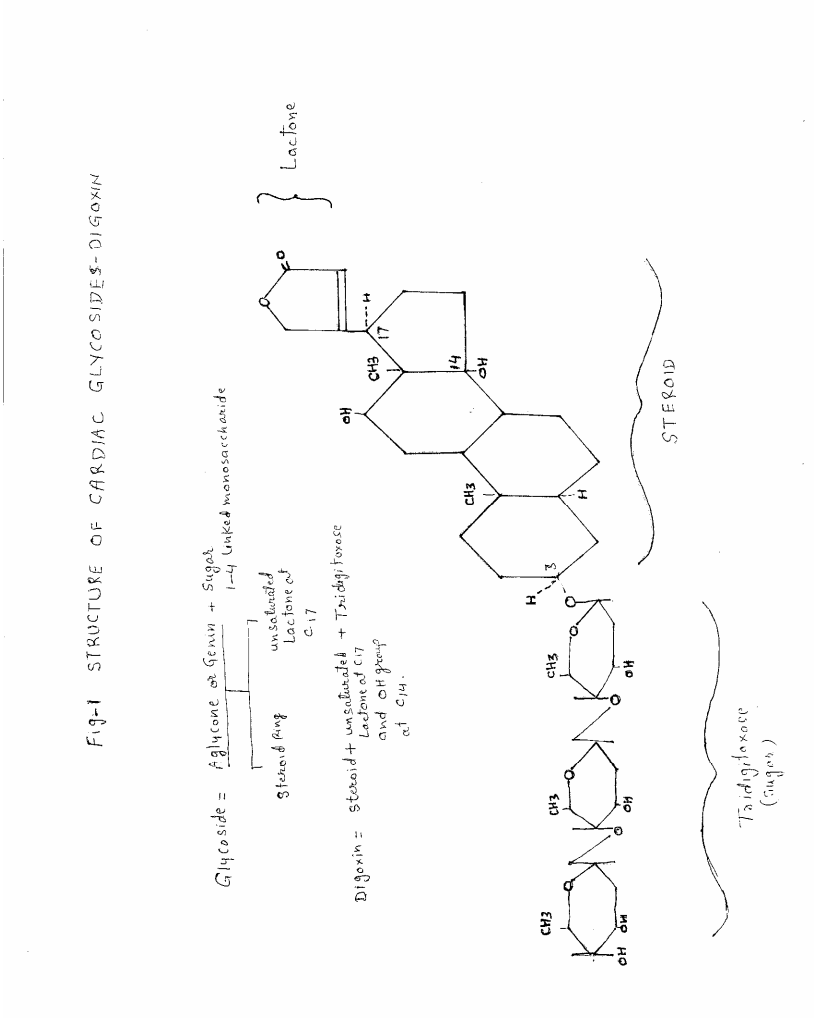
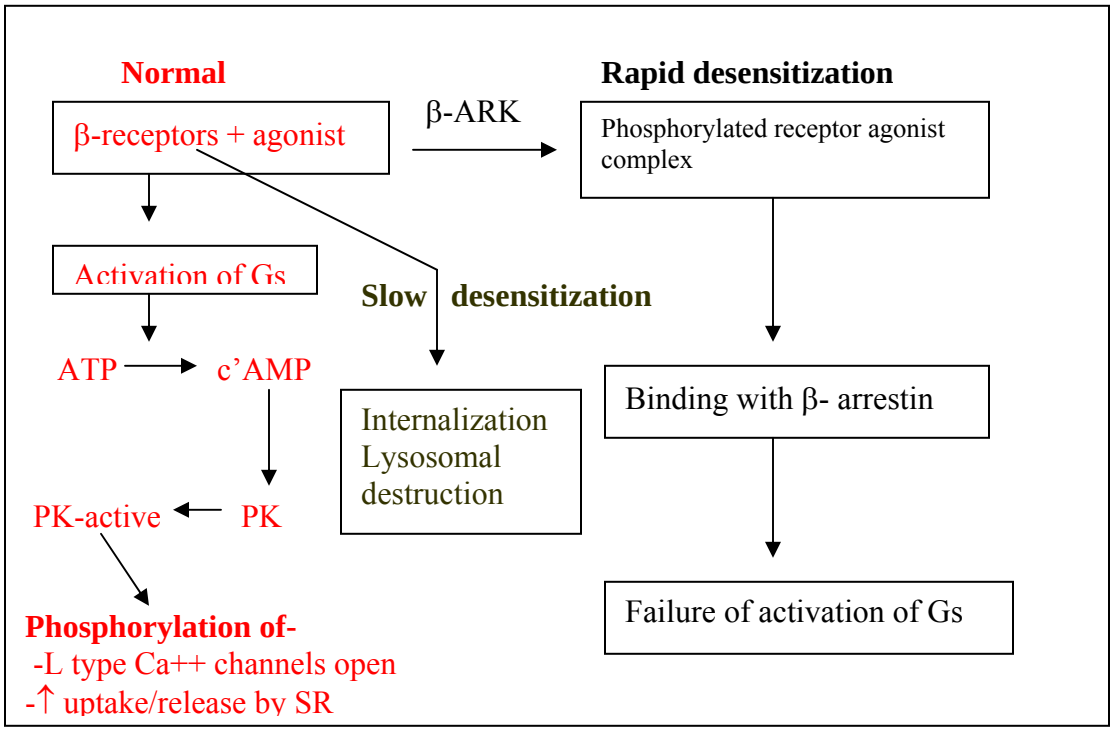


Fig. 1: Structure of Cardiac Glycosides: Digoxin

Pharmacological Actions

The pharmacological actions of digitalis include direct and indirect effects on cardiovascular system. The cardiac effects are most important actions responsible for therapeutic uses (Flow diagram 3).



Flow diagram 3: Pathways of β-receptor down regulation in CHF

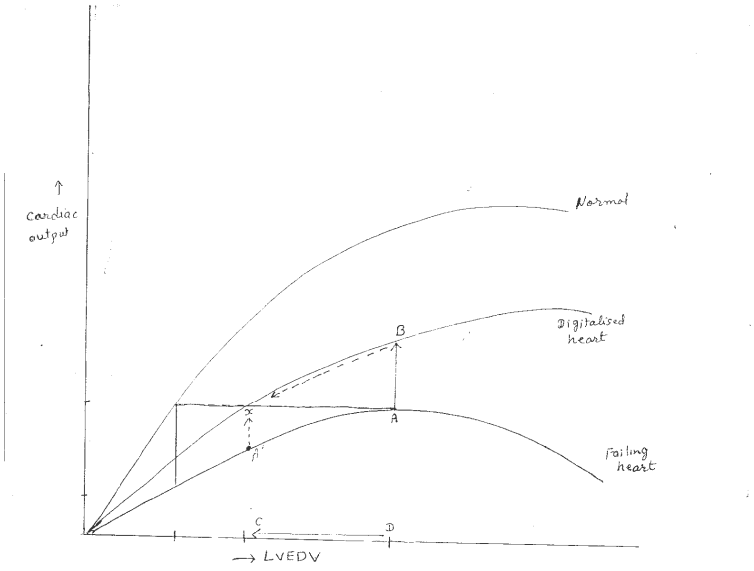
Cardiac Actions

In normal persons, administration of digitalis may increase cardiac output (CO) to some extent but there is peripheral vasoconstriction by direct vascular smooth muscle contraction and sodium accumulation inside smooth muscle cells (see mechanism of action). This raises peripheral vascular resistance (PVR) and after load on heart so rise in CO is nullified. However, in failing heart there are important effects of digitalis. These effects are mechanical effects in the form of increased cardiac contractility and reduction in the size of dilated heart. In addition there are direct electrophysiological effects but effects of digitalis on autonomic nervous system modify them.

