Chapter 38 Cardiac Glycosides and Drugs for Heart Failure

CARDIAC GLYCOSIDES

These are glycosidic drugs having *cardiac inotropic* property. They increase myocardial contractility and output in a hypodynamic heart without a proportionate increase in O_2 consumption. Though other drugs are now more important in the treatment of congestive heart failure (CHF), the cardiac glycosides were the primary drugs till the 1970s, and are still valuable for many patients, when combined with others.

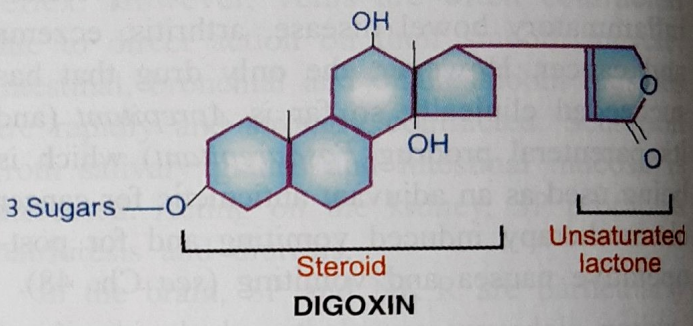
William Withering, a Birmingham physician, tried an extract of 'foxglove' (*Digitalis*) and found it to be remarkably effective in some cases of dropsy (edema). He published his classic monograph in 1785 and ascribed the beneficial effect to an action on the kidney. Cushney and Mackenzie, in the beginning of 20th century, established its action on the heart and its use in congestive heart failure (CHF).

Cardiac glycosides are found in several plants and in toad skin *(Bufotoxin)*. *Digitalis lanata* is the source of *Digoxin*, the only glycoside that is currently in use. Others like *Digitoxin* (from *Digitalis purpurea*) and *Ouabain* (from *Strophanthus gratus*), etc. are no longer clinically used or marketed.

By convention the term, 'Digitalis' has come to mean 'a cardiac glycoside'.

Chemistry

The cardiac glycosides consist of an *aglycone (genin)* to which are attached one or more *sugar* (glucose or digitoxose) moieties.



DIGOXIN

The aglycone consists of a cyclopentanoperhydrophenanthrene (steroid) ring to which is attached a 5 or 6 membered unsaturated lactone ring.

Pharmacological actions

All digitalis glycosides have qualitatively similar action. Digoxin is described as prototype.

1. Heart Digoxin has direct effects on myocardial contractility and electrophysiological properties. In addition, it has vagomimetic action, reflex effects due to alteration in haemodynamics and direct CNS effects altering sympathetic activity.

Force of contraction Digoxin causes a dose dependent increase in force of contraction of heart—a positive inotropic action. This is especially seen in the failing heart which is exquisitely sensitive. Systole is shortened, diastole is prolonged. When a normal heart is subjected to increased impedance to outflow, it generates increased tension so that stroke volume is maintained upto considerably higher values of

impedance (Fig. 38.1), while the failing heart is not able to do so and the stroke volume progressively decreases. The digitalized failing heart regains some of its capacity to contract more forcefully when subjected to increased resistance to ejection. There is more complete emptying of failing and dilated ventricles—cardiac output is increased and end-diastolic volume is reduced.

Rate Heart rate is decreased by digoxin. Bradycardia is more marked in CHF patients because improved circulation (due to positive inotropic action) restores the diminished vagal tone and abolishes sympathetic overactivity. In addition, digitalis slows the heart by vagal (increase in vagal tone) and extravagal (direct depression of SA and AV nodes) actions.

Electrophysiological properties

(a) *Action potential (AP):* The effects are illustrated diagrammatically in Fig. 38.2.

- The resting membrane potential (RMP) is progressively decreased (to less negative values) with increasing doses.
- The rate of 0 phase depolarization is reduced resulting in slowing of conduction. This action is most marked in A-V node and bundle of His.
- The slope of phase-4 depolarization is increased in the PFs—ectopic automaticity is enhanced—latent pacemakers become overt at high doses producing extrasystoles. High doses of digoxin produce coupled beats by another mechanism: the RMP shows oscillations during phase-4; when their magnitude is sufficient enough, delayed after-depolarizations result (*see* Fig. 39.1). The SA and A-V node automaticity is reduced at therapeutic concentrations by vagal action which hyperpolarizes these cells and reduces their phase-4 slope.
- The action potential duration (APD) is reduced (primarily at phase-2) and amplitude of AP is diminished.

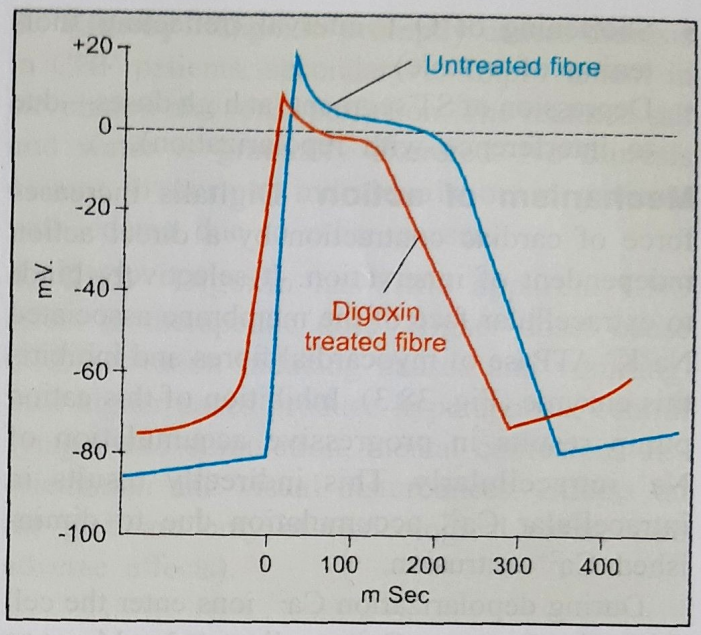


Fig. 38.2: Effect of digoxin on Purkinje fibre action potential

(b) *Effective refractory period (ERP):*

Atrium
- decreased by vagal action
- increased by direct action

Vagal action normally predominates, causes inhomogeneity; allows the atria to respond at a higher rate and in an asynchronous manner.

A-V node and bundle of His — Increased by direct, vagomimetic and antiadrenergic actions; the maximum rate at which impulses can be transmitted is reduced.

Ventricle—ERP is abbreviated by direct action.

(c) *Conduction:* A-V conduction is demonstrably slowed by therapeutic doses. At high doses, intraventricular conduction in PFs is also depressed by uncoupling of gap junctions.

(d) *ECG :* Therapeutic doses of digoxin produce changes in the ECG. These are accentuated at high doses which may also produce arrhythmias.

- Decreased amplitude or inversion of T wave.
- Increased P-R interval (due to slowing of A-V conduction), A-V block at toxic doses.

