SECTION 8

# CARDIOVASCULAR DRUGS

## Chapter 36a

# Cardiac Electrophysiological Considerations

Drugs having their major action on heart or blood vessels, or those used primarily for cardiovascular disorders are designated cardiovascular drugs. They can act directly on the cardiovascular structures or through autonomic/central nervous system, kidney, autacoids or hormones which regulate cardiovascular function.

## CARDIAC ELECTROPHYSIOLOGY

The properties which are especially important for understanding drug action on heart are:

**1. Impulse generation** Electrophysiologically, two types of myocardial fibres can be distinguished (Fig. VIII.1).

(a) *Nonautomatic fibres* These are the ordinary working myocardial fibres; cannot generate an impulse of their own. During diastole, the resting membrane potential remains stable (approximately 90 mv negative inside). When stimulated, they depolarize very rapidly (fast 0 phase) with considerable overshoot (+ 30 mv) → rapid return to near isoelectric level (phase-1) → maintenance of membrane potential at this level for a considerable period (phase-2, plateau phase) during which $Ca^{2+}$ ions flow in and bring about contraction → relatively rapid repolarization (phase-3) during which membrane $Na^{+}K^{+}$ pump gets activated and tends to restore ionic distribution to the resting pattern. Resting membrane potential, once attained, does not decay (stable phase-4).

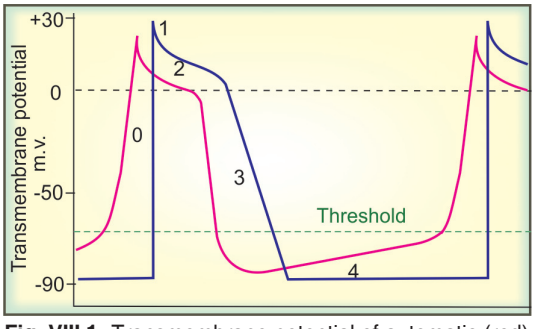



**Fig. VIII.1:** Transmembrane potential of automatic (red) and nonautomatic (purple) myocardial fibres recorded through intracellular electrodes

(b) *Automatic fibres* These are present in the sinoatrial (SA) and atrioventricular (A-V) nodes, and in the His-Purkinje system, i.e. especialized conducting tissue. In addition, patches of automatic tissue are present in the interatrial septum, A-V ring and around openings of the great veins. The most characteristic feature of these fibres is *phase*-4 or *slow diastolic depolarization*, i.e. after repolarizing to the maximum value, the membrane potential decays spontaneously. When it reaches a critical threshold value—sudden depolarization occurs automatically. Thus, they are capable of generating their own impulse. The rate of impulse generation by a particular fibre depends on the value of maximal diastolic potential, the slope of phase-4 depolarization and the value of threshold potential.

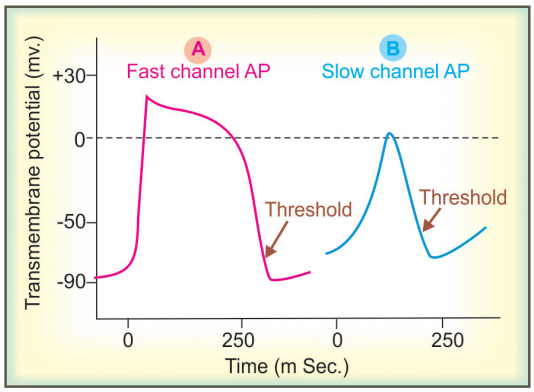



**Fig. VIII.2:** (A) Fast channel action potential (AP) in a Purkinje fibre, (B) Slow channel action potential in a SA node fibre

Normally, the SA node has the steepest phase-4 depolarization, undergoes self-excitation and propagates the impulse to rest of the heart. In other words, it acts as the *pacemaker*. Other automatic fibres which are also undergoing phase-4 depolarization, but at a slower rate, receive the propagated impulse before reaching threshold value and remain as *latent pacemakers.*

*Two types of action potential (AP)* are possible. These are depicted in Fig. VIII.2. Their characteristics are given in Table VIII.1.

The slow channel AP is characterised by:

(a) Initiation at a higher threshold (less negative level).
(b) Slower depolarization during 0 phase.
(c) Less overshoot, low amplitude.
(d) Very slow propagation, decremental conduction and a low safety factor for conduction.
(e) Can arise and propagate in fibres too depolarized to support fast channel responses.

Slow channel AP in SA node, A-V node, etc. has a shorter duration and phases 1–3 are not clearly demarkated. Slow channel AP can occur in Purkinje fibres (PF) also, but this has a much longer duration with a prominent plateau phase.

**2. Conduction** The rate of conduction through a fibre is a function of its *membrane responsiveness*, which is defined by rate of rise of AP (dv/dt) as a function of membrane potential at which activation occurs (Fig. VIII.3); a more completely polarized membrane depolarizes faster because more $Na^+$ channels have recovered (voltage-dependent reactivation). This type of relationship is seen in atrial, ventricular and Purkinje fibres (fast channel fibres which depolarize by $Na^+$ current), but not in SA and A-V nodal cells which remain refractory for some time even after attainment of maximal resting potential ($Ca^{2+}$ channel reactivation is time-dependent).

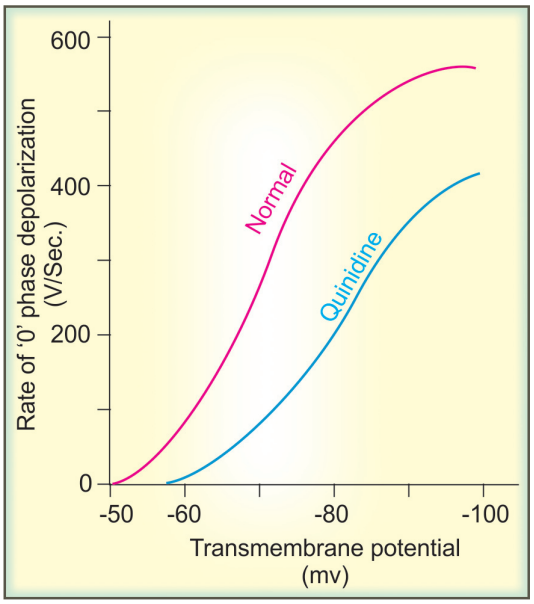
The $Na^+$ channels get progressively inactivated as the resting membrane potential (RMP) drops over the –80 to –60 mV range. Consequently, less negative the RMP at which activation occurs, fewer are the $Na^+$ channels available for activation—slope of '0' phase depolarization, AP amplitude and conduction velocity are reduced.

A drug which reduces the slope of 0 phase (at any given resting membrane potential) will shift the membrane responsiveness curve to the right and impede conduction. The reverse occurs with a drug that shifts the curve to the left. Membrane responsiveness curve can also be altered by disease.

**TABLE VIII.1 Characteristics of fast channel and slow channel action potentials**

| | | *Fast channel AP* | *Slow channel AP* |
|---|---|---|---|
| 1. | Sites of occurrence | Atria, ventricles, Purkinje fibres | SA and A-V nodes, round A-V ring, coronary sinus opening |
| 2. | Predominant ion moving in 0 phase | $Na^+$ | $Ca^{2+}$ |
| 3. | Activation-inactivation kinetics | Fast | Slow |
| 4. | Channel reactivation | Voltage-dependent | Time-dependent |
| 5. | Activation potential (threshold voltage) | –60 to –70 mv | –45 to –55 mv |
| 6. | Conduction velocity | 0.5–5 m/sec | 0.01–0.1 m/sec |
| 7. | ERP–APD* relationship | ERP < APD | ERP > APD |
| 8. | Selective channel blocker | Tetrodotoxin, Local anaesthetics | Verapamil, Diltiazem, $Mn^{2+}$ |

*ERP—Effective refractory period; APD—Action potential duration.




**VIII.3:** Membrane responsiveness curve of a myocardial fibre showing the relationship between membrane polarization and dv/dt of 0 phase. Note the depressant action of quinidine

Small cells at the upper margin of A-V node have very low conduction velocity (20 mm/sec). Normally Purkinje fibres (PFs) have the highest conduction velocity (4000 mm/sec) except near their junction with the ventricular fibres 'gate region', or if they change over from fast channel to slow channel response.

**3. Excitability** This property of a fibre is defined by the strength of stimulus required to elicit a response or to produce an AP. Hyperpolarization decreases excitability while small reductions in resting membrane potential increase excitability by respectively increasing and decreasing the gap between it and the threshold potential. Thus, in fast channel fibres excitability is generally super-normal during the end of phase-3. However, when the resting membrane potential is reduced to a value below the threshold potential, the fibre becomes inexcitable.

**4. Refractory period** Pharmacologically, the effective refractory period (ERP) which is the minimum interval between two propagating APs, is the most important. It is closely related to the AP duration (APD). An AP can be evoked in fast channel fibres even before complete repolarization, because $Na^+$ channels recover in a voltage-dependent manner above the threshold potential. As such ERP/APD is <1. By contrast, the $Ca^{2+}$ channels recover in a time-dependent manner progressively after the fibre has fully repolarized. Thus, in slow channel fibres ERP/APD is > 1. Most antiarrhythmic drugs increase ERP/APD ratio.

### Autonomic influences on cardiac electrophysiology and contractility

It would be profitable to recapitulate the influence of sympathetic and parasympathetic stimulation on variables of cardiac function, because many cardiovascular drugs have indirect/secondary autonomic effects (Table VIII.2).

**TABLE VIII.2** Autonomic influences on cardiac electrophysiology and contractility

| *Parameter* | *Effect of stimulation* | |
|---|---|---|
| | *Parasympathetic (ACh)* | *Sympathetic (Adr)* |
| 1. Automaticity | | |
| SA node | Bradycardia | Tachycardia |
| Ectopic ventricular | — | Enhanced |
| 2. Refractory period | | |
| Atria | Shortened (inhomogeneous) | Shortened |
| Conducting tissue | Prolonged | Shortened |
| 3. Conductivity | Decreased | Enhanced |
| 4. Contractility | Decreased (little effect on ventricle) | Increased |

# Chapter 36b Drugs Affecting Renin-Angiotensin System and Plasma Kinins

## RENIN-ANGIOTENSIN SYSTEM

*Angiotensin-II* (Ang II) is an octapeptide generated in the plasma from a precursor plasma $\alpha_2$ globulin, which is involved in electrolyte, blood volume and pressure homeostasis. Pressor action of kidney extracts was known since the turn of the 19th century. The active material was termed '*Renin*'. In the 1940s renin was shown to be an enzyme which acted indirectly by producing a pressor principle from plasma protein. Subsequently, it became clear that the product of renin action was an inactive decapeptide *angiotensin-I* (Ang I) which was converted to the active octapeptide Ang II by an *angiotensin converting enzyme (ACE)*. The renin-angiotensin system (RAS) has attracted considerable attention over the past 30 years, particularly after the development of ACE inhibitor *captopril*.

**Circulating renin-angiotensin system** The generation and metabolism of Ang II in circulation is depicted in Fig. 36.1. Normally, the amount of renin in plasma acts as the limiting factor for Ang II generation. The plasma t½ of renin is 15 min. The biological potency of Ang I is only 1/100 that of Ang II, but it is rapidly converted into the latter by ACE which is a *dipeptidyl carboxypeptidase,* an ectoenzyme located primarily on the luminal surface of vascular endothelial cells (especially in lungs). Circulating Ang II also has a very short t½ (1 min). The

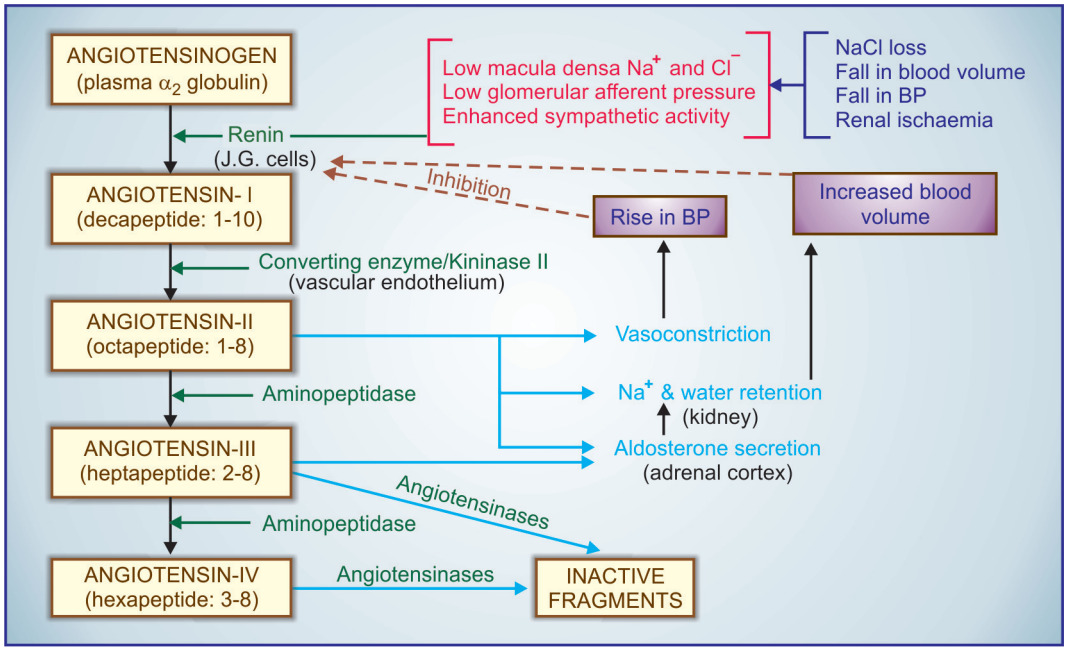



**Fig. 36.1:** Physiological regulation of electrolyte balance, plasma volume and blood pressure by the renin-angiotensin system

first degradation product produced by the action of an aminopeptidase is the heptapeptide termed *Angiotensin-III* (Ang III). It is 2–10 times less potent than Ang II, except in stimulating aldosterone secretion, in which it is equipotent. Ang III is again attacked by another amino-peptidase, and the resulting hexapeptide (3-8) is called Ang IV which has very different central (and some peripheral) actions elicited through a specific $AT_4$ receptor. Both Ang III and Ang IV are broken into inactive fragments by nonspecific peptidases termed *angiotensinases*.

## Tissue (local) renin-angiotensin systems

*Extrinsic local RAS* Apart from Ang II generated in circulation as described above, blood vessels capture circulating angiotensinogen and renin to produce Ang II at the surface of their wall. This Ang II diffuses to act locally on the angiotensin receptors producing localized responses.

*Intrinsic local RAS* Many tissues, especially heart, blood vessels, brain, kidneys, adrenals possess the capacity to synthesize all components of RAS within their cells. They generate Ang II and III intracellularly as per physiological need and pathological status. These signal molecules are instrumental in regulating organ function, cell growth (hypertrophy), cell death (apoptosis), remodeling and fibrosis.

The local RAS operate in several organs in addition to the liver and kidney dependent circulating RAS.

*Prorenin and (Pro) renin receptor (PRR)* Renin is synthesized in juxtaglomerular (JG) cells of kidney and in tissues expressing local RAS as a larger peptide *pre-prorenin*. In response to appropriate stimuli both prorenin and renin are secreted; the former in much larger quantities. The concentration of prorenin in circulation is 5–10 fold higher than that of renin. Till recently, prorenin was considered to be only the inactive precursor of renin, but now it is recognized to be active in its own right.

Prorenin is activated both enzymatically and non-enzymatically (*see* Fig. 36.2). The enzymatic

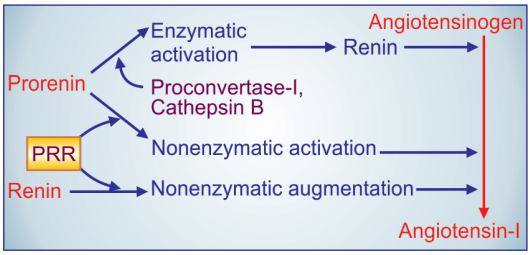



**Fig. 36.2:** Activation of prorenin and augmentation of renin in the tissue (local) renin-angiotensin system. PRR—(Pro) renin receptor

activation is carried out by proteases like proconvertase-1/Cathepsin B, which cleave off the hindering 'propeptide' to produce renin with exposed catalytic domain. This activation is irreversible. Nonenzymatic and reversible activation occurs by binding of prorenin to another cell surface protein called (*Pro) renin receptor (PRR)*, because it binds renin as well. The PRR is richly expressed in heart, blood vessels, kidney, brain, eye and liver. Binding of prorenin to PRR brings about a conformational change, the 'propeptide' segment unfolds and the catalytic domain is exposed. When renin binds to PRR, its catalytic activity is augmented several fold. however, prorenin/renin can dissociate from PRR to return to their original state. Nonenzymatic activation of prorenin plays a major role in local RAS, where prorenin exerts effects *via* Ang II dependent and Ang II independent pathways (Fig. 36.3).

(a) *Ang II dependent pathway*: Activation of prorenin/renin generates Ang I which is converted to Ang II by ACE. Ang II acts on AT receptors on the tissue cells to produce effects on cell growth, inflammation, apoptosis, etc.

(b) *Ang II independent pathway*: Binding of prorenin/renin to PRR on cell surface directly triggers intracellular signalling *via* activation of MAP kinase, plasminogen activator-inhibitor-1 (PAI-1), JAK-STAT pathway, transcription factors, protooncogenes, etc. to regulate cell growth, collagen deposition, fibrosis and apoptosis. Overactivity of RAS *via* such signalling

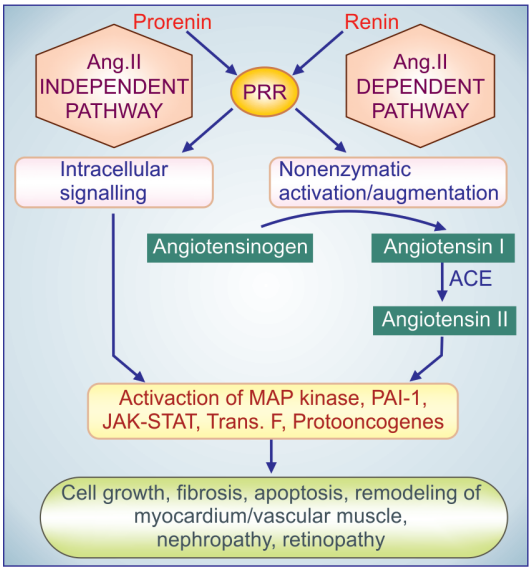



**Fig. 36.3:** (Pro) renin receptor (PRR) mediated action of tissue prorenin/renin through angiotensin II (Ang II) dependent and Ang II independent pathways.
PAI-1—Plasminogen activator inhibitor-1;
Trans. F—Transcription factors

abundantly contributes to pathological changes and end-organ damage in many conditions like hypertensive vascular/ventricular hypertrophy, post-infarction myocardial fibrosis and remodeling, congestive heart failure, nephropathy, retinopathy, etc. The ratio of circulating prorenin to renin is markedly elevated in diabetes, which may be causative in nephropathy and retinopathy.

### Alternative (ACE-independent) pathway of Ang II production

In addition to the primary pathway described above, small quantities of Ang I and Ang II can be produced from angiotensinogen by the action of other proteases like cathepsin. Moreover, chymase can convert (although at a much slower rate) Ang I to Ang II, particularly in heart and kidney.

### Other angiotensin peptides

In addition to Ang II and Ang III some other biologically active angiotensin peptides are produced in small quantities whose physio-pathological role is not well understood.

*Angiotensin IV (Ang IV)* It is a hexapeptide (Ang 3-8) produced by removal of arginine from aminoterminal of Ang III by an aminopeptidase. Ang IV inhibits an insulin regulated aminopeptidase (IRAP) which is considered to be its specific receptor and is labelled *$AT_4$ receptor*. Binding of Ang IV to IRAP prevents degradation of neuropeptides involved in cognitive function and memory in animals. Thus Ang IV improves memory. Some vascular, renal and other peripheral effects of Ang IV have also been described.

*Angiotensin (1-7)* This heptapeptide can be produced from Ang I or Ang II by the action of another carboxy-peptidase labelled ACE 2. In animals, Ang (1-7) produces effects which are in general opposite to those of Ang II, including NO-dependent vasodilatation, antithrombotic, anti-ischaemic and antiproliferative effects by binding to a protooncogene receptor. The clinically used ACE inhibitors do not inhibit ACE 2. Rather, when these drugs are given levels of Ang (1-7) are increased due to diversion of Ang I from ACE and inhibition of degradation of Ang (1-7).

Attempts are being made to therapeutically exploit the Ang II related peptides.

## ACTIONS

**1. CVS** The most prominent action of Ang II is vasoconstriction—produced directly as well as by enhancing Adr/NA release from adrenal medulla/adrenergic nerve endings and by increasing central sympathetic outflow. In addition, it inhibits reuptake of NA and augments responsiveness of vascular smooth muscle to it. Vasoconstriction involves arterioles and venules and occurs in all vascular beds. However, it is less marked in cerebral, skeletal muscle, pulmonary and coronary vessels. Ang II induced vasoconstriction promotes movement of fluid from vascular to extravascular compartment. Ang II injected i.v. is much more potent than NA as a pressor agent. No tachyphylaxis is seen in the pressor action of Ang II; rather long-term infusion of low concentration of Ang II produces progressive and sustained rise in BP by its renal effects promoting salt and water reabsorption, as well as by enhancing endothelin generation.

Ang II increases force of myocardial contraction by promoting $Ca^{2+}$ influx. Though, it can increase heart rate by enhancing sympathetic activity, reflex bradycardia predominates in the intact animal. Cardiac output is often reduced and cardiac work is increased (due to rise in peripheral resistance). In contrast to NA, Ang II does not activate latent pacemakers. As such, it has little arrhythmogenic propensity.

Ang II acting on a chronic basis induces hypertrophy, hyperplasia and increased intercellular

matrix production in the myocardium and vascular smooth muscle by direct cellular effects involving expression of proto-oncogenes and transcription of several growth factors. Indirectly, volume overload and increased t.p.r. caused by Ang II contributes to the hypertrophy and remodeling (abnormal redistribution of muscle mass) in heart and blood vessels. Long standing hypertension increases vessel wall as well as intimal thickness and causes ventricular hypertrophy. Fibrosis and dilatation of infarcted area with hypertrophy of the noninfarcted ventricular wall is seen after myocardial infarction. Progressive cardiac myocyte death and fibrotic transformation occurs in CHF. These changes are important risk factors for cardiovascular morbidity and mortality. ACE inhibitor therapy retards/reverses many of these changes imparting a pivotal role to Ang II in vascular and ventricular hypertrophy, apoptosis and remodeling. As described above, the local RAS and prorenin-PRR systems are crucial in these responses.

**2. Smooth muscles** Ang II contracts many visceral smooth muscles *in vitro*, but *in vivo* effects are insignificant.

**3. Adrenal cortex** Ang II and Ang III are trophic to the zona glomerulosa of adrenal cortex. They enhance synthesis and release of aldosterone which acts on distal tubule in kidney to promote $Na^+$ reabsorption and $K^+/H^+$ excretion. These effects are exerted at concentrations lower than those required to cause vasoconstriction.

**4. Kidney** In addition to exerting indirect effect on kidney through aldosterone, Ang II promotes $Na^+/H^+$ exchange in proximal tubule → increased $Na^+$, $Cl^-$ and $HCO_3^-$ reabsorption. Further, Ang II reduces renal blood flow and GFR, and produces intrarenal haemodynamic effects which normally result in $Na^+$ and water retention. However, an opposite effect has been observed in cirrhotics and renovascular disease patients in whom it increases GFR by stongly constricting glomerular efferent vessels.

**5. CNS** It has been noted that systemically administered Ang II can gain access to certain periventricular areas of the brain to induce drinking behaviour and ADH release—both of which would be conducive to plasma volume expansion. Ang II also increases central sympathetic outflow, which contributes to the pressor response. Brain has its own tissue RAS and generates Ang II locally as well.

**6. Peripheral sympathetic structures** Ang II enhances sympathetic activity by peripheral action as well. It releases Adr from adrenal medulla, stimulates autonomic ganglia and increases the output of NA from adrenergic nerve endings.

**Angiotensin receptors and transducer mechanisms** Specific Ang II receptors are expressed on the surface of target cells. Two subtypes ($AT_1$ and $AT_2$) have been differentiated pharmacologically: *Losartan* is a selective $AT_1$ antagonist, while PD 123177 is a selective $AT_2$ antagonist. Both subtypes are GPCRs. However, all major effects of Ang II are mediated by $AT_1$ receptor. Ang III also activates $AT_1$ and $AT_2$ receptors, but is a much weaker agonist at most sites, except on adrenal cortex causing aldosterone release.

The $AT_2$ receptor is abundantly expressed in foetal tissues. In adults, it has been demonstrated in vascular endothelium, adrenal medulla, kidney and some brain areas. The functional role of $AT_2$ receptor is not well delineated, but is generally opposite to that of $AT_1$ receptor. Activation of $AT_2$ receptor causes NO-dependent vasodilatation, promotes apoptosis, myocardial fibrosis, inhibits cell proliferation and may lower BP.

Other angiotensin peptides like Ang IV and Ang (1-7) act on their own ($AT_4$ and *Mas* respectively) receptors.

The $AT_1$ GPCR utilizes different transducer mechanisms in different tissues. By coupling with Gq protein the phospholipaseC–$IP_3$/DAG–intracellular $Ca^{2+}$ release mechanism underlies vascular and visceral smooth muscle contraction by activating myosin light chain kinase (MLCK). In addition, membrane $Ca^{2+}$ channels are activated. Enhanced $Ca^{2+}$ movement also induces aldosterone synthesis/release, cardiac inotropy, depolarization of adrenal medullary/autonomic ganglionic cell resulting in CA release/ sympathetic discharge. DAG activates protein kinase C (PKC) which

phosphorylates several intracellular proteins and augments the above responses as well as participates in promotion of cell growth. In liver and kidney, Ang II inhibits adenylyl cyclase by $AT_1$ coupled to Gi protein. The intrarenal homeostatic action involves phospholipase $A_2$ activation and PG/LT production.

In many tissues, especially myocardium, vascular smooth muscle and fibroblasts, $AT_1$ receptor also mediates long-term effects of Ang II on cell growth. Ang II activates MAP kinase, TAK2 tyrosine protein kinase, PKC and utilizes the JAK-STAT pathway which together enhance expression of proto-oncogenes, transcription factors and growth factors. As a result, cell growth is promoted and more intercellular matrix is synthesized.