Mechanical Action (cardiotonic or inotropic)

This is the most important action of digitalis in CHF. Digitalis improves cardiac contractility, increasing force of contraction so that the stroke volume and cardiac output increase and heart ejects blood into systemic circulation more efficiently. The time spent in systole is reduced. The heart rate is reduced also so a greater time is spent in diastole. This improves coronary flow and pumping action of heart further. The dilated heart reduces in size. Since a large heart requires more energy for generating similar tension (Laplace law), therefore digitalis improves cardiac performance at the expense of less energy utilization (as if it tones the failing heart). Hence digitalis is called as cardiotonic drug. This is unlike the actions of a cardiac stimulant

(isoprenaline) that increases force of contraction and heart rate-*as if a galloping but tired horse is being whipped to run still faster, which it is unable to do (Diagram)!* This is because cardiac stimulants increase oxygen requirement of a failing heart also. These salutary effects of digitalis are depicted in Fig 2, which shows upward shift of Frank-Starling curve on digitalization. Haemodynamic improvement is seen in the form of shift of fluid from extravascular to intravascular compartment, diuresis, reduction in dyspnea, edema and increased exercise capacity.



Digitalis increases cardiac output (A→B) and thus reduces heart size (B→X). Vasodilators and diuretics reduce preload (D→C) and increase cardiac output (A'→X)

Fig. 2: Frank-Starling Curves of normal, failing and digitalized Heart

Effects on Heart Rate

Digitalis reduces tachycardia in CHF by direct and indirect actions. There is haemodynamic improvement, which reduces sympathetic overactivity in CHF. The heart rate is reduced by direct suppressive effect and provagal action of digitalis on SA node. The vagal activation is due to a number of reasons:

1. Central vagal stimulation
2. Sensitization of baroreceptors and nodose ganglia
3. Facilitation of muscarinic transmission in cardiac myocytes.

Reduction in heart rate in atrial fibrillation is due to predominant AV nodal suppressive action of digitalis.

Electrophysiological effects of digitalis

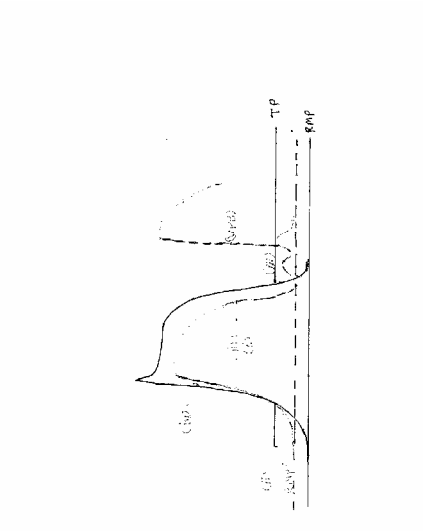
These include the changes in heart rate, rhythm and antiarrhythmic effects. The effects are direct and indirect (altered autonomic influences on heart) actions of digitalis. Direct effects are observed as different actions on SA & AV nodes, Atria, Purkinje's fibers (PF) and ventricular myocardium (VM). Each of these tissues shows changes in automaticity, excitability,

conductivity and refractoriness (Table 2). These direct actions are modified largely by stimulation of cardiac vagus.

Table 2: Main electrophysiological effects of digoxin

Property	**Atrium**	**AV Node**	**PF / Ventricle**
ERP	Reduced (vagal)	Increased (vagal)	Reduced (direct)
Conduction velocity	Increased (vagal)	Reduced (vagal)	Minimal depression
Automaticity	Increasd (directly & adrenergic overactivity)	Increased (direct)	Increased (direct); ectopic activity

Automaticity and excitability: The automaticity and excitability of PF and VM are increased by elevation of Resting membrane potential (RMP) and increased slope of phase-4 of AP (Fig 3). This is more prominent in higher doses and predisposes to extrasystoles and ventricular tachycardia. Intracellular Na+ and Ca++ accumulation activate the latent pacemakers. The automaticity of atrial and SA/AV node is reduced, predominantly by vagal action.



i. Shortened AP in atrial tissues
ii. Less negative resting membrane potential (RMP') in high dose
iii. Unstable phase-4; DADs induced premature depolarization in toxic doses (VPB).
iv. Reduced rate of rise of action potential.

These direct effects are modified by prominent autonomic effects on heart.

Fig. 3: Digitalis induced changes in Cardiac Action Potential: overall changes

Refractory period: The effective refractory period (ERP) of atria is reduced (decreased APD) by vagal action predominantly. ERP of PF and VM is also reduced but mainly by direct action. The most important action of digitalis is *prolongation of ERP of AV node* by both, direct and vagal action. This is the responsible for rate reduction in atrial fibrillation (AF). Minor resting depolarizations induced by digitalis render AV node more refractory.

Conduction velocity: The conduction velocity is increased in atrial tissues by vagal action but it is *markedly reduced in AV node by direct, vagal and antiadrenergic actions.* The does not allow a number of weak impulses to travel down the AV node(concealed conduction) thus producing a '*traffic jam'*. This effect is useful in reducing ventricular rate in atrial fibrillation higher dose causes AV blocks.

Afterpotentials: In more than therapeutic doses, delayed after depolarizatons (DADs) during phase-4 occur due to Ca++ overloading and K+ depletion in myocytes. The consequences of DADs are-

a. Interference with cyclic ionic movements across cell membrane, affecting normal contractions.
b. Some of the DADs may reach threshold of excitation and evoke ventricular premature beats (VPBs) which contract heart less forcefully further reducing efficiency of heart and
c. A few DADs may generate more DADs resulting in sustained VT or ventricular fibrillation(VF).

ECG effects: In full therapeutic doses prolongation of PR interval (AV nodal block), shortening of QT interval and ST segment scooping with/without T wave inversion are observed. Toxic doses can cause a variety of arrhythmias.

Mechanism of Action of digitalis

Normal ionic changes in a cardiac cycle: Role of Na+ , Ca++ and Na+K+ATPase : Fig. 4 shows the key role of intracellular sodium in promoting Ca++ accumulation and contractility. Normally during contraction, .Sodium ion enters the cells in exchange of K+ to depolarize the cell membrane. Ca++ accumulates in the cytoplasm by entry through L-type of Ca++ channels and release of Ca++ from sarcoplasmic reticulum(SR) The Ca++ so accumulated initiates actin-myosin interaction. During repolarization (diastolic) phase, 3Na+ are exchanged with 2K+ so that intracellular K+ is restored, Na+ is extruded and RMP becomes negative. This exchange is done by the active Na+K+ATPase pump. An electric gradient is created across cell membrane which causes a continuous exchange of Ca++/3Na+, so that Ca++ efflux is accompanied by Na+ influx. This influxed Na+ is then exchanged with K+ as described above.

Consequences of inhibition of Na+K+ATPase enzyme by digitalis: Most of the therapeutic and toxic effects can be explained by reversible inhibition of Na+K+ ATPase enzyme (pump) located in the cardiac cell membrane. Digitalis binds with α-subunit of the Na+K+ATPase enzyme and phosphorylates the β-aspartate thereby inactivating it. It is to be noted that extracellular potassium promotes dephosphorylation and thus reduces digitalis binding. About 30% of the enzyme must be inhibited for adequate therapeutic actions. Inhibition of enzyme is slow so the inotropic action is gradual in onset.

When digitalis is administered, it **inhibits** the Na+K+ATPase pump thereby accumulating Na+ inside cells. Since Na+ is now more inside (sizeable transmembrane gradient is not generated to extrude Ca++) no exchange will occur with Ca++ and this results in *Ca++ accumulation inside cell*. Intracellular Ca++ *augments* Ca++ accumulation further by 3 mechanisms:

a. Opening of voltage gated L type Ca++ channels allowing Ca++ entry in cell

with each cardiac cycle.

b. Release of sarcoplasmic Ca++ by opening of Ca++ channels of sarcoplasmic reticulum . This is called as *triggered release of Ca++*.

c. Ca++ accumulation in cytoplasm progressively increases in subsequent cycles. A part of it is taken back by SR leading to Ca++ overloading , which further increases 'triggered release' of Ca++ susequently.