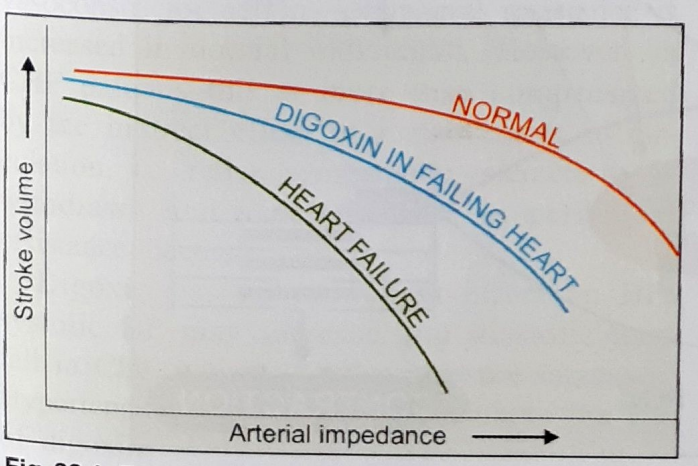


Fig. 38.1: Relationship between peripheral resistance and stroke output in normal and failing heart, and the action of digoxin on failing heart

- Shortening of Q-T interval (reflecting shortening of systole).
- Depression of ST segment (at high doses—due to interference with repolarization).

Mechanism of action Digitalis increases force of cardiac contraction by a direct action independent of innervation. It selectively binds to extracellular face of the membrane associated Na^+K^+ ATPase of myocardial fibres and inhibitis this enzyme (Fig. 38.3). Inhibition of this cation pump results in progressive accumulation of Na^+ intracellularly. This indirectly results in intracellular Ca^{2+} accumulation due to diminished Ca^{2+} extrusion.

During depolarization Ca^{2+} ions enter the cell driven by the steep Ca^{2+} gradient (>1 mM extracellular to < 100 nM cytosolic during diastole) through voltage sensitive L type Ca^{2+} channels. This triggers release of larger amount of Ca^{2+} stored in sarcoplasmic reticulum (SR) through a calcium-activated calcium channel known as *Ryanodine receptor calcium channel 2 (RYR2)* → cytosolic Ca^{2+} increases transiently to about 500 nM (calcium transients) triggering contraction by activating troponin C on myofibrils. The *sarcoplasmic-endoplasmic reticular Cal. ATPase 2 (SERCA2)* is then activated which pumps Ca^{2+} back into the SR, where it is stored loosely bound to calsequestrin (CalS). In the normal state SERCA remains inhibited by a cytosolic protein phospholamban (PLN). Phosphorylation of PLN by PK_A removes this inhibition and SERCA becomes active. A fraction of Ca^{2+} (equal to that which entered from outside during depolarization) is extruded mainly by $3Na^+/1Ca^{2+}$ exchange transporter (*NCX-antiporter*) and to a lesser extent by sarcolemmal Ca^{2+} pump (Ca^{2+} ATPase). During phase 3 of AP, membrane Na^+K^+ATPase moves 3 intracellular Na^+ ions for 2 extracellular K^+ ions. The slight (1–1.5 mM) increase in cytosolic Na^+ over normal (8–10 mM) due to

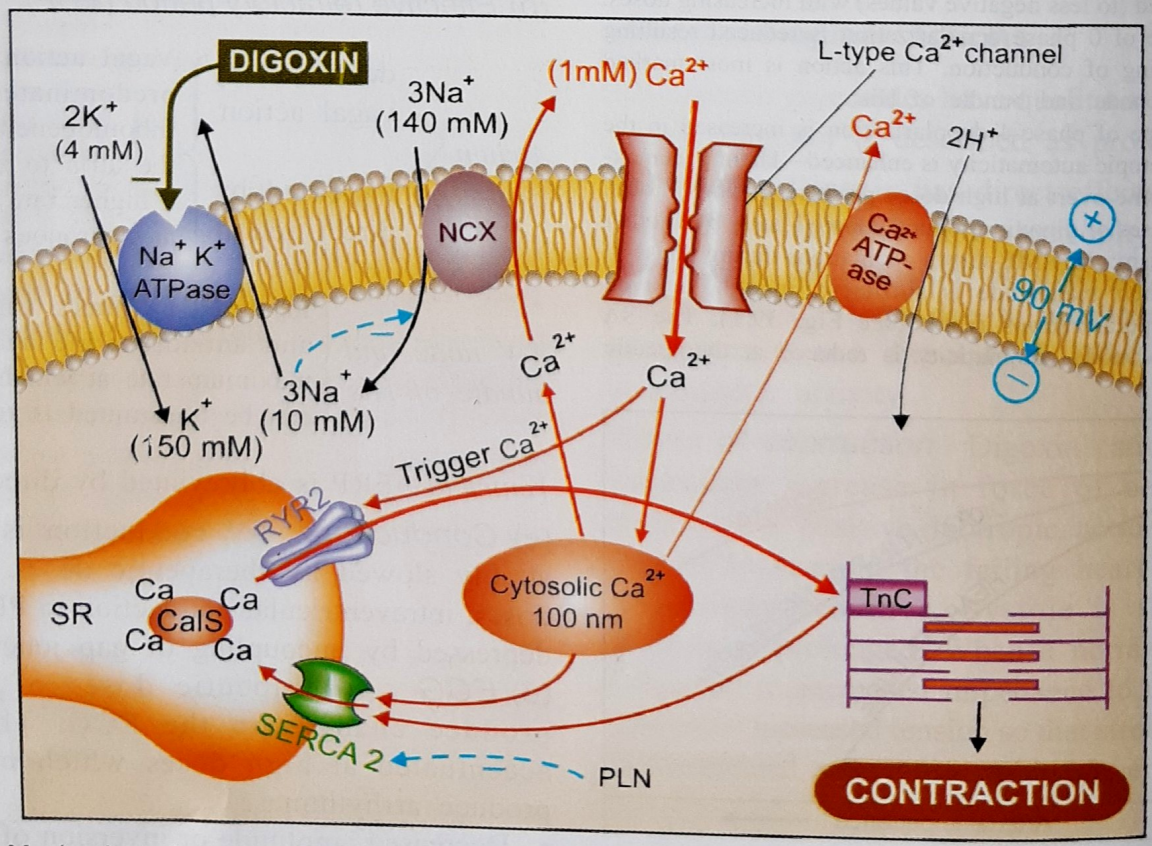


Fig. 38.3: Mechanism of positive inotropic action of digoxin
SR—Sarcoplasmic reticulum; TnC—Troponin C; NCX—Na^+-Ca^{2+} exchanger; RyR2—Ryanodine receptor calcium channel 2; PLN—Phospholamban; SERCA2—Sarcoplasmic-endoplasmic reticulum calcium ATPase 2, CalS—Calsequestrin.

partial inhibition of Na^+K^+ATPase by digoxin reduces transmembrane gradient of Na^+ which drives the extrusion of Ca^{2+}. The excess Ca^{2+} remaining in cytosol is taken up into SR which progressively get loaded with more Ca^{2+} so that subsequent calcium transients are augmented.

The relationship of cytosolic [Na^+] and [Ca^{2+}] is such that a small percentage increase in Na^+ concentration leads to a large percentage increase in Ca^{2+} concentration. Moreover, raised cytosolic Ca^{2+} induces greater entry of Ca^{2+} through voltage sensitive Ca^{2+} channels during the plateau phase. It has been shown that 1 mM rise in cytosolic [Na^+] results in 20–30% increase in the tension developed by ventricular fibres.

Binding of glycoside to Na^+K^+ATPase is slow. Moreover, after Na^+K^+ATPase inhibition, Ca^{2+} loading occurs gradually. As such, inotropic effect of digitalis takes hours to develop, even after i.v. administration.