## PATHOPHYSIOLOGICAL ROLES

1. *Mineralocorticoid secretion* There is no doubt that Ang II (also Ang III) is the physiological stimulus for aldosterone secretion from adrenal cortex. It also exerts trophic influence on the glomerulosa cells so that effects are augmented under conditions which persistently raise Ang II levels.

2. *Electrolyte, blood volume and pressure homeostasis* The RAS plays an important role in maintaining electrolyte composition and volume of extracellular fluid (*see* Fig. 36.1). Changes that lower blood volume or blood pressure, or decrease $Na^+$ content induce renin release by three mechanisms.

(i) *Intrarenal baroreceptor pathway:* By decreasing tension in the afferent glomerular arterioles, it operates partly through increased production of prostaglandins (PGs) and partly *via* stretch sensitive ion channels.

(ii) *Macula densa pathway:* Low $Na^+$ and $Cl^-$ concentration in the tubular fluid sensed by macula densa cells triggers this pathway. It has been found that COX-2 and neuronal nitric oxide synthase (nNOS) are induced in macula densa cells by $Na^+$ depletion → release of $PGE_2$ and $PGI_2$ is enhanced both due to increased amount of COX-2 as well as its activation by NO. The locally released PGs act on juxtaglomerular cells to promote renin secretion.

(iii) *β adrenoceptor pathway*: Baroreceptor and other reflexes which increase sympathetic impulses to JG cells activate $\beta_1$ adrenoceptors expressed on their surface → increased intracellular cAMP triggers renin release.

Increased renin is translated into increased plasma Ang II which produces acute rise in BP by vasoconstriction, and more long-lasting effects by directly as well as indirectly increasing $Na^+$ and water reabsorption in the kidney. Rise in BP in turn inhibits renin release : the *long-loop negative feedback mechanism*. It has been shown that Ang II can be formed within the kidney and exerts important local regulatory effects. A *short-loop negative feedback mechanism* operates within the kidney : activation of $AT_1$ receptors on JG cells inhibits renin release directly. Long-term stabilization of BP despite varying salt and water intake appears to be achieved through these mechanisms.

The mechanisms of regulation of renin release have important pharmacological implications:

- ACE inhibitors and $AT_1$ antagonists enhance renin release by interfering with both the short-loop and long-loop negative feedback mechanisms.
- Vasodilators and diuretics stimulate renin release by lowering BP.
- Loop diuretics increase renin production by reducing entry of $Na^+$ and $Cl^-$ into macula densa cells.
- Central sympatholytics and β blockers decrease renin release by interfering with the β adrenoceptor pathway.
- NSAIDs, including selective COX-2 inhibitors, and nNOS inhibitors decrease renin release by inhibiting PG production → cause $Na^+$ and water retention.

3. *Development of hypertension* The RAS is directly involved in renovascular hypertension: plasma renin activity (PRA) is raised in most patients. In essential hypertension also it appears to have a permissive role, though PRA may be

either raised or low. Since ACE inhibitors consistently lower BP in hypertensives, the involvement of this system appears to be more widespread. A positive correlation between circulating angiotensinogen levels and essential hypertension has also been found. Several evidences point to causation of pregnancy-induced hypertension (preeclampsia) by production of autoantibodies which activate $AT_1$ receptor. The role of Ang II in hypertrophy/remodeling of heart and blood vessels is now well recognized (*see* above).

4. *Secondary hyperaldosteronism* The RAS is instrumental in the development of secondary hyperaldosteronism.

5. *CNS* Ang II can be formed locally in the brain and may function as transmitter or modulator. Regulation of thirst, hormone release and sympathetic outflow may be the responses mediated.

Ang II is not available commercially, and not used clinically.

**Inhibition of renin-angiotensin system**

This can be achieved by:

1. Sympathetic blockers (β blockers, adrenergic neurone blockers, central sympatholytics)—decrease renin release.
2. Direct renin inhibitors (DRIs): block renin action—interfere with generation of Ang I from angiotensinogen (rate limiting step).
3. Angiotensin converting enzyme (ACE) inhibitors—prevent generation of the active principle Ang II.
4. Angiotensin receptor blockers (ARBs)—antagonise the action of Ang II on target cells.
5. Aldosterone antagonists—block mineralocorticoid receptors.

## ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Teprotide was the first ACE inhibitor to be synthesized taking a lead from the bradykinin potentiating factor (BPF) found in pit viper venom and the finding that the kininase II was also ACE. Teprotide, a nonapeptide inhibited generation of Ang II from Ang I and lowered BP. However, it had limitations of parenteral administration and brief duration of action.

Captopril, an orally active dipeptide analogue was introduced in 1977 and quickly gained wide usage. A multitude of ACE inhibitors have since been added, of which—*captopril, enalapril, lisinopril, benazepril, ramipril, fosinopril, quinapril, trandolapril, imidapril* and *perindopril* are available in India. Many others are marketed elsewhere.The pharmacology of captopril is described as prototype, since most of its effects are class effects common to all ACE inhibitors.

### Captopril

It is a sulfhydryl containing dipeptide surrogate of proline which abolishes the pressor action of Ang I but not that of Ang II: does not block $AT_1$ or $AT_2$ receptors.

ACE is a relatively nonspecific enzyme; splits off a dipeptidyl segment from several peptides including bradykinin, substance P, a natural stem cell regulating peptide, etc. in addition to Ang I. As such, captopril increases plasma kinin levels and potentiates the hypotensive action of exogenously administered bradykinin. Pretreatment with $B_2$ kinin receptor antagonist has shown that kinins do contribute to the acute vasodepressor action of ACE inhibitors, but they appear to have little role in the long-term hypotensive effect, probably because, firstly kinins play only a minor role, if at all, in BP regulation, and, secondly another enzyme 'Kininase I' (which also degrades bradykinin) is not inhibited by captopril. Nevertheless, elevated kinins (and PGs whose synthesis is enhanced by kinins) may be responsible for cough and angioedema induced by ACE inhibitors in susceptible individuals. ACE inhibitors interfere with degradation of substance P also. Rise in the level of stem cell regulator peptide caused by ACE inhibitors could, in part, be responsible for their cardioprotective effect in CHF.

Captopril lowers BP, but in the short-term, magnitude of response is dependent on $Na^+$ status and the level of RAS activity. In normotensive $Na^+$ replete individuals, the fall in BP attending initial few doses of ACE inhibitors is modest.

This is more marked when $Na^+$ has been depleted by dietary restriction or diuretics, because renin level is high. In CHF also, the renin level is raised and antihypertensive doses of captopril cause marked fall in BP initially. ACE inhibitor therapy in these situations has to be initiated at much lower doses. A greater fall in BP occurs in renovascular, accelerated and malignant hypertension as well. In essential hypertension it has been found that RAS is overactive in 20%, normal in 60% and hypoactive in the rest. Thus, it contributes to maintenance of vascular tone in over 80% cases and its inhibition results in lowering of BP. Treatment with ACE inhibitors causes feed back increase in renin release resulting in overproduction of Ang I. Since its conversion to Ang II is blocked, Ang I is diverted to produce more Ang (1-7) which has vasodilator property, and could contribute to the BP lowering action of ACE inhibitors. While the initial fall in BP is dependent on renin and Ang II levels, in the long-term no correlation has been observed between plasma renin activity (PRA) and magnitude of fall in BP due to captopril.

Captopril induced hypotension is a result of decrease in total peripheral resistance. The arterioles dilate and compliance of larger arteries is increased. Both systolic and diastolic BP fall. It has no effect on cardiac output. Cardiovascular reflexes are not interfered with and there is little dilatation of capacitance vessels. As such, postural hypotension is not a problem. Reflex sympathetic stimulation does not occur despite vasodilatation, and ACE inhibitors can be safely used in patients with ischaemic heart disease. The renal blood flow is not compromized even when BP falls substantially. This is due to greater dilatation of renal vessels (Ang II markedly constricts them). Cerebral and coronary blood flow are also not compromized.

Reflex (postural) changes in plasma aldosterone are abolished and basal levels are somewhat decreased as a consequence of loss of its regulation by Ang II. However, physiologically sufficient mineralocorticoid is still secreted under the influence of ACTH and plasma $K^+$. Levels of plasma renin and Ang I are increased as a compensatory measure, but the physiological significance of this appears to be minor (most actions are exerted through generation of Ang II).

**Pharmacokinetics** About 70% of orally administered captopril is absorbed. Presence of food in stomach reduces its bioavailability. Penetration in brain is poor. It is partly metabolized and partly excreted unchanged in urine. The plasma t½ is ~2 hours, but actions last for 6–12 hours.

**Adverse effects** The adverse effect profile of all ACE inhibitors is similar. Captopril is well tolerated by most patients, especially if daily dose is kept below 150 mg.

- *Hypotension:* an initial sharp fall in BP occurs especially in diuretic treated and CHF patients; persistent hypotension may be troublesome in MI patients.

**TABLE 36.1 Comparative features of some ACE inhibitors**

| | *Captopril* | *Enalapril* | *Lisinopril* | *Fosinopril* | *Perindopril* | *Ramipril* |
|---|---|---|---|---|---|---|
| 1. Chemical nature | Sulfhydryl | Carboxyl | Carboxyl | Phosphinate | Carboxyl | Carboxyl |
| 2. Activity status | Active | Prodrug | Active | Prodrug | Prodrug | Prodrug |
| 3. Bioavailability (as active form) | 70% | 50% | 25% | 30% | 30–50% | 60% |
| 4. Time to peak action | 1 hr | 4–6 hr | 6–8 hr | 3–5 hr | 6 hr | 3–6 hr |
| 5. Elimination t½* | 2 hr | 11 hr | 12 hr | 12 hr | 25–30 hr | 8–48 hr |
| 6. Mode of excretion | Renal | Renal | Renal | Renal/hepatic | Renal | Renal |
| 7. Duration of action | 6–12 hr | 24 hr | ≥ 24 hr | 24 hr | > 24 hr | >24 hr |
| 8. Daily dose (mg) | 25–150 | 2.5–40 | 5–40 | 10–40 | 2–8 | 1.25–10 |

* t½ including that of active metabolite

- *Hyperkalaemia:* more likely in patients with impaired renal function and in those taking $K^+$ sparing diuretics, NSAIDs or β blockers. In others significant rise in plasma $K^+$ is rare.
- *Cough:* a persistent brassy cough occurs in 4–16% patients within 1–8 weeks, often requires discontinuation of the drug—subsides 4–6 days thereafter. It is not dose related and appears to be caused by inhibition of bradykinin/substance P breakdown in the lungs of susceptible individuals.
- *Rashes, urticaria:* occur in 1–4% recipients; but do not usually warrant drug discontinuation.
- *Angioedema*: resulting in swelling of lips, mouth, nose, larynx may develop within hours to few days in 0.06–0.5% patients; may cause airway obstruction. This can be treated with Adr, antihistaminics and corticosteroids according to need.
- *Dysgeusia:* reversible loss or alteration of taste sensation due to captopril occurs in few patients. A still lower incidence with other ACE inhibitors has been noted.
- *Foetopathic:* foetal growth retardation, hypoplasia of organs and foetal death may occur if ACE inhibitors are given during later half of pregnancy. A recent report indicates 2.7-fold higher malformation rate in foetuses exposed to ACE inhibitors in the first trimester. ACE inhibitors must be stopped when the woman conceives.
- *Headache, dizziness, nausea and bowel upset:* each reported in 1–4% patients.
- *Granulocytopenia and proteinuria:* are rare, but warrant withdrawal. Renal disease predisposes to these adverse effects. However, ACE inhibitors retard diabetic nephropathy, reduce attendant proteinuria, and are renoprotective.
- *Acute renal failure:* is precipitated by ACE inhibitors in patients with bilateral renal artery stenosis due to dilatation of efferent arterioles and fall in glomerular filtration pressure. ACE inhibitors are contraindicated in such patients.

### Interactions

- Diuretics synergise with the hypotensive action of ACE inhibitors by depleting $Na^+$ and raising renin levels. In diuretic treated patients, the starting dose of ACE inhibitors should be low.
- Indomethacin (and other NSAIDs) attenuate the hypotensive action by retaining salt and water. Incidents of renal failure have been reported when a NSAID was given to patients (especially elderly) receiving ACE inhibitor + diuretic.
- Hyperkalaemia can occur if $K^+$ supplements/ $K^+$ sparing diuretics are given with captopril.
- Antacids reduce bioavailability of captopril.
- ACE inhibitors reduce $Li^+$ clearance and predispose to its toxicity.

*Dose:* 25 mg BD, increased gradually upto 50 mg TDS according to response. In patients on diuretics and in CHF patients it is wise to start with 6.25 mg BD to avoid marked fall in BP initially. Tablets should be taken 1 hr before or 2 hr after a meal.

Captopril has become less popular due to need for twice/thrice daily dosing and possibly higher incidence of side effects compared to other ACE inhibitors.

ANGIOPRIL 25 mg tab, ACETEN, CAPOTRIL 12.5, 25 mg tab.

## OTHER ACE INHIBITORS

All ACE inhibitors have the same pharmacological actions, therapeutic uses and spectrum of adverse effects, drug interactions and contraindications. Differences among them are primarily pharmacokinetic, reflected in time course of action. No single drug is superior to others.

**Enalapril** This is the second ACE inhibitor to be introduced. It is a prodrug, deesterified in the liver to *enalaprilat* (a tripeptide analogue), which is not used as such orally because of poor absorption, but is marketed as injectable preparation in some countries. Enalapril has the same pharmacological, therapeutic and adverse effect profile as captopril, but may offer certain advantages:

1. More potent, effective dose 5–20 mg OD or BD.
2. Its absorption is not affected by food.

3. Onset of action is slower (due to need for conversion to active metabolite), less liable to cause abrupt first dose hypotension.
4. Has a longer duration of action: most hypertensives can be treated with single daily dose.
5. Rashes and loss of taste are probably less frequent.

ENAPRIL, ENVAS, ENAM 2.5, 5, 10, 20 mg tab.

**Lisinopril** It is the lysine derivative of enalaprilat; does not require hydrolysis to become active ACE inhibitor. Its oral absorption is slow (making first dose hypotension less likely) and incomplete, but unaffected by food. The duration of action is considerably longer, permitting single daily dose and ensuring uniform hypotensive action round the clock. A reduction in venous return, cardiac contractility and cardiac output has been noted after few weeks of lisinopril use.
LINVAS, LISTRIL, LIPRIL 2.5, 5, 10 mg tab, LISORIL 2.5, 5, 10, 20 mg tab.

**Perindopril** Another long-acting ACE inhibitor with a slow onset of action: less chance of first dose hypotension. Though 66–95% of orally administered perindopril is absorbed, only about 20% is converted to the active metabolite *perindoprilat*. Extensive metabolism to other inactive products occurs. Efficacy and tolerance of perindopril are similar to other ACE inhibitors.
COVERSYL 2, 4 mg tab.

**Fosinopril** This ACE inhibitor is unique in being a phosphinate compound that is glucuronide conjugated and eliminated both by liver and kidney. The t½ is not altered by renal impairment and the dose remains the same. However, like most others, it is a prodrug suitable for once daily administration. First dose hypotension is more likely.
*Dose:* Initially 10 mg (elderly 5 mg) OD; maximum 40 mg/day.
FOSINACE, FOVAS 10, 20 mg tabs.

**Ramipril** The distinctive feature of this long-acting ACE inhibitor is its extensive tissue distribution. Greater inhibition of local RAS has been claimed. However, whether this confers any therapeutic advantage is not known. The plasma t½ of its active metabolite ramiprilat is 8–18 hours, but terminel t½ is longer due to slow release of tissue bound drug.
CARDACE, RAMIRIL, CORPRIL, R.PRIL 1.25, 2.5, 5 mg caps.

**Quinapril** A prodrug carboxyl ACE inhibitor that is rapidly and completely converted in the liver to the active form Quinaprilat. Like ramiprilat, it is highly bound to the tissue ACE and exhibits a biphasic plasma t½ of 2 hours and 24 hours. Elimination occurs in urine and bile in a ratio of 2:1.
*Dose:* 10–40 mg/day
ACCUPRIL-H: Quinapril 20 mg + hydrochlorothiazide 12.5 mg tab.

**Trandolapril** It is a carboxyl prodrug that is 40–60% bioavailable in the active form. Absorption is delayed but not decreased by food. The peak effect occurs at 4–6 hours. It is partly metabolized and eliminated both in urine and faeces. The plasma t½ of active metabolite is biphasic 10–24 hours, suitable for once daily dosing.
*Dose:* 2–4 mg (max 8 mg) OD; ZETPRIL 1, 2 mg tabs.

**Imidapril** The oral bioavailability of this long-acting prodrug ACE inhibitor is 40%, which is reduced by taking the drug with meals. The peak effect occurs at 6–8 hours and plasma t½ is >24 hours.
*Dose:* Initially 5 mg OD taken 1 hour before food; usual maintenance dose 10 mg OD.
TANATRIL 5, 10 mg tabs.

**Benazepril** Another nonsulfhydryl prodrug ACE inhibitor; has a bioavailability of 37% and is excreted by kidney with a t½ of 10–12 hr.
*Dose:* 10 mg initially, max 20–40 mg/day;
BENACE 5, 10, 20 mg tab.

## USES

**1. Hypertension** The ACE inhibitors are first line drugs in all grades of hypertension, but the angiotensin receptor blockers (ARBs) have now surpassed them in popularity. About 50% patients of essential hypertension respond to monotherapy with ACE inhibitors and majority of the rest to their combination with diuretics or β blockers.

The hypotensive effect of lower doses develops gradually over 2–3 weeks. They offer the following advantages:

- Free of postural hypotension, electrolyte disturbances, feeling of weakness and CNS effects.
- Safety in asthmatics, diabetics and peripheral vascular disease patients.
- Long-term ACE inhibitor therapy has the potential to reduce incidence of type 2 diabetes in high risk subjects.
- Secondary hyperaldosteronism and $K^+$ loss due to diuretics is prevented.
- Renal blood flow is well maintained.
- Left ventricular hypertrophy and increased wall-to-lumen ratio of blood vessels that occurs in hypertensive patients is reversed.
- No hyperuricaemia, no deleterious effect on plasma lipid profile.
- No rebound hypertension on withdrawal.
- Minimum worsening of quality of life parameters like general wellbeing, work performance, sleep, sexual performance, etc.

Large multicentric trials have confirmed that ACE inhibitors reduce cardiovascular morbidity and increase life expectancy of hypertensive patients. It appears that by their specific effect on myocardial and vascular cell growth/remodeling, they have greater protective potential than other classes of antihypertensive drugs.

ACE inhibitors are highly effective and first choice drugs in renovascular and resistant hypertension. They are particularly suitable for diabetic hypertensives in whom they reduce cardiovascular complications more than other antihypertensive drugs, probably by improving endothelial function.

**2. CHF** ACE inhibitors cause both arteriolar and venodilatation in CHF patients; reduce afterload as well as preload. Haemodynamic measurements in severe CHF patients have shown reduction in right atrial pressure, pulmonary arterial pressure, pulmonary capillary wedge pressure, systemic vascular resistance, systolic wall stress and systemic BP. Though they have no direct myocardial action, stroke volume and cardiac output are increased, while heart rate is reduced. Diuresis occurs initially and the accumulated salt and water are lost due to improved renal perfusion and abolition of mineralocorticoid mediated $Na^+$ retention. Cardiac work as measured by heart rate × pressure product is reduced; thereby, exercise capacity of CHF patients is enhanced. Beneficial effects are well sustained with chronic therapy and the NYHA functional class of most patients is improved.

Robust multicentric trials have shown that ACE inhibitors retard the progression of left ventricular systolic dysfunction and prolong survival of CHF patients of all grades (I to IV). Mortalility is reduced by ~ 20% in symptomatic CHF patients. Unless contraindicated, ACE inhibitors are now advocated by several professional bodies, including American Heart Association and American College of Cardiology, as first line drugs in all patients with symptomatic as well as asymptomatic left ventricular inadequacy. A diuretic, β blocker with or without digitalis may be added according to need. ACE inhibitors reduce episodes of decompensation, myocardial infarction and sudden death. In addition to improved haemodynamics, long-term benefits of ACE inhibitors accrue from withdrawal of Ang II mediated ventricular hypertrophy, remodeling, accelerated myocyte apoptosis and fibrosis. Indirect benefits occur due to reduction in sympathetic activation and aldosterone levels.

The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial on 3164 heart failure patients (NYHA class II to IV) has shown that high dose lisinopril (32.5–35 mg/day) given for 39–58 months was more effective in reducing all cause mortality, hospitalization for heart failure and risk of MI than lower dose (2.5–5 mg/day). To afford maximum protection against progression of heart failure, the dose of ACE inhibitors needs to be titrated to nearly the upper limit of recommended dose range, as shown in other mega trials like GISSI-3, SOLVD, AIRE, etc. as well. ACE inhibitors are effective in reducing development of ventricular dysfunction, heart failure and related mortality in post-MI patients also (SAVE, TRACE, AIRE trials).

**3. Myocardial infarction (MI)** Several mega-trials have established that oral ACE inhibitors administered while MI is evolving (within 24 hr

of an attack) and continued for 6 weeks reduce early as well as long-term mortality, irrespective of presence or absence of systolic dysfunction, provided hypotension is avoided. In high risk patients and those with latent or overt ventricular dysfunction (CHF) extension of therapy continues to afford survival benefit over years. In unstable angina/non-ST segment elevation MI (NSTEMI), long-term ACE inhibitor therapy reduces recurrent MI and need for coronary angioplasty (SAVE and SOLVD trials), though no benefit was apparent in the short-term (ISIS-4 study). Current evidence shows that if there are no contraindications, all MI patients stand to gain from ACE inhibitor therapy, though magnitude of benefit is greatest in those having associated hypertension and/or diabetes.

**4. Prophylaxis in high cardiovascular risk subjects** The results of Heart Outcomes Prevention Evaluation (HOPE) study in 9297 post-MI and other high risk subjects, but having no left ventricular dysfunction or heart failure have shown that ramipril reduced cardiac death and MI or stroke by 22% over a period of 4.5 years. Risk of developing heart failure or diabetes was also reduced. These results have been confirmed by the EUROPA trial and appear to hold true even for patients who have undergone coronary revascularization (APRES trial). Thus, ACE inhibitors are protective in high cardiovascular risk subjects even when there is no associated hypertension or left ventricular dysfunction. Protective effect is exerted both on myocardium as well as vasculature; may involve improved endothelial function, and is independent of hypotensive action.

**5. Diabetic nephropathy** Prolonged ACE inhibitor therapy has been found to prevent or delay end-stage renal disease in type I as well as type II diabetics. Albuminuria (an index of glomerulopathy) remains stable in those treated with ACE inhibitor, but aggravates in untreated diabetics. Treated patients have higher creatinine clearance, require less dialysis and have longer life expectancy. Benefits appear to be due to haemodynamic (systemic and intrarenal) as well as abnormal mesangial cell growth attenuating effects of ACE inhibitors. They reduce intraglomerular pressure and hyperfiltration. ACE inhibitors arrest/partly reverse any degree of albuminuria, but benefits in type 2 diabetics are rather limited once macroalbuminuria has set in. The RAS seems to accentuate micro- and macrovascular complications in diabetics, and ACE inhibitors have specific organ protective effect by attenuating the same. All patients with diabetic nephropathy, whether hypertensive or normotensive, deserve ACE inhibitor therapy. Deterioration of retinopathy in diabetics also appears to be retarded by ACE inhibitors.

*Nondiabetic nephropathy* There is evidence now that chronic renal failure due to nondiabetic causes may also be improved by ACE inhibitors. These drugs reduce proteinuria by decreasing pressure gradient across glomerular capillaries as well as by altering membrane permeability. This retards disease progression. Among hypertensive nephropathy patients the incidence of doubling of serum creatinine or end stage renal failure is significantly lower in those treated with ACE inhibitors than those treated with other antihypertensive drugs.

**6. Scleroderma crisis** The marked rise in BP and deterioration of renal function in scleroderma crisis is mediated by Ang II. ACE inhibitors produce dramatic improvement and are life saving in this condition.

*Captopril test* This test has been devised to obviate the need for renal angiography for diagnosis of renovascular hypertension. The basis of the test is—acute blockade of Ang II formation by captopril results in a reactive increase in PRA which is much higher in renovascular compared to essential hypertension. However, this test is only of adjunctive value.

## ANGIOTENSIN ANTAGONISTS (Angiotensin receptor blockers or ARBs)

Over the past 2 decades, several nonpeptide orally active $AT_1$ receptor blockers (ARBs) have been developed as alternatives to ACE inhibitors. These include *losartan, candesartan*, *valsartan,*

*telmisartan, olmesartan* and *irbesartan*. Selective antagonists of $AT_2$ receptors as well as combined $AT_1$ + $AT_2$ antagonists have also been produced, but are not used clinically.

**Losartan** It is a competitive antagonist and inverse agonist, 10,000 times more selective for $AT_1$ than for $AT_2$ receptor; does not block any other receptor or ion channel, except thromboxane $A_2$ receptor (has some platelet antiaggregatory property). All overt actions of Ang II, *viz*. vasoconstriction, central and peripheral sympathetic stimulation, release of aldosterone and Adr from adrenals, renal actions promoting salt and water reabsorption, central actions like thirst, vasopressin release and growth-promoting actions on heart and blood vessels are blocked. No inhibition of ACE has been noted.

Pharmacologically, ARBs differ from ACE inhibitors in the following ways:

- They do not interfere with degradation of bradykinin and other ACE substrates: no rise in level or potentiation of bradykinin, substance P occurs. Consequently, ACE inhibitor related cough is rare.
- They result in more complete inhibition of $AT_1$ receptor activation, because responses to Ang II generated *via* alternative pathways and consequent $AT_1$ receptor activation (which remain intact with ACE inhibitors) are also blocked.
- They result in indirect $AT_2$ receptor activation. Due to blockade of $AT_1$ receptor mediated feedback inhibition—more Ang II is produced which acts on $AT_2$ receptors that remain unblocked. ACE inhibitors result in attenuation of both $AT_1$ and $AT_2$ receptor activation.
- ARBs cause little increase in the level of Ang (1-7) which is raised by ACE inhibitors, since Ang (1-7) is partly degraded by ACE.

The impact of these differences on clinical efficacy and therapeutic value of the two classes of RAS inhibitors is not known.

Losartan causes fall in BP in hypertensive patients which lasts for 24 hours, while HR remains unchanged and cardiovascular reflexes are not interfered. No significant effect on plasma lipid profile, carbohydrate tolerance, insulin sensitivity has been noted. A mild probenecid-like uricosuric action is produced.