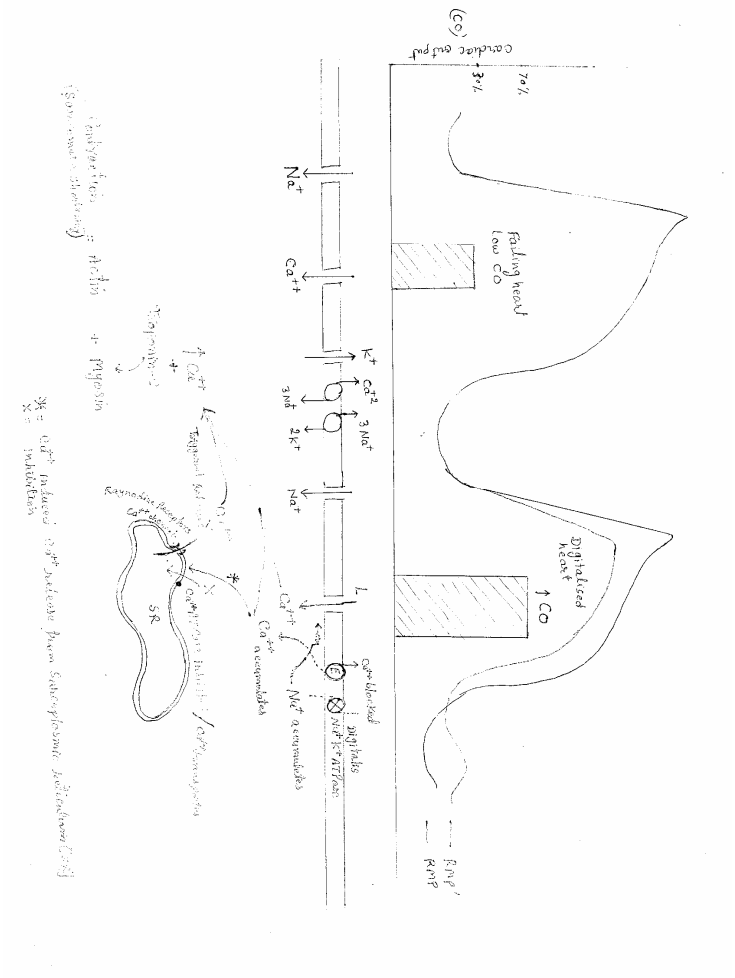


Fig. 4: Mechanism of action of Digitalis

The relationship between Na+ and Ca++ is such that a minute increase in intracellular Na+ causes greater accumulation of Ca++ in side heart muscle cell. The net result is increased availability of cytosolic Ca++ to bind with troponin-C and activation of myosin which intedigitates with actin to generate tension (forceful contractions). Intracellular Na+ accumulation explains elevation of RMP (less negative), increased excitability and while Ca++ accumulation explains increased automaticity in ectopic tissues, and inotropic action of digitalis. The Na+K+ATPase pump present in the neurons of retina, kidney and vascular smooth muscles may also be blocked by digoxin. This explains some of the extracardiac actions of digitalis.

Digoxin-Potassium interaction: Extracellular potassium reduces binding of digoxin on enzyme by dephosphorylation of binding site of α- subunit. Hypokalemia increases digoxin binding, effects and toxicity of digoxin. Therefore, hypokalemia should be avoided and if present must be corrected. Elevated serum potassium levels raise threshold of excitation and reduce automaticity by further reducing RMP (more negative). Severe hypokalemia may decrease tubular secretion of digoxin.

Autonomic effects of digitalis

Reduction in sympathetic overactivity in heart failure: In CHF, digitalis reduces adrenergic activity by improving cardiac output and tissue perfusion. There is a fall in noradrenaline levels and rennin secretion. The reduction adrenergic activity is noted much earlier to clinical improvement. In higher doses, digitalis may raise adrenergic activity by central stimulation and it may contribute to the genesis of cardiac arrhythmias.

Cholinergic stimulation: Digitalis increases vagal effects on heart, slows AV conduction and suppresses SA activity as discussed above. In larger doses diarrhea and vomiting is due to vagal actions on gut.

Other actions: There is improvement in venous return and reduction in oedema. Coronary flow improves by greater time spent in diastole and raised cardiac output. Digitalis increases urine output in CHF. Diuretic action is due to:

a. Increased renal blood flow as a result of haemodynamic improvement.
b. Shift of tissue fluid to vascular compartment
c. Reduced influence of adrenergic-renin-angiotensin axis on kidney and
d. Reduced tubular reabsorption of Na+.

In toxic doses, digoxin has CNS effects also.

Pharmacokinetics: Both digoxin and digitoxin are well absorbed orally. The biovailability of digoxin varies from 60%-90% depending on the formulation. Digoxin is absorbed from a small segment of upper gut (small window of absorption). Therefore, *prokinetics (metoclopramide) reduce and anticholinergics increase* bioavailability of digoxin. A portion of digoxin is inactivated into dihydrodigoxin by gut bacteria, therefore antibacterial may increase bioavailability of digoxin. Digitalis is distributed widely in tissues and thus has a high volume of distribution. The concentration in myocardial and skeletal muscles is 20-50 times that of plasma. The elimination half-life of digoxin is 36 hours. That means if loading dose is not given, then the steady state plasma level is achieved in 6-7 days (4-5 half-lives). Digoxin is mainly excreted unchanged by kidney and daily clearance is about 30% of the dose. The clearance of digoxin is higher in children (2-3 times) and lower in elderly. The comparative pharmacokinetics of digoxin and digitoxin are given in the Table 3.

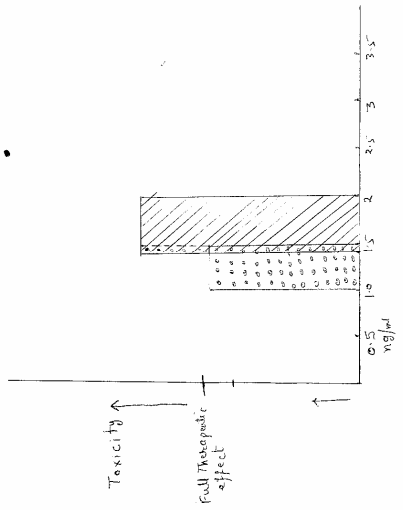
Table 3: Comparative pharmacokinetics of digoxin and digitoxin*

S.No	Parameter	Digoxin	Digitoxin
1	Source	D.lanata	D.lanata, D.purpurea
2	Absorption %	60-90	90-100
3	Protein binding %	25	90

4	Half-life (days)	1.5-1.7	6-7
5	Route of elimination-main	Renal	Fecal
6	Daily clearance %	30	15
7	Lipid solubility	Low	High
8	Enterohepatic cycling	Minimal	Marked
9	Therapeutic concentration	0.5-1.5 ng/ml	10-35 ng/ml
10	Average digitalizing dose	1-2 mg	0.8-1.2 mg
11	Average maintenance dose	0.125-0.25 mg/day	0.05-0.2 mg/day

*** Digitoxin is rarely used now days**

Therapeutic drug monitoring: Digitalis has a narrow safety margin. Even a full therapeutic dose may prove to be toxic for some patients (Fig.5). Therefore, a close clinical and laboratory monitoring is required to avoid toxicity. Earlier, a plasma level above 2 ng/ml was considered to be toxic. Since, plasma levels above 1.5 ng/ml are associated with considerable toxicity, a plasma level between 1.0-1.5 ng/ml is therapeutically useful and dose is adjusted accordingly. Even a level as low as 1 ng/ml carries a 5% risk of toxicity. Because of low therapeutic index, digoxin loading dose, although rarely used now a days, is given in 3 divided doses in one day. The usual oral dose, without a loading schedule, is 0.125-0.25 (½-1 tablet) per day. Oral loading dose of digoxin is 0.5 mg given 8 hourly for 3 doses. Intravenous loading dose is rarely used now a day.