Inhibition of Na^+K^+ ATPase is clearly involved in the toxic actions of digitalis. At high doses, there is depletion of intracellular K^+; and digitalis toxicity is partially reversed by infusing K^+, because K^+ decreases binding of glycoside to Na^+K^+ ATPase. Excessive Ca^{2+} loading of SR results in spontaneous cycles of Ca^{2+} release and uptake producing oscillatory delayed after-depolarizations and after-contractions. Since both therapeutic and toxic effects of digoxin are due to myocardial Ca^{2+} loading, these are inseparable and therapeutic index of digoxin is low.

2. Blood vessels Digoxin has weak direct vasoconstrictor action—peripheral resistance is increased in normal individuals. However, in CHF patients this is more than compensated by the indirect effect of improvement in circulation, i.e. reflex sympathetic overactivity is withdrawn and a net decrease in peripheral resistance occurs.

Digoxin has no prominent effect on BP: systolic BP may increase and diastolic may fall in CHF patients—pulse pressure increases. Hypertension is no contraindication to the use of digoxin.

Therapeutic doses of digoxin have no significant effect on coronary circulation—coronary insufficiency is no contraindication to its use.

3. Kidney Digoxin promptly causes diuresis in CHF patients, secondary to improvement in circulation and renal perfusion. The retained salt and water is gradually excreted. No diuresis occurs in normal individuals or in patients with edema due to other causes.

4. CNS Digoxin has little apparent CNS effect in therapeutic dose. Higher doses cause CTZ activation inducing nausea and vomiting. Still higher doses produce hyperapnoea, central sympathetic stimulation, mental confusion, disorientation and visual disturbances. Effects on the g.i.t. are only of toxicological nature (*see* adverse effects).

Pharmacokinetics

The pharmacokinetic features of digoxin are listed in Table 38.1.

Bioavailability of digoxin tablets from different manufacturers may differ. Presence of food in stomach delays absorption of digoxin. The volume of distribution is large (6–8 L/Kg). It is concentrated in the heart (~20 times than plasma), skeletal muscle, liver and kidney.

Table 38.1: Pharmacokinetic features of digoxin

		DIGOXIN
1.	Oral absorption	60–80%
2.	Plasma protein binding	25%
3.	**Time course of action***	
	–Onset	15–30 min
	–Peak	2–5 hr
	–Duration	2–6 days
4.	Plasma t½	40 hr
5.	Therapeutic concn.	0.5–1.4 ng/ml
6.	Toxic concn.	> 2 ng/ml
7.	Daily maintenance dose	0.125–0.5 mg
8.	Daily elimination**	35%
9.	Route of elimination (predominant)	Renal excretion
10.	Route of administration	Oral, i.v.

* Of full digitalizing dose given i.v.;
** fraction of total amount present in the body.

Digoxin is primarily excreted unchanged by the kidney: mainly by glomerular filtration; rate of excretion is altered parallel to creatinine clearance. Its t½ is prolonged in elderly patients and in those with renal insufficiency: dose has to be reduced.

Digoxin is a cumulative drug. When maintenance doses are given from the beginning, steady state levels and full therapeutic effect are attained after 4 × t½, i.e. 6–7 days.

Digoxin: DIGOXIN 0.25 mg tab., 0.05 mg/ml pediatric elixir, 0.5 mg/2 ml inj. LANOXIN, SANGOXIN 0.25 mg tab, CARDIOXIN 0.25 mg tab, 0.5 mg/2 ml inj.

Adverse effects

Toxicity of digitalis is high, margin of safety is low (therapeutic index 1.5–3). About 25% patients receiving digoxin therapy develop one or other toxic symptom. The manifestations are:

Extracardiac Anorexia, nausea, vomiting and abdominal pain are usually reported first: are due to gastric irritation, mesenteric vasoconstriction and CTZ stimulation. Diarrhoea can also occur. Fatigue, malaise, headache, mental confusion, restlessness, hyperapnoea, disorientation, psychosis and visual disturbances are the other complaints. Skin rashes and gynaecomastia are rare.

Cardiac Almost every type of arrhythmia can be produced by digoxin: pulsus bigeminus is common; others are nodal and ventricular extrasystoles, ventricular tachycardia and terminally ventricular fibrillation. Partial to complete A-V block may be the sole cardiac toxicity, or it may accompany other arrhythmias. Severe bradycardia, atrial extrasystoles, AF or AFl have also been noted. In about 2/3 patients showing toxicity, extracardiac symptoms precede cardiac toxicity.

Treatment Further doses of digoxin must be stopped at the earliest sign of toxicity; nothing more needs to be done in many patients, especially if the manifestations are only extracardiac.

(a) For tachyarrhythmias When caused by chronic use of digoxin and diuretics (both induce K^+ depletion)—infuse KCl 20 m.mol/hour (max. 100 m.mol) i.v. or give orally in milder cases. High extracellular K^+ decreases binding of the glycosides to Na^+K^+ATPase by favouring a conformation of the enzyme that has lower affinity for the glycoside, and K^+ tends to antagonize digitalis induced enhanced automaticity. When toxicity is due to acute ingestion of large doses of digoxin, plasma K^+ may be high; it should not be given from outside. In any case, it is desirable to measure serum K^+ to guide KCl therapy. K^+ is contraindicated if higher degree of A-V block is present, because complete A-V block and ventricular asystole may be precipitated.

(b) For ventricular arrhythmias Lidocaine i.v. repeated as required is the drug of choice. It suppresses the excessive automaticity, but does not accentuate A-V block. Quinidine, procainamide and propafenone are contraindicated.

(c) For supraventricular arrhythmias Propranolol may be given i.v. or orally depending on the urgency.

(d) For A-V block and bradycardia The treatment of choice is cardiac pacing through a temporarily inserted pacemaker. Atropine 0.6–1.2 mg i.m. may help.

Cardioversion by DC shock is contraindicated because severe conduction defects may be unmasked in the digitalis intoxicated heart.

Digoxin antibody Digoxin specific antibody is highly effective in reversing cardiotoxicity due to digoxin as well as many other related glycosides. The Fab fragment has been marketed in Europe as DIGIBIND (38 mg vial), DIGIFAB (40 mg/vial). It is nonimmunogenic because it lacks the Fc fragment. Given by i.v. infusion it has markedly improved the survival of seriously digitalis intoxicated patients.

Precautions and contraindications

- *Hypokalemia*: enhances digitalis toxicity.
- *Elderly, renal or severe hepatic disease*: patients are more susceptible to digoxin toxicity.
- *Thyrotoxicosis*: patients are more prone to develop digitalis arrhythmias, while digoxin elimination is slowed in hypothyroid patients.
- *Ventricular tachycardia*: digitalis is contraindicated because it may precipitate ventricular fibrillation.
- *Partial A-V block*: may be converted to complete A-V block by digoxin.
- *Wolff-Parkinson-White syndrome*: Digoxin is contraindicated because it decreases the ERP of bypass tract in 1/3 patients. In them rapid atrial impulses may be transmitted to ventricles → VF may occur. Digoxin can increase the chances of reentry by slowing

conduction in the normal A-V bundle and accelerating it in the aberrant pathway.