*Pharmacokinetics* Oral absorption of losartan is not affected by food, but bioavailability is only 33% due to first pass metabolism. It is partially carboxylated in liver to an active metabolite (E3174) which is a 10–30 times more potent noncompetitive $AT_1$ receptor antagonist. After oral ingestion peak plasma levels are attained at 1 hr for losartan and at 3–4 hours for E3174. Both compounds are 98% plasma protein bound, do not enter brain and are excreted by the kidney. The plasma t½ of losartan is 2 hr, but that of E3174 is 6–9 hr. No dose adjustment is required in renal insufficiency, but dose should be reduced in presence of hepatic dysfunction.

*Adverse effects* Losartan is well tolerated; has side effect profile similar to placebo. Like ACE inhibitors it can cause hypotension and hyperkalemia, but first dose hypotension is uncommon. Though, a few reports of dry cough have appeared, losartan is considered to be free of cough and dysgeusia inducing potential. Patients with a history of ACE inhibitor related cough have taken losartan without recurrence. Angioedema is reported in fewer cases. Headache, dizziness, weakness and upper g.i. side effects are mild and occasional. However, losartan has fetopathic potential like ACE inhibitors—not to be administered during pregnancy.

*Dose:* 50 mg OD, rarely BD; in liver disease or volume depleted patients 25 mg OD; addition of hydrochlorothiazide 12.5–25 mg enhances its effectiveness.

LOSACAR, TOZAAR, ALSARTAN 25, 50 mg tabs.

**Candesartan** It has the highest affinity for the $AT_1$ receptor and produces largely unsurmountable antagonism, probably due to slow dissociation from the receptors or receptor desensitization. Elimination occurs by both hepatic metabolism and renal excretion with a t½ of 8-12 hours: action lasts 24 hours.

*Dose:* 8 mg OD (max 8 mg BD), liver/kidney impairment 4 mg OD.

CANDESAR 4, 8, 10 mg tab., CANDILONG, CANDESTAN 4, 8 mg tabs.

**Irbesartan** The oral bioavailability of this ARB is relatively high. It is partly metabolized and excreted mainly in bile. The t½ is ~12 hours.
*Dose:* 150–300 mg OD.
IROVEL, IRBEST 150, 300 mg tabs.

**Valsartan** The $AT_1$ receptor affinity of valsartan is similar to that of losartan. Its oral bioavailability averages 23% and food interferes with its absorption. Elimination occurs mainly by the liver in unchanged form with a t½ of 6–9 hours; action lasts 24 hours.
*Dose:* 80–160 mg OD 1 hour before meal (initial dose in liver disease 40 mg).
DIOVAN, STARVAL, VALZAAR 40, 80, 160 mg tabs.

**Olmesartan** Another potent ARB with high affinity for $AT_1$ receptor. It is available as an ester prodrug which is completely hydrolysed during absorption from the gut. It is eliminated in urine as well as in bile with a t½ of ~12 hours. No dose adjustment is needed in liver or kidney disease, unless it is severe.
*Dose:* 20–40 mg OD; OLMAT 20, 40 mg tabs.

**Telmisartan** The $AT_1$ receptor blocking action of telmisartan is similar to losartan, but it does not produce any active metabolite. After an oral dose, peak action occurs in 3 hours and action lasts > 24 hours. It is largely excreted unchanged in bile; dose reduction is needed in liver disease.
*Dose:* 20–80 mg OD.
TELMA, TELSAR, TELVAS 20, 40, 80 mg tabs.

### Uses of ARBs

The ARBs have the same overall range of clinical utility as ACE inhibitors, but the suitability/efficacy of one over the other is not clearly defined; may depend on the condition being treated and/or specific features of the patient. The value of combined use of ACE inhibitors and ARBs *versus* monotherapy is also still unsettled.

*Hypertension* Losartan and other ARBs are now first line drugs, comparable in efficacy and desirable features to ACE inhibitors, with the advantage of not inducing cough and a lower incidence of angioedema, rashes and dysgeusia. As such, they are more commonly prescribed now than ACE inhibitors, though superiority of one over the other is not established. Like ACE inhibitors, the maximum antihypertensive effect is reached in 2–4 weeks and ventricular/vascular hypertrophy/remodeling is arrested/reversed similarly.

The Losartan intervention for endpoint reduction in hypertension (LIFE, 2002) study has found losartan to be more effective than β-blockers in reducing stroke among > 9000 hypertensive patients with left ventricular hypertrophy, and is approved for stroke prevention. In cirrhotics, losartan has been found to control portal hypertension.

*CHF* The ARBs afford clear-cut symptomatic relief as well as survival benefit in CHF. However, their relative value compared to ACE inhibitors, especially in long-term morbidity and mortality reduction, is still uncertain.

A number of large randomized endpoint trials like Evaluation of losartan in the elderly (ELITE, 1997), ELITE-II (2000), OPTIMAAL (2002), Valsartan in acute MI (VALIANT, 2003) have produced inconsistent results. Some find ACE inhibitors more effective, others find ARBs more effective, while still others find them equieffective. For CHF, the current consensus is to use ACE inhibitors as the first choice drugs and to reserve ARBs for those who fail to respond well or who develop cough/angioedema/other intolerance to ACE inhibitors.

*Myocardial infarction* The evidence so far indicates that utility of ARBs in MI, including long-term survival, is comparable to ACE inhibitors. However, the latter are generally used first, since there is greater experience with them.

*Diabetic nephropathy* Several studies have confirmed that ARBs are renoprotective in type 2 diabetes mellitus, independent of BP lowering. The magnitude of benefit is comparable to ACE inhibitors, but because of better tolerability profile, many consider ARBs to be the first choice now.

*Combination of ACE inhibitors with ARBs*

There are theoretical reasons to combine an ACE inhibitor with an ARB to obtain more complete suppression of RAS and achieve added cardioprotection in CHF or renoprotection in diabetic nephropathy. These are:

- Ang II is generated in several tissues (especially heart and kidney) by non-ACE mechanisms, whose effect can be blocked by ARBs.

- ACE inhibitors produce bradykinin and Ang (1-7) related vasodilatation and other effects that are not produced by ARBs.
- ARBs cause compensatory increase in Ang II production that can be checked by ACE inhibitors.
- ARBs enhance unblocked $AT_2$ receptor mediated effects that can be prevented by concurrent ACE inhibition.

Additional haemodynamic and symptomatic improvement over short-term has been obtained in CHF with addition of an ARB to exhisting ACE inhibitor therapy. However, several large randomized trials including Randomized evaluation of strategies for left ventricular dysfunction (RESOLVD, 1999), Valsartan heart failure trial (VAL-He FT, 2001), CHARM-additive trial (2003), VALIANT (2003) trial, Ongoing Telmisartan alone and in combination with ramipril global endpoint trial (ON TARGET, 2008) of combinations of ARBs and ACE inhibitors *Vs* their monotherapy in affording mortality and other endpoint benefits in CHF have yielded discordant results. Thus, it is not yet clarified whether long-term use of ARB + ACE inhibitor combination is advisable or not.

In non-diabetic renal disease, the Combination treatment of ARB and ACE inhibitor randomized trial (COOPERATE, 2003) has concluded that ARB + ACE inhibitor combination therapy retards progression of non-diabetic renal disease to a greater extent compared with their monotherapy.

## DIRECT RENIN INHIBITOR

### Aliskiren

Direct renin inhibitors (DRIs) are the latest class of RAS inhibitory drugs, of which only one member *Aliskiren* has become available for the treatment of cardiovascular and renal diseases in which ACE inhibitors and ARBs are currently used. Aliskiren is a nonpeptide which binds selectively to the catalytic site of renin and competitively blocks the access of angiotensinogen to this site → Ang I is not produced and the chain of RAS is interrupted. While the concentration of renin in plasma is increased by feed back, the plasma renin activity (PRA) is decreased. Ang I and Ang II levels fall.

Aliskiren causes fall in BP which is more marked in the $Na^+$ depleted subjects with high basal PRA. Similar to ACE inhibitors, plasma aldosterone levels are lowered accompanied by mild natriuresis and a tendency to $K^+$ retention. The antihypertensive efficacy of aliskiren is equivalent to that of ACE inhibitors or ARBs. Combination of these drugs with aliskiren produces greater fall in BP, at least in the short term. This may be due to blockade of rise in PRA caused by ACE inhibitors/ARBs. The pattern of haemodynamic effect of aliskiren resembles ACE inhibitors; postural hypotension is not a problem.

Trials so far have shown that aliskiren can reduce hypertensive left ventricular hypertrophy and benefit CHF patients, but its value compared to ACE inhibitors/ARBs as monotherapy and as additional drug remains to be determined. Aliskiren has renoprotective effect as well in hypertension and diabetes mellitus. Its long-term benefits and comparative position in relation to ACE inhibitors/ARBs is being evaluated.

At present, aliskiren is recommended as an alternative antihypertensive drug (for those who do not respond/do not tolerate 1st line drugs) and in combination with others for greater BP lowering.

*Pharmacokinetics* Aliskiren is administered orally, but bioavailability is very low due to active extrusion of absorbed drug by P-glycoprotein. The drug is mainly eliminated in faeces; small amount in urine. The plasma t½ is > 24 hours, and its BP lowering effect persists for days after regular intake.

*Adverse effects* Aliskiren produces few and mild side effects—mainly dyspepsia, abdominal pain, loose motions, headache and dizziness. Acute hypotension, hyperkalaemia, cough, angioedema and rashes are much less frequent than with ACE inhibitors. Aliskiren is contraindicated during pregnancy.

*Dose:* 150–300 mg OD; RASILEZ 150 mg tab; RASILEZ-HC: along with hydrochlorothiazide.

## PLASMA KININS (Bradykinin and Kallidin)

Plasma kinins are polypeptides split off from a plasma globulin *Kininogen* by the action of specific enzymes *Kallikreins*. The two important plasma kinins, *Kallidin* (decapeptide) and *Bradykinin* (nonapeptide) were discovered around 1950 by two independent lines of investigation into the hypotensive activity of urine and certain snake venoms. These and other biological fluids were found to act indirectly: they contained enzymes which generated active substances in the plasma.

Kinins are generated by proteolytic reactions triggered by tissue injury, inflammation, allergic reaction, etc., and play important mediator roles.

**Generation and metabolism** Kininogens are $\alpha_2$ globulins present in plasma which also contains inactive kininogenase *prekallikrein*.

Prekallikrein is activated by Hageman factor (factor XII) which itself is activated by tissue injury and contact with surfaces having negative charge, e.g. collagen, basement membrane, bacterial liposaccharides, urate crystals, etc. *Plasmin* facilitates contact activation of Hageman factor (Fig. 36.4). Kinins are also generated by trypsin, proteolytic enzymes in snake and wasp venoms and by kallikrein present in kidney, pancreas and other tissues. Bradykinin is generated from high molecular weight (HMW) kininogen by the action of plasma kallikrein, because HMW-kininogen does not cross the capillaries. On the other hand, kallidin can be produced from both low molecular weight (LMW) kininogen as well as HMW-kininogen by the action of tissue kallikreins. Bradykinin can also be generated from kallidin on the removal of lysine residue by an aminopeptidase.

Plasma and tissues also contain kininogenase inhibitory factors of which *complement (C1) esterase inhibitor* is the most important. Moreover, kallikreins are normally present in their inactive forms. Thus, physiologically only small amounts of kinins are generated in plasma and tissues.

Kinins are very rapidly degraded, primarily in lungs, but also in other tissues and have a t½ of < 1 min. The principal degrading enzyme is *Kininase* II, also known as 'angiotensin-II converting enzyme' (ACE) which splits off 2 amino acids from the carboxyterminal of the peptide chain. Another carboxypeptidase *Kininase I* removes only one amino acid (arginine) producing selective $B_1$ receptor agonistic metabolites (desArg bradykinin and desArg kallidin) which are further degraded by other peptidases.

### ACTIONS

Bradykinin and kallidin have similar actions.

**1. CVS** Kinins are more potent vasodilators than ACh and histamine. The dilatation is mediated through endothelial NO and $PGI_2$ generation, and involves mainly the arterioles. Larger arteries, most veins and vessels with damaged endothelium are constricted through direct action on the smooth muscle. In addition, they can release histamine and other mediators from mast cells. Injected i.v. kinins cause flushing, throbbing

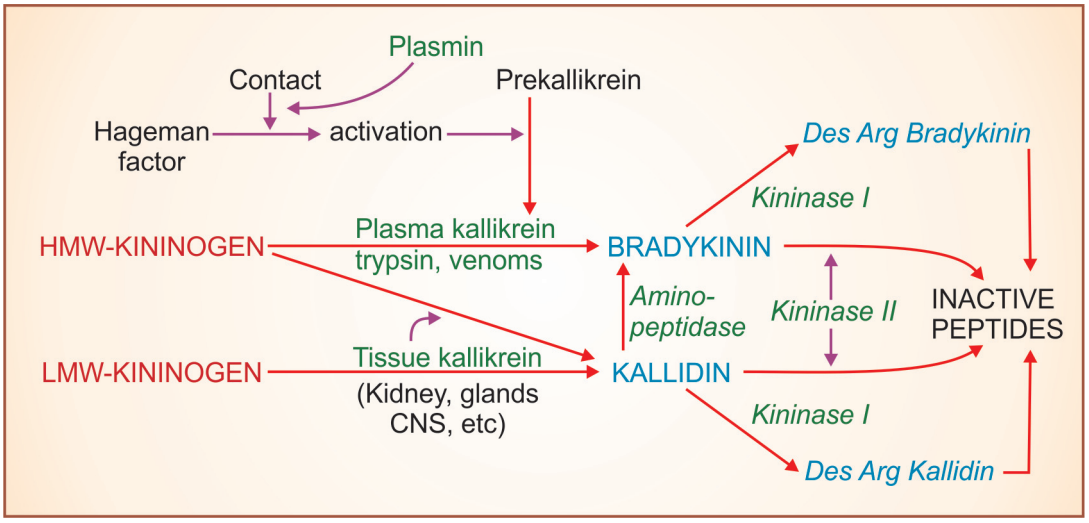



**Fig. 36.4:** Generation and degradation of plasma kinins
HMW—High molecular weight; LMW—Low molecular weight

headache and fall in BP. They markedly increase capillary permeability due to separation of endothelial cells → exudation and inflammation occurs if they are injected in a tissue. Intradermal injection produces wheal and flare (similar to histamine).

Kinins have no direct action on heart; reflex stimulation occurs due to fall in BP.

**2. Smooth muscle** Kinin-induced contraction of intestine is slow (*bradys*—slow, *kinein*—to move). They cause marked bronchoconstriction in guineapigs and in asthmatic patients. Action on other smooth muscles is not prominent, some may be relaxed also.

**3. Neurones** Kinins strongly stimulate nerve endings that transmit pain and produce a burning sensation. Applied to blister base/injected intraperitoneally or in the brachial artery, bradykinin produces intense, transient pain and has been used in analgesic testing.

Kinins release CAs from adrenal medulla. Injected directly in brain they produce a variety of effects including enhanced sympathetic discharge. They increase permeability of the blood-brain barrier.

**4. Kidney** Kinins increase renal blood flow as well as facilitate salt and water excretion by action on tubules. The diuretic effect of furosemide is reduced by kinin $B_2$ receptor antagonists, indicating participation of locally generated kinins in this response.

**Kinin receptors** Existance of two types of kinin receptors ($B_1$, $B_2$) has been established. Bradykinin and Kallidin are selective agonists of $B_2$ receptors, while their des-Arg metabolites generated by the action of kininase I are selective agonists of $B_1$ receptor. Most of the kinin actions in noninflamed tissues are mediated by $B_2$ receptors which are constitutively present on:

(i) Visceral smooth muscle—contraction of intestine, uterus, airway.
(ii) Vascular endothelium—NO release, vasodilatation, increased permeability.
(iii) Sensory nerves—acute pain.

The $B_2$ receptor is a GPCR coupled to Gq and Gi proteins which utilizes the phospholipaseC—$IP_3$/DAG—intracellular $Ca^{2+}$ mobilization transducer mechanism. Endothelial NO synthase (eNOS) is activated causing vasodilatation. Certain responses to kinins, e.g. bronchoconstriction and renal vasodilatation are attenuated by pretreatment with PG synthesis inhibitors (aspirin). Kinin induced acute pain involves $B_2$ receptors. Aspirin injected i.p. before bradykinin through the same cannula blocks its algesic action. These responses are mediated by phospholipase A activation—release of arachidonic acid and generation of PGs.The activated Gq protein also mediates production of NFκB and triggering of MAP kinase pathway leading to generation of pro-inflammatory mediators.

The $B_1$ receptor is located on the smooth muscle of large arteries and veins—mediates contraction of these vessels, but is expressed minimally in normal tissues. Inflammation induces synthesis of $B_1$ receptors, which colocalize with kininase I enzyme, so that the $B_1$ agonistic des-Arg kinins are produced locally. Activated $B_1$ receptor also transduces through Gq and Gi proteins and produces similar responses, especially enhanced PG synthesis, leukocyte recruitment, activation of inducible NOS (iNOS) and chronic pain in inflammed tissues.

## PATHOPHYSIOLOGICAL ROLES

1. *Mediation of inflammation* Kinins produce all the signs of inflammation—redness, exudation, pain and leukocyte mobilization. Tissue injury can cause local kinin production which then sets in motion the above defensive and reparative processes. Activation of $B_1$ receptors on macrophages induces production of IL-1, TNF-α and other inflammatory mediators.

Kinins appear to play important role in allergic inflammation manifesting as angioedema, rhinitis and asthma.

2. *Mediation of pain* By directly stimulating nerve endings and by increasing PG production, kinins appear to serve as mediators of pain. The $B_2$ antagonists block acute pain produced by bradykinin, but induced $B_1$ receptors appear to mediate pain of chronic inflammation.

3. *Functional hyperemia* (in glands during secretion) and *regulation of microcirculation*—especially in kidney may be occurring through local kinin production.

4. Production of kinins is integrated with *clotting, fibrinolysin* and *complement* systems. Kallikreins may have roles in these systems which are independent of kinin production.

5. Kinins appear to play no significant role in the regulation of normal BP. However, they may serve to oppose overactive RAS and exert antiproliferative influence on cardiac and vascular muscle in hypertensive states.

Potentiation of endogenous bradykinin appears to partly account for the cardioprotective effect of ACE inhibitors. Recent evidence indicates that ischaemic preconditioning which limits tissue damage during myocardial infarction involves kinins.

6. Kinins cause closure of ductus arteriosus, dilatation of foetal pulmonary artery and constriction of umbilical vessels.

Thus, they may be involved in adjusting from foetal to neonatal circulation.

7. Kinins play a major role in the development of angioedema. They also appear to be involved in *shock, rhinitis, asthma, ACE inhibitor induced cough, carcinoid, postgastrectomy dumping syndrome,* fluid secretion in *diarrhoea, acute pancreatitis* and certain *immunological* reactions.

Because of evanescent and unpleasant actions, kinins have no clinical use.

## Bradykinin antagonists

After characterization of $B_1$ and $B_2$ kinin receptors, several peptide and nonpeptide kinin antagonists have been produced. The synthetic peptide HOE 140 (icatibant) is a selective $B_2$ antagonist, resistant to kinin degrading enzymes and having longer t½. The compound *FR 173657* and some others are orally active nonpeptide $B_2$ antagonists that have helped in defining the pathophysiological roles of kinins and have undergone limited trials as analgesic, antiinflammatory drugs and in pancreatitis, head injury, etc. Icatibant has been recently approved in Europe for symptomatic treatment of hereditary angioedema.

### ☞ PROBLEM DIRECTED STUDY

**36.1** A 65-year-male was diagnosed to be suffering from congestive heart failure (CHF). He had pitting edema of feet, dyspnoea and cough on mild exertion, fatigue, engorged neck veins, soft enlargement of liver, pulmonary congestion and mild cardiac dilatation. The pulse was 100/min, respiration 20/min and BP 130/86 mm of Hg. He was prescribed—

Tab furosemide 40 mg once daily in the morning

Tab captopril 25 mg twice daily, morning and evening.

After 2 hours of taking the medicines, he started passing increased quantity of urine and in the next few hours he gradually started feeling weakness, nausea, sweating and fainted while walking to the toilet. The pulse was recorded as 110/min and BP 80/40 mm Hg.

(a) What could be the cause of sudden onset symptoms and the marked fall in BP?

(b) Is the choice of drugs incorrect?

(c) How could such adverse event be prevented?

(d) What immediate management is required?

(see Appendix-1 for solution)

# Chapter 37 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. Thus, efficiency of failing heart is increased. In contrast, *'cardiac stimulants'* (Adr, theophylline) increase $O_2$ consumption rather disproportionately and tend to decrease myocardial efficiency.

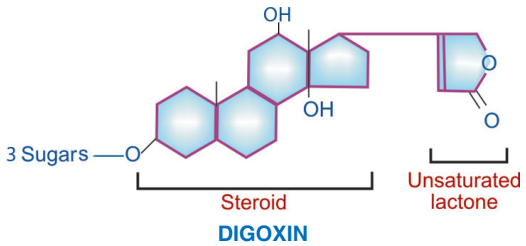
William Withering, a Birmingham physician, learnt that a decoction containing 'foxglove' (*Digitalis*) with other herbals, prepared by an old lady, relieved dropsy. He tried extract of foxglove alone and found it to be remarkably effective in some cases. He published his classic monograph 'An account of the Foxglove and some of its medicinal uses: with practical remarks on dropsy and other diseases' 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 *Strophan thus 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** Digitalis 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* Digitalis 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. There is increased velocity of tension development and higher peak tension can be generated. 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. 37.1), 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. However, therapeutic doses of digoxin do not increase resting tension (tone) in myocardial fibres.

*Rate* Heart rate is decreased by digitalis. Bradycardia is more marked in CHF patients

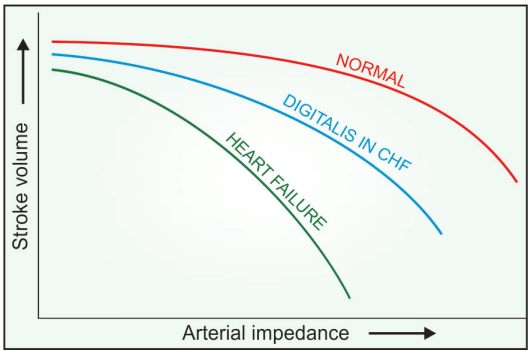



**Fig. 37.1:** Relationship between peripheral resistance and stroke output in normal and failing heart, and the action of digitalis on failing heart

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 and extravagal actions.

*Vagal* tone is increased reflexly by sensitization of baroreceptors, as well as by stimulation of vagal centre.

*Extravagal* A direct depressant action on SA and A-V nodes. This component of bradycardia is not reversed by atropine.

*Electrophysiological properties* The electrophysiological effects of digitalis on different types of cardiac fibres differ quantitatively and qualitatively. The Purkinje fibres, automatic and conducting tissues are more sensitive. In addition to direct effects, the indirect autonomic influences are important in the *in situ* heart.

(a) *Action potential (AP)*: The effects are illustrated diagrammatically in Fig. 37.2.

- The resting membrane potential (RMP) is progressively decreased (to less negative values) with increasing doses. Excitability is enhanced at low doses but depressed at toxic doses because $Na^+$ channels are inactivated.
- 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—

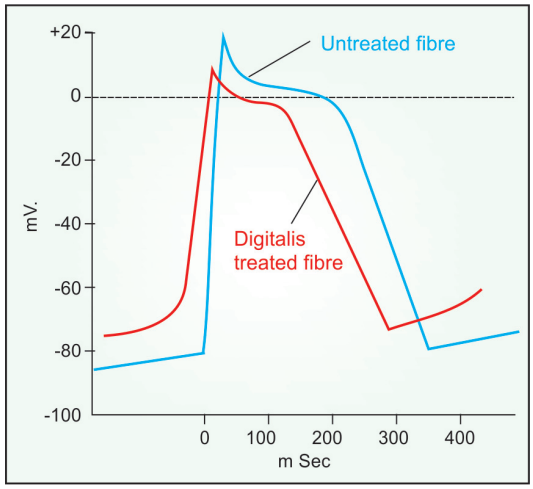



**Fig. 37.2:** Effect of digitalis on Purkinje fibre action potential

latent pacemakers become overt at high doses producing extrasystoles. High doses of digitalis 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. 38.1). 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. Toxic doses markedly reduce RMP of SA nodal cells by direct action and stop impulse generation.

- The action potential duration (APD) is reduced (primarily at phase-2) and amplitude of AP is diminished.

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

*Atrium*
- decreased by vagal action — Vagal action normally predominates, causes inhomogeneity; allows the atria to respond at a higher rate and in an asynchronous manner.
- 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 digitalis produce changes in the ECG. These are accentuated at high doses—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.
- 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. 37.3). Inhibition of this cation pump results in progressive accumulation of $Na^+$ intracellularly. This indirectly results in intracellular $Ca^{2+}$ accumulation.

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 Ryanodine calcium channel 2 (RYR2) → cytosolic $Ca^{2+}$ increases transiently to about 500 nM (calcium transients) → triggers 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. A fraction (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

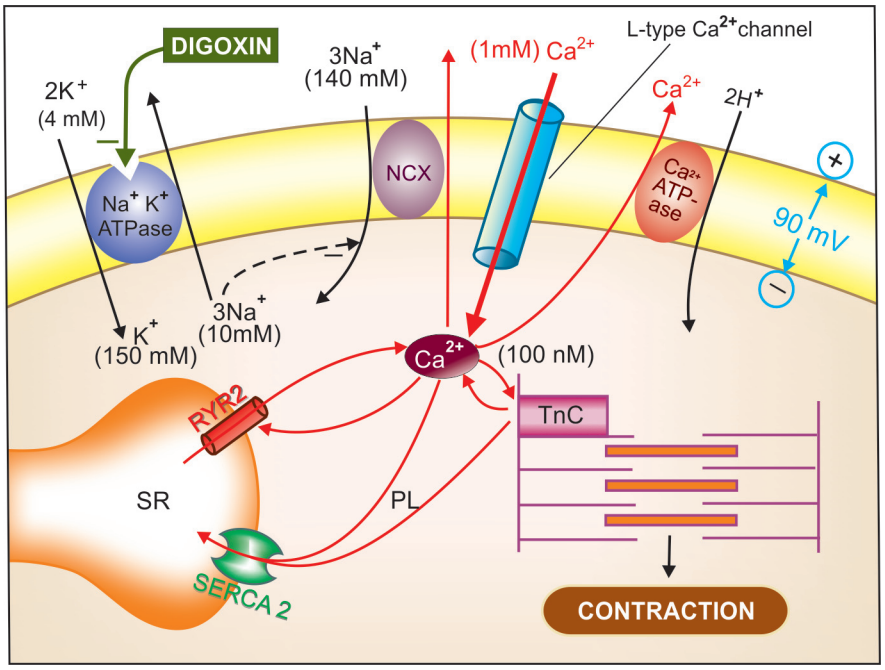



**Fig. 37.3:** Mechanism of positive inotropic action of cardiac glycosides. SR—Sarcoplasmic reticulum; TnC—Troponin C; NCX—$Na^+$-$Ca^{2+}$ exchanger; RyR2—Ryanodine receptor calcium channel 2; PL—Phospholamban; SERCA2—Sarcoplasmic-endoplasmic reticulum calcium ATPase 2.