In full therapeutic doses some toxicity is inevitable (hatched-dotted intersection). A plasma level above 1.5 ng is now considered to toxic level

Fig. 5: Narrow Safety Margin of Digoxin

Drug interactions: There are many drugs that adversely interact with digoxin, altering its pharmacokinetic and pharmacodynamic profiles (Table 4).

Table 4: Drug interactions and mechanisms

S.No	Interacting drug	Effect on digoxin	Mechanism
1	Quinidine	2-3 times↑ in Plasma level	Reduced renal/nonrenal clearance, displacement from tissue binding sites.
2	Kaluretic diuretics	↑Toxicity	Hypokalemia-see text
3	Amiodarone	↑Plasma level	Reduced renal/nonrenal clearance
4	Verapamil	↓Pulse rate, asystole, ↑toxicity	Additive AV nodal inhibition Reduced clearance
5	Antibacterials	↑Bioavailability	Reduced gut inactivation
6	Adrenergic drugs	Tachyarrhythmias	↑Myocardial sensitivity
7	Propranolol	More bradycardia, ↓ Inotropic action	Additive AV nodal depression, Opposite effect on contractility.

Therapeutic uses of digitalis: The indications of digitalis (digoxin) have changed markedly. It was used as a first line drug in CHF but as the outcome of many large-scale clinical trials indicated no reduction in mortality, the use of digoxin has declined as a first line drug. At present main indications of digoxin are:

1. Chronic CHF with atrial fibrillation- Digoxin reduces heart rate by AV block and increases cardiac output.
2. Chronic CHF with normal sinus rhythm (NSR)- Digoxin provides limited clinical benefits from congestive manifestations. It increases cardiac output gradually even when given in smaller doses without loading dose. In this way toxicity is reduced. It is considered to be an *add-on* drug to provide longer inotropic support in patients already on ACE-Is/ARBs, β-blockers and diuretics, if patient is symptomatic and in systolic failure with low ejection fraction.

> **Limitations of digoxin:** The digoxin Investigation Group (DIG-1997) studied the effect of digoxin on survival in CHF. Overall, there was no difference in mortalily between digoxin and no-digoxin groups. Less hospital admissions were there with digoxin. The risk of death was increased with digoxin (in patients with plasma level >1.4 ng/ml). Other studies also support these findings. The pathological changes in CHF are not reversed by digitalis

3. Chronic atrial fibrillation without CHF: In this condition the main objective is to reduce ventricular rate by digoxin. It increases AV nodal ERP and reduces conduction by establishing a greater degree of AV block so that weak impulses are not effectively transmitted to ventricles. This action is further supported by addition of small dose of propranolol (10-20 mg 3-4 times a day) cautiously.

4. Paroxysmal atrial tachycardia: Digoxin is an alternative agent only. The main drugs used are adenosine, verapamil or diltiazem.
5. Atrial flutter: Digoxin is less often used in this condition. It may convert flutter to fibrillation that is easier to treat. As in atrial fibrillation, digoxin reduces heart rate in atrial flutter also.
6. Left ventricular failure: In past IV lanatoside-C was used in acute LVF. Its use is supplanted by IV nitroglycerine, frusemide and nasiritide. Oral digoxin may be required for a longer inotropic support in some cases.

Factors altering digoxin response: Digoxin effects are altered by a number of factors, the most important being systemic diseases (Table 5). Digoxin is less effective or ineffective in tight mitral stenosis, high output heart failure due to severe anemia or thyrotoxicosis, cor pulmonale and acute rheumatic carditis. The electrolyte disturbance (particularly hypokalemia, hypomagnesemia & hypercalcemia), myocardial ischaemia, acute hypoxemia, and acid-base disturbances markedly alter digoxin response. The most important factor for maintenace doses is adequate renal function. This necessitates dose adjustments according to the renal function (creatinine clearance).

Table 5: Systemic disorders modifying digoxin effects: Increased toxicity

S.No	Disorder	Mechanism
1	Lean body mass-elderly	Reduced skeletal muscle pool of digoxin
2	Renal impairment	Reduced clearance
3	Chronic lung disease	Hypoxia, electrolyte disturbance,sympathetic overactivity and acidosis
4	Hypothyroidism	Reduced metabolism
5	Hypokalemia	More binding of digoxin on Na+K+ATPase
6	Hypomagnesemia	More digoxin binding on Na+K+ATPase
7	Myocardial infarction Myocarditis	Myocardium is more sensitive. May ↑ infarct size by increased cardiac work Coronary constriction.

Adverse effects and toxicity

Full loading and maintenance doses of digoxin may cause toxic manifestations. There are cardiac and extracardiac manifestations, the latter appear earlier. GIT manifestations are anorexia, nausea and vomiting. Vomiting is due to central and peripheral (stomach) effects. Diarrhoea may occur due to direct intestinal smooth muscle contractions as a result of Na+K+ pump inhibition.

Cardiac toxicity: Palpitations, syncope and dizziness may be due to rhythm disturbances. Digoxin characteristically causes AV junctional(nodal) rhythm and ventricular extrasystoles, notably bigeminy. Paroxysmal atrial tachycardia with variable AV block is another arrhythmia characteristically observed in digoxin toxicity. Severe bradycardia, SA arrest and VT can also occur. In fact any arrhythmia occurring after digoxin use may be attributed to it and treated accordingly.

CNS manifestations of toxicity are headache, fatigue, visual disturbance (redgreen hues & scotoma), optic neuritis, vertigo, numbness, paresthesia, confusion and rarely hallucinations. Uncommonly, digoxin causes gynecomastia due to estrogen like (steroidal structure) action. Contraindications to digitalis are given in Table 6.

Treatment of digitalis toxicity: First of all digitalis should be stopped immediately. Estimation of serum electrolytes, particularly potassium levels, and quick correction is important. Hypokalemia should be corrected by oral potassium chloride 4-6 gm given in 3-4 divided doses as a syrupy liquid. Intravenous potassium is needed in urgent situations and 20-40 mEq of potassium can be infused in 5% dextrose solution in 2-4 hours under ECG control. If AV blocks are present, IV potassium is avoided because AV refractoriness is increased and AV block may be aggravated. In this situation disodium edetate(calcium chelating agent) appear to be a good choice. Symptomatic bradycardia requires IV atropine.

Table 6: Contraindications

Absolute	**Condition**	**Reason**
	Hypertrophic obstructive cardiomyopathy	↑ contractility increases outflow tract obstruction
	Atrial fibrillation in WPW syndrome	Worsening of tachycardia by accelerating conduction in bypass tract
	AV nodal blocks and sick-sinus syndrome	Asystole, Complete heart block
	Diastolic heart failure (DHF)	EF is high in DHF, No improvement in LVH
Relative	High output failure	
	Myocarditis	
	Post MI failure	
	Acute glomerulonephritis	

Sometimes temporary pacing is needed. Supraventricular tachycardia (usually associated with varying blocks) requires phenytoin because it facilitates AV conduction. Propranolol 1 mg slow IV can also be used. In ventricular tachyarrhythmias, IV lidocaine is required but phenytoin is also effective. Quinidine, verapamil and amiodarone should be avoided because these may increase toxicity by reducing clearance of digoxin. Absorption of unabsorbed digoxin can be reduced by activated charcoal (50-100 gm) or by cholestyramine.

Digoxin antibodies (Digibind):

These have FAB fraction of sheep or bird antibodies against digoxin and are effective in neutralizing overdose effects when given intravenously.

Dose calculations:

Total body burden of digoxin = Amount ingested X Bioavailability (80%)

$$\text{Dose of FAB antibodies} = \frac{\text{Digoxin body burden} \times \text{Molecular mass of antibodies (50,000 Daltons)}}{\text{Molecular mass of digoxin (781 Daltons)}}$$

One vial contains about 40 mg and is sufficient against 0.5 - 0.6 mg of digoxin

Digoxin antibodies are indicated in severe intoxication (poisoning) and when hyperkalemia complicates the picture. These are more effective in ventricular tachycardia. The duration of action is short therefore; antibodies have to be repeated after 24 hours.