Interactions

1. *Diuretics*: cause hypokalemia which increases the risk of digitalis arrhythmias; potassium supplements should be given prophylactically.
2. *Calcium*: synergises with digitalis → precipitates toxicity.
3. *Quinidine*: reduces binding of digoxin to tissue proteins as well as its renal and biliary clearance by inhibiting efflux transporter P-glycoprotein → plasma concentration of digoxin is doubled → toxicity can occur. *Verapamil, diltiazem, captopril, propafenone* and *amiodarone* also increase plasma concentration of digoxin to variable extents.
4. *Adrenergic drugs*: can induce arrhythmias in digitalized patients; both increase ectopic automaticity.
5. Digoxin absorption may be reduced by *metoclopramide, sucralfate, antacids, neomycin, sulfasalazine*. Absorption of digoxin is increased by atropinic drugs, including tricyclic antidepressants.
6. *Propranolol, verapamil, diltiazem and disopyramide:* may additively depress A-V conduction and oppose positive inotropic action.

Uses

The two main indications of digoxin are heart failure and control of ventricular rate in atrial fibrillation/flutter. Its use in heart failure is described in the next section on treatment of heart failure.

Cardiac arrhythmias

Atrial fibrillation (AF), atrial flutter (AFl)

Digoxin can be used for controlling ventricular rate in AF and AFl, whether associated with CHF or not, but it is incapable of curing the arrhythmia, i.e. does not revert it to sinus rhythm. Often, AFl may be converted into AF because digoxin abbreviates atrial ERP and makes it more inhomogeneous.

Digoxin reduces ventricular rate in AF and AFl by decreasing the number of impulses that are able to pass down the A-V node and bundle of His. It increases ERP of A-V node by direct, vagomimetic and antiadrenergic actions: the minimum interval between consecutive impulses that can successfully traverse the conducting tissue is prolonged.

Digoxin may be used for long-term ventricular rate control in persistent or permanent AF/AFl, but is not the preferred drug for rapid control of heart rate. Oral or i.v. β blocker (e.g. metoprolol) or a non-DHP calcium channel blocker (CCB) diltiazem/verapamil given orally or i.v. (depending on the urgency) are the preferred drugs. The short-acting i.v. β blocker esmolol is preferred for haemodynamically unstable patients. Digoxin is not only slow to act (takes 1–6 hours even after i.v. injection), but also less effective. However, it is preferred when AF/AFl is attended by heart failure. Digoxin decreases ventricular rate in a dose dependent manner and abolishes the pulse deficit in AF. The maintenance dose in persistent or permanent AF/AFl can be determined by titrating with heart rate, which should not be allowed to decrease to ≤ 60 per min at rest. Digoxin can also be combined with the β blocker/CCB, if a single drug fails to lower the heart rate to the desired levels.

Paroxysmal supraventricular tachycardia (PSVT) It is a common arrhythmia with a rate 150–200/min and 1 : 1 A-V conduction. It is mostly due to reentry involving the A-V node. Digoxin may be injected i.v. It increases vagal tone and depresses the path through the A-V node, or the ectopic focus, and terminates the arrhythmia (success in 1/3 cases). Adenosine, verapamil or esmolol injected i.v. are more effective, less toxic and act faster, therefore preferred.

TREATMENT OF HEART FAILURE

Heart failure occurs when cardiac output is insufficient to meet the demands of tissue perfusion, or is able to do so only by elevating filling pressure. It is a progressive disease with gradually deteriorating cardiac performance. Heart failure may primarily be due to systolic dysfunction or diastolic dysfunction.

Systolic dysfunction This refers to deficient pumping action of ventricles, i.e. ventricles are unable to develop sufficient wall tension to eject adequate quantity of blood and get progressively dilated. This makes the ventricle further inefficient according to the Laplace equation:

$$\text{Wall tension} = \text{Intraventricular pressure} \times \text{ventricular radius}$$

i.e. to generate the same ejection pressure a dilated ventricle has to develop higher wall tension. Thus, a self-perpetuating vicious cycle is set up and ejection fraction (EF) is progressively reduced (usually to <40%). The most important cause of systolic dysfunction is coronary artery disease (CAD), myocardial infarction (MI) and loss of functioning myocardium. Other causes are valvular incompetence, dilated cardiomyopathy, viral (including HIV) myocarditis, tachyarrhythmias (mostly AF), etc.

Diastolic dysfunction The ventricular wall is thickened and unable to relax normally during diastole; ventricular filling is impaired and stroke volume is reduced, but the EF may be normal.

Long standing hypertension is the most common cause of left ventricular hypertrophy (LVH) and subsequent diastolic dysfunction. It is mostly associated with ageing and myocardial stiffening. Aortic stenosis, hypertrophic cardiomyopathy, A-V shunts and congenital heart disease are the other important causes.

However, most patients, especially long standing cases, have both systolic and diastolic dysfunction. Symptomatically also both are similar. Several compensatory mechanisms are brought into action to overcome the reduced cardiac output (CO). These include:

- Elevation of filling pressure by Frank-Starling compensation to increase stroke volume (*see* Fig. 38.4); but this may produce congestive symptoms, i.e. venous engorgement, hepatic enlargement, peripheral edema, pulmonary congestion → dyspnoea, renal congestion → oliguria.
- Augmentation of sympathetic tone resulting in β receptor mediated cardiac stimulation and α receptor mediated vasoconstriction. However, prolonged β receptor activation promotes cardiac myocyte apoptosis and fibrotic change. Vasoconstriction increases cardiac afterload and tends to restrict CO.
- Activation of RAS causes further vasoconstriction and LVH. Myocardial remodeling, cell death and fibrotic transformation are direct consequences of long term exposure to raised Ang II.
- Over production of aldosterone promotes Na^+ retention, K^+ loss and fibroblast proliferation which contributes to ventricular remodeling.
- Endothelin production is also increased which reinforces vasoconstriction as well as cardiac and vascular myocyte proliferation followed by fibrotic change.
- Heart failure also triggers release of natriuretic peptides ANP and BNP due to atrial and ventricular distention, which tend to oppose vasoconstriction and Na^+ retention.

After initial haemodynamic benefit, the compensatory ventricular hypertrophy becomes counter productive, because it alters ventricular geometry, hampers ventricular filling and predisposes to ischaemia. Nevertheless, the counter-regulatory neurohumoral mechanisms described above do provide targets for drug therapy to retard the progression of disease in heart failure.