$K^+$ ions. The slight (1–1.5 mM) increase in cytosolic $Na^+$ over normal (8–10 mM) due to partial inhibition of $Na^+K^+$ATPase by digitalis 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 $Ca^{2+}$ → 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 after-depolarizations and after-contractions. Since both therapeutic and toxic effects of digitalis are due to myocardial $Ca^{2+}$ loading, these are inseparable and therapeutic index is low.

**2. Blood vessels** Digitalis has mild 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.

Digitalis 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 digitalis.

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

**3. Kidney** Diuresis occurs promptly 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** Digitalis has little apparent CNS effect in therapeutic dose. Higher doses cause CTZ activation → nausea and vomiting. Still higher doses produce hyperapnoea, central sympathetic stimulation, mental confusion, disorientation and visual disturbances.

## PHARMACOKINETICS

The pharmacokinetic features of digoxin are listed in Table 37.1.

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

Digoxin is primarily excreted unchanged by the kidney: mainly by glomerular filtration; rate

**TABLE 37.1 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.

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 is the only cardiac glycoside available widely and used clinically now.

*Digoxin: DIGOXIN 0.25 mg tab., 0.05 mg/ml pediatric elixir, 0.5 mg/2 ml inj. LANOXIN 0.25 mg tab, CARDIOXIN, DIXIN 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). Higher cardiac mortality has been reported among patients with steady-state plasma digoxin levels > 1.1 ng/ml but still within the therapeutic range during maintenance therapy. About 25% patients 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. 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 digitalis: pulsus bigeminus, 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; in the rest serious cardiac arrhythmias are the first manifestation.

**Treatment** Further doses of digoxins 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 digitalis 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* Atropine 0.6–1.2 mg i.m. may help; otherwise cardiac pacing is recommended.

Cardioversion by DC shock is contraindicated because severe conduction defects may be unmasked in the digitalis intoxicated heart. Attempts to enhance the elimination of digoxin by diuretics or haemodialysis are not very effective.

**Digoxin antibody** Developed for measuring plasma concentration of digoxin by radioimmunoassay, it has been found effective in treating toxicity as well. Digoxin specific antibody crossreacts with digitoxin also. The Fab fragment has been marketed in Europe as DIGIBIND (38 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. The digoxin-Fab complex is rapidly excreted by kidney.

## PRECAUTIONS AND CONTRAINDICATIONS

(a) *Hypokalemia*: enhances digitalis toxicity.

(b) *Elderly, renal or severe hepatic disease*: patients are more susceptible to digoxin toxicity.

(c) *Myocardial ischaemia*: severe arrhythmias are more likely.

(d) *Thyrotoxicosis*: patients are more prone to develop digitalis arrhythmias.

(e) *Myxoedema*: these patients eliminate digoxin more slowly; cumulative toxicity can occur.

(f) *Ventricular tachycardia*: digitalis is contraindicated because it may precipitate ventricular fibrillation.

(g) *Partial A-V block*: may be converted to complete A-V block by digoxin.

(h) *Acute myocarditis*: Diphtheria, acute rheumatic carditis, toxic carditis—inotropic response to digitalis is poor, more prone to arrhythmias.

(i) *Wolff-Parkinson-White syndrome*: Digitalis 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. Digitalis 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.
7. *Succinylcholine*: can induce arrhythmias in digitalized patients.

## USES

The two main indications of digitalis are CHF and control of ventricular rate in atrial fibrillation/flutter.

### 1. Congestive heart failure

CHF occurs when cardiac output is insufficient to meet the demands of tissue perfusion or does so by elevating filling pressure. Heart failure may primarily be due to systolic dysfunction or diastolic dysfunction.

*Systolic dysfunction* The ventricles are dilated and unable to develop sufficient wall tension to eject adequate quantity of blood. This occurs in ischaemic heart disease, valvular incompetence, dilated cardiomyopathy, myocarditis, tachyarrhythmias (mostly atrial fibrillation).

*Diastolic dysfunction* The ventricular wall is thickened and unable to relax properly during diastole; ventricular filling is impaired because of which output is low. It occurs in sustained hypertension, aortic stenosis, congenital heart disease, A-V shunts, hypertrophic cardiomyopathy.

However, most patients, especially long-standing CHF, have both systolic and diastolic dysfunction. Cardiac glycosides afford only symptomatic relief, primarily in systolic dysfunction. Best results are obtained when myocardium is not primarily deranged, e.g. in hypertension, valvular defects or CHF due to rapid heart rate in atrial fibrillation. Poor response and more toxicity is likely when the myocardium has been damaged by ischaemia, inflammation or degenerative changes and in thiamine deficiency, as well as in high output failure (in anaemia).

Cardiac glycosides are incapable of reversing the pathological changes of CHF or even arresting their progress. Associated with hypertrophy, cardiac muscle undergoes remodeling which may involve changes in various functional proteins such as myosin, creatine kinase, $Na^+K^+$ATPase, matrix components, etc. as a result of altered myocyte gene function. Cardiac glycosides do not affect remodeling.

Because of lower inotropic state, the failing heart is able to pump much less blood at the normal filling pressure (Fig. 37.4), more blood remains in the ventricles at the end of systole. The venous return is added to it and Frank-Starling compensation is utilized to increase filling pressure: the heart may be able to achieve the required stroke volume, but at a filling pressure which produces congestive symptoms (venous engorgement, edema, enlargement of liver, pulmonary congestion → dyspnoea, renal congestion → oliguria).

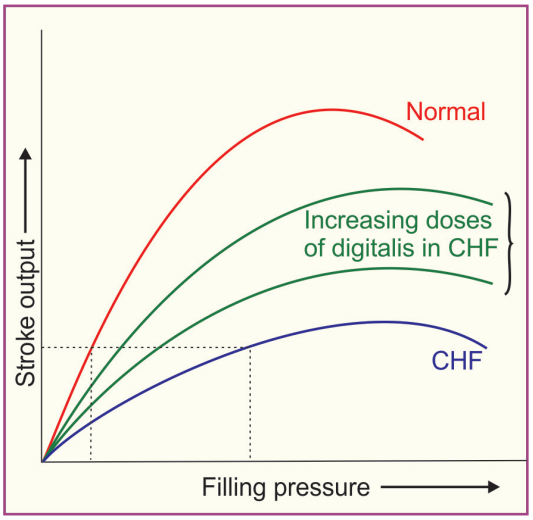



**Fig. 37.4:** Relationship between filling pressure and cardiac output in normal and failing heart. Digitalis tends to shift the curve towards normal

Digitalis 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. 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.

A dilated ventricle automatically becomes inefficient according to 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. By reducing end diastolic volume (due to better emptying), digitalis restores efficiency of translation of cardiac work into cardiac output. That is why $O_2$ consumption does not increase proportionately.

*Dosage* In mild to moderate heart failure, 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. Intravenous digoxin is seldom required now for CHF. When imperative 0.25 mg may be injected slowly with continuous ECG, BP and CVP monitoring.

There is some recent evidence that maintenance therapy with sub-maximal inotropic doses (producing steady-stage digoxin levels < 1 ng/ml) may benefit by counteracting neurohumoral activation of CHF, without risk of toxicity.

**Current status of digitalis** Before the introduction of high ceiling diuretics, ACE inhibitors and β blockers, digitalis was considered an indispensible part of anti-CHF treatment. It is not so now. Many mild-to-moderate cases are managed without digitalis. Now ACE inhibitors/ARBs, β adrenergic blockers and diuretics are the standared treatment. However, digitalis is still the most effective drug capable of relieving symptoms of CHF and restoring cardiac compensation, especially in patients with dilated heart and low ejection fraction. All patients who remain symptomatic even while receiving ACE inhibitor/ARB, β blocker and diuretic should be treated with digitalis. Uncertainty exists in the area of maintenance therapy, i.e. after decompensation has been corrected in patients with sinus rhythm and not having atrial fibrillation (AF).

Two large trials—Randomized assessment of digoxin on inhibition of angiotensin converting enzyme (RADIANCE, 1993) and Prospective randomized study of ventricular failure and efficacy of digoxin (PROVED, 1993) on CHF patients in sinus rhythm showed that discontinuation of digitalis resulted in reduced exercise capacity and haemodynamic deterioration in a significant number of cases despite continued use of diuretic with or without ACE inhibitor. However, digitalis could be withdrawn without haemodynamic deterioration in 60% (not receiving ACE inhibitor) and in 72% (receiving ACE inhibitor) patients.

Thus, if stable clinical state has been maintained for 2–3 months, withdrawal of digitalis may be attempted. Early reinstitution of digitalis is recommended if cardiac status declines.

Continued digitalis 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 digitalis decreases overall mortality in CHF patients, though episodes of decompensation and heart failure deaths are reduced. The two major limitations in the use of cardiac glycosides are low margin of safety and lack of effect on neuro-humoral contributors to pathogenesis of CHF.

### 2. Cardiac arrhythmias

*Atrial fibrillation (AF)* Digitalis is used for controlling ventricular rate in AF, whether associated with CHF or not. However, it is incapable of curing AF, i.e. does not revert it to sinus rhythm, even perpetuates it.

Digitalis reduces ventricular rate in AF by decreasing the number of impulses that are able to pass down the A-V node and bundle of His.
(a) 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 increased.
(b) Because of the relatively long ERP of A-V node, many of the atrial impulses (~500/min) falling in the relative refractory period get extinguished by decremental conduction. These concealed impulses, nevertheless, leave the upper margin of A-V node refractory for a further period. Digoxin increases the number of concealed impulses and indirectly prolongs the interval between any two impulses that are successfully conducted to the ventricle.

When digoxin is given in AF, average ventricular rate decreases in a dose-dependent manner and pulse deficit is abolished. It is particularly effective in controlling ventricular rate at rest, but has less effect during exercise. Thus, it is preferred in sedentary patients. For physically active patients, β blockers/verapamil/diltiazem provide better rate control. If a single drug fails to decrease the heart rate to the desired level, one out of propranolol/verapamil/diltiazem may be combined with digoxin.

*Atrial flutter (AFl)* The atrial rate is 200–350/min (less than that in AF), but atrial contractions are regular and synchronous. A variable degree of A-V block, depending on the mean ERP of A-V node, is naturally established. Digitalis enhances this A-V block, reduces ventricular rate and prevents sudden shift of A-V block to a lower degree. Ventricular rate control in AFl is generally an interim measure before it is abolished by cardioversion/radiofrequency ablation/anti-arrhythmic drugs, or when definitive therapy is not possible. For rate control, a β blocker/verapamil/diltiazem are mostly used. Digoxin is employed in patients with CHF, or as an addon drug in case of inadequate rate control with β blocker, etc. Digitalis may convert AFl to AF by reducing atrial ERP and making it inhomogeneous. This is a welcome response because control of ventricular rate is easier in AF (graded response occurs) than in AFl (A-V block shifts in steps).

*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 SA or A-V node. A parenteral glycoside may be injected i.v.—increases vagal tone and depresses the path through the SA/A-V node, or the ectopic focus, and terminates the arrhythmia (success in 1/3 cases). Adenosine and verapamil are more effective, less toxic and act faster. Digitalis is now reserved for preventing recurrences in selected cases.

## TREATMENT OF CHF

There are two distinct goals of drug therapy in CHF:

(a) Relief of congestive/low output symptoms and restoration of cardiac performance. This can be achieved by:
*Inotropic drugs*—Digoxin, dobutamine/dopamine, amrinone/milrinone

*Diuretics*—Furosemide, thiazides
*RAS inhibitors*—ACE inhibitors/ARBs
*Vasodilators*—hydralazine, nitrate, nitroprusside
*β blocker*—Metoprolol, bisoprolol, carvedilol, Nebivolol

(b) Arrest/reversal of disease progression and prolongation of survival, possible with:
*ACE inhibitors/ ARBs, β blockers*
*Aldosterone antagonist*—Spironolactone, eplerenone

Important nonpharmacological measures are rest and salt restriction.

Rest reduces peripheral needs, but should be advised only till compensation is restored, beyond that it may lower myocardial reserve and be counterproductive. Salt restriction limits edema formation and is advised in all grades of CHF. The underlying cause of CHF, if treatable like hypertension, myocardial ischaemia, valvular defects, A-V shunts, arrhythmias, thyrotoxicosis, anaemia, should be corrected.

Till 1980 drugs available for CHF (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 CHF. Drugs developed thereafter (ACE inhibitors/ARBs, β adrenergic blockers, aldosterone antagonists, etc.) impact the neurohumoral perpetrators of CHF, myocardial apoptosis, fibrosis, 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. 37.5. The current pattern of use of drugs in various stages of heart failure is summarized in Fig. 37.6.

## Diuretics

Almost all cases of symptomatic CHF 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. In advanced CHF after chronic use, resistance may develop to even high ceiling diuretics. Addition of a thiazide/ metolazone/spironolactone to furosemide may overcome the resistance. Thiazide alone has very limited role in CHF. Diuretics:

(a) Decrease preload and improve ventricular efficiency by reducing circulating volume.

(b) 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

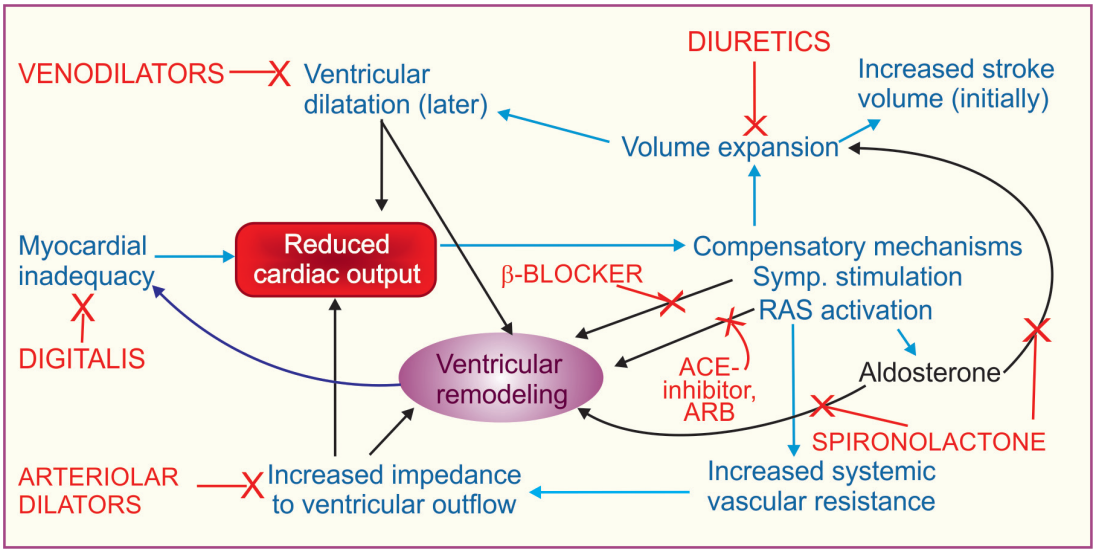



**Fig. 37.5:** The vicious cycle in CHF: compensatory mechanisms evoked in response to reduced cardiac output themselves perpetuate failure and contribute to remodeling responsible for disease progression. The parameter which is improved by different therapeutic measures is indicated

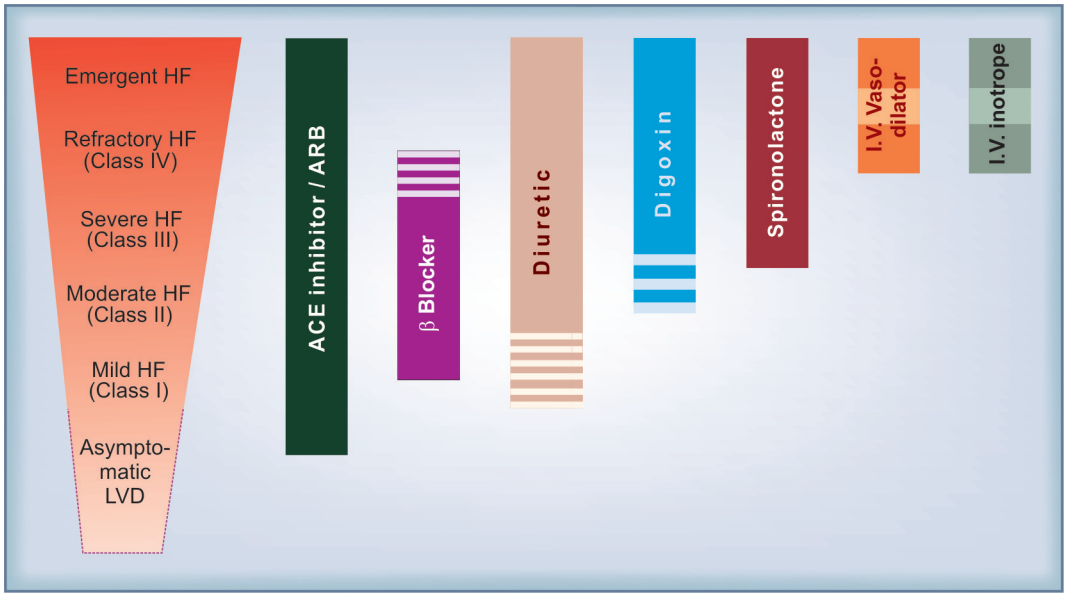



**Fig. 37.6:** Current pattern of clinical use of various classes of drugs in different stages of heart failure (HF)
LVD—Left ventricular dysfunction; ACE—Angiotensin converting enzyme; ARB—Angiotensin receptor blocker



obviated the need for i.v. digitalization. Further, most mild cases can be maintained symptom free on diuretics without recourse to chronic digitalis therapy. 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. They 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. On the other hand, 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 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 when diuretic is stopped. 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 CHF, the ACE inhibitors and ARBs are the sheet anchor of drug therapy in CHF (*see* p. 504 and 507). They afford symptomatic as well as disease modifying benefits in CHF 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 as well as in subjects with asymptomatic systolic dysfunction. They are thus recommended for all grades of CHF, unless contraindicated, or if renal function deteriorates by their use (mainly in those with decresed renal blood flow/renal artery stenosis).

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

## Vasodilators

Vasodilators were first used i.v. to treat acute heart failure that occurs in advanced cases or following MI, and serve to tide over crisis. Their use by oral route has been extended to long-term therapy of chronic CHF, but vasodilators other than ACE inhibitors/ARBs have only limited utility. Vasodilators with differing profiles of arteriolar and venodilator action are available (*see* box).

(i) *Preload reduction: Nitrates* cause pooling of blood in systemic capacitance vessels to reduce ventricular end-diastolic pressure and volume. With reduction in size of ventricles, effectiveness of myocardial fibre shortening in causing ejection of blood during systole improves (Laplace relationship). Controlled 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, lowering of preload (by vasodilators + strong diuretics) beyond a limit 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 even weaker ventricular contraction is able to pump more blood; systolic wall stress is reduced. It is effective in forward failure when cardiac index (CI = min output/body surface area) is low (< 2.5 L/min/m$^2$) without a marked increase in CVP (< 18 mm Hg). Marked tachycardia, worsening of myocardial ischaemia and fluid retention limit long-term use of hydralazine monotherapy.

Minoxidil is a more potent arteriolar dilator, but has found little use in heart failure; so has nicorandil a more specific pot. channel opener. Trials of the three prototype calcium channel blockers verapamil, diltiazem and nifedipine in systolic dysfunction have been disappointing, even negative with occasional worsening of symptoms and increase in mortality. This may be due to reflex sympathetic activation (nifedipine) or negative inotropic property (verapamil, diltiazem). Verapamil, however, is useful in diastolic dysfunction due to hypertrophic cardiomyopathy. Trials with long-acting and more vasoselective dihydropyridines (felodipine, amlodipine) have also not been encouraging.

| Venodilators (primarily ↓ preload) | Route (for CHF) |
|---|---|
| Glyceryl trinitrate | s.l./i.v. |
| Isosorbide dinitrate | s.l./oral |
| **Arteriolar dilators (primarily ↓ afterload)** | |
| Pot. channel openers | |
| Hydralazine | oral/i.v. |
| Minoxidil | i.v. |
| Nicorandil | – |
| Cal. channel blockers | – |
| **Mixed dilators (↓ pre- and afterload)** | |
| ACE inhibitors | oral |
| ARBs ($AT_1$ receptor antagonists) | oral |
| $\alpha_1$ blocker (Prazosin) | — |
| PDE 3 inhibitors | |
| Amrinone, Milrinone | i.v. |
| Nitroprusside sod. | i.v. |

(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 acts by both the above mechanisms, i.e. 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. Titrated i.v. infusion of nitroprusside is employed in conjunction with a loop diuretic + i.v. inotropic drug to tideover crisis in severely decompensated patients. For symptomatic treatment of acute heart failure, choice of i.v. vasodilator (glyceryl trinitrate or hydralazine or nitroprusside) depends on the primary haemodynamic abnormality in individual 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 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. Hydralazine alone or a nitrate alone have not proven useful in the treatment of chronic heart failure. However, when combined they supplement each other and nitrate tolerance is attenuated by hydralazine. Severe CHF patients already receiving ACE inhibitors + digoxin + diuretic have obtained extra benefit from addition of hydralazine with or without a nitrate.

For reasons not known, the $\alpha_1$ blocker *prazosin* has not been able to afford prognostic benefit.

## β-Adrenergic blockers

Extensive studies over the past 30 years have established the utility of $\beta_1$ blockers (mainly metoprolol, bisoprolol, nebivolol) and the nonselective β + selective $\alpha_1$ blocker carvedilol in mild to moderate CHF treated with ACE inhibitor ± diuretic, digitalis.

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 immediate hemodynamic action of β blockers is to depress cardiac contractility and ejection fraction, these parameters gradually improve over weeks. After a couple of months ejection fraction 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 CHF, as well as due to prevention of sinister arrhythmias. Incidence of sudden cardiac death as well as that due to worsening CHF is decreased. β blockers lower plasma markers of activation of sympathetic, renin-angiotensin systems and endothelin-1.

However, β blocker therapy in CHF 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.
- 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 recommenced at lower doses followed by uptitration after compensation is retored. Conventional therapy should be continued along with them.
- Starting dose should be very low—then titrated upward as tolerated to the target level (carvedilol 50 mg/day, bisoprolol 10 mg/day, metoprolol 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.
- A long-acting preparation (e.g. sustained release metoprolol) or 2–3 times daily dosing to produce round-the-clock β blockade should be selected.
- 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 CHF, 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.
(d) Enhancement of cardiotoxic and remodeling effect of sympathetic overactivity.

The aldosterone antagonist spironolactone is a weak diuretic (*see* Ch. 41), but can benefit CHF by antagonizing the above effects of aldosterone.

In addition to several small studies, a large Randomised aldactone evaluation study (RALES, 1999) conducted on 1663 NYHA class III and IV patients having left ventricular ejection fraction ≤ 35% has confirmed the additional survival benefit (30%) of spironolactone when added to conventional therapy with ACE inhibitors + other drugs. A subsequent trial (EPHESUS, 2003) using another aldosterone antagonist *eplerenone* in post acute MI heart failure has further substantiated the mortality and anti-remodeling benefit over and above that of ACE inhibitors ± β blockers.

Though ACE inhibitors themselves lower aldosterone levels, this effect is incomplete and short lasting. Current evidence suggests the following regarding spironolactone/eplerenone therapy in CHF:

- It is indicated as add-on therapy to ACE inhibitors + other drugs in moderate-to-severe CHF.
- It can retard disease progression, reduce episodes of decompensation and death due to heart failure as well as sudden cardiac deaths, over and above the protection afforded by ACE inhibitors/ARBs ± β blockers.
- Only low doses (12.5–25 mg/day) of spironolactone should be used to avoid hyperkalaemia; particularly because of concurrent ACE inhibitor/ARB therapy.
- It may help restoration of diuretic response to furosemide when refractoriness has developed.

The onset of benefit of aldosterone/antagonist in CHF is slow. It is contraindicated in renal insufficiency because of risk of hyperkalemia—requires serum $K^+$ monitoring. Gynaecomastia occurs in a number of male patients treated with spironolactone. This can be avoided by using eplerenone. Aldosterone antagonists are a significant additional therapeutic measure in moderate-severe CHF with prognostic benefits.

## Sympathomimetic inotropic drugs (*see* Ch. 9)

Drugs with β adrenergic and dopaminergic D1 agonistic actions have positive inotropic and (at low doses) vasodilator properties which may be utilized to combat emergency pump failure.

*Dobutamine* (2–8 µg/kg/min) a relatively selective $\beta_1$ agonist with prominent inotropic action is the preferred drug for i.v. infusion in acute heart failure accompanying myocardial infarction (MI), cardiac surgery as well as to tide over crisis in advanced decompensated CHF.

*Dopamine* (3–10 µg/kg/min by i.v. infusion) has been used in cardiogenic shock due to MI and other causes. While dobutamine does not raise (may lower) systemic vascular resistance and is preferred in heart failure, dopamine tends to increase afterload, especially at higher rates of infusion (>5 µg/kg/min) and has limited utility in patients who are not in shock. Low rates of dopamine infusion (~2 µg/kg/min) cause selective renal vasodilatation (D1 agonistic action) which improves renal perfusion and g.f.r. This can restore diuretic response to i.v. furosemide in refractory CHF.

These drugs afford additional haemodynamic support over and above vasodilators, digitalis and diuretics, but benefits are short-lasting. Due to development of tolerance and cardiotoxic potential when used regularly, these drugs have no role in the long-term management of CHF.

## Phosphodiesterase 3 inhibitors

Theophylline is a phosphodiesterase inhibitor that is non-selective for different isoforms of this enzyme which degrades intracellular cAMP and cGMP. Intravenous aminophylline had been used in past for acute left ventricular failure with limited benefits, but unacceptable toxicity.