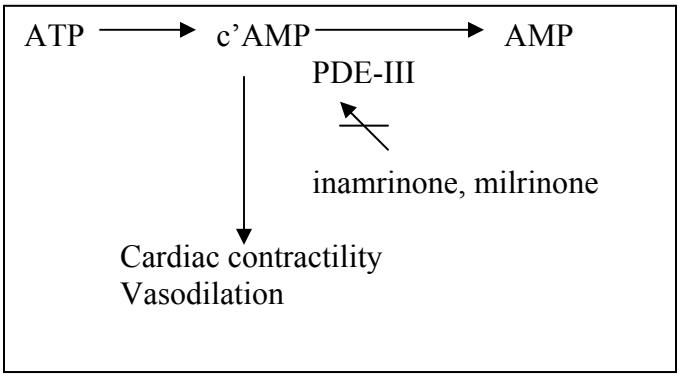
Other Inotropic Drugs

Dobutamine: It is a derivative of dopamine and has β_1-agonistic action. It increases cardiac contractility but heart rate does not rise much in usual doses. It is therefore a cardiotonic agent. It reduces sympathetic activity in CHF. It must be given intravenously in a dose of 2.5 μg/kg/minute and can be increased upto 20 μg/kg/minute. It may stimulate vascular β_2 receptors and thus causes hypotension. A simultaneous dopamine infusion raises blood pressure and renal output in cardiogenic shock. It is indicated in the treatment of acute heart failure with systolic dysfunction and pump failure in acute myocardial infarction. It is also used in β-blocker poisoning and, as a short-term inotropic drug in severe acute decompensation in chronic heart failure and during cardiac surgery. A portable pump is being evaluated currently, for home-based therapy of intractable heart failure awaiting cardiac transplantation. A major limitation of dobutamine is tolerance to inotropic action. Therefore, it is infused for 1-3 days only. Adverse effects are cardiac rhythm disturbances, hypotension, nausea and vomiting.

Dopamine: It is used in shock to raise blood pressure and to improve renal perfusion by acting on renal vascular dopaminergic receptors in low doses causing renal vasodilation. The response to diuretics is restored by low dose infusion of dopamine. A higher dose stimulates heart by β_1 agonist action and in still higher doses α-adrenergic action causes peripheral vasoconstriction and raises PVR. In refractory heart failure with hypotension it is used in a dose of 0.5-1.0 μg/kg/minute and dose increased upto 5-10 μg/kg/minute. It is contraindicated in ventricular extrasystoles and VT.

Other inotropes are dopexamine and ibopamine. Dopexamine increases CO and renal blood flow by stimulating β_2 and dopamine receptors. It also inhibits reuptake of noradrenaline. Ibopamine is a prodrug and is rapidly converted into active inotropic intermediate

Inodilators (Phophodiesterase –III inhibitors): This group of drugs includes bipyridines such as inamrinone, milrinone, enoximone and vesnarinone. Pimobendan and levosimendan are Ca++ sensitizers with inodilatory actions. Inodilators are the drugs, which have inotropic and vasodilatory actions together. The general mechanism of action is given below.



PDE-III inhibitors elevate intracellular c'AMP levels and cardiac contractility by increasing cyclic release of Ca++ from sarcoplasmic stores and cytosolic calcium. In the blood vessels, rise in c'AMP is associated with smooth muscle relaxation. Thus, there is venous and arterial dilatation. The diastolic relaxation is also hastened. Heart rate usually does not change.
NB: *Theophylline is a nonselective PDE inhibitor and sildenafil inhibits PDE-V in penile tissues.*

Inamrinone (Amrinone): It inhibits PDE-III in heart, blood vessels and other smooth muscles. i.v. infusion increases cardiac output and reduces ventricular end-diastolic pressure. It may be of some use in acute heart failure. Unfortunately, tolerance develops rapidly limiting its use. Adverse effects are nausea, vomiting and tachyarrhythmia. Liver enzymes are elevated and *thrombocytopenia* is seen in about 10% cases. Because of these unwanted effects it is no longer used.

Milrinone: It is a bipyridine and is more selective inhibitor of PDE-III than amrinone. It is about 10 times more potent and can be used orally. Its half-life is short (1 hour). It does not cause thrombocytopenia so is a preferred inotrope. In acute heart failure i.v. milrinone is given as a freshly prepared solution in a dose of 50 μg/kg in 10 minutes, initially and then as an infusion at a rate of 0.25-1.00 μg/kg/minute for 1-2 days. It can be given concurrently with ACE-Is, dobutamine or dopamine. Although it provides short-term improvement but the results of clinical trials show that no additional benefit is accrued by milrinone therapy and it causes lethal arrhythmias. It is contraindications are same as with digoxin. Currently, milrinone is tried as a continuous infusion by a portable devise, which a patient with intractable heart failure may use at home.

Enoximone: It is a newer derivative which can be used in acute heart failure resistant to conventional drugs. It is given in a dose of 90 μg/kg/minute initially, then 5-10 μg/kg/minute.

Role of vasodilators in CHF
There is increased preload and afterload in CHF (Flow diagram 1). Reduction in pre- and after-loads is beneficial in heart failure because cardiac work is reduced. Different vasodilators have been used to dilate venous and arterial beds. Table 7 shows the vasodilating drugs used in CHF. These agents shift the Frank-Starling curve to the left (Fig 2) and reduce ventricular end-diastolic volume and pressure.

Table 7: Vasodilator drugs used in CHF

Predominant venodilators:	Organic nitrates(NTG and ISDN)
Predominent arterial dilators:	Hydralazine, calcium channel blockers, (amlodipine,nifedipine)
Mixed dilators:	ACE-Is, ARBs, sodium nitroprusside, α-blockers, nesiritide.

- *Some β-blockers have vasodilating action (labetalol, carvedilol)*
- *IV frusemide and morphine have venodilatory action (not classified as vasodilators)*

Venodilators are useful when predominant symptom is dyspnoea and pulmonary congestion. By reducing venous return, left ventricular filling pressure is reduced, pulmonary congestion decreases and forward output increases. Nitroglycerin (NTG) and isosorbide dinitrate-ISDN (sublingually, orally or IV) are very important drugs for the treatment of acute LVF with pulmonary oedema. i.v. NTG is used at a rate of 2-5 μg/min. It is interesting to note that rapid i.v. frusemide reduces dyspnoea in LVF much earlier to diuretic effects and this benefit is attributed to venodilatory effects. Oral ISDN with hydralazine was used as balanced vasodilator earlier. This combination is found to be effective in reducing mortality by 20-43% when given along with other drugs in resistant CHF.

Arterial dilators are effective when main symptom is fatigue due to low cardiac output and PVR is raised. Hydralazine may be given to those who cannot tolerate ACE-Is but now a days ARBs have taken over it. Hydralazine has some direct inotropic action and increases renal blood flow also. Usually small dose of 10-25 mgs is given three times a day then increased to a maximum of 300 mg. It may also reverse nitrate tolerance by its antioxidant action (reduces generation of superoxides).

Sodium nitroprusside is a balanced dilator. It is an inorganic compound, a prodrug, which is converted by guanylate-c'GMP system to NO that acts as a dilator. It is used for quick reduction of blood pressure in emergency and to improve cardiac output in severe CHF associated with low output and pulmonary congestion. It reduces preload and afterload of failing heart with pressure overload thus reduces wall stress. It is given as a freshly prepared solution protected from light (light sensitive) at a rate of 0.25-1.5 μg/kg/minute. Its adverse effects are hypotension, thiocyanate toxicity (confusion, abdominal pain, lactic acidosis, convulsions), and methemoglobinemia. Other vasodilators are used less often

Nesiritide: A family of endogenous neurohormones such as atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type peptide) are secreted by atrial and ventricular myocytes. BNP is secreted in response to stretch and its circulating levels parallel with severity of heart failure. Circulating BNP opposes actions of angiotensin-II and noradrenaline. Recombinant form of human-BNP has diuretic, natriuretic and vasodilatory actions. Vasorelaxation is mediated by activation of guanylate cyclase and production of NO. Nasiritde has a short half-life of 18 minutes and has to be given i.v.. It is administrered in a dose of 25 μg/kg initially and then as an infusion of 0.01-0.03 μg/kg/minute. It is as effective as NTG in acute LVF and does not have arrhythmogenic potential. It reduces right and left ventricular EDVs and pulmonary capillary pressure. There is fall in PVR, rise in cardiac output and diuresis in acute heart failure. It dose not have chronotropic and inotropic actions. Hypotension may occur on rapid IV administration.