There are two distinct goals of drug therapy in heart failure:

A. Relief of congestive/low output symptoms, restoration of cardiac performance and treatment of acute decompensation. This can be achieved by:

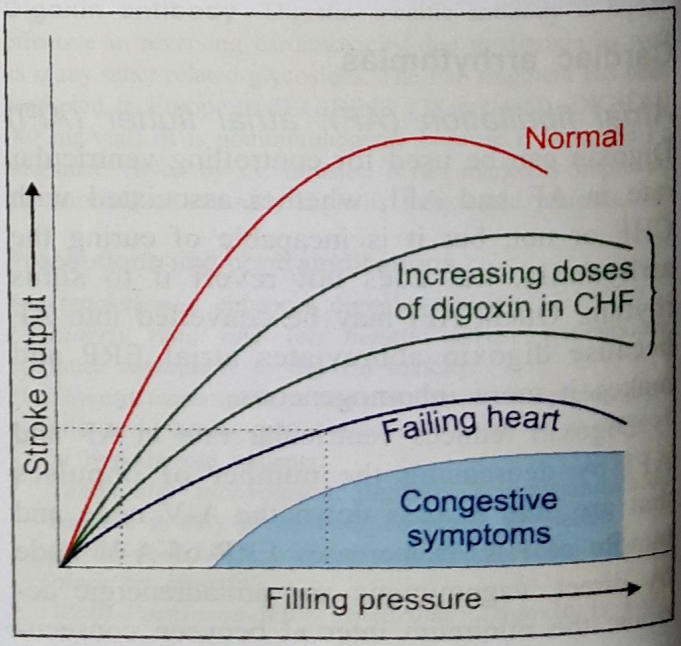


Fig. 38.4: Relationship between filling pressure and cardiac output in normal and failing heart. Digoxin tends to shift the curve towards normal

Inotropic drugs—Digoxin, dobutamine/dopamine, inamrinone/milrinone
Diuretics—Furosemide, thiazides, metolazone
RAS inhibitors—ACE inhibitors/ARBs
Vasodilators—Hydralazine, nitrate, nitroprusside
Synthetic BNP—Nesiritide
β blocker—Metoprolol, bisoprolol, carvedilol, nebivolol

B. Arrest/reversal of disease progression and prolongation of survival. This is possible with:
ACE inhibitors/ ARBs,
β blockers
Aldosterone antagonist—Spironolactone, eplerenone
Neprilysin inhibitor—Sacubitril

Till 1980 drugs available for heart failure (digitalis and diuretics) addressed only the consequences of CHF, but not its genesis. As such, these drugs while affording symptomatic relief, did not modify the course of heart failure. Drugs developed thereafter (ACE inhibitors/ARBs, β adrenergic blockers, aldosterone antagonists, etc.) impact the neurohumoral perpetrators of heart failure, myocardial apoptosis, fibrosis, remodeling, matrix abnormalities, etc. in addition to haemodynamic effects, and have become the primary therapeutic modality.

The pathophysiological mechanisms that perpetuate heart failure and contribute to disease progression, along with site of drug action are depicted in Fig. 38.5. The current pattern of use of drugs in various stages of heart failure is summarized in Fig. 38.6.

Diuretics

Almost all cases of symptomatic heart failure are treated with a diuretic. *High ceiling diuretics* (furosemide, bumetanide) are the diuretics of choice for mobilizing edema fluid; later they may be continued in low doses. However, resistance may develop to even high ceiling diuretics after prolonged use in advanced heart failure. Addition of metolazone or spironolactone to furosemide may overcome the resistance. Thiazide alone has very limited role in CHF. Diuretics:

- Decrease preload and improve ventricular efficiency by reducing circulating volume.

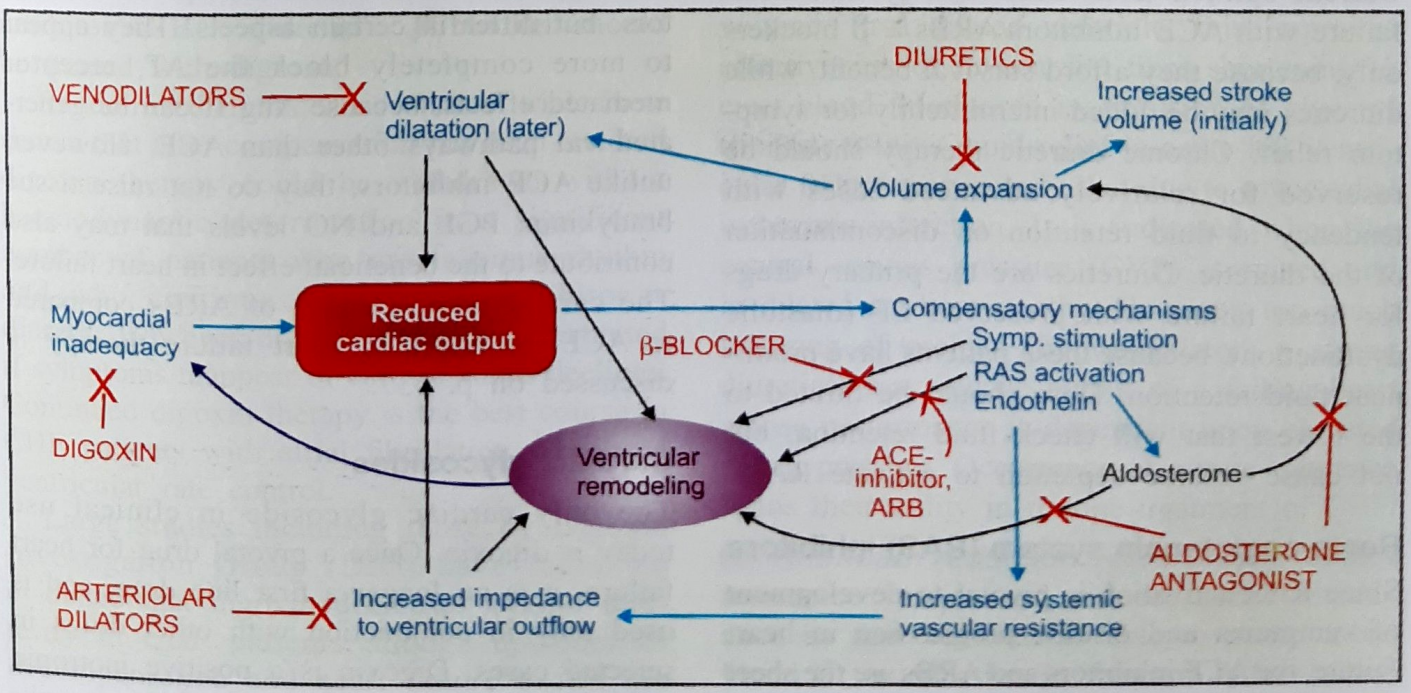


Fig. 38.5: The vicious cycle in heart failure: compensatory mechanisms evoked in response to reduced cardiac output themselves perpetuate failure and contribute to remodeling responsible for disease progression. The parameter which is improved by different therapeutic measures is indicated
ACE—Angiotensin convertnig enzyme; ARB—Angiotensin receptor blocker; RAS—Renin-angiotensin system

- Remove peripheral edema and pulmonary congestion.

Intravenous furosemide promptly increases systemic venous capacitance and produces rapid symptomatic relief in acute left ventricular failure. It has, in conjunction with vasodilators, virtually obviated the need for i.v. digoxin. On the other hand, most mild cases of heart failure can be maintained symptom free on diuretics without recourse to any other medication, though concurrent use of ACE inhibitor. ARB is recommended to retard disease progression. However, diuretics have no role in asymptomatic left ventricular dysfunction, and brisk diuresis can worsen some cases whose cardiac output is critically dependent upon volume overload. Diuretics do not influence the disease process in CHF, though they may dramatically improve symptoms. Despite decades of experience, no prognostic benefit has been demonstrated for diuretics. Moreover, they may cause activation of RAS (if hypovolemia occurs) which has adverse cardiovascular consequences. Chronic diuretic therapy tends to cause hypokalaemia, alkalosis and carbohydrate intolerance. Current opinion is to treat mild systolic heart failure with ACE inhibitors/ARBs ± β blockers only, because they afford survival benefit, while diuretics may be added intermittently for symptom relief. Chronic diuretic therapy should be reserved for relatively advanced cases with tendency to fluid retention on discontinuation of the diuretic. Diuretics are the primary drugs for heart failure with preserved EF (diastolic dysfunction), because these patients have prominent fluid retention. Dose should be titrated to the lowest that will check fluid retention, but not cause volume depletion to activate RAS.