**Inamrinone (amrinone)** It is chemically and pharmacologically distinct from digitalis and catecholamines. 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 $Ca^{2+}$. It does not inhibit $Na^+K^+$ATPase, and its action is independent of tissue catecholamines as well as adrenergic receptors.

The two most important actions of amrinone are *positive inotropy* and direct *vasodilatation*: 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. amrinone action starts in 5 min and lasts 2–3 hours; elimination t½ is 2–4 hours. It increases cardiac index, left ventricular ejection fraction and decreases peripheral vascular resistance, CVP, left ventricular end diastolic volume and pressure accompanied by mild tachycardia and slight fall in BP.

*Adverse effects* Thrombocytopenia is the most prominent and dose related side effect, but is mostly transient and asymptomatic.
Nausea, diarrhoea, abdominal pain, liver damage, fever and arrhythmias are the other adverse effects.

*Use* Though amrinone is active orally, its oral use 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 digitalis, diuretics and vasodilators.
*Dose:* 0.5 mg/kg bolus injection followed by 5–10 µg/kg/min i.v. infusion (max. 10 mg/kg in 24 hours). 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 40–80 min.

Thrombocytopenia is not significant. In long term prospective trials, increased mortality has been reported with oral milrinone also. Milrinone is preferred over amrinone and 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.

**Nesiritide** This recombinant brain natriuretic peptide (BNP) has been approved for i.v. use 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; reduces ventricular filling pressure. Additional haemodynamic and symptomatic improvement can be obtained for short-periods, but no long-term benefits are evident in CHF.

**Tolvaptan** This is an orally active nonpeptide vasopressin $V_2$ receptor antagonist introduced recently 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 benefits have been noted.



## ☞ PROBLEM DIRECTED STUDY

**37.1** 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 of 28%. A diagnosis of moderate grade congestive heart failure due to dilated cardiomyopathy 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)

# Chapter 38 Antiarrhythmic Drugs

These are drugs used to prevent or treat irregularities of cardiac rhythm.

Nearly 3 out of 4 patients of acute myocardial infarction (MI) and about half of those given a general anaesthetic exhibit at least some irregularity of cardiac rhythm. Arrhythmias are the most important cause of sudden cardiac death. However, only few arrhythmias need to be treated with antiarrhythmic drugs.

Abnormal automaticity or impaired conduction or both underlie cardiac arrhythmias. The generation and propagation of cardiac impulse and properties of excitability and refractoriness are described on p. 492 to 494. Ischaemia, electrolyte and pH imbalance, mechanical injury, stretching (due to heart failure), neurogenic and drug influences, including antiarrhythmic drugs themselves, can cause arrhythmias by altering electrophysiological properties of cardiac fibres.

Important mechanisms of cardiac arrhythmias are:

**A. Enhanced/ectopic pacemaker activity** The slope of phase-4 depolarization may be increased pathologically in the automatic fibres or such activity may appear in ordinary fibres. Ectopic impulse may also result from current of injury. Myocardial cells damaged by ischaemia become partially depolarized: a current may flow between these and normally polarized fibres (injury current) and initiate an impulse.

**B. After-depolarizations** These are secondary depolarizations accompanying a normal or premature action potential (AP), Fig. 38.1.

*Early after-depolarization (EAD)* Repolarization during phase-3 is interrupted and membrane potential oscillates. If the amplitude of oscillations is sufficiently large, neighbouring tissue is activated and a series of impulses are propagated. EADs are frequently associated with long Q-T interval due to slow repolarization and markedly prolonged APs. They result from depression of delayed rectifier $K^+$ current.

*Delayed after-depolarization (DAD)* After attaining resting membrane potential (RMP) a secondary deflection occurs which may reach threshold potential and initiate a single premature AP. This generally results from $Ca^{2+}$ overload (digitalis toxicity, ischaemia-reperfusion).

Because an AP is needed to trigger after-depolarizations, arrhythmias based on these have been called *triggered arrhythmias.*

**C. Reentry** Due primarily to abnormality of conduction, an impulse may recirculate in the heart and cause repetitive activation without the need for any new impulse to be generated. These are called *reentrant arrhythmias*.

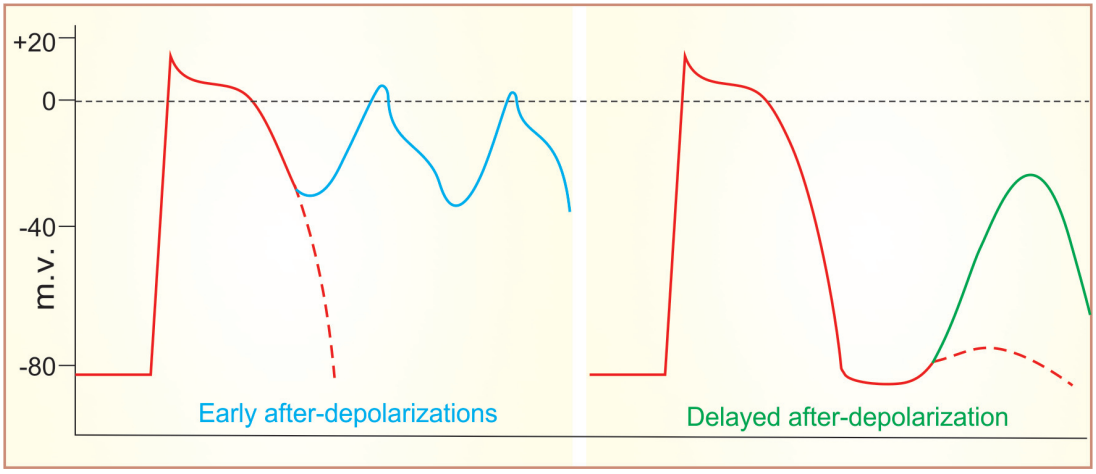



**Fig. 38.1:** Action potential in a nonautomatic ventricular fibre (in red) followed by early or delayed after-depolarizations.

(i) *Circus movement reentry* It occurs in an anatomically defined circuit. A premature impulse, temporarily blocked in one direction by refractory tissue, makes a one-way transit around an obstacle (natural orifices in the heart, A-V nodal region) or through an abnormal tract, finds the original spot in an advanced state of recovery and reexcites it, setting up recurrent activation of adjacent myocardium (Fig. 38.2). This type of reentry is often responsible for PSVT, atrial flutter and atrioventricular reciprocal rhythm in WPW.

Reentry occurring in an anatomically fixed circuit can be permanently cured by radiofrequency catheter ablation of the defined pathway.

(ii) *Functional reentry* In this type of reentry there is no fixed 'obstacle' or 'pathway'. Rather, a functional obstacle (core of the circuit) and unidirectional conduction pathway is created by a premature impulse which travels through electrophysiologically inhomogeneous myocardium. On encountering refractory tissue in one direction, the wavefront travels through partially recovered fibres—gets markedly slowed and can set up small reentry circuits which may constantly shift location. Functional reentry may be responsible for ventricular extrasystoles, polymorphic ventricular tachycardia, atrial/ventricular fibrillation.

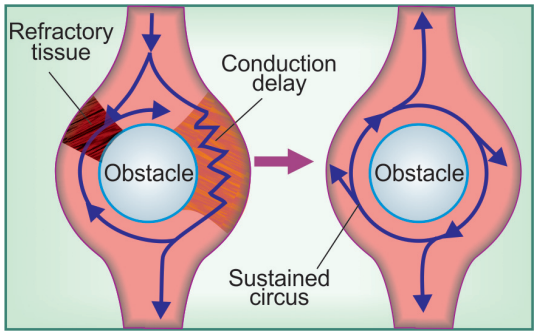



**Fig. 38.2:** Diagrammatic depiction of circus movement reentry in atrium

For reentry to occur, the path length of the circuit should be greater than the wave length (ERP × conduction velocity) of the impulse. Slow conduction in the reentrant circuit may be caused by:

(a) Partial depolarization of the membrane—decreased slope of phase 0 depolarization, i.e. depressed fast channel response.

(b) Cells changing over from fast channel to slow channel depolarization which conducts extremely slowly. When a fibre is depolarized to a RMP of about –60 mv, the $Na^+$ (fast) channels are inactivated, but the fibre can still develop $Ca^{2+}$ (slow) channel response.

Reentry can be abolished both by marked slowing of conduction (converting unidirectional block to bidirectional block) as well as by acceleration of impulse (retrograde impulse reaches so early as to meet refractory tissue).

(iii) *Fractionation of impulse* When atrial ERP is brief and inhomogeneous (under vagal overactivity), an impulse generated early in diastole gets conducted irregularly over the atrium, i.e. it moves rapidly through fibres with short ERP (which have completely recovered) slowly through fibres with longer ERP (partially recovered) and not at all through those still refractory. Thus, asynchronous activation of atrial fibres occurs → atrial fibrillation (AF). This arrhythmia must be initiated by a premature depolarization, but is self sustaining, because passage of an irregular impulse leaves a more irregular refractory trace and perpetuates the inhomogeneity of ERPs.

The important cardiac arrhythmias are:

1. *Extrasystoles (ES)* are premature ectopic beats due to abnormal automaticity or after-depolarization arising from an ectopic focus in the atrium (AES), A-V node (nodal ES) or ventricle (VES). The QRS complex in VES is broader and abnormal in shape.
2. *Paroxysmal supraventricular tachycardia (PSVT)* is sudden onset episodes of atrial tachycardia (rate 150–200/min) with 1:1 atrioventricular conduction: mostly due to circus movement type of reentry occurring within or around the A-V node or using an accessory pathway between atria and ventricle (Wolff-Parkinson-White syndrome or WPW).
3. *Atrial flutter (AFl)* Atria beat at a rate of 200–350/min and there is a physiological 2:1 to 4:1 or higher A-V block (because A-V node cannot transmit impulses faster than 200/min). This is mostly due to a stable re-entrant circuit in the right atrium, but some cases may be due to rapid discharge of an atrial focus.
4. *Atrial fibrillation (AF)* Atrial fibres are activated asynchronously at a rate of 350–550/min (due to electrophysiological inhomogeneity of atrial fibres), associated with grossly irregular and often fast (100–160/min) ventricular response. Atria remain dilated and quiver like a bag of worms.
5. *Ventricular tachycardia (VT)* is a run of 4 or more consecutive ventricular extrasystoles. It may be a sustained or nonsustained arrhythmia, and is due either to discharges from an ectopic focus, after-depolarizations or single site (monomorphic) or multiple site (polymorphic) reentry circuits.

6. *Torsades de pointes* (French: twisting of points) is a life-threatening form of polymorphic ventricular tachycardia with rapid asynchronous complexes and an undulating baseline on ECG. It is generally associated with long Q-T interval.
7. *Ventricular fibrillation (VF)* is grossly irregular, rapid and fractionated activation of ventricles resulting in incoordinated contraction of its fibres with loss of pumping function. It is fatal unless reverted within 2–5 min; is the most common cause of sudden cardiac death.
8. *Atrio-ventricular (A-V) block* is due to depression of impulse conduction through the A-V node and bundle of His, mostly due to vagal influence or ischaemia.
   *First degree A-V block:* Slowed conduction resulting in prolonged P-R interval.
   *Second degree A-V block:* Some supraventricular complexes are not conducted: drop beats.
   *Third degree A-V block:* No supraventricular complexes are conducted; ventricle generates its own impulse; complete heart block.

**Proarrhythmic potential of antiarrhythmic drugs**

Most antiarrhythmics can themselves be the cause of serious arrhythmias, especially during long-term prophylactic use. Two multicentric trials 'Cardiac Arrhythmia Suppression Trial I and II' (CAST I, II, 1991, 1992) showed that post-MI patients randomized to receive on a long-term basis encainide, flecainide, moricizine had higher incidence of sudden death, though initially the same drugs had suppressed VES in these patients. It is possible that during transient episodes of ischaemia, the intraventricular conduction slowing action of these drugs gets markedly accentuated resulting in VT and VF. Similar increased mortality has been reported by the "Mortality in the survival with D-sotalol (SWORD) trial. It is therefore not prudent to try and suppress all extrasystoles/arrhythmias, especially those not causing symptoms, with chronic prophylactic antiarrhythmic therapy. Only the β blockers and amiodarone have been found to decrease cardiac mortality in the long term.

## CLASSIFICATION

Antiarrhythmic drugs act by blocking myocardial $Na^+$, $K^+$ or $Ca^{2+}$ channels. Some have additional or even primary autonomic effects. Classification of antiarrhythmic drugs has been difficult, because many drugs have more than one action. Vaughan Williams and Singh (1969) proposed a 4 class system which takes into account the primary electrophysiological action of a drug that may serve to indicate the type of clinical effects and therapeutic utility. However, different drugs within a class have their own specific set of properties.

A simplified clinical classification of antiarrhythmic drugs is given at the end of the chapter.

**Drugs that prolong Q-T interval**
(have potential to precipitate Torsades de pointes)

| | | |
|---|---|---|
| 1. | *Antiarrhythmics* | : Quinidine, procainamide, disopyramide, propafenone, amiodarone |
| 2. | *Antimalarials* | : Quinine, mefloquine, artemisinin, halofantrine |
| 3. | *Antibacterials* | : Sparfloxacin, moxifloxacin |
| 4. | *Antihistaminics* | : Terfenadine, astemizole, ebastine |
| 5. | *Antidepressants* | : Amitryptyline and other tricyclics |
| 6. | *Antipsychotics* | : Thioridazine, pimozide, aripiprazole, ziprasidone |
| 7. | *Prokinetic* | : Cisapride |

## CLASS I

The primary action of drugs in this class is to limit the conductance of $Na^+$ (and $K^+$) across cell membrane—a local anaesthetic action. They also reduce rate of phase-4 depolarization in automatic cells.

### SUBCLASS IA

The subclass IA containing the oldest antiarrhythmic drugs *quinidine* and *procainamide* are open state $Na^+$ channel blockers which also moderately delay channel recovery (channel recovery time $\tau_{recovery}$ 1–10s), suppress A-V conduction and prolong refractoriness. The $Na^+$ channel blockade is greater at higher frequency (premature depolarization is affected more). These actions serve to extinguish ectopic pacemakers that are often responsible for triggered arrhythmias and abolish reentry by converting unidirectional block into bidirectional block.

**Antiarrhythmic drugs**

| Class | Actions | Drugs |
|---|---|---|
| I. | *Membrane stabilizing agents ($Na^+$ channel blockers)* | |
| | A. *Moderately decrease dv/dt of 0 phase* | Quinidine, Procainamide, Disopyramide |
| | B. *Little decrease in dv/dt of 0 phase* | Lidocaine, Mexiletine |
| | C. *Marked decrease in dv/dt of 0 phase* | Propafenone, Flecainide |
| II. | *Antiadrenergic agents* (β *blockers*) | Propranolol, Esmolol, Sotalol (also class III) |
| III. | *Agents widening AP* (*prolong repolarization and ERP*) | Amiodarone, Dronedarone<br>Dofetilide, Ibutilide |
| IV. | *Calcium channel blockers* | Verapamil, Diltiazem |

Note: Class IA agents also have Class III property; Propranolol has Class I action as well; sotalol has both Class II and Class III actions.

*In addition*

1. *For PSVT* : Adenosine, Digoxin
2. *For A-V block* : Sympathomimetics—Isoprenaline, etc.
   Anticholinergics—Atropine.
3. Digitalis is used in AF, AFl and PSVT to control ventricular rate.

### Quinidine

It is the dextro isomer of the antimalarial alkaloid quinine found in cinchona bark. In addition to $Na^+$ channel blockade, quinidine has cardiac antivagal action which augments prolongation of atrial ERP and minimizes RP disparity of atrial fibres. A-V node ERP is increased by direct action of quinidine, but decreased by its antivagal action; overall effect is inconsistent. Quinidine depresses myocardial contractility; failure may be precipitated in damaged hearts.

*ECG:* Quinidine increases P-R and Q-T intervals and tends to broaden QRS complex. Changes in the shape of T wave may be seen reflecting effect on repolarization.

*Mechanism of action:* Quinidine blocks myocardial $Na^+$ channels in the open state—reduces automaticity and maximal rate of 0 phase depolarization in a frequency dependent manner. Prolongation of APD is due to $K^+$ channel block, while lengthening of ERP is caused by its moderate effect on recovery of $Na^+$ and $K^+$ channels. At high concentrations it also inhibits L type $Ca^{2+}$ channels. Quinidine decreases the availability of $Na^+$ channels as well as delays their reactivation.

The other actions of quinidine are fall in BP (due to weak α adrenergic blockade and direct cardiac depression), decreased skeletal muscle contractility, augmented uterine contractions, vomiting, diarrhoea and neurological effects like ringing in ears, vertigo, deafness, visual disturbances and mental changes (Cinchonism). Like its levo isomer, it has antimalarial action, and has been used as a parenteral alternative to quinine for falciparum malaria. The important drug interactions of quinidine are:

- Rise in blood levels and toxicity of digoxin due to displacement from tissue binding and inhibition of P-glycoprotein mediated renal and biliary clearance of digoxin.
- Marked fall in BP in patients receiving vasodilators.
- Risk of *torsades de pointes* is increased by hypokalaemia caused by diuretics.
- Synergistic cardiac depression with β-blockers, verapamil, $K^+$ salts.
- Quinidine inhibits CYP2D6: prolongs t½ of propafenone and inhibits conversion of codeine to morphine.

*Use:* Though quinidine is effective in many atrial and ventricular arrhythmias, it is seldom used now, because of risk of adverse effects, including that of *torsades de pointes*, sudden cardiac arrest or VF; idiosyncratic angioedema, vascular collapse, thrombocytopenia, etc. In a dose of 100–200 mg TDS quinidine may rarely be used to maintain sinus rhythm after termination of AF or AFI.

QUINIDINE SULPHATE 200 mg tab; QUININGA 300 mg tab, 600 mg/2 ml inj; NATCARDINE 100 mg tab.

### Procainamide

It is orally active amide derivative of the local anaesthetic procaine, with cardiac electrophysiological actions almost identical to those of quinidine, *viz.* slowing of 0 phase depolarization and impulse conduction, prolongation of APD, ERP, QRS complex and Q-T interval. Significant differences between the two are:

- It is less effective in suppressing ectopic automaticity.
- It causes less marked depression of contractility and A-V conduction.
- Antivagal action is absent.
- It is not an α blocker: causes less fall in BP; at high doses, fall in BP is due to ganglionic blockade.

*Pharmacokinetics* Oral bioavailability of procainamide is about 75%, peak plasma concentration occurs in 1 hour. It is metabolized in liver, primarily by acetylation to N-acetyl-procainamide (NAPA) which has no $Na^+$ channel blocking property but blocks $K^+$ channels and prolongs repolarization: APD is lengthened. There are fast and slow acetylators of procainamide (as there are for isoniazid). Plasma t½ is relatively short (3–4 hours).

*Dose:* For abolition of arrhythmia—0.5–1 g oral or i.m. followed by 0.25–0.5 g every 2 hours; or 500 mg i.v. loading dose (25 mg/min injection) followed by 2 mg/kg/hour. Maintenance dose—0.5 g every 4–6 hours.
PRONESTYL 250 mg tab., 1 g/10 ml inj.

*Adverse effects* Gastrointestinal tolerance of procainamide is better than quinidine, but nausea and vomiting do occur. CNS: weakness, mental confusion and hallucinations are noted at higher doses.
Flushing and hypotension are seen on rapid i.v. injection. Cardiac toxicity, ability to cause *torsades de pointes* are similar to quinidine.
Hypersensitivity reactions are rashes, fever, angioedema. Agranulocytosis and aplastic anaemia is rare.
Long-term high dose procainamide therapy can cause systemic lupus erythematosus (SLE), especially in slow acetylators.

*Use* Procainamide (i.v.) is occasionally used to terminate monomorphic VT and some supraventricular arrhythmias. Many WPW reciprocal VTs respond and it has been used to prevent recurrences of VF. However, procainamide is not suitable for prolonged oral therapy because of poor efficacy and high risk of lupus.

### Disopyramide

It is a quinidine like Class IA drug that has prominent cardiac depressant and anticholinergic actions, but no α adrenergic blocking property. Disopyramide usually has no effect on sinus rate because of opposing direct depressant and antivagal actions. Prolongation of P-R interval and QRS broadening are less marked.

*Pharmacokinetics* Bioavailability of oral disopyramide is about 80%. It is partly metabolized in liver by dealkylation, nearly half is excreted unchanged in urine; plasma t½ is 6–8 hrs. The t½ is increased in patients of MI and in renal insufficiency.

*Dose:* 100–150 mg 6–8 hourly oral.
NORPACE 100, 150 mg cap, REGUBEAT 100 mg tab.

*Adverse effects* Disopyramide causes less g.i. effects. Anticholinergic side effects are the most prominent: dry mouth, constipation, urinary retention (especially in elderly males) and blurred vision.
Depression of cardiac contractility is more prominent. Cardiac decompensation and hypotension may occur in patients with damaged hearts because it also increases peripheral resistance, so that cardiac output may be markedly decreased.
Contraindications are—sick sinus, cardiac failure and prostate hypertrophy.

*Use* The primary indication of disopyramide is as a second line drug for prevention of recurrences of ventricular arrhythmia. It may also be used for maintenance therapy after cardioversion of AF or AFl.

## SUBCLASS IB

These drugs block $Na^+$ channels more in the inactivated than in the open state, but do not delay channel recovery (channel recovery time < 1S). They do not depress A-V conduction or prolong (may even shorten) APD, ERP and Q-T.

### Lidocaine (Lignocaine)

It is the most commonly used local anaesthetic (*see* Ch. 26). In addition, it is a popular anti-arrhythmic in intensive care units.

The most prominent cardiac action of lidocaine is suppression of automaticity in ectopic foci. Enhanced phase-4 depolarization in partially depolarized or stretched PFs, and after-depolarizations are antagonized, but SA node automaticity is not depressed.

The rate of 0 phase depolarization and conduction velocity in A-V bundle or ventricles is not decreased. Lidocaine decreases APD in PF and ventricular muscle, but has practically no effect on APD and ERP of atrial fibres. Atrial reentry is not affected. However, it can suppress reentrant ventricular arrhythmias either by abolishing one-way block or by producing two way block.

Lidocaine is a blocker of inactivated $Na^+$ channels more than that of open state. As such,

it is relatively selective for partially depolarized cells and those with longer APD (whose $Na^+$ channels remain inactivated for longer period). While normal ventricular and conducting fibres are minimally affected, depolarized/damaged fibres are significantly depressed. Brevity of atrial AP and lack of lidocaine effect on channel recovery might explain its inefficacy in atrial arrhythmias.

Lidocaine has minimal effect on normal ECG; QT interval may decrease. It causes little depression of cardiac contractility or arterial BP. There are no significant autonomic actions: all cardiac effects are direct actions.

*Pharmacokinetics* Lidocaine is inactive orally due to high first pass metabolism in liver. Action of an i.v. bolus lasts only 10–20 min because of rapid redistribution. It is hydrolysed, deethylated and conjugated; metabolites are excreted in urine. Metabolism of lidocaine is hepatic blood flow dependent.

The t½ of early distribution phase is 8 min while that of later elimination phase is nearly 2 hours. Its t½ is prolonged in CHF, because of decrease in volume of distribution and hepatic blood flow.

*Dose and preparations* Lidocaine is given only by i.v. route: 50–100 mg bolus followed by 20–40 mg every 10–20 min or 1–3 mg/min infusion.
XYLOCARD, GESICARD 20 mg/ml inj. (5, 50 ml vials).
These preparations for cardiac use contain no preservative. The local anaesthetic preparations should not be used for this purpose.

Propranolol prolongs t½ of lidocaine by reducing hepatic blood flow. Cimetidine also increases plasma levels of lidocaine.

*Adverse effects* The main toxicity is dose related neurological effects:
Drowsiness, nausea, paresthesias, blurred vision, disorientation, nystagmus, twitchings and fits.
Lidocaine has practically no proarrhythmic potential and is the least cardiotoxic antiarrhythmic. Only excessive doses cause cardiac depression and hypotension.

*Use* Lidocaine is safe if given by slow i.v. injection; is used to suppress VT and prevent VF. It is ineffective in atrial arrhythmias. Because of rapidly developing and titratable action it is a good drug in the emergency setting, e.g. arrhythmias following acute MI or during cardiac surgery. In acute MI, i.v. infusion of lidocaine can prevent VF, but a metaanalysis has shown that it fails to improve survival; may even increase short term mortality. Therefore, lidocaine is no longer administered prophylactically to all MI patients, but may be used in selected cases, and to treat ventricular arrhythmias when they occur.

Efficacy of lidocaine in chronic ventricular arrhythmia is poor, but it suppresses VT due to digitalis toxicity, for which it is used because it does not worsen A-V block.

### Mexiletine

It is a local anaesthetic and an orally active antiarrhythmic; chemically and pharmacologically similar to lidocaine. Automaticity in PF is reduced both by decreasing phase-4 slope and by increasing threshold voltage. By reducing the rate of 0 phase depolarization in ischaemic PF it may convert one-way block to two-way block.

Mexiletine is almost completely absorbed orally, 90% metabolized in liver and excreted in urine; plasma t½ 9–12 hours.

Bradycardia, hypotension and accentuation of A-V block may attend i.v. injection of mexiletine.
Neurological side effects—tremor, nausea and vomiting are common; dizziness, confusion, blurred vision, ataxia can occur.

*Dose:* 100–250 mg i.v. over 10 min., 1 mg/min infusion.
Oral: 150–200 mg TDS with meals.
MEXITIL 50, 150 mg caps, 250 mg/10 ml. inj.

*Use* Parenteral mexiletine may be used in post-infarction sinister ventricular arrhythmias as alternative to lidocaine. Oral use to chronically suppress VES/VT is of questionable merit.

## SUBCLASS IC

These are the most potent $Na^+$ channel blockers with more prominent action on open state and the longest recovery times (> 10S). They markedly delay conduction, prolong P-R interval, broaden QRS complex, but have variable effect on APD. Drugs of this subclass have high

proarrhythmic potential when administered chronically; sudden deaths have occurred.

**Propafenone** By blocking $Na^+$ channels propafenone considerably depresses impulse transmission and has profound effect on His-Purkinje as well as accessory pathway conduction. Anterograde as well as retrograde conduction in the bypass tract of WPW syndrome is retarded. Propafenone prolongs APD and has β adrenergic blocking property—can precipitate CHF and bronchospasm. Sino-atrial block has occurred occasionally.