Role of β-blockers in CHF

In past, β-blockers were considered to be contraindicated in heart failure because of their acute negative inotropic effect causing further decompensation in CHF. However, considering the immense role of sympathetic overactivity (Table-8) and β-receptor dysregulation in pathophysiology of CHF, β-blockers appear to be logical choice for reversing structural and functional changes in CHF. In fact, the results of several carefully conducted clinical trials show that β-blockers reduce all cause mortality by 35-40%, reduce hospitalizations, worsening of CHF

and prevent sudden death. There is increased exercise capacity and CO rises gradually along with a fall in heart rate. Full benefits occur slowly over a period of 2-4 weeks. Initial doses of β-blockers are very small and dose increments are done gradually once in 2-4 weeks (Box)

β-Blocker dose titration: daily dose-increments once in 1-2 weeks

- Carvedilol: 3.125mg initially, then 6.25 to 25 mg
- Bisoprolol: 1.25 mg → 2.5 → 3.75 → 5.0 → 7.5 mg
- Metoprolol-XL: 12.5 mg → 25 → 50 → 100 → 150 → 200 mg

Table 8: Abnormalities of Adrenergic System in CHF

1. **Downregulation of β-receptors**
   It occurs due to persistent adrenergic overactivity. The functional receptors decrease and thus reduced formation of cAMP leads to poor contractility. A compensatory increase in β_3 receptors produces excessive NO, which has negative inotropic action on heart.
2. **Abnormal β-receptor signaling**
   Increased activity of β-ARK (β-adrenergic receptor kinase) forms inhibitory Gi and inhibits β_1 receptor activity.
3. **Cyclic influx** of Ca++ in sarcopalsmic reticulum is disturbed so its cyclic release is less which leads to poor contractile power.
4. **Catecholamines** have direct myocardial toxicity, Ca++ overloading, cell membrane damage and distrurbed ionic movement across myocytes.
5. Catecholamines are arrhythmogenic.
6. There is induction of apoptosis with loss of contractile elements.

These drugs have proved to be beneficial in many ways and are now a part of standard drug treatment of CHF, along with ACE-Is and diuretics.

1. Reduction in cardiac contractions reduces wall stress, increase diastolic time for adequate cardiac filling and reduce tachycardia.
2. Reduce cardiac excitation due to sympathetic overactivity thus prptect myocardium.
3. Reverse defects in β-receptor signaling (c'AMP, β-ARK), ultimately improves c'AMP production which enhances cardiac contractions.
4. Carvedilol reduces β_3 overactivity (β_3 receptors have negative inotropic effects) and has antioxidant property also.
5. Antiarrhythmic actions of β-blockers prevent arrhythmia-induced sudden death.
6. Anti apoptotic and anti-remodeling actions are important for reversal of structural changes in CHF.
7. Overactive renin-angiotensin system is normalized.
8. Reduced β_1 receptor gene expression. Reversal of downregulation of β_1 receptors on chronic administration.

These drugs are indicated when patient is receiving ACE-Is, diuretics and still is in NYHA functional class-II or III and requires therapy for low cardiac output, then gradual addition of β-blockers improves cardiac output and long-term survival. Carvedilol has a greater effect on mortality reduction than metoprolol. They should not be stopped abruptly and are not given if there is:

1. low systolic blood pressure (<90 mmHg)
2. Frank CHF with oedema
3. Chronic obstructive pulmonary disease or bronchial asthma
4. Uncontrolled diabetes mellitus
5. Volume depletion.

Vasopeptidase inhibitors: As stated earlier ANP and BNP are released from myocardium in CHF to induce diuresis and oppose the adverse effects of angiotensin-II. These peptides are inactivated by neutral endopeptidase enzyme (NEP) present in kidney, lungs and liver .Inhibition of metabolism of natriuretic peptides increases their levels in blood and prolongs their diuretic and natriuretic actions. Some newer drugs are capable of inhibiting both ACE and NEP enzymes and produce beneficial vasodilatory action in CHF (box). There is increase in blood natriuretic peptide levels and reduced formation of angiotensin-II. This reduces vasoconstrictor response and also reduce peripheral vascular resistance.

Angiotensin-I	ANP and Bradykinin
ACE ←X (Omapatrilat) X→	NEP
Angitensin-II	Inactive products

Omapatrilat, sampatrilat and fasidotrilat are dual inhibitors of ACE and NEP enzymes and have been tried in CHF and hypertension.

Role of diuretics in CHF

These drugs are time-tested drugs for CHF and increase urine output, reducing oedema and breathlessness in heart failure. There is reduction in blood volume (preload) also.

Thiazides: Thiazides are effective in mild to moderate CHF. Hydrochlorothiazide (HCTZ) is commonly used agent. The diuretic dose of HCTZ is higher than antihypertensive doses. Clopamide, chlorthalidone and metolazone are other agents. Thiazides are not effective when GFR is low. Metolazone acts even when GFR is low. A small dose of K+retaining diuretic is also added to reduce hypokalemic effect. If thiazides fail or there is severe CHF then loop diuretics are needed. Thiazides show synergism with frusemide and combination is used in diuretic resistant oedema.

Loop diuretics: Frusemide, bumetanide, torasemide and ethacrynic acid are potent diuretics, which inhibit Na+K+2Cl- symporter in the ascending limb of loop of Henle. As such these agents are effective even when GFR is low. Frusemine is started in low dose of 20-40 mg/day and dose increased to achieve desired volume reduction. Frusemide and bumetanide are short acting that means if these are given as a single morning dose then action wears off by afternoon and there is post dose retention of Na+ from all segments of nephron. This Na+ retention causes

loss of diuretic efficacy and can be avoided by giving frusemide twice a day. Hypokalemia can be prevented by combining loop diuretics with spironolactone,amiloride or triamterene. Frusemide is the diuretic of choice in acute left ventricular failure/pulmonary oedema. It rapidly reduces dyspnoea and pulmonary congestion by its venodilatory action that is observed earlier to diuretic effect. It is given as 20-40 mg i.v. and may also be given by continuous infusion at a rate of 10 mg/hr. This method reduces risk of ototoxicity and there is sustained natriuretic action.

Limitations of diuretics: Diuretics increase renin and angiotensin-II secretion because of reduction in blood volume. Chronic use causes electrolyte disturbances (hypokalemia), raise LDL and uric acid levels and worsen diabetes mellitus. There is no reduction in mortality on long-term use. Diuretic resistance may occur. Comparative pharmacology is given in Table 9.

Table 9: Comparative pharmacology of diuretics used in CHF

	Thiazides	**Frusemide**	**Bumetanide**	**Torsemide**
Onset of action	1-2 hr	10-20 min	30 min	30-60 min
Duration	16-24 hr	4-6 hr	4-5 hr	7-8 hr
Dose-interval	Once	Twice	Once/twice	Once
Maximal efficacy	Low/medium	high	high	high
Equivalent dose	50 mg	40 mg	1 mg	10 mg
Hypokalemia	More than loop diuretics	Less than thiazides	Yes	Less than Frusemide in small doses

Role of Aldosterone antagonists

Aldosterone levels are markedly raised (10-20 times normal) in heart failure. It is responsible for some of haemodynamic (volume overload, sodium retention & oedema) and structural changes. Aldosterone induced cellular and subcellular changes in heart failure are given in Table-10.