Renin-angiotensin system (RAS) inhibitors

Since RAS activation is pivotal to development of symptoms and disease progression in heart failure, the ACE inhibitors and ARBs are the sheet anchor of drug therapy in CHF (*see* p. 534 and 537). They afford symptomatic as well as disease modifying benefits in heart failure by causing vasodilatation, retarding/preventing ventricular hypertrophy, myocardial cell apoptosis, fibrosis, intercellular matrix changes and remodeling. In addition to decreasing Ang II production, ACE inhibitors raise the level of kinins which stimulate generation of cardioprotective NO and PGs. Symptomatic and prognostic benefits of ACE inhibitors/ARBs have been established in mild to severe (NYHA class I to IV) CHF with reduced EF, as well as in subjects with asymptomatic systolic dysfunction. An overall 20% reduction in mortality has been obtained by the use of ACE inhibitors in heart failure. They are thus recommended for all grades of CHF, unless contraindicated, or if renal function deteriorates by their use (mainly in those with renal artery stenosis). However, no prognostic benefit or improved outcome has been obtained with them in patients of heart failure with preserved EF.

ACE inhibitor therapy is generally started at low doses (to avoid initial hypotension) which are gradually increased to obtain maximum benefit or to near the highest recommended doses.

The ARBs are an alternative to ACE inhibitors, but differ in certain aspects. They appear to more completely block the AT_1 receptor mediated effects, because Ang II can be generated *via* pathways other than ACE. However, unlike ACE inhibitors, they do not raise tissue bradykinin, PGI_2 and NO levels that may also contribute to the beneficial effect in heart failure. The current relative status of ARBs compared to ACE inhibitors in heart failure therapy is discussed on p. 537.

Cardiac glycosides

The only cardiac glycoside in clinical use today is digoxin. Once a pivotal drug for heart failure, it is no longer a first line drug, and is used only in conjunction with other drugs in selected cases. Digoxin is a positive inotropic drug which affords symptomatic relief, primarily in systolic dysfunction or when CHF is due to AF with rapid heart rate. It is incapable of

reversing or retarding the pathological changes of heart failure or affording prognostic benefit.

Digoxin induced enhancement of contractility increases ventricular ejection and shifts the curve relating stroke output to filling pressure towards normal, so that adequate output may be obtained at a filling pressure that does not produce congestive symptoms (*see* Fig. 38.4). Improved tissue perfusion results in withdrawal of sympathetic overactivity → heart rate and central venous pressure (CVP) are lowered towards normal. Compensatory mechanisms retaining Na^+ and water are inactivated, diuresis occurs and edema is cleared. Liver regresses, pulmonary congestion is reduced → dyspnoea abates, cyanosis disappears. Low output symptoms like decreased capacity for muscular work are mitigated. Thus, digoxin is the most effective drug capable of relieving symptoms of systolic failure and restoring cardiac compensation, especially in patients with dilated heart and low EF. However, patients with preserved EF and heart failure due to diastolic dysfunction usually do not respond to digoxin or to other inotropic drugs. All patients with low EF who remain symptomatic while receiving ACE inhibitor/ARB + diuretic ± β blocker should be treated with digoxin.

Randomized multicentric clinical trials have shown that after compensation has been restored digoxin therapy could be withdrawn without haemodynamic deterioration in a significant number of patients who are in sinus rhythm and who continue taking ACE inhibitor + diuretic. However, digoxin should be reinstituted if symptoms reappear or cardiac status declines. Continued digoxin therapy is the best course in CHF patients with atrial fibrillation who need ventricular rate control.

Large studies including those by Digoxin Investigation Group (DIG) have found no evidence that digoxin decreases overall mortality in CHF patients, though episodes of decompensation and heart failure deaths are reduced, but incidence of sudden death may increase. The two major limitations in the use of cardiac glycosides are low margin of safety and lack of effect on neurohumoral contributors to pathogenesis of heart failure.

Dosage Digoxin therapy is now initiated with the estimated maintenance doses (0.125–0.25 mg/day) without any loading dose. Full response takes 5–7 days to develop when steady-state is reached. In case of inadequate response, the dose is increased to 0.375 and 0.5 mg/day at weekly intervals. Reduction in heart rate and relief of heart failure symptoms are the best guide to dosing.

If an early response is required, a loading dose of 0.75–1.25 mg spread over 24–48 hours may be given in the beginning, but requires close monitoring.

Vasodilators

The direct acting vasodilators are primarily useful in the treatment of acute heart failure that occurs episodically in advanced cases, or that follows acute MI, and are infused i.v. for short periods to tide over crisis. The utility of long-term oral vasodilator therapy in chronic heart failure is quite limited. Vasodilators can be differentiated into those which primarily dilate veins (nitrates), or those which mainly dilate arterioles (hydralazine), or which dilate both (sod. nitroprusside).

(i) ***Preload reduction:*** *Nitrates* cause pooling of blood in systemic capacitance vessels to reduce ventricular end-diastolic pressure and volume. In a dilated ventricle, this improves effectiveness of myocardial fibre shortening to eject blood. Monitored i.v. infusion of glyceryl trinitrate affords rapid relief in acute left ventricular failure, particularly that due to myocardial ischaemia/infarction. It is indicated when the central venous pressure (CVP) is raised and in dilated cardiomyopathy. However, too much lowering of preload (by vasodilators + strong diuretics) may reduce output of a failing heart whose performance is dependent upon elevated filling pressure. Occurrence of nitrate tolerance limits their utility in routine treatment of CHF.

(ii) ***Afterload reduction*** *Hydralazine* dilates resistance vessels and reduces aortic impedance so that ventricle is able to pump more blood. It is effective in forward failure when cardiac index is low (< 2.5 L/min/m^2) without a marked increase in CVP (< 18 mm Hg). Marked tachycardia, worsening of myocardial