Propafenone is absorbed orally and undergoes variable first pass metabolism; there being *extensive* or *poor* metabolizers because the major metabolic isoenzyme CYP2D6 is deficient in poor metabolizers. CYP2D6 inhibitors like fluoxetine increase its bioavailability and plasma concentration. Bioavailability and t½ differs considerably among individuals. Some metabolites are active. Side effects are nausea, vomiting, bitter taste, constipation and blurred vision. As mentioned above, it can worsen CHF, asthma and increase the risk of sudden death.

Propafenone is used for prophylaxis and treatment of ventricular arrhythmias, reentrant tachycardias involving AV node/accessory pathway and to maintain sinus rhythm in AF. However, it can occasionally increase ventricular rate in AFl by slowing atrial rate and allowing 1:1 A-V transmission. Some reentrant VTs may also be worsened.

*Dose:* 150 mg BD–300 mg TDS;
RHYTHMONORM 150 mg tab.

**Flecainide** It is the prototype class IC antiarrhythmic which markedly delays $Na^+$ channel recovery. In contrast to propafenone, flecainide has no consistent effect on APD and no β adrenergic blocking property. It suppresses VES, VT, WPW tachycardia and prevents recurrences of AF and PSVT. But in the CAST study it was found to increase mortality in patients recovering from MI; can itself provoke arrhythmias during chronic therapy. It is reserved for resistant cases of paroxysmal AF and for life-threatening sustained VT in patients not having associated CHF.

## CLASS II

The primary action of class II drugs is to suppress adrenergically mediated ectopic activity.

**Propranolol** (*see* Ch. 10) It is the most commonly selected β blocker for treatment and prevention of cardiac arrhythmias; has some quinidine like direct membrane stabilizing action at high doses. However, in the clinically used dose range—antiarrhythmic action is exerted primarily because of cardiac adrenergic blockade. In a normal resting individual propranolol has only mild depressant action on SA node automaticity, but marked decrease in the slope of phase-4 depolarization and automaticity occurs in SA node, PF and other ectopic foci when the same has been increased under adrenergic influence. The other most important action is to prolong the ERP of A-V node (an antiadrenergic action). This impedes A-V conduction so that no paradoxical tachycardia can occur when atrial rate is reduced in AF or AFl.

Slow channel responses and after-depolarizations that have been induced by catecholamines (CAs) are suppressed. Reentrant arrhythmias that involve A-V node (many PSVTs) or that are dependent on slow channel/depressed fast channel response may be abolished by its marked depressant action on these modalities.

The most prominent ECG change is prolongation of PR interval. Depression of cardiac contractility and BP are mild.

*Administration* For rapid action, propranolol may be injected i.v. 1 mg/min (max. 5 mg) under close monitoring. The usual oral antiarrhythmic dose is 40–80 mg 2–4 times a day.

*Use* Propranolol is very useful in treating inappropriate sinus tachycardia. Atrial and nodal ESs, especially those provoked by emotion or exercise are suppressed by propranolol, but need to be treated only when symptomatic and disturbing. Propranolol is less effective than adenosine and verapamil for termination of PSVT (success rate ~ 60%), but can be used to prevent recurrences.

Propranolol rarely abolishes AF or AFl, but is used to control ventricular rate. It is highly effective in sympathetically mediated arrhythmias seen in pheochromocytoma and during anaesthesia

with halothane. Digitalis induced tachyarrhythmias may be suppressed.

Non-sustained VT may be treated with a β blocker (propranolol, esmolol), but its efficacy in terminating sustained VT is low. However, propranolol may prevent recurrences of VT and its antiischaemic action may be protective. Prophylactic treatment with β blockers reduces mortality in post-MI patients. Propranolol or esmolol injected i.v. may terminate *torsades de pointes*. Along with a class IA or IC drug, it may be used for WPW reciprocal rhythms.

**Sotalol** (*see* p. 148) It is a nonselective β blocker having prominent Class III action of prolonging repolarization by blocking cardiac inward rectifier $K^+$ channels. It is not a $Na^+$ channel blocker—does not depress conduction in fast response tissue, but delays A-V conduction and prolongs its ERP. Sotalol is effective in polymorphic VT, some WPW arrhythmias and for maintaining sinus rhythm in AF/AFl. Due to prolongation of APD and Q-T, risk of dose-dependent *torsades de pointes* is the major limitation. It is contraindicated in patients with long Q-T interval.

**Esmolol** (*see* p. 149) This quick and short acting $\beta_1$ blocker administered i.v. is very useful for emergency control of ventricular rate in AF/AFl. It can terminate supraventricular tachycardia, and is mainly used for arrhythmias associated with anaesthesia where rapidly developing β adrenergic blockade is desired.

MINIBLOCK 100 mg/10 ml, 250 mg/10 ml inj.; 0.5 mg/kg in 1 min followed by 0.05–0.2 mg/kg/min i.v. infusion.

## CLASS III

The characteristic action of this class is prolongation of repolarization (phase-3); AP is widened and ERP is increased. The tissue remains refractory even after full repolarization: reentrant arrhythmias are terminated.

### Amiodarone

This unusual iodine containing highly lipophilic long-acting antiarrhythmic drug exerts multiple actions:

- Prolongs APD and Q-T interval attributable to block of myocardial delayed rectifier $K^+$ channels. This also appears to reduce non-uniformity of refractoriness among different fibres.
- Preferentially blocks inactivated $Na^+$ channels (like lidocaine) with relatively rapid rate of channel recovery: more effective in depressing conduction in cells that are partially depolarized or have longer APD.
- Partially inhibits myocardial $Ca^{2+}$ channels, has noncompetitive β adrenergic blocking property and alters thyroid function. Thus amiodarone is a multichannel blocker with some additional activities.

Conduction is slowed and ectopic automaticity is markedly depressed, but that of SA node is only slightly affected. Effect of oral doses on cardiac contractility and BP are minimal, but i.v. injection frequently causes myocardial depression and hypotension.

Despite prolongation of APD, the arrhythmia (*torsades de pointes*) provoking potential of amiodarone is low, probably because it does not exhibit 'reverse use-dependence' of APD prolongation or because of its multiple antiarrhythmic mechanisms. The prolongation of APD by other class III drugs is more marked at slower rates of activation (encouraging EAD) than at higher rates (reverse use-dependence), while with amiodarone it is independent of rate of activation.

*Pharmacokinetics* Amiodarone is incompletely and slowly absorbed from the g.i.t. On daily oral ingestion the action develops over several days, even weeks. However, on i.v. injection, action develops rapidly. It accumulates in muscle and fat from which it is slowly released and then metabolized in liver mainly by CYP3A4. One metabolite is active. The duration of action is exceptionally long; t½ 3–8 weeks.

*Dose*: Amiodarone is mainly used orally 400–600 mg/day for few weeks, followed by 100–200 mg OD for maintenance therapy. 100–300 mg (5 mg/kg) slow i.v. injection over 30–60 min.

CORDARONE, ALDARONE, EURYTHMIC 100, 200 mg tabs, 150 mg/3 ml inj.

*Use* Amiodarone is effective in a wide range of ventricular and supraventricular arrhythmias including PSVT, nodal and ventricular tachycardia,

AF, AFl, etc. Resistant VT and recurrent VF are the most important indications. It is also used to maintain sinus rhythm in AF when other drugs have failed. Rapid termination of ventricular (VT and VF) and supraventricular arrhythmias can be obtained by i.v. injection. WPW tachyarrhythmia is terminated by suppression of both normal and aberrant pathways.

Long duration of action makes amiodarone suitable for chronic prophylactic therapy. Apart from propranolol, it is the only antiarrhythmic drug which in the long term has been found to reduce sudden cardiac death. Because of high and broad spectrum efficacy and relatively low proarrhythmic potential, amiodarone is a commonly used antiarrhythmic, despite its organ toxicity.

*Adverse effects* These are dose-related and increase with duration of therapy. Fall in BP, bradycardia and myocardial depression occurs on i.v. injection and after drug cumulation.

Nausea, gastrointestinal upset may attend oral medication, especially during the loading phase.

Photosensitization and sun burn like skin pigmentation occurs in about 10% patients.

Corneal microdeposits are common with long-term use, may cause headlight dazzle, but are reversible on discontinuation.

Pulmonary alveolitis and fibrosis is the most serious toxicity of prolonged use, but is rare if daily dose is kept below 200 mg.

Peripheral neuropathy generally manifests as weakness of shoulder and pelvic muscles. Liver damage is rare. Amiodarone interferes with thyroid function in many ways including inhibition of peripheral conversion of $T_4$ to $T_3$ and interaction with thyroid hormone receptor. Goiter, hypothyroidism and rarely hyperthyroidism may develop on chronic use.

*Interactions* Amiodarone can increase digoxin and warfarin levels by reducing their renal clearance. Additive A-V block can occur in patients receiving β blockers or calcium channel blockers. Inducers and inhibitors of CYP3A4 respectively decrease and increase amiodarone levels.

**Dronedarone** This is a recently introduced noniodinated congener of amiodarone, less toxic, but also less effective class III antiarrhythmic. Clinical utility of dronedarone is limited to supraventricular arrhythmias; primary indication being maintenance of sinus rhythm in haemodynamically stable patients of paroxysmal/non-permanent AF, and to control ventricular rate during AF/AFl.

In clinical trials, recurrence time for AF was increased by 2–3 times in dronedarone recipients. Like amiodarone, dronedarone is a multichannel blocker, inhibits delayed rectifier and other types of cardiac $K^+$ channels, inward $Na^+$ channel and L-type $Ca^{2+}$ channel. The noncompetitive β adrenergic blocking activity is more marked compared to amiodarone, but it does not interfere with thyroid function. It increases myocardial APD, ERP and slows A-V conduction.

Dronedarone is less lipophilic and is metabolized by CYP3A4 and CYP2D6; inhibitors of these isoenzymes (Ketoconazole, erythromycin, metoprolol, etc.) markedly increase its blood levels. The elimination t½ is 24 hours. Side effects are mainly gastrointestinal disturbances, bradycardia, weakness, cough and dermatological reactions. Though it prolongs Q-T interval, risk of *torsades de pointes* is very low. Hypothyroidism, pulmonary fibrosis and peripheral neuropathy does not occur. Dronedarone is contraindicated in moderate-to-severe CHF, 2nd/3rd degree A-V block and in permanent AF.

*Dose*: 400 mg BD oral; MULTAQ 400 mg tab.

*Note:* On the basis of two clinical trials PALLAS and ATHENA, the US-FDA in Dec 2011 issued a safety alert that dronedarone should not be used in AF patients who cannot and will not be converted to sinus rhythm (permanent AF), because it doubles the rate of stroke, heart failure and cardiovascular death in such patients. If during dronedarone therapy the patient is found to have AF, he should either be cardioverted or dronedarone should be stopped. A recent meta-analysis has also noted unfavourable cardiovascular and mortality outcomes with dronedarone, especially in patients with cardiovascular risk factors.

**Dofetilide** This newer antiarrhythmic prolongs APD and ERP by selectively blocking rapid component of delayed rectifier $K^+$ current without affecting other channels or receptors; has no autonomic or peripheral actions. It is therefore labelled as *pure* class III antiarrhythmic.

Oral dofetilide can convert AF or AFl to sinus rhythm in ~30% cases, but is more effective in maintaining sinus rhythm in converted patients—its primary indication. Significantly, chronic therapy with dofetilide in patients with high risk of sudden cardiac death/post MI cases has not increased mortality, despite provoking *torsades de pointes* in some recipients. It is mainly excreted unchanged in urine and produces few side effects.

**Ibutilide** is another new class III antiarrhythmic used i.v. for pharmacological conversion of AFl and AF to sinus rhythm. Efficacy is higher in recent onset AF/AFl and in AFl compared to AF. Induction of *Torsades de pointes* is a risk.

## CLASS IV

The primary action of this class of drugs is to inhibit $Ca^{2+}$ mediated slow channel inward current.

### Verapamil

Of the many $Ca^{2+}$ channel blockers, verapamil has the most prominent cardiac electrophysiological action (Table 38.1). It blocks L type $Ca^{2+}$ channels and delays their recovery. Its antiarrhythmic aspects are described here, while other aspects are covered in Ch. 39 and 40.

The basic action of verapamil is to depress $Ca^{2+}$ mediated depolarization. This suppresses automaticity and reentry dependent on slow channel response. Phase-4 depolarization in SA node is reduced resulting in bradycardia. Reflex sympathetic stimulation due to vasodilatation partly counteracts the direct bradycardia producing action. Delayed after-depolarizations in PFs are dampened.

The most consistent action of verapamil is prolongation of A-V nodal ERP. As a result A-V conduction is markedly slowed (P-R interval increases) and reentry involving A-V node is terminated. Intraventricular conduction, however, is not affected. Verapamil has negative inotropic action due to interference with $Ca^{2+}$ mediated excitation-contraction coupling in myocardium.

#### *Uses and precautions*

1. PSVT—Verapamil can terminate attacks of PSVT; 5 mg i.v. over 2–3 min is effective in ~ 80% cases. However, i.v. verapamil carries the risk of marked bradycardia, A-V block, cardiac arrest and hypotension. It should not be used if PSVT is accompanied with hypotension or CHF. For preventing recurrences of PSVT, verapamil 60 to 120 mg TDS may be given orally.
2. To control ventricular rate in AF or AFl; Verapamil causes a dose dependent (40–120 mg TDS oral) reduction in ventricular rate in AF and AFl, and is a first line drug for this purpose. In case of inadequate response, digoxin may be added to it. Verapamil can also be injected i.v. for emergency control of ventricular rate in AF and AFl.

Reentrant supraventricular and nodal arrhythmias are susceptible to verapamil, but it is contraindicated in broad QRS complex WPW tachycardia in which it may abbreviate the ERP of bypass tract. A class IA (procainamide) or IC (propafenone) drug which prolongs ERP of bypass tract and depresses conduction is to be combined with verapamil so as to concurrently depress A-V conduction.

Verapamil has poor efficacy in ventricular arrhythmias. In contrast to β blockers, verapamil

**TABLE 38.1 Electrophysiological actions of calcium channel blockers**

| | *Verapamil* | *Diltiazem* | *Nifedipine* |
|---|---|---|---|
| 1. SA node automaticity | ↓ | ↓,– | — |
| 2. Ventricular automaticity | ↓,– | — | — |
| 3. ERP : atrial | — | — | — |
| : A-V nodal | ↑↑ | ↑ | ↑↓ |
| : ventricular | — | — | — |
| : bypass tract | ↑↓ | ↑↓ | — |
| 4. ECG : R-R interval | ↑ | ↑↓ | ↓ |
| P-R interval | ↑ | ↑ | — |

↑ : increase; ↓ : decrease; —: no change

prophylaxis does not reduce mortality in post-MI patients. In some patients of VT, i.v. injection of verapamil has precipitated VF: therefore contraindicated. It is also not recommended for digitalis toxicity, because additive A-V block may occur. It is contraindicated in partial heart block and sick sinus.

CALAPTIN 40, 80 mg tab; 120, 240 mg SR tab, 5 mg/2 ml inj.

**Diltiazem** The direct cardiac actions of diltiazem are similar to those of verapamil. However, bradycardia and depression of cardiac contractility are less marked. It is an alternative to verapamil for termination as well as prophylaxis of PSVT.

For rapid control of ventricular rate in AF or AFl, i.v. diltiazem is preferred over verapamil, because it can be more easily titrated to the target heart rate, causes less hypotension or myocardial depression and can be used even in the presence of mild-to-moderate CHF.

DILZEM 30, 60, 90 mg tabs, 25 mg/5 ml inj.



### Drugs for PSVT

An attack of PSVT can be terminated by reflex vagal stimulation through Valsalva maneuver, splashing ice cold water on face, hyperflexion (head between knees), etc. Alternatively, or if it does not work, the drug of choice is adenosine (i.v.). Other alternatives are i.v. injection of verapamil/diltiazem/esmolol. To prevent recurrences, oral therapy with verapamil, diltiazem or propranolol alone or combined with digoxin may be prescribed.

### Adenosine

Administered by rapid i.v. injection (over 1–3 sec) either as the free base (6–12 mg) or as ATP (10–20 mg), adenosine terminates within 30 sec. more than 90% episodes of PSVT involving the A-V node. It activates ACh sensitive $K^+$ channels and causes membrane hyperpolarization through interaction with A1 type of adenosine GPCRs on SA node (pacemaker depression → bradycardia), A-V node (prolongation of ERP → slowing of conduction) and atrium (shortening of AP, reduced excita-bility). It indirectly reduces $Ca^{2+}$ current in A-V node. Depression of the reentrant circuit through A-V node is responsible for termination of majority of PSVTs. Adrenergically induced DADs in ventricle are also suppressed. Coronary dilatation occurs transiently.

ADENOJECT, ADENOCOR 3 mg adenosine (base) per ml in 2 ml and 10 ml amp.

Adenosine has a very short t½ in blood (~10 sec) due to uptake into RBCs and endothelial cells where it is converted to 5-AMP and inosine. Almost complete elimination occurs in a single passage through coronary circulation. Injected ATP is rapidly converted to adenosine. Dipyridamole potentiates its action by inhibiting uptake, while theophylline/ caffeine antagonize its action by blocking adenosine receptors. Higher doses may be required in heavy tea/coffee drinkers. Patients on carbamazepine are at greater risk of developing heart block. Advantages of adenosine for termination of PSVT are:

- Efficacy equivalent to or better than verapamil.
- Action lasts < 1 min; adverse effects (even cardiac arrest, if it occurs) are transient.
- No haemodynamic deterioration; can be given to patients with hypotension, CHF or those receiving β blockers. Verapamil is contra-indicated in these situations.
- Safe in wide QRS tachycardia (verapamil is unsafe).
- Effective in patients not responding to verapamil.

However, adenosine produces transient dyspnoea, chest pain, fall in BP and flushing in 30–60% patients; ventricular standstill for few sec or VF occurs in some patients. Bronchospasm may be precipitated in asthmatics; verapamil is the drug of choice for such patients. Adenosine has to be rapidly injected in a large vein and has brief action. Therefore, it is not suitable for prophylaxis in recurrent cases.

*Other uses of adenosine*

(a) Diagnosis of tachycardias dependent on A-V node.
(b) To induce brief coronary vasodilatation during certain diagnostic/interventional procedures.
(c) To produce controlled hypotension during surgery.

### Drugs for A-V Block

The definitive treatment of chronic heart block is pacing with an implanted cardiac pacemaker. Drugs are of value only for acute/transient A-V block and as an interim measure.

*Atropine:* When A-V block is due to vagal overactivity, e.g. digitalis toxicity, some cases of MI; it can be improved by atropine 0.6–1.2 mg i.m. Atropine abbreviates A-V node ERP and increases conduction velocity in bundle of His.

*Sympathomimetics* (Adr, isoprenaline): These drugs may overcome partial heart block by facilitating A-V conduction and shortening ERP of conducting tissues.

They may also be used in complete (3rd degree) heart block to maintain a sufficient idioventricular rate (by increasing automaticity of ventricular pacemakers) till external pacemaker can be implanted.

## Choice and use of antiarrhythmic drugs

Mere detection of an arrhythmia does not necessitate treatment.

Asymptomatic arrhythmias and those which do not jeopardize haemodynamics, e.g. most AES and occasional VES, first degree A-V block, bundle branch block, etc. in an otherwise normal heart, do not require antiarrhythmic treatment; reassurance is enough. If a patient is particularly disturbed by AES, propranolol is the best option. Chronic prophylactic therapy with class I and class IV antiarrhythmics does not appear to afford survival benefit, except in few selected cases. Only propranolol and to some extent amiodarone have been shown to reduce cardiovascular mortality in the long-term. On the other hand, vigorous therapy is indicated when:

- Arrhythmia is life-threatening, e.g. sustained VT, *torsades de pointes,* VF.
- Arrhythmia is causing hypotension, breathlessness, activity limitation or cardiac failure.
- Palpitation is marked, e.g. in PSVT, sustained VT, AF, *torsades de pointes.*
- When simple arrhythmia may lead to more serious ones, e.g. after MI (warning arrhythmias).

In the above situations antiarrhythmics are mostly needed for short periods. Majority of antiarrhythmic drugs have narrow margin of safety. A simple clinical classification of antiarrhythmic drugs is presented in the box below.

The selection of an antiarrhythmic in a patient depends on:

(a) ECG diagnosis

(b) Possible mechanism underlying the arrhythmia

(c) Mechanism of action and range of antiarrhythmic activity of the drug

(d) Pharmacokinetic profile of the drug.

(e) Haemodynamic effects of the drug.

The aim is to improve cardiovascular function either by restoring sinus rhythm, or by controlling ventricular rate, or by conversion to a more desirable pattern of electrical and mechanical activity.

Despite extensive investigation, choice of an antiarrhythmic is still largely empirical. A practical guide to the choice and use of antiarrhythmic drugs is summarized in the box on next page.

**Clinical classification of antiarrhythmic drugs**

| *Supraventricular arrhythmias only* | *Supraventricular and ventricular arrhythmias* | | *Ventricular arrhythmias only* |
|---|---|---|---|
| Adenosine | Amiodarone | Procainamide | Lidocaine |
| Verapamil | β blockers | Disopyramide | Mexiletine |
| Diltiazem | Propranolol | Quinidine | |
| Dronedarone | Sotalol | Flecainide | |
| Digoxin | Esmolol | Propafenone | |

**Choice of antiarrhythmics for cardiac arrhythmias**

| *Arrhythmia* | *Clinical objective* | *Drug(s)* |
|---|---|---|
| 1. Atrial extrasystoles<br>Symptomatic | : Suppression, symptom relief | No drug if asymptomatic or non-disturbing<br>Propranolol (only if disturbing) |
| 2. Paroxysmal supraventricular tachycardia (PSVT) | : Termination of PSVT<br>: Prevention of recurrence | i.v. adenosine/verapamil/diltiazem/esmolol<br>Oral verapamil/diltiazem/propranolol/sotalol |
| 3. Atrial fibrillation (AF) | : Reversal to SR (for paroxysmal/persistent AF)<br>: Maintenance of SR<br>: Ventricular rate control (for permanent AF/during recurrence of AF)<br>: Urgent vent. rate control | Cardioversion<br>i.v. amiodarone<br>Sotalol/propafenone/amiodarone/dronedarone/disopyramide<br>oral verapamil/diltiazem/propranolol ± digoxin<br>i.v. esmolol/verapamil/amiodarone |
| 4. Atrial flutter (AFl) | : Reversal to SR<br>: Ventricular rate control | Cardioversion, radiofrequency ablation, Propafenone (after rate control with verapamil/propranolol)<br>Propranolol/verapamil/diltiazem ± digoxin or Amiodarone |
| 5. Wolff-Parkinson-White syndrome (WPW) tachycardia | : Termination<br>: Maintenance<br>- narrow QRS<br>- wide QRS | Radiofrequency ablation, cardioversion<br><br>Propafenone/procainamide<br>Propafenone + verapamil/propranolol or Amiodarone/sotalol |
| 6. Acute-MI arrhythmia<br>Bradycardia<br>Vent. extrasystoles/tachycardia | : Reversal to normal rate<br>: Abolition to prevent serious arrhythmia | Atropine (i.v.)—no effect—Pacing<br>i.v. Lidocaine/procainamide/amiodarone<br>Cardioversion (if haemodynamically unstable) |
| 7. Chronic vent. tachycardia<br>Nonsustained VT<br>Sustained VT | : Suppression<br>: Abolition<br>: Maintenance therapy (prevention of VF/arrest) | Propranolol/amiodarone (oral)<br>i.v. Amiodarone ± propranolol or cardioversion or propafenone/lidocaine (i.v.)<br>Amiodarone/sotalol<br>Implantable defibrillator |
| 8. Ventricular fibrillation (VF) | : Termination<br>: Recurrence prevention | Defibrillation ± amiodarone (i.v.)<br>Amiodarone (oral)/propranolol |

SR—Sinus rhythm

## ☞ PROBLEM DIRECTED STUDY

**38.1** A sales executive aged 55 years presented with palpitation felt off-and-on, both during activity as well as at rest for the last one month or so. He also complained of tiredness and anxiety. The pulse was irregular in volume and frequency with average rate 104/min, respiration 20/min, BP 130/84 mm Hg, apex beat was irregular, with an average rate 120/min. Heart sounds were irregular, but there was no murmur. The ECG showed atrial fibrillation (AF) with no sign of ischaemia. A diagnosis of persistent AF was made, and it was decided to electrically cardiovert him. He was put on warfarin sod. 5 mg twice daily for 2 days followed by 5 mg once daily and dose to be adjusted to an INR between 2–2.5. This was to be maintained for 1 month before attempting cardioversion.

(a) Why the patient has been put on warfarin therapy before attempting cardioversion?

(b) Can some drug be given to control and regularize his heart rate in the mean time? If so, which drug(s)?

(c) If electrical cardioversion does not succeed, can some drug be given to revert him to sinus rhythm (SR)?

(d) After cardioversion, can some drug(s) be given to maintain SR and prevent recurrence of AF?

(see Appendix-1 for solution)

# Chapter 39 Antianginal and Other Anti-ischaemic Drugs

## ANTIANGINAL DRUGS

Antianginal drugs are those that prevent, abort or terminate attacks of angina pectoris.

**Angina pectoris** Is a pain syndrome due to induction of an adverse oxygen supply/demand situation in a portion of the myocardium. Two principal forms are recognized:

(a) *Classical angina* (common form) Attacks are predictably provoked (stable angina) by exercise, emotion, eating or coitus and subside when the increased energy demand is withdrawn. The underlying pathology is—severe arterio-sclerotic affliction of larger coronary arteries (conducting vessels) which run epicardially and send perforating branches to supply the deeper tissue (Fig. 39.1). The coronary obstruction is 'fixed'; blood flow fails to increase during increased demand despite local factors mediated dilatation of resistance vessels (Fig. 39.2) and ischaemic pain is felt. Due to inadequacy of ischaemic left ventricle, the end diastolic left ventricular pressure rises from 5 to about 25 mm Hg—produces subendocardial 'crunch' during diastole (blood flow to the subendocardial region occurs only during diastole) and aggravates the ischaemia in this region. Thus, a form of acutely developing and rapidly reversible left ventricular failure results which is relieved by taking rest and reducing the myocardial workload.

Drugs that are useful, primarily reduce cardiac work (directly by acting on heart or indirectly by reducing preload hence end diastolic pressure, and afterload). They may also cause favourable redistribution of blood flow to the ischaemic areas.