Table 10: Effects of aldosterone in the pathogenesis of CHF

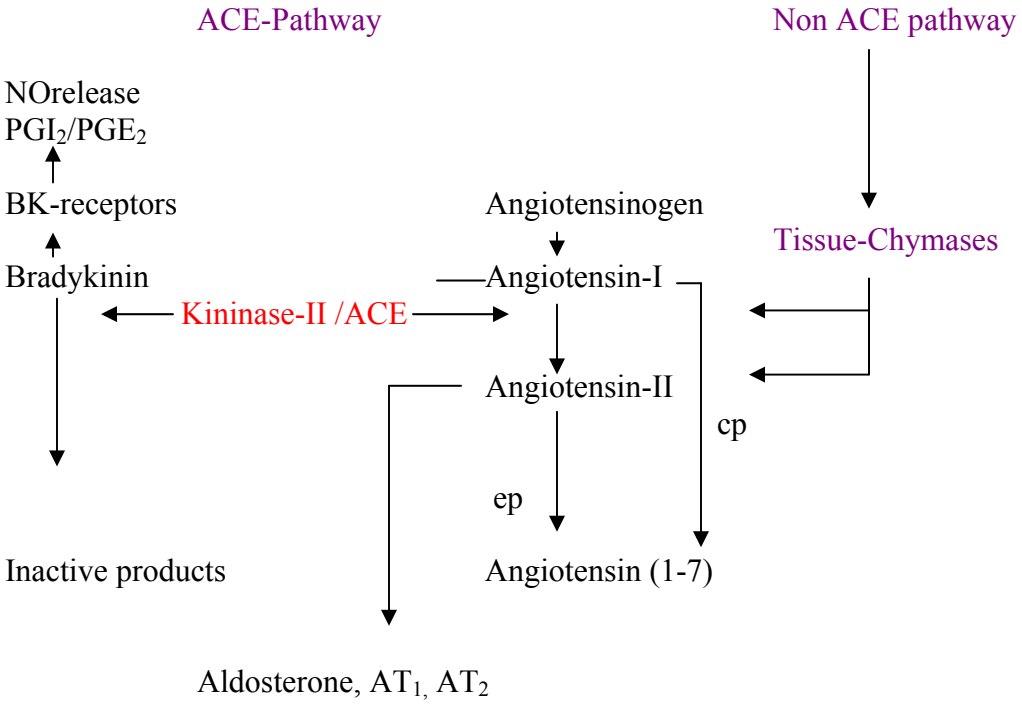
Effect of aldosterone	**Mechanism**
• Remodelling induced-LV dysfunction	Proliferation of fibroblasts, myocardial fibrosis.
• Increased peripheral vascular resistance/afterload	Perivascular fibrosis, ↑ vascular reactivity, ↑ Vascular wall sodium
• Increased blood volume,	Sodium & fluid retention
• Edema	increased back-pressure
• Increased excitability, ventricular arrhythmia, sudden death.	Loss of K+ & Mg++, NE reuptake inhibition, Na+ channel dysfunction, Hypersensitive baroreceptor reflex.

Aldosterone antagonists (spironolactone and eplerenone) can reverse the structural and functional changes induced by aldosterone excess in CHF. Spironolactone is a mild K+ conserving diuretic, which is given with thiazides or loop acting diuretics to antagonize their hypokalemic effects. It has shown a significant additional improvement as reduction in hospitalization, mortality by 30% and prevention of progression of heart failure when added in low doses (25 mg/day) with ACE-Is, diuretics, digoxin and β-blockers in resistant cases of CHF. This beneficial effect is not due to reduction in edema alone but mainly due to reduction in myocardial fibrosis and remodeling.

Eplerenone: It is another K+sparing diuretic is also found to be as effective in improving left ventricular function given after myocardial infarction in a dose of 25-50 mg/day. The advantage with eplerenone is that it does not have endocrine adverse effects (gynecomastia, impotence, menstrual disturbance) of spironolactone.

Role of angiotensin converting enzyme inhibitors (ACE-Is)

Angiotensin-II (A-II) formation is increased in CHF. Tissues can generate angiotensin-II by ACE and non ACE pathways (Flow Diagram 4). A-II has multiple deleterious effects on cardiovascular system (Table-11). It is responsible for hypertrophy, remodeling and rise in peripheral vascular resistance (PVR). Renin-angiotensin system is activated early in the course of CHF and plays critical role in haemodynamic and structural changes in chronic CHF.



cp= carboxypeptidase ; ep= endopeptidase

The brain, heart, blood vessels and adrenals can synthesize A-II by ACE and non-ACE (chymases) pathways. Non-ACE pathways form about 60% of A-II in heart.

Flow diagram 4: Tissue Angiotensin-II generation by ACE and Non-ACE pathways

Table-11.Structural and haemodynamic alterations caused by Angiotensin-II

Haemodynamic changes:	**Mechanism**
Raised PVR	A-II is a potent direct vasoconstrictor
Increased pre/afterload	Increased sympathetic activity
Raised LV wall-tension	Increases NE release
	Reduced reuptake of released NE
	Increased vascular responsiveness to NE
	Increased central sympathetic discharge
	Catecholamine release from adrenals
	Increased ganglionic transmission
Alterations in Renal function	
Sodium and water retention	Aldosterone secretion
	Reduced tubular Na+ reabsorption
Renal vascular changes	
GFR and urine output changed	Direct effect
	NE effect
	Efferent glomerular vasoconstriction
	Reduced medullary flow
Structural changes in heart	
Hypertrophy and remodeling	Expression of proto-oncogenes by AT_1 receptors
Concentric-new sarcomeres added in parallel.	Production of growth factors
Eccentric—addition of sarcomeres in series; new contractile proteins added to existing sarcomeres.	Synthesis of extracellular matrix proteins
	Fibroblast proliferation by AT_1 receptors
	Hypertrophy of myocytes
	Cytokine activation
Structural changes in blood vessels	
Raised PVR	Intimal thickening
	Reduced lumen:wall ratio
	Smooth muscle hypertrophy
	Fibrosis
Most of these actions are mediated by AT_1 receptors.	

ACE-Is are indicated in patients with systolic dysfunction (EF<40%) and are considered to be the first drug of choice for the treatment of mild to severe heart failure (NYHA class I-IV). There is reduction in systemic vascular resistance (preload), heart size, and ventricular end diastolic pressure. Cardiac output increases gradually. Diuresis occurs with reduction in oedema and body weight. Heart rate is reduced and exercise capacity is increased. Patients report increased well-being. The functional class changes (say from III to I). These beneficial effects are maintained with continuous use. Overall mortality is reduced by 20%-40% as is evident from large controlled multicentric trials (Table-12).

Table 12: Major Outcome Trials

Trial name	Outcome
The cooperative northern Scandinavian Enalapril Survival Study (CONSENSUS) (N.Eng.J.Med., 1987;316:1429-1435)	40% reduction in mortality in 6 months.
Survival and Ventricular Enlargement trial (SAVE) (N.Eng.J.Med.,1992;327:669-677)	20% reduction in mortality, 36% reduction in progression to severe heart failure.
Acute Infarction Ramipril Efficacy(AIRE) (Lancet., 1993;342:821-828)	27% reduction in mortality in 6 months.
Study of left ventricular dysfunction SOLVD-treatment with enalapril (N.Eng.J.Med.,1991;325:293-302)	18% mortality reduction in 40 months
SOLVD-prevention with enalapril (N.Eng.J.Med.,1992;327:685-691)	37% reduction in risk of CHF.
Extended SOLVD (Lancet.,2003;361:1843-1848)	Death risk reduced by 10%.

In asymptomatic patients, ACE-Is delay occurrence of frank CHF and hospitalization. They can be given with β-blockers, diuretics and digoxin. The usual doses are given in Table-13. In patients already receiving diuretics, the dose should be reduced and then added according to need. This is because in a volume depleted (diuretics) patient ACE activity is high and thus ACE-Is act as more potent agents causing hypotension. ACE-Is are effective in diastolic dysfunction when used along with other agents. These beneficial effects are attributed to the reductions in levels of A-II, aldosterone and sympathetic over-activity.