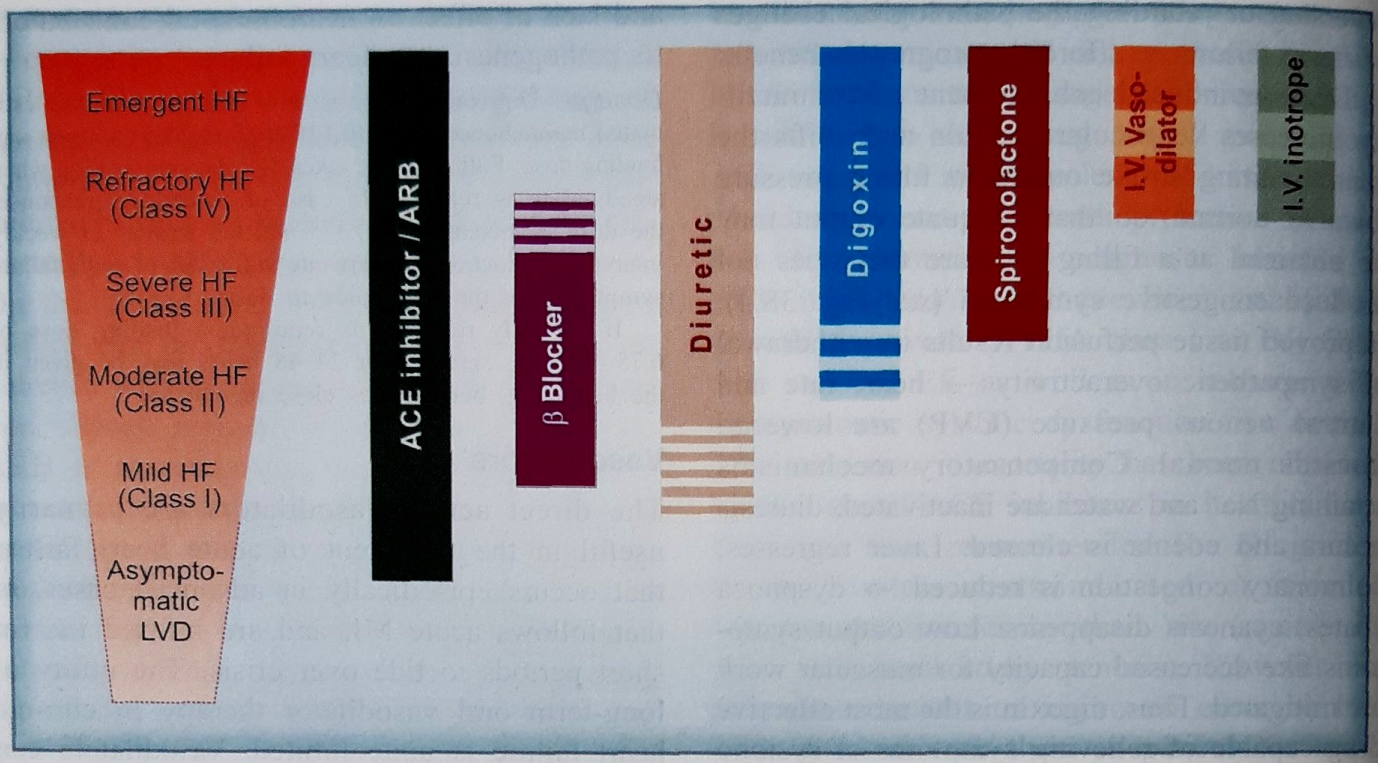


Fig. 38.6: Current pattern of clinical use of various classes of drugs in different stages of heart failure (HF)
LVD—Left ventricular dysfunction; ACE—Angiotensin converting enzyme; ARB—Angiotensin receptor blocker

ischaemia and fluid retention limit long-term use of hydralazine monotherapy.

(iii) *Pre- and after load reduction* *Sod. nitroprusside* is a high efficacy i.v. dilator with equal action on the two types of vessels. It reduces ventricular filling pressure as well as systemic vascular resistance. Cardiac output and renal blood flow are increased. The action is very fast and brief. Careful i.v. infusion of nitroprusside may be employed in conjunction with a loop diuretic + i.v. inotropic drug to tideover crisis in severely decompensated patients.

In the long term oral therapy, survival benefit has been obtained only with a combination of hydralazine + isosorbide dinitrate, but the ACE inhibitors and ARBs alone are clearly superior in this regard. Hydralazine causes more marked renal vasodilatation. Along with isosorbide dinitrate it may be selected for patients with renal insufficiency, low renal blood flow or renal artery stenosis, who cannot tolerate ACE inhibitors or ARBs. Isosorbide dinitrate and hydralazine supplement each other when combined. African-American patients with severe CHF who are already receiving ACE inhibitors + digoxin + diuretic have obtained extra survival benefit from addition of hydralazine + nitrate.

β-Adrenergic blockers

Extensive studies over the past 30 years have established the utility of β_1 blockers (mainly metoprolol, bisoprolol, nebivolol) and the nonselective β + selective α_1 blocker carvedilol in mild to moderate CHF treated with ACE inhibitor ± diuretic, digitalis. They afford survival benefit, and are now part of standard therapy of CHF.

A large number of randomized trials including Metoprolol in dilated cardiomyopathy trial (1993), US carvedilol trial (1996), MERIT-HF trial (1999), CIBIS-II trial (1999), CAPRICORN trial (2001), COPERNICUS trial (2002) have demonstrated subjective, objective, prognostic and mortality benefits of the above named β blockers over and above that afforded by ACE inhibitors + diuretic ± digitalis.

Though the early hemodynamic action of β blockers is to depress cardiac contractility and EF, these parameters gradually improve over weeks. After a couple of months EF is generally higher than baseline, and slow upward titration of dose

further improves cardiac performance. The hemodynamic benefit is maintained over long-term and hospitalization/mortality due to worsening cardiac failure, as well as all cause mortality is reduced. The benefits appear to be due to antagonism of ventricular wall stress enhancing, apoptosis promoting and pathological remodeling effects of excess sympathetic activity (occurring reflexly) in heart failure, as well as due to prevention of sinister arrhythmias. Incidence of sudden cardiac death as well as that due to worsening heart failure is decreased. β blockers lower plasma markers of activation of sympathetic, renin-angiotensin systems and endothelin-1.

However, β blocker therapy in heart failure requires caution, proper patient selection and observance of several guidelines:

- Greatest utility of β blockers has been shown in mild to moderate (NYHA class II, III) cases of dilated cardiomyopathy with systolic dysfunction in which they are now routinely coprescribed unless contraindicated. In one recent study (SENIORS, 2009) nebivolol has been found effective in both systolic as well as diastolic failure.
- Encouraging results (upto 35% decrease in mortality) have been obtained in class IV cases as well, but use in severe failure could be risky and needs constant monitoring.
- There is no place for β blockers in decompensated patients. β blockers should be stopped during an episode of acute heart failure and reinstituted gradually after compensation is restored. Conventional therapy should be continued along with them.
- Starting dose should be very low because the early negative inotropic action may precipitate failure. Dose is then titrated upward as tolerated to the target level (carvedilol 50 mg/day, bisoprolol 10 mg/day, metoprolol SR 200 mg/day) or near it, for maximum protection.
- In few patients any attempt to introduce a β blocker results in worsening of heart failure. β blockers should not be used in such patients.
- Survival benefit has been demonstrated with sustained release (SR) metoprolol which provides round-the-clock β blockade, but not with short acting metoprolol.
- There is no evidence of benefit in asymptomatic left ventricular dysfunction.

Aldosterone antagonist (Spironolactone, Eplerenone)

Over the past 2 decades it has been realized that rise in plasma aldosterone in heart failure, in addition to its well known Na^+ and water retaining action, is an important contributor to disease progression by direct and indirect effects:

(a) Expansion of e.c.f. volume → increased cardiac preload.

(b) Fibroblast proliferation and fibrotic change in myocardium → worsening systolic dysfunction and pathological remodeling.

(c) Hypokalemia and hypomagnesemia → increased risk of ventricular arrhythmias and sudden cardiac death.

The aldosterone antagonist spironolactone is a weak diuretic (*see* Ch. 42), but can benefit CHF by antagonizing the above effects of aldosterone.

Two large randomized trials (RALES, 1999 with spironolactone, and EPHESUS, 2003 with eplerenone) conducted on NYHA class III and IV heart failure have demonstrated the mortality and anti-remodeling benefit of these drugs over and above that of ACE inhibitors ± β blockers.