(b) *Variant/Prinzmetal/Vasospastic angina* (uncommon form) Attacks occur at rest or during sleep and are unpredictable. They are due to

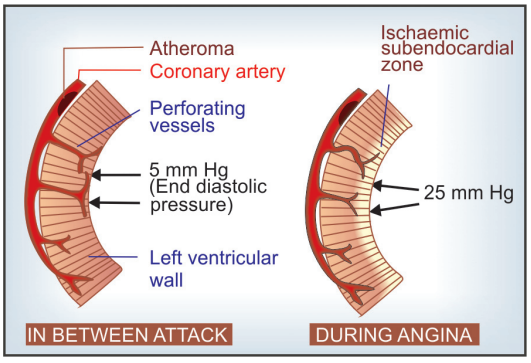



**Fig. 39.1:** Diagrammatic representation of subendocardial 'crunch' during an attack of angina

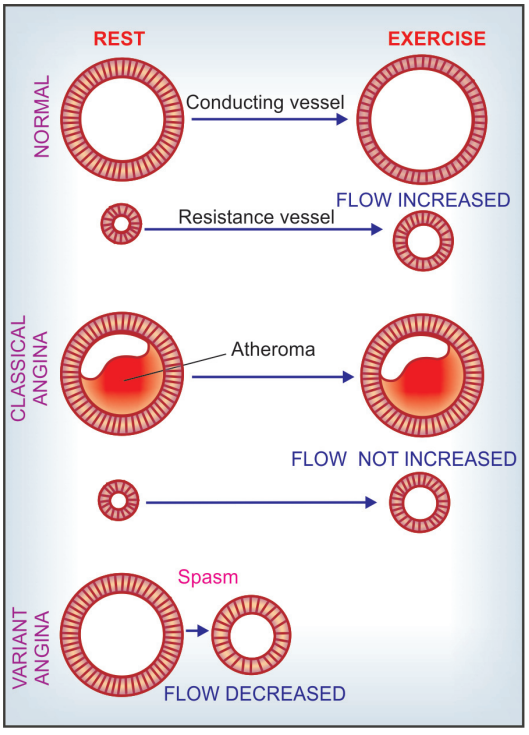



**Fig. 39.2:** Diagrammatic representation of coronary artery calibre changes in classical and variant angina

recurrent localized (occasionally diffuse) coronary vasospasm (Fig. 39.2) which may be superimposed on arteriosclerotic coronary artery disease. Abnormally reactive and hypertrophied segments in the coronary arteries have been demonstrated. Drugs are aimed at preventing and relieving the coronary vasospasm.

*Unstable angina (UA)* with rapid increase in duration and severity of attacks is mostly due to rupture of an atheromatous plaque attracting platelet deposition and progressive occlusion of the coronary artery; occasionally with associated coronary vasospasm.

Chronically reduced blood supply causes atrophy of cardiac muscle with fibrous replacement (reduced myocardial work capacity → CHF) and may damage conducting tissue to produce unstable cardiac rhythms. Antianginal drugs relieve cardiac ischaemia but do not alter the course of coronary artery pathology: no permanent benefit is afforded. On the other hand, aspirin, ACE inhibitors and statins (hypocholesterolaemic) can modify coronary artery disease and improve prognosis.

*Glyceryl trinitrate*, the drug unsurpassed in its ability to abort and terminate anginal attack, was introduced by Murrell in 1879. Other organic nitrates were added later, but a breakthrough was achieved in 1963 when propranolol was used for chronic prophylaxis. The calcium channel blockers have been a major contribution of the 1970s. A number of vasodilator and other drugs have been promoted from time to time, but none is as uniformly effective. Some potassium channel openers (nicorandil), metabolic modulator (trimetazidine) and late $Na^+$ current inhibitor (ranolazine) have been introduced lately.

## CLASSIFICATION

1. *Nitrates*
   (a) *Short acting:* Glyceryl trinitrate (GTN, Nitroglycerine)
   (b) *Long acting*: Isosorbide dinitrate (short acting by sublingual route), Isosorbide mononitrate, Erythrityl tetranitrate, Pentaerythritol tetranitrate
2. *β Blockers* Propranolol, Metoprolol, Atenolol and others.
3. *Calcium channel blockers*
   (a) *Phenyl alkylamine*: Verapamil
   (b) *Benzothiazepine:* Diltiazem
   (c) *Dihydropyridines:* Nifedipine, Felodipine, Amlodipine, Nitrendipine, Nimodipine, Lacidipine, Lercanidipine, Benidipine
4. *Potassium channel opener* Nicorandil
5. *Others* Dipyridamole, Trimetazidine, *Ranolazine, Ivabradine, Oxyphedrine*

### *Clinical classification*

A. *Used to abort or terminate attack* GTN, Isosorbide dinitrate (sublingually).
B. *Used for chronic prophylaxis* All other drugs.

## NITRATES (GTN as prototype)

All organic nitrates share the same action; differ only in time course. The only major action is direct nonspecific smooth muscle relaxation.

*Preload reduction* The most prominent action is exerted on vascular smooth muscle. Nitrates dilate veins more than arteries → peripheral pooling of blood → decreased venous return, i.e. preload on heart is reduced → end diastolic size and pressure are reduced → decreased cardiac work according to *Laplace relationship*—which describes the effectiveness of ventricular wall tension in elevating intraventricular pressure and the extent to which fibre shortening results in systolic ejection.

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

Thus, reduction in ventricular radius decreases the tension that must be generated in the ventricular wall—hence decreased $O_2$ consumption. Reduction in cardiac output (c.o.) occurs at rest but is less marked during angina due to better ventricular emptying. The decrease in end diastolic pressure abolishes the subendocardial crunch by restoring the pressure gradient across ventricular wall due to which subendocardial perfusion occurs during diastole. It is through their action on peripheral veins that nitrates exert major beneficial effects in classical angina.

*Afterload reduction* Nitrates also produce some arteriolar dilatation → slightly decrease total peripheral resistance (t.p.r.) or afterload on heart; BP falls somewhat; systolic more than diastolic (reflex sympathetic activity tends to maintain diastolic BP). This action contributes to the reduction in cardiac work which is directly proportional to aortic impedance.

With usual doses, and if the patient does not stand still (which favours pooling of blood in the legs), tachycardia is not prominent. With large doses and if the mean BP falls significantly, reflex sympathetic stimulation occurs → tachycardia, increased cardiac contractility → increased cardiac work → angina may be precipitated. Fainting and cold sweat occur due to cerebral ischaemia. All these can be prevented by lying down and raising the foot end.

*Redistribution of coronary flow* In the arterial tree, nitrates preferentially relax bigger conducting (angiographically visible) coronary arteries than arterioles or resistance vessels. This pattern of action may cause favourable redistribution of blood flow to ischaemic areas in angina patients. Dilatation of conducting vessels all over by nitrate along with ischaemia-induced dilatation of autoregulatory resistance vessels only in the ischaemic zone increases blood flow to this area (*see* Fig. 39.4B), while in the non-ischaemic zones, resistance vessels maintain their tone → flow does not increase, or may decrease to compensate for increased flow to ischaemic zone. In fact, nitrates do not appreciably increase total coronary flow in angina patients.

*Mechanism of relief of angina* The relaxant effect on larger coronary vessels is the principal action of nitrates benefiting variant angina by counteracting coronary spasm. In classical angina undoubtedly the primary effect is to reduce cardiac work by action on peripheral vasculature, though increased blood supply to ischaemic area may contribute. Exercise tolerance of angina patients is improved because the same amount of exercise causes lesser augmentation of cardiac work.

*Heart and peripheral blood flow* Nitrates have no direct stimulant or depressant action on the heart. They dilate cutaneous (especially over face and neck → flushing) and meningeal vessels causing headache. Splanchnic and renal blood flow decreases to compensate for vasodilatation in other areas. Nitrates tend to decongest lungs by shifting blood to systemic circulation.

*Other smooth muscles* Bronchi, biliary tract and esophagus are mildly relaxed. Effect on intestine, ureter, uterus is variable and insignificant.

**Mechanism of action** Organic nitrates are rapidly denitrated enzymatically in the smooth muscle cell to release the reactive free radical *nitric oxide (NO)* which activates cytosolic guanylyl cyclase → increased cGMP → causes dephosphorylation of myosin light chain kinase (MLCK) through a cGMP dependent protein kinase (Fig. 39.3). Reduced availability of phosphorylated (active) MLCK interferes with activation of myosin → it fails to interact with actin to cause contraction. Consequently relaxation occurs. Raised intracellular cGMP may also reduce $Ca^{2+}$ entry—contributing to relaxation.

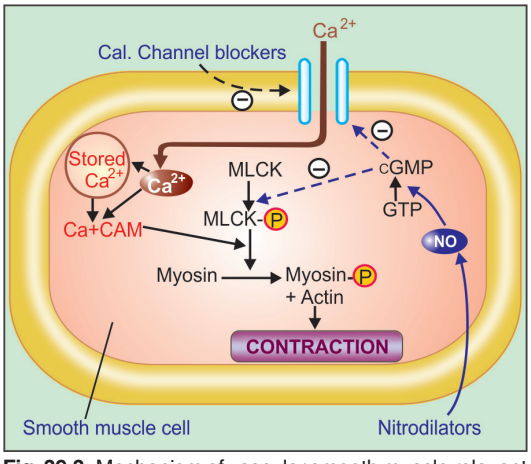



**Fig. 39.3:** Mechanism of vascular smooth muscle relaxant action of nitrodilators like glyceryl trinitrate and calcium channel blockers; (- - - →) Inhibition
CAM—Calmodulin; NO—Nitric oxide; MLCK—Myosin light chain kinase; MLCK-P—Phosphorylated MLCK; GTP—Guanosine triphosphate; cGMP—Cyclic guanosine monophosphate

Veins express greater amount of mitochondrial aldehyde dehydrogenase, the enzyme that generates NO from GTN, than arteries. This may account for the predominant venodilator action. It has been suggested that preferential dilatation of epicardial conducting arteries over autoregulatory arterioles is also due to differential distribution of nitrate metabolizing enzymes in these vessels.

*Platelets* Though platelets are poor in mitochondrial aldehyde dehydrogenase, the NO generated from nitrates activates cGMP production in platelets as well, leading to a mild antiaggregatory effect. This action may be valuable in unstable angina.

**Pharmacokinetics** Organic nitrates are lipid-soluble: well absorbed from buccal mucosa, intestines and skin. Ingested orally, all except isosorbide mononitrate undergo extensive and variable first pass metabolism in liver. They are rapidly denitrated by a glutathione reductase and a mitochondrial aldehyde dehydrogenase. The partly denitrated metabolites are less active, but have longer t½. Though nitrates have been traditionally classified into short-acting and long-acting, it is the rate of absorption from the site of administration and the rate of metabolism that govern the duration of action of a particular nitrate. For example, GTN and isosorbide dinitrate are both short-acting from sublingual but longer-acting from oral route.

**Adverse effects** These are mostly due to vasodilatation.

1. Fullness in head, throbbing headache; some degree of tolerance develops on continued use.
2. Flushing, weakness, sweating, palpitation, dizziness and fainting; these are mitigated by lying down. Erect posture and alcohol accentuate these symptoms.
3. Methemoglobinemia: is not significant with clinically used doses. However, in severe anaemia, this can further reduce $O_2$ carrying capacity of blood.
4. Rashes are rare, though relatively more common with pentaerythritol tetranitrate.

*Tolerance* Attenuation of haemodynamic and antiischaemic effect of nitrates occurs in a dose and duration of exposure dependent manner if they are continuously present in the body. This tolerance weans off rapidly (within hours) when the body is free of the drug. Clinically, no significant tolerance develops on intermittent use of sublingual GTN for attacks of angina. However, it may become important when GTN is used orally, transdermally or by continuous i.v. infusion round the clock, as well as with the use of long acting agents, especially sustained release formulations. Cross tolerance occurs among all nitrates. Tolerance occurs more readily with higher doses.

The mechanism of nitrate tolerance is not well understood. Reduced ability to generate NO due to depletion of cellular SH radicals has been demonstrated experimentally. However, thiol replinishing agents only partially overcome nitrate tolerance. This form of therapy has not met clinical success. Other changes which interfere with NO production could be involved. Products formed during generation of NO inhibit mitochondrial aldehyde dehydrogenase. Activation of compensatory mechanisms including volume expansion, sympathetic and renin-angiotensin system stimulation or other humoral pathways as well as oxidative stress due to free radicals generated during denitration may contribute to nitrate tolerance.

The most practical way to prevent nitrate tolerance is to provide nitrate free intervals everyday.

*Dependence* On organic nitrates is now well recognized. Sudden withdrawal after prolonged exposure has resulted in spasm of coronary and peripheral blood vessels. MI and sudden deaths have been recorded. Angina threshold is lowered during the nitrate free interval in some patients: episodes of angina may increase. In such patients an antianginal drug of another class should be added. Withdrawal of nitrates should be gradual.

**Interactions** Sildenafil causes dangerous potentiation of nitrate action: severe hypotension, MI and deaths are on record (*see* p. 304). Additive hypotension is also possible when nitrate is given to a patient receiving other vasodilators.

## INDIVIDUAL DRUGS

### 1. Glyceryl trinitrate (GTN, Nitroglycerine)

It is a volatile liquid which is adsorbed on the inert matrix of the tablet and rendered nonexplosive. The tablets must be stored in a tightly closed glass (not plastic) container lest

the drug should evaporate away. The sublingual route is used when terminating an attack or aborting an imminent one is the aim. The tablet may be crushed under the teeth and spread over buccal mucosa. It acts within 1–2 min (peak blood level in 3–6 min) because of direct absorption into systemic circulation (bypassing liver where almost 90% is metabolized).

Plasma t½ is 2 min, duration of action depends on the period it remains available for absorption from buccal mucosa. When anginal pain is relieved, the remaining part of tablet may be spit or swallowed. A sublingual spray formulation has been recently marketed—acts more rapidly than sublingual tablet. Hepatic metabolizing capacity can be overwhelmed by administering a large dose (5–15 mg) orally. Sustained release oral capsules containing much larger amounts of GTN can be used for chronic prophylaxis.

Nitroglycerine is readily absorbed from the skin. In the early 1970s, cutaneous application as ointment was found to produce haemodynamic effects for 4–6 hours. A transdermal patch in which the drug is incorporated into a polymer bonded to adhesive plaster (*see* p. 6) has been developed which provides steady delivery for 24 hours. It starts working within 60 min and has a bioavailability of 70–90%. However, development of tolerance and dependence may jeopardise its value. It is advised that the patch be taken off for 8 hours daily. A transmucosal dosage form which has to be stuck to the gums under the upper lip has also been produced—acts in 5 min and releases the drug for 4–6 hours.

Intravenous infusion of GTN provides rapid, steady, titratable plasma concentration for as long as desired. It has been successfully used for unstable angina, coronary vasospasm, LVF accompanying MI, hypertension during cardiac surgery, etc. Begin with 5 µg/min, adjust according to need. Early institution of infusion may limit the size of infarct in MI.

**2. Isosorbide dinitrate** It is a solid but similar in properties to GTN; can be used sublingually at the time of attack (slightly slower

**TABLE 39.1 Organic nitrates available for angina pectoris**

| *Drug* | *Preparations* | *Dose & route* | *Duration of action* |
|---|---|---|---|
| 1. GTN (Nitroglycerine) | ANGISED 0.5 mg tab | 0.5 mg sublingual | 10–30 min |
| | NITROLINGUAL, GTN SPRAY 0.4 mg per spray | 0.4–0.8 mg s.l. spray | 10–30 min |
| | ANGISPAN-TR 2.5, 6.5 mg SR cap. | 5–15 mg oral | 4–8 hr |
| | NITROCONTIN, CORODIL 2.6, 6.4 mg tabs. | | |
| | NITRODERM-TTS 5 or 10 mg patch | One patch for 14–16 hr per day | Till applied, max 24 hr. |
| | MYOVIN, MILLISROL, NITROJECT 5 mg/ml inj | 5–20 µg/min i.v. | Till infused |
| 2. Isosorbide dinitrate | SORBITRATE 5, 10 mg tab, ISORDIL 5 mg sublingual & 10 mg oral tab. | 5–10 mg sublingual<br>10–20 mg oral | 20–40 min<br>2–3 hr |
| | DITRATE 5, 10 mg tab; 20, 40 mg SR tab | 20–40 mg oral | 6–10 hr |
| 3. Isosorbide-5-mononitrate | MONOTRATE 10, 20, 40 mg tab, 25, 50 mg SR tabs<br>5-MONO, MONOSORBITRATE 10, 20, 40 mg tab. | 20–40 mg oral | 6–10 hr |
| 4. Erythrityl-tetranitrate | CARDILATE 5, 15 mg tab | 15–60 mg oral | 4–6 hr |
| 5. Pentaerythritol-tetranitrate | PERITRATE 10 mg tab<br>PERITRATE-SA 80 mg SR tab | 10–40 mg oral<br>80 mg oral | 3–5 hr<br>8–12 hr |

in action than GTN, peak in 5–8 min) as well as orally for chronic prophylaxis. Presystemic metabolism on oral administration is pronounced and variable. The t½ is 40 min, but sustained release formulation may afford protection for 6–10 hours. Last dose should not be taken later than 6 PM to allow nitrate level to fall during sleep at night.

**3. Isosorbide mononitrate** This is an active metabolite of isosorbide dinitrate. When administered orally it undergoes little first pass metabolism: bioavailability is high, interindividual differences are minimal and it is longer acting (t½ 4–6 hr). Last dose is to be taken in the afternoon; SR tablet once a day in the morning.

**4. Erythrityl tetranitrate and pentaerythritol tetranitrate** These are longer-acting nitrates used only for chronic prophylaxis. Sustained release oral preparations are now available for 2–3 times a day dosing.

There has been considerable scepticism in the past about the efficacy of orally administered long-acting nitrates. Studies with high doses have shown that firstpass metabolism in liver can be saturated and haemodynamic effects lasting 4–6 hours do occur.

## USES

1. *Angina pectoris* Nitrates are effective in classical as well as variant angina. For aborting or terminating an attack, sublingual GTN tablet or spray, or isosorbide dinitrate is taken on 'as and when required' basis. GTN produces relief within 3 min in 75% patients, the rest may require another dose or take longer (upto 9 min). Nitrates increase exercise tolerance and postpone ECG changes of ischaemia. Longer-acting formulations (oral, transdermal) of GTN or other nitrates are used on regular schedule for chronic prophylaxis. However, development of tolerance and dependence may limit the usefulness of this approach: 6–8 drug free hours daily are advisable. Moreover, chronic nitrate therapy in angina does not decrease cardiac mortality. In terms of prognostic benefit chronic prophylactic therapy with CCBs is superior to long-acting nitrates in variant angina.

2. *Acute coronary syndromes (ACS)* These are characterized by rapid worsening of anginal status of the patient : include unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI). It needs aggressive therapy with a combination of drugs intended to prevent further coronary occlusion, increase coronary blood flow and decrease myocardial stress (oxygen demand). Nitrates are useful by decreasing preload (myocardial work) as well as by increasing coronary flow (dilatation and antagonism of coronary spasm, if present). Initially GTN is given sublingually, but if pain persists after 3 tablets 5 min apart, i.v. infusion of GTN is started. The role of nitrates appears to be limited to relief of pain, because no mortality benefit has been demonstrated in large randomized clinical trials such as GISSI-3 (1994) and ISIS-4 (1995).

Antiplatelet drugs like aspirin, clopidogrel, $GPII_b/III_a$ antagonists, with or without heparin are the primary measures in UA/NSTEMI. The β blockers are indicated in all patients (if there are no contraindications) to reduce myocardial oxygen demand. A CCB is indicated only when coronary spasm is not effectively counteracted by the nitrate. Revascularization by thrombolytics/coronary angioplasty with stents/coronary bypass surgery is considered in high risk patients.

3. *Myocardial infarction (MI)* Administered by carefully titrated i.v. infusion to avoid hypotension and tachycardia, GTN is frequently used during evolving MI with the aim of relieving chest pain, pulmonary congestion and limiting the area of necrosis by favourably altering $O_2$ balance in the marginal partially ischaemic zone (a consequence of preload reduction). However, evidence that it decreases mortality is not robust; prognostic benefits appear marginal. Proper patient selection is important. GTN should not be administered if:

- Systolic BP is < 90 mm Hg
- Heart rate is < 50 or > 100 beats/min
- Right ventricular infarction is suspected

- Hypotension caused by nitrate limits the administration of β blockers which have more powerful salutary effects.*
- Patient has taken sildenafil in the past 24 hours.

4. *CHF and acute LVF* The role of vasodilators in CHF is described in Ch. 37. Nitrates afford relief by venous pooling of blood (which can be aided by sitting posture while managing acute LVF or severe chronic CHF) → reduced venous return (preload) → decreased end diastolic volume → improvement in left ventricular function by *Laplace law* and regression of pulmonary congestion. Intravenous GTN is the preparation of choice for emergency use. Rate of infusion must be guided by continuous haemodynamic monitoring.

5. *Biliary colic* due to disease or morphine—responds to sublingual GTN or isosorbide dinitrate.

6. *Esophageal spasm* Sublingual GTN promptly relieves pain. Nitrates taken before a meal facilitate feeding in esophageal achalasia by reducing esophageal tone.

7. *Cyanide poisoning* Nitrates generate methaemoglobin which has high affinity for cyanide radical and forms cyanomethaemoglobin. However, this may again dissociate to release cyanide. Therefore, sodium thiosulfate is given to form Sod. thiocyanate which is poorly dissociable and is excreted in urine.

Cytochrome and other oxidative enzymes are thus protected from cyanide; even that which has complexed CN is reactivated. However, early treatment is critical. The antidotes should be repeated as required.

Haemoglobin
↓ ← Sod. nitrite (10 ml of 3% solution i.v.)
Methaemoglobin
↓ ← Cyanide
Cyanomethaemoglobin
↓ ← Sod. thiosulfate (50 ml of 25% solution i.v.)
Methaemoglobin + Sod. thiocyanate
↓
Excreted in urine

Sodium nitrite is used for this purpose because it is a very weak vasodilator; large doses (>300 mg) sufficient to generate enough methaemoglobin can be injected i.v. without producing hypotension.

## β BLOCKERS (*see* Ch. 10)

These drugs do not dilate coronaries or other blood vessels; total coronary flow is rather reduced due to blockade of dilator $\beta_2$ receptors. However, flow to the ischaemic subendocardial region is not reduced because of favourable redistribution and decrease in ventricular wall tension. β blockers act by reducing cardiac work and $O_2$ consumption as a consequence of decreased heart rate, inotropic state and mean BP. This is marginal at rest. More importantly, β blockers limit increase in cardiac work that occurs during exercise or anxiety by antiadrenergic action on heart.

All β blockers are nearly equally effective in decreasing frequency and severity of attacks and in increasing exercise tolerance in classical angina, but cardioselective agents (atenolol, metoprolol) are preferred over nonselective $\beta_1$ + $\beta_2$ blockers (e.g. propranolol). The latter are particularly prone to worsen variant angina due to unopposed α receptor mediated coronary constriction that may accentuate the coronary spasm. Long term β blocker therapy clearly lowers risk of sudden cardiac death among ischaemic heart disease patients.

In angina pectoris, β-blockers are to be taken on a regular schedule; not on 'as and when required' basis. The dose has to be individualized. Abrupt discontinuation after chronic use may precipitate severe attacks, even MI.



* American Heart Association/American College of Cardiology guidelines for the management of patients with acute myocardial infarction. *Circulation* **2004**, *110*, 588-636.

**Voltage sensitive calcium channels**

| | L-type (Long lasting current) | T-type (Transient current) | N-type (Neuronal) |
|---|---|---|---|
| 1. Conductance | 25 pS | 8 pS | 12–20 pS |
| 2. Activation threshold | High | Low | Medium |
| 3. Inactivation rate | Slow | Fast | Medium |
| 4. Location and function | • Excitation-contraction coupling in cardiac and smooth muscle<br>• SA, A-V node—conductivity<br>• Endocrine cells—hormone release<br>• Neurones—transmitter release | • SA node—pacemaker activity<br>• 'T' current and repetitive spikes in thalamic and other neurones<br>• Endocrine cells—hormone release<br>• Certain arteries—constriction | • Only on neurones in CNS, sympathetic and myenteric plexuses—transmitter release |
| 5. Blocker | Nifedipine, diltiazem, verapamil | Mibefradil, flunarizine, ethosuximide | ω-Conotoxin |



*Unstable angina (UA)/Non-ST-elevation MI (NSTEMI)* Unless contraindicated, β blockers are routinely used in UA/NSTEMI. However, they should be given only after starting nitrate ± calcium channel blocker to counteract coronary vasospasm, if present (β blockers carry the risk of worsening coronary vasospasm). β blockers reduce myocardial $O_2$ demand and afford additional benefit by reducing risk of impending MI/sudden cardiac death.

## CALCIUM CHANNEL BLOCKERS

Verapamil was developed in Germany in 1962 as a coronary dilator. It had additional cardiodepressant property, but its mechanism of action was not known. Fleckenstein (1967) showed that it interfered with $Ca^{2+}$ movement into the cell. In the subsequent years, a large number of chemically diverse $Ca^{2+}$ channel blockers (CCBs) with different pharmacological profiles have been produced.

Three important classes of calcium channel blockers are examplified by:

Verapamil—a *phenyl alkylamine*, hydrophilic papaverine congener.

Nifedipine—a *dihydropyridine* (lipophilic).

Diltiazem—a hydrophilic *benzothiazepine*.

The dihydropyridines (DHPs) are the most potent $Ca^{2+}$ channel blockers, and this subclass has proliferated exceptionally.

### Calcium channels

Three types of $Ca^{2+}$ channels have been described in smooth muscles (other excitable cells as well):

(a) *Voltage sensitive channel* Activated when membrane potential drops to around –40 mV or lower.

(b) *Receptor operated channel* Activated by Adr and other agonists—independent of membrane depolarization (NA contracts even depolarized aortic smooth muscle by promoting influx of $Ca^{2+}$ through this channel and releasing $Ca^{2+}$ from sarcoplasmic reticulum).

(c) *Leak channel* Small amounts of $Ca^{2+}$ leak into the resting cell and are pumped out by $Ca^{2+}$ATPase. Mechanical stretch promotes inward movement of $Ca^{2+}$, through the leak channel or through separate *stretch sensitive channel.*

The *voltage sensitive $Ca^{2+}$ channels* are heterogeneous: three major types have been identified (*see* box):

All voltage sensitive $Ca^{2+}$ channels are membrane spanning funnel shaped glycoproteins that function as ion selective valves. They are composed of a major $\alpha_1$ subunit which encloses the ion channel and other modulatory subunits like $\alpha_2$,β, γ and δ. In L-type $Ca^{2+}$ channels each subunit exists in multiple isoforms which may be site specific, e.g.

Skeletal muscle L-channels are: $\alpha_{1s}$ . $\alpha_2/\delta_a$ . $\beta_1$ . $\gamma$
Cardiac muscle L-channels are: $\alpha_{1ca}$ . $\alpha_2/\delta_c$ . $\beta_2$
Smooth muscle L-channels are: $\alpha_{1cb}$ . $\alpha_2/\delta$ . $\beta_3$

Even smooth muscle L-channels differ between vascular and nonvascular. Moreover, distribution may be heterogeneous in different parts of the vascular bed.

Only the voltage sensitive L-type channels are blocked by the CCBs. The 3 groups of CCBs *viz.* phenylalkylamines (verapamil), benzothiazepine (diltiazem) and dihydropyridines

(nifedipine) bind to their own specific binding sites on the $\alpha_1$ subunit; all restricting $Ca^{2+}$ entry, though characteristics of channel blockade differ. Further, different drugs may have differing affinities for various site specific isoforms of the L-channels. This may account for the differences in action exhibited by various CCBs. The vascular smooth muscle has a more depolarized membrane (RMP about –40 mV) than heart. This may contribute to vascular selectivity of certain CCBs.

## PHARMACOLOGICAL ACTIONS AND ADVERSE EFFECTS

The common property of all three subclasses of CCBs is to inhibit $Ca^{2+}$ mediated slow channel component of action potential (AP) in smooth/cardiac muscle cell. The two most important actions of CCBs are:

(i) Smooth muscle (especially vascular) relaxation.
(ii) Negative chronotropic, inotropic and dromotropic action on heart.

**Smooth muscle** Smooth muscles depolarize primarily by inward $Ca^{2+}$ movement through voltage sensitive channel. These $Ca^{2+}$ ions trigger release of more $Ca^{2+}$ from intracellular stores and together bring about excitation-contraction coupling through phosphorylation of myosin light chain as depicted in Fig. 39.3. The CCBs cause relaxation by decreasing intracellular availability of $Ca^{2+}$. They markedly relax arterioles but have mild effect on veins. Extravascular smooth muscle (bronchial, biliary, intestinal, vesical, uterine) is also relaxed.

The dihydropyridines (DHPs) have the most marked smooth muscle relaxant and vasodilator action; verapamil is somewhat weaker followed by diltiazem.

Nitrendipine and few other DHPs have been shown to release NO from endothelium and inhibit cAMP-phosphodiesterase resulting in raised smooth muscle cAMP. These additional mechanisms may account for their predominant smooth muscle relaxant action. Released endothelial NO may exert antiatherosclerotic action.

**Heart** In the working atrial and ventricular fibres, $Ca^{2+}$ moves in during the plateau phase of AP and releases more $Ca^{2+}$ from sarcoplasmic reticulum. This $Ca^{2+}$ surge causes contraction through binding to troponin—allowing interaction of myosin with actin (*see* Fig. 37.3). The CCBs would thus have negative inotropic action.

The 0 phase depolarization in SA and A-V nodes is largely $Ca^{2+}$ mediated. Automaticity and conductivity of these cells appear to be dependent on the rate of recovery of the $Ca^{2+}$ channel.

The L-type $Ca^{2+}$ channels activate as well as inactivate at a slow rate. Consequently, $Ca^{2+}$ depolarized cells (SA and A-V nodal) have a considerably less steep 0 phase and longer refractory period. The recovery process which restores the channel to the state from which it can again be activated (Fig. 39.4) by membrane depolarization is delayed by verapamil and diltiazem (resulting in depression of pacemaker activity and conduction), but not by DHPs (they have no negative chronotropic/dromotropic action). Moreover, channel blockade by verapamil is enhanced at higher rates of stimulation, that by nifedipine is independent of frequency, while diltiazem is intermediate. Thus, verapamil slows sinus rate and A-V conduction, but nifedipine does not. Effect of diltiazem on sinus node automaticity and A-V conduction is similar to that of verapamil.

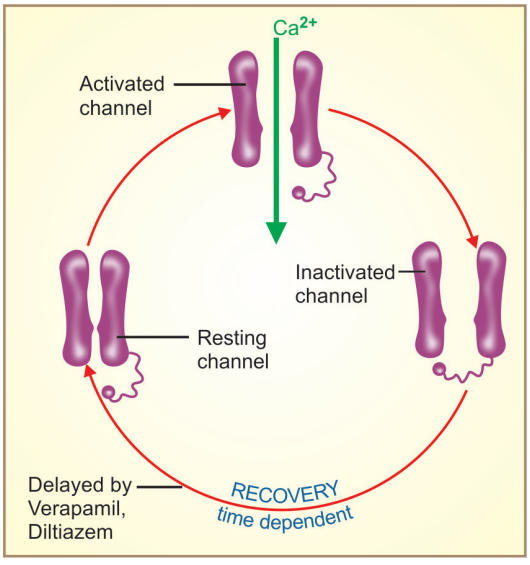



**Fig. 39.4:** Activation–inactivation–recovery cycle of cardiac $Ca^{2+}$ channels

**TABLE 39.2** Comparative properties of representative calcium channel blockers

| | | *Verapamil* | *Nifedipine* | *Diltiazem* |
|---|---|---|---|---|
| 1. | Channel blocking potency | ++ | +++ | + |
| 2. | Frequency dependence of channel blockade | ++ | – | + |
| 3. | Channel recovery rate | Much delayed | No effect | Delayed |
| 4. | Cardiac effects (*In vivo* at usual clinical doses) | | | |
| | Heart rate | ↓ | ↑ | ↓, – |
| | A-V conduction velocity | ↓↓ | – | ↓↓ |
| | Contractility | –, ↓ | ↑ | ↓,↑ |
| | Output | –, ↓ | ↑ | –, ↑ |
| 5. | Vascular smooth muscle relaxation | ++ | +++ | + |
| 6. | Clinical use in | Arrhythmia<br>Angina<br>(Hypertension) | Angina<br>Hypertension | Angina<br>Hypertension<br>Arrhythmia |

The relative potencies to block slow channels in smooth muscle do not parallel those in the heart. The DHPs are more selective for smooth muscle L channels. At concentrations which cause vasodilatation they have negligible negative inotropic action which is most prominent in verapamil. Diltiazem causes less depression of contractility than verapamil. Important differences between the three representative CCBs are summarized in Table 39.2. Their cardiac electrophysiological effects are compared in Table 38.1.

**Verapamil** It dilates arterioles and has some α adrenergic blocking activity—decreases t.p.r. but BP is only modestly lowered. The pronounced direct cardiodepressant effect is partially offset *in vivo* by reflex effects of peripheral vasodilatation. The HR generally decreases, A-V conduction is slowed, but c.o. is maintained by reflex sympathetic stimulation and reduction in aortic impedance. However, ventricular contractility may be markedly impaired in CHF patients. Coronary flow is increased.

*Dose:* 40–160 mg TDS oral, 5 mg by slow i.v. injection. CALAPTIN 40, 80 mg tabs, 120, 240 mg SR tabs, 5 mg/2 ml inj. VASOPTEN 40, 80, 120 mg tab.

*Adverse effects* Nausea, constipation and bradycardia are more common than with other CCBs, while flushing, headache and ankle edema are less common. Hypotension is occasional and tachycardia (common with DHPs) is absent. It can accentuate conduction defects (contraindicated in 2nd and 3rd degree A-V block) and precipitate CHF in patients with preexisting disease. Cardiac arrest has occurred on i.v. injection and when it is given to patients with sick sinus.

*Interactions* Verapamil should not be given with β blockers—additive sinus depression, conduction defects or asystole may occur.
It increases plasma digoxin level by decreasing its excretion: toxicity can develop.
It should not be used along with other cardiac depressants like quinidine and disopyramide.

**Diltiazem** It is somewhat less potent vasodilator than nifedipine and verapamil, and has modest direct negative inotropic action, but direct depression of SA node and A-V conduction are equivalent to verapamil. Usual clinical doses produce consistent fall in BP with little change or decrease in HR. Large dose or i.v. injection decreases t.p.r. markedly which may elicit reflex cardiac effects. Diltiazem dilates coronaries.

*Dose:* 30–60 mg TDS–QID oral; DILZEM, 30, 60 mg tabs, 90 mg SR tab; 25 mg/5 ml inj; ANGIZEM 30, 60, 90, 120, 180 mg tab, DILTIME 30, 60 mg tab; 90, 120 mg SR tab.

*Adverse effects* Side effects are milder, but the profile is similar to verapamil. Like verapamil, it also increases plasma digoxin level.

Diltiazem should not be given to patients with preexisting sinus, A-V nodal or myocardial disease. Only low doses should be given to patients on β blockers.

**Nifedipine** It is the prototype DHP with a rapid onset and short duration of action. The overriding action of nifedipine is arteriolar dilatation → t.p.r. decreases, BP falls. The direct depressant action on heart requires much higher dose, but a weak negative inotropic action can be unmasked after β blockade. As described above, it does not depress SA node or A-V conduction. Reflex sympathetic stimulation of heart predominates producing tachycardia, increased contractility and c.o. No decrease in venous return along with lowering of afterload aids increase in c.o. Coronary flow is increased.

*Dose:* 5–20 mg BD–TDS oral.

CALCIGARD, DEPIN, NIFELAT 5, 10 mg cap, also 10 mg, 20 mg S.R. (RETARD) tab; ADALAT RETARD 10, 20 mg SR tab.

*Adverse effects* Frequent side effects are palpitation, flushing, ankle edema, hypotension, headache, drowsiness and nausea. These are related to peaks of drug level in blood: can be minimized by low starting dose or fractionation of dose or use of retard formulation. Ankle edema is not due to fluid retention, but because of greater dilatation of precapillary than postcapillary vessels. Nifedipine has paradoxically increased the frequency of angina in some patients. Higher mortality among post MI patients has been confirmed. However, it has been safely administered with β blockers and digoxin.

By its relaxant effect on bladder nifedipine can increase urine voiding difficulty in elderly males. Gastroesophageal reflux may be worsened by all DHPs due to relaxation of lower esophageal sphincter. It has also been reported to hamper diabetes control by decreasing insulin release.

### Other dihydropyridines (DHPs)

All DHPs have pharmacodynamic profile similar to nifedipine. However, minor differences in organ selectivity and major differences in pharmacokinetic characteristics exhist (Table 39.3). The slower and longer acting ones induce less reflex sympathetic stimulation. Tachycardia, propensity to increase cardiac work, flushing, headache, dizziness are subdued. They are the favoured DHPs because of milder side effects and because increased mortality among post-MI patients is reported with the regular short-acting nifedipine formulation.

**Felodipine** It differs from nifedipine in having greater vascular selectivity, larger tissue distribution and longer t½. The extended release preparation is suitable for once daily administration.

*Dose:* 5–10 mg OD, max. 10 mg BD.

FELOGARD, PLENDIL, RENDIL 2.5, 5, 10 mg ER tab.

**Amlodipine** Pharmacokinetically it is the most distinct DHP and the most popular. Oral absorption is slow, but complete; peak blood level occurs. after 6 to 9 hr—the early vasodilator side effects (palpitation, flushing, headache, postural dizziness) are largely avoided. Because of less extensive and less variable first pass metabolism, its oral bioavailability is higher and more consistent. Volume of distribution and t½ are exceptionally long: diurnal fluctuation in blood level is small and action extends over the next morning.

*Dose:* 5–10 mg OD; AMLOPRES, AMCARD, AMLOPIN, MYODURA 2.5, 5, 10 mg tabs.

*S(–)Amlodipine* The single enantiomer preparation is effective at half the dose and is claimed to cause less ankle edema.

*Dose:* 2.5–5 mg OD;

S-NUMLO, S-AMCARD, ASOMEX, ESAM 2.5, 5 mg tabs.

**Nitrendipine** A DHP with oral bioavailability of 10–30% and elimination t½ of 4–12 hours. It has been shown to release NO from the endothelium and inhibit cAMP phosphodiesterase. These may be the additional mechanisms of vasodilator action. The endothelial NO may retard atherosclerosis. Ventricular contractility and A-V conduction are not depressed. Nitrendipine is indicated in hypertension and angina pectoris.

*Dose:* 5–20 mg OD; NITREPIN, CARDIF 10, 20 mg tabs.

**Lacidipine** A highly vasoselective newer DHP suitable for once daily administration. It is claimed to attain higher concentration in vascular smooth muscle membrane, and is approved only for use as antihypertensive.

*Dose:* 4 mg OD, increase to 6 mg OD if required.
LACIVAS, SINOPIL 2, 4 mg tabs.

**Nimodipine** It is a short-acting DHP which penetrates blood-brain barrier very efficiently due to high lipid solubility. As such, it is believed to selectively relax cerebral vasculature and is approved for prevention and treatment of neurological deficit due to cerebral vasospasm following subarachnoid haemorrhage or ruptured congenital intracranial aneurysms. Side effects are headache, flushing, dizziness, palpitation and nausea.

*Dose:* 30–60 mg 4–6 hourly for 3 weeks following subarachnoid haemorrhage; VASOTOP, NIMODIP, NIMOTIDE 30 mg tab; 10 mg/50 ml inj.

**Lercanidipine** Another DHP similar to nifedipine, but with longer duration of action. Peak plasma concentrations occur at 1.5–3 hrs; t½ is 5–10 hours. It is indicated in hypertension at a dose of 10–20 mg OD.
LEREZ, LERKA 10, 20 mg tabs.

**Benidipine** A long-acting DHP that owes its long duration of action to slow dissociation from the DHP receptor on the smooth muscle cell. Marketed only in India and Japan, it is indicated in hypertension and angina pectoris.
*Dose:* 4–8 mg OD; CARITEC 4, 8 mg tab.

## PHARMACOKINETICS

The pharmacokinetic parameters of representative $Ca^{2+}$ channel blockers are tabulated in Table 39.3.

All are 90–100% absorbed orally, peak occurring at 1–3 hr (except amlodipine 6–9 hr). The oral bioavailability of $Ca^{2+}$ channel blockers is incomplete with marked inter- and intra-individual variations. This is due to high first pass metabolism (modest and less variable for amlodipine). All are highly plasma protein bound (min.: diltiazem 80%, max.: felodipine 99%).

The $Ca^{2+}$ channel blockers are high clearance drugs with extensive tissue distribution. All are > 90% metabolized in liver and excreted in urine. Some metabolites are active. The elimination t½ are in the range of 2–6 hr, but that of amlodipine is exceptionally long; followed by lacidipine, nitrendipine and felodipine.

On chronic use verapamil decreases its own metabolism—bioavailability is nearly doubled and t½ is prolonged.

## USES

Calcium channel blockers can be safely given to patients with obstructive lung disease and peripheral vascular disease in whom β blockers are contraindicated. The problem of rebound worsening of angina on withdrawal after chronic use is less marked with CCBs than with β blockers.

1. *Angina pectoris* All CCBs are effective in reducing frequency and severity of *classical as well as variant angina.* Benefit in classical angina appears to be primarily due to reduction in cardiac work: mainly as a result of reduced afterload and the BP × HR product. Though, they can increase coronary flow in normal individuals, this is unlikely to be significant in patients with fixed arterial obstruction. Exercise tolerance is increased.

**TABLE 39.3 Pharmacokinetic characteristics of calcium channel blockers**

| | Drug | Bioavailability | Vd (L/Kg) | CL (L/hr/Kg) | Active metabolite | Elimin. t½ (hr) |
|---|---|---|---|---|---|---|
| 1. | Verapamil | 15–30% | 5.0 | 0.9 | Yes | 4–6 |
| 2. | Diltiazem | 40–60% | 3.0 | 0.7 | Yes | 5–6 |
| 3. | Nifedipine | 30–60% | 0.8 | 0.42 | Minor | 2–5 |
| 4. | Felodipine | 15–25% | 10.0 | 1.0 | None | 12–18 |
| 5. | Amlodipine | 60–65% | 21.0 | 0.42 | None | 35–45 |

Many controlled studies and metaanalysis have concluded that myocardial ischaemia may be aggravated by short-acting DHPs. This may be due to decreased coronary flow secondary to fall in mean arterial pressure, reflex tachycardia and coronary steal. The direct cardiac effect of verapamil and diltiazem to reduce $O_2$ requirement. In addition, less marked reflex sympathetic stimulation makes them unlikely to aggravate ischaemia.

Trials using high dose regular short-acting nifedipine formulation have reported increased mortality among MI patients. The sudden rush of sympathetic activity evoked by each dose of these preparations has been held responsible for the deleterious effect. The slow and long-acting DHPs do not share this disadvantage. There is some evidence that verapamil and diltiazem reduce reinfarction and mortality in MI patients (similar to that achieved by β blockers) with uncompromised ventricular function.

*Myocardial infarction:* The concensus opinion is against use of CCBs in evolving MI as well as to prevent further attacks, but verapamil/diltiazem may be employed for secondary prophylaxis when β blockers are contraindicated.

The capacity of CCBs to prevent arterial spasm is undoubtedly responsible for the beneficial effect in *variant angina.* Reduction of cardiac $O_2$ demand would also work in the same direction. No significant difference in efficacy among different CCBs has been noted in angina pectoris.

CCBs are not a first line treatment of *unstable angina,* but may be used as add on therapy to nitrates when coronary vasospasm is prominent and is not counteracted by nitrate alone. Antiplatelet drugs and β blockers + a nitrate are the primary drugs which reduce infarction and mortality in UA. Use of nifedipine/DHPs in non β blocked patients is to be avoided.

2. *Hypertension* All DHPs, diltiazem and verapamil are among the first line drugs for hypertension (*see* Ch. 40).

3. *Cardiac arrhythmias* Verapamil and diltiazem are highly effective in PSVT and for control of ventricular rate in supraventricular arrhythmias (*see* Ch. 38).

4. *Hypertrophic cardiomyopathy* The negative inotropic action of verapamil can be salutary in this condition.

5. *Other uses* Nifedipine is an alternative drug for premature labour (*see* p. 333). Verapamil has been used to suppress nocturnal leg cramps. The DHPs reduce severity of Raynaud's episodes.

## DRUG COMBINATIONS IN ANGINA

Along with any of the drugs used for chronic prophylaxis of angina, sublingual short-acting nitrate is allowed on 'as and when' required basis to abort and terminate anginal attacks when they occur. In addition to the symptomatic treatment with antianginal drugs, therapy aimed at modifying course of coronary artery disease (CAD), and at cardioprotection with antiplatelet drugs, statins and ACE inhibitors is advised by professional guidelines. The β blockers ward-off attacks of angina as well as afford cardioprotection.

Of the three major classes of antianginal drugs described above, generally one agent is used initially; choice depends on the stage and severity of disease, associated cardiac/other medical conditions and individual acceptability of side effects. The antianginal efficacy and tolerability of long-acting nitrates (including transdermal GTN), β blockers and long-acting CCBs is similar. However, direct comparative studies have found β blockers to achieve greater reduction in the number of anginal attacks than CCBs, but objective measurements and outcome were not different. When monotherapy is unable to provide adequate relief in tolerated doses, concurrent use of 2 or 3 drugs may be required.

I. β blocker + long-acting nitrate combination is rational in classical angina because:

(a) Tachycardia due to nitrate is blocked by β blocker.
(b) The tendency of β blocker to cause ventricular dilatation is counteracted by nitrate.
(c) The tendency of β blocker to reduce total coronary flow is opposed by nitrate.

II. The above advantages may also be obtained by combining a slow acting DHP (in place of nitrate) with β blocker. The DHPs are particularly suitable if there is an element of coronary vasospasm in classical angina. However, verapamil or diltiazem should not be used with β blocker since their depressant effects on SA and A-V node may add up.

III. Nitrates primarily decrease preload, while CCBs have a greater effect on afterload and on coronary flow. Their concurrent use may decrease cardiac work and improve coronary perfusion to an extent not possible with either drug alone. This combination may be especially valuable in severe vasospastic angina, and when β blockers are contraindicated.

IV. In the more severe and resistant cases of classical angina, combined use of all the three classes is indicated. Since their primary mechanism of benefit is different, supraadditive results may be obtained.

- Nitrates primarily decrease preload.
- CCBs mainly reduce afterload + increase coronary flow.
- β blockers decrease cardiac work primarily by direct action on heart.

Verapamil/diltiazem should be avoided in such combinations.

In randomized comparative studies, combinations have been found superior to monotherapy only in more severe cases, but not in mild angina. Recent evidence suggests a greater role of reflex vasospasm of arteriosclerotic segments of coronary arteries in precipitating attacks of angina. As such, coronary dilator action of DHPs/nitrates may be more relevant.

## POTASSIUM CHANNEL OPENERS

Minoxidil and diazoxide are $K^+$ channel openers which were used earlier in severe hypertension and hypertensive emergencies. Novel $K^+$ channel openers like *nicorandil, pinacidil* and *cromakalim* have been developed in the 1990s.

The chemical (intracellular 150 mM *vs* extracellular 4–5 mM) and electrical (inside –90 mV) gradients for $K^+$ across the plasma membrane are in opposite directions. As such, depending on the channel, this ion can move in either direction. Such movement is regulated by multiple types of $K^+$ channels, *viz:*

- Voltage dependent $K^+$ channel
- ATP activated $K^+$ channel
- $Ca^{2+}$ activated $K^+$ channel
- Receptor operated $K^+$ channel
- $Na^+$ activated $K^+$ channel
- Cell volume sensitive $K^+$ channel

These channels regulate $K^+$ movement outward as well as inward, serve diverse functions and exhibit different sensitivities to drugs. As such, $K^+$ channel openers exhibit considerable diversity in action.

The above mentioned drugs open ATP activated $K^+$ channels in smooth muscles. Their most prominent action is hyperpolarization and relaxation of vascular as well as visceral smooth muscle. The hypotensive $K^+$ channel opener diazoxide reduces insulin secretion, while sulfonylureas promote insulin release by blocking $K^+$ channels in pancreatic β cells. *Nicorandil* has been introduced as an antianginal drug in the 1990s.

**Nicorandil** This dual mechanism antianginal drug activates ATP sensitive $K^+$ channels ($K_{ATP}$) thereby hyperpolarizing vascular smooth muscle. The vasodilator action is partly antagonized by $K^+$ channel blocker glibenclamide. Like nitrates it also acts as a NO donor—relaxes blood vessels by increasing cGMP. Thus, arterial dilatation is coupled with venodilatation. Coronary flow is increased; dilatation of both epicardial conducting vessels and deeper resistance vessels has been demonstrated. No significant cardiac effects on contractility and conduction have been noted.

Beneficial effects on angina frequency and exercise tolerance comparable to nitrates and CCBs have been obtained in stable as well as vasospastic angina. Nicorandil is believed to exert cardioprotective action by simulating *'ischaemic preconditioning'* as a result of activation of mitochondrial $K_{ATP}$ channels. Ischaemic preconditioning in a phenomenon in which brief periods of ischaemia and reperfusion exert a cardioprotective effect on subsequent total vascular occlusion, and involves opening of mito.$K_{ATP}$ channels.

A large 'Impact of nicorandil in angina' (IONA, 2002) randomized trial found nicorandil to reduce acute coronary events in high risk stable angina patients.

Nicorandil is well absorbed orally, nearly completely metabolized in liver and is excreted in urine. It exhibits biphasic elimination; the initial rapid phase t½ is 1 hour and later slow phase t½ is 12 hours.

*Side effects* of nicorandil are flushing, palpitation, weakness, headache, dizziness, nausea

and vomiting. Large painful aphthous ulcers in the mouth, which heal on stopping nicorandil have been reported. Nitrate like tolerance does not occur with nicorandil, but it has the potential to interact with sildenafil.

*Dose:* 5–20 mg BD; NIKORAN, 5, 10 mg tabs, 2 mg/vial, 48 mg/vial inj; KORANDIL 5, 10 mg tabs.

Though nicorandil is an alternative antianginal drug, its efficacy and long term effects are less well established. It has failed to acquire wide acceptance, but may be useful in resistant angina when combined with other drugs. Administered i.v. during angioplasty for acute MI, it is believed to improve outcome.

## OTHER ANTIANGINAL DRUGS

**1. Dipyridamole** It is a powerful coronary dilator; increases total coronary flow by preventing uptake and degradation of adenosine which is a local mediator involved in autoregulation of coronary flow in response to ischaemia. It dilates resistance vessels and abolishes autoregulation, but has no effect on larger conducting coronary vessels. Cardiac work is not decreased because venous return is not reduced. BP is minimally altered. Accordingly, it fails to relieve anginal symptoms or avert ECG changes.

The pharmacological success but therapeutic failure of dipyridamole has been explained on the basis of 'coronary steal' phenomenon (Fig. 39.5C). By dilating resistance vessels in nonischaemic zone as well, it diverts the already reduced blood flow away from the ischaemic zone.

Dipyridamole inhibits platelet aggregation. By potentiating $PGI_2$ and increasing cAMP in platelets, it enhances antiaggregatory influences. Though not useful as an antianginal drug, it is being employed for prophylaxis of coronary and cerebral thrombosis in post-MI and post-stroke patients, as well as to prevent thrombosis in patients with prosthetic heart valves (*see* Ch. 44).

*Dose*: 25–100 mg TDS; PERSANTIN, CARDIWELL 25, 75, 100 mg tab.

**2. Trimetazidine** This antianginal drug acts by nonhaemodynamic mechanisms. There is no effect on determinants of myocardial $O_2$ consumption, such as HR and BP, both at rest as well as during exercise, but angina frequency is reduced and exercise capacity is increased. In patients not adequately controlled by long-acting nitrate/β blocker/CCB, addition of trimetazidine further reduced anginal attacks and increased exercise duration. The mechanism of action of trimetazidine is uncertain, but it may improve cellular tolerance to ischaemia by:

- Inhibiting mitochondrial long chain 3-ketoacyl-CoA-thiolase (LC3-KAT) a key enzyme in fatty acid oxidation—thereby reducing fatty acid metabolism and increasing glucose metabolism in myocardium. Ischaemic myocardium shifts to utilizing fatty acid as substrate, thereby increasing requirement of $O_2$ for the same amount of ATP generated. Since oxidation of fatty acid requires more $O_2$, shift back of substrate to glucose would reduce $O_2$ demand.Trimetazidine has been labelled as pFOX (fatty acid oxidation pathway) inhibitor.
- Limiting intracellular acidosis and $Na^+$, $Ca^{2+}$ accumulation during ischaemia.
- Protecting against $O^{\cdot}$ free radical induced membrane damage.

Trimetazidine is absorbed orally, partly metabolized and largely excreted unchanged in urine; t½ is 6 hr. It is generally well tolerated; side effects