Table 13: ACE-Is and ARBs: Doses

ACE-Is	ARBs
Captopril 25-50 mg three times a day	Losartan 12.5-100 mg once a day
Enalapril 2.5-10 mg twice a day	Candesartan 4-16 mg twice a day
Benazepril 10-20 mg twice a day	Valsartan 40-160 mg per day
Lisinopril 2.5-10 mg once a day	Irbesartan 150-300 mg a day
Perindopril 2-8 mg once a day	Telmisartan 20-40 mg once a day
Ramipril 1.25-10 mg once a day	
Fosinopril 5-10 mg once/twice a day	
Trandolapril 0.5-4 mg once a day.	

Beneficial effects of ACE-Is: ACE-Is are indicated in all grades of severity of heart failure with EF<40% and left ventricular dysfunction after myocardial infarction. They are indicated even in

asymptomatic patients with low ejection fraction because these agents reduce occurrence of clinical heart failure. In addition ACE-Is have protective effects in coexistent conditions like diabetic mellitus (nephropathy and retinopathy). There are several benefits with these drugs:

1. Reversal of A-II induced cardiac structural and functional changes.
2. Reduction in preload and afterload with subsequent reduction in cardiac work.
3. Reduction in adrenergic overactivity and aldosterone secretion
4. Reduced myocardial fibrosis
5. Improvement in well-being and quality of life.

Adverse effects of ACE-Is: Hypotension may occur if diuretics are already given. Dry cough occurs in about 10-20% cases and is due to bradykinin-induced secretion of prostaglandins. It is ameliorated by use of NSAIDs (sulindac, aspirin), iron supplementation or by small doses of nifedipine. Hyperkalemia is due to reduced aldosterone. Fetopathy (particularly second and third trimester use- oligohydramnios, pulmonary hypoplasia, neonatal oliguria and death). Fetal growth requires activity of AT_1 receptors and severe reduction in placental blood flow an fetal growth retardation is noted with ACE-Is. Maculopapular skin rash, angioedema, neutropenia and dysguesia occur more frequently with captopril. Proteinuria may occur while proteinuria due to diabetic nephropathy is reduced. Rarely glycosuria, cholestatasis and hepatotoxicity may also occur.

Angiotensin receptor blockers (ARBs) in CHF

These agents competitively block the AT_1 receptors, which are responsible for mediation of actions of angiotensin-II. Candesartan induced block is surmountable while with others there is insurmountable block of AT_1 receptors. ARBs are found to be as effective as ACE-Is and are indicated when the latter are not tolerated because of dry cough, angioedema or drug rashes. AT_2 receptors are not blocked by ARBs so that these receptors continue to exert cardioproective and antiproliferative effects. ARBs are slow acting thus full effects occur in 3-4 weeks. Use of ACE-Is and ARBs together have complete blockade and additive beneficial effects on hypertrophy, remodeling and cardiac performance in CHF and are being evaluated intensively. There are certain differences between these two groups of drugs (Table-14).

Table 14: Differences between ACE-IS and ARBs

Parameter	ACE-Is	ARBs
1. Angiotensin-II levels	Reduced	Increased
2. Bradykinin action	Potentiated	Unaffected
3. AT1 receptors	Not affected	Blocked
4. AT2 receptor activity (cardioprotective effects)	Reduced	Increased (remain unblocked)
5. A-II generation by alternative (chymase). route	Generated.	Generated but effects blocked.
6. ACE escape*	ACE escape.	No ACE escape
7. Cough, angioedema, dysguesia.	More frequent	Rare

*ACE-escape- ACE-inhibitors do not affect formation of angiotensin-II by alternate pathways (nonACE pathways) as shown in Flow diagram-4. Therefore angiotensin-II/aldosterone levels return back to baseline.

Contraindications and precautions with ACE-Is and ARBs: Pregnancy, renal failure, bilateral renal arterial stenosis, renal artery stenosis in single kidney and hyperkalemia are contraindications for both groups.

Drugs which worsen CHF: Table-15 lists the drugs which can worsen preexisting CHF and thus should be avoided.

Table 15: Drugs which may worsen CHF

Drug	**Effect on heart**
Verapmil and diltiazem	Myocardial depression
β-blockers	Acute decompensation in untreated caes
Doxorubicin(Adriamycin) Daunomycin	Cardiomyopathy
Alcohol*	Myocardial damage
High dose cyclophosphamide	Myocardial damage
Cocaine abuse	Myocardial damage
Methysegide	Endocardial fibrosis
NSAIDs, Pioglitazone, Carbenoxolone.	Fluid retention and weight gain
Fenfluramine	Valvular damage and fibrosis

* Chronic intake in larger quantities

Diagram-horse cart: A horse drawing a loaded cart uphill has to perform a greater work. The work can be reduced by –

1. Reducing load on the cart (Preload reduction).
2. Reducing the speed and giving rest to horse (cardiotonic agents).
3. Diverting horse cart to a level running road (Afterload reduction).

Suggested Readings

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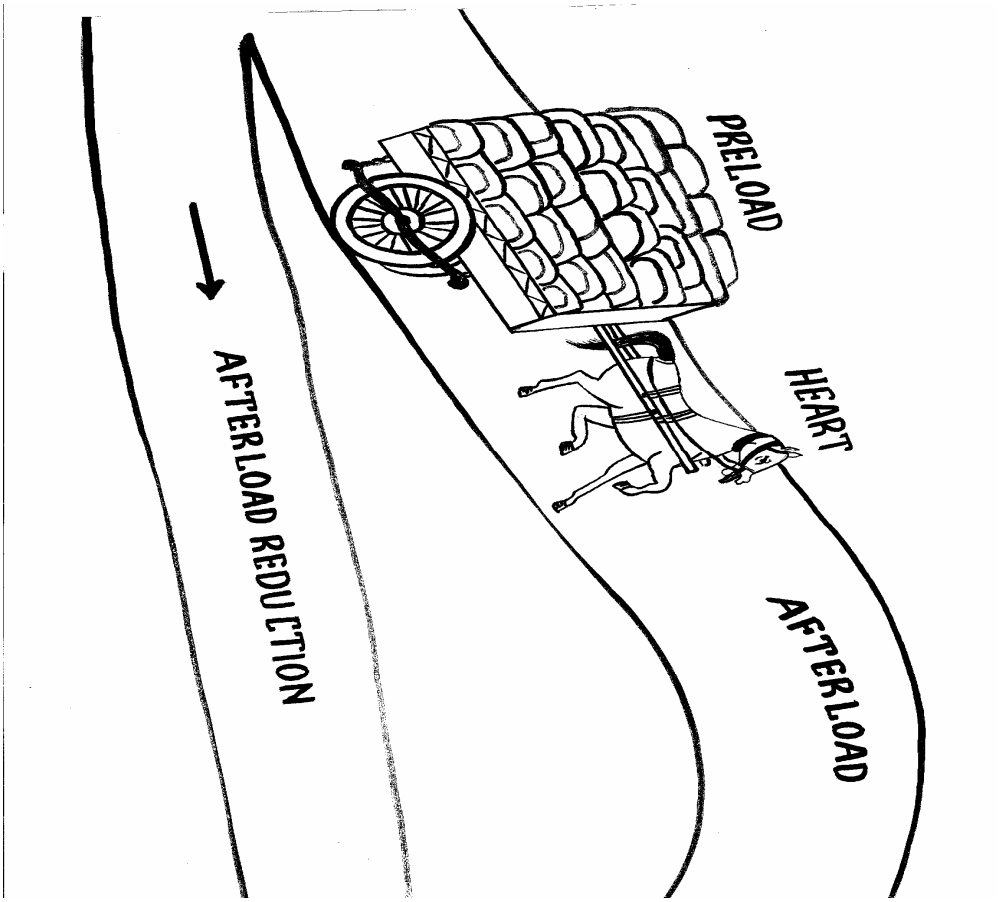

Diagram-Horse-cart, indicating how reductions in preload and afterload and increasing contractility improves cardiac performance