Though ACE inhibitors themselves lower aldosterone levels, this effect is incomplete and needs to be enhanced in moderate-to-severe heart failure with low EF. Current recommendation regarding spironolactone/eplerenone therapy in CHF is:

- They are to be used as add-on therapy to ACE inhibitors + other drugs in moderate-to-severe heart failure with reduced EF. Their role in patients with preserved EF is uncertain.
- They can retard disease progression, reduce episodes of decompensation and death due to heart failure as well as sudden cardiac deaths.

- Only low doses (12.5–25 mg/day) of spironolactone/eplerenone should be used to avoid hyperkalaemia.
- They may help restoration of diuretic response to furosemide when refractoriness has developed.

Gynaecomastia occurs in a number of male patients treated with spironolactone. This can be avoided by using eplerenone.

Ivabradine This pure bradycardia producing antianginal drug (*see* p. 600) has been approved recently for use in stable grade II to IV heart failure patients who are in sinus rhythm and have heart rate >70 per min with systolic dysfunction (ER <35%). It works by slowing the heart and improving ventricular filling. Ivabradine is specifically indicated for patients with contraindications to β blockers, or in those who do not achieve heart rate reduction to <75/min with an adequate dose of β blocker alone. It is given in addition to standard therapy with ACE inhibitor, diuretic, aldosterone antagonist, etc., and has been shown to decrease the composite end points of hospitalization and cardiovascular mortality (SHIFT trial 2010). However, it lacks the cardioprotective property of β blockers.

Sympathomimetic inotropic drugs (see Ch. 9)

Drugs with β adrenergic and dopaminergic D1 agonistic actions have positive inotropic property which may be utilized to combat emergency pump failure.

Dopamine and dobutamine (*see* p. 146–47) infused i.v. act promptly and afford additional haemodynamic support over and above vasodilators, digoxin and diuretics, but benefits are short-lasting. They are particularly useful when heart failure is accompanied by low BP. Due to development of tolerance and their cardiotoxic potential when used for prolonged therapy, these drugs have no role in the long-term management of CHF.

Phosphodiesterase 3 inhibitors

Inamrinone (amrinone) This bipyridine derivative is a selective phosphodiesterase 3 (PDE3) inhibitor. The PDE3 isoenzyme is specific for intracellular degradation of cAMP in heart, blood vessels and bronchial smooth muscles. Amrinone increases myocardial cAMP and transmembrane influx of Ca^{2+}. Both these actions may underlie its positive inotropic property.

The two most important actions of inamrinone are *positive inotropy* and direct *vasodilatation*. It has been called an 'inodilator'. Both preload and afterload on the heart is reduced. Compared to dobutamine, proportionately greater decrease in systemic vascular resistance is noted.

In CHF patients i.v. inamrinone acts rapidly and its action lasts for 2–3 hours; elimination t½ is 2–4 hours. It increases cardiac output and decreases peripheral vascular resistance, CVP and left ventricular end diastolic volume, accompanied by mild tachycardia and slight fall in BP.

Thrombocytopenia is the most prominent and dose related adverse effect, because of which inamrinone is seldom used now. Nausea, diarrhoea, abdominal pain, liver damage, fever and arrhythmias are the other adverse effects.

Use of oral inamrinone in maintenance therapy of CHF has been abandoned, because efficacy was lost and mortality was increased in comparison to placebo.

It is indicated only for short-term i.v. use in severe and refractory CHF, as an additional drug to conventional therapy with digoxin, diuretics and vasodilators.

AMICOR, CARDIOTONE 5 mg/ml (as lactate) 20 ml amp.

Milrinone Related to inamrinone, it has similar action but is more selective for PDE3, and is at least 10 times more potent. It is shorter-acting with a t½ of ~80 min.

Thrombocytopenia is not significant. In long term prospective trials, increased mortality has been reported with oral milrinone as well. Milrinone is preferred over inamrinone, but should be restricted to short-term use only.

Dose: 50 μg/kg i.v. bolus followed by 0.4–1.0 μg/kg/min infusion.

PRIMACOR IV 10 mg/10 ml inj.

Levosimendan

This inotropic drug acts by sensitizing myocardial troponin C to Ca^{2+}, as well as by inhibiting PDE3. As such, the inotropic effect occurs even in patients receiving β blockers, and is not associated with a change in cytosolic Ca^{2+} concentration. It also opens ATP-sensitive K^+ channels in vascular smooth muscle cells to cause vasodilatation. Thus, it is another 'inodilator', Haemodynamic improvement in heart failure is both due to increase in cardiac contractility as well as reduction in preload and afterload.

Levosimendan infused i.v. is primarily indicated for short-term treatment of acutely decompensated severe chronic heart failure. Though it relieved symptoms of heart failure, but survival rate was not improved. The most common side effect is hypotension which may last for few days due to its active metabolite that has long t½.

SECTION 8

Nesiritide *(see p. 553)* This recombinant brain natriuretic peptide (BNP) is being used by continuous i.v. infusion to relieve dyspnoea and other symptoms in refractory CHF. It enhances salt and water excretion and is a potent vasodilator with profile of action similar to i.v. glyceryl trinitrate; i.e. reduces ventricular filling pressure. Added to the standard therapy, additional haemodynamic and symptomatic improvement can be obtained for short-periods, but no long-term benefits are evident in CHF.

Sacubitril-Valsartan combination

Sacubitril is an orally active neprilysin inhibitor which prevents the degradation of endogenous ANP, BNP and other vasodilator peptides, producing vasodilatation, natriuresis and diuresis. Combined with the ARB valsartan, it has been recently approved for use in advanced heart failure to decrease the incidence of death and acute decompensation (*see* p. 553). A greater reduction in hospitalization and mortality compared to enalapril has been reported.

Tolvaptan

This is an orally active nonpeptide vasopressin V_2 receptor antagonist introduced for the correction of water retention and hyponatremia occurring in 'syndrome of inappropriate ADH secretion' (SIADH) as well as in advanced CHF. In clinical trials on CHF patients with hyponatremia, tolvaptan has afforded short-term improvement by increasing water excretion, restoring serum Na^+ and relieving dyspnoea. However, no long-term benefit has been noted.

PROBLEM DIRECTED STUDY

38.1 A 72-year-old man presents with swelling over ankle and feet, also noticeable over face in the morning, shortness of breath and palpitation on walking ~100 m, weakness, fatigue and cough at night. The pulse is 110/min, BP 114/78 mm Hg, there is pitting edema over feet, liver is enlarged 2 cm below costal margin, neck veins are filled upto 3 cm above clavicle, crepitations are heard at the base of lungs, apex beat is in the 6th intercostal space and heart sounds are muffled. Chest X-ray and echocardiography show enlarged cardiac shadow and an ejection fraction (EF) of 28%. A diagnosis of moderate grade heart failure due to dilated cardiomyopathy with reduced EF is made. The doctor prescribed bed rest, salt restriction and:

Tab enalapril 5 mg twice a day

Tab furosemide 40 mg in the morning

(a) Can the patient be prescribed any other drug to hasten relief of symptoms? If so, which drug and in what dosage?

(b) Should the dose of enalapril be changed over time or should it be withdrawn, if so when?

(c) Should a β adrenergic blocking drug be added to the treatment regimen concurrently?

(see Appendix-1 for solution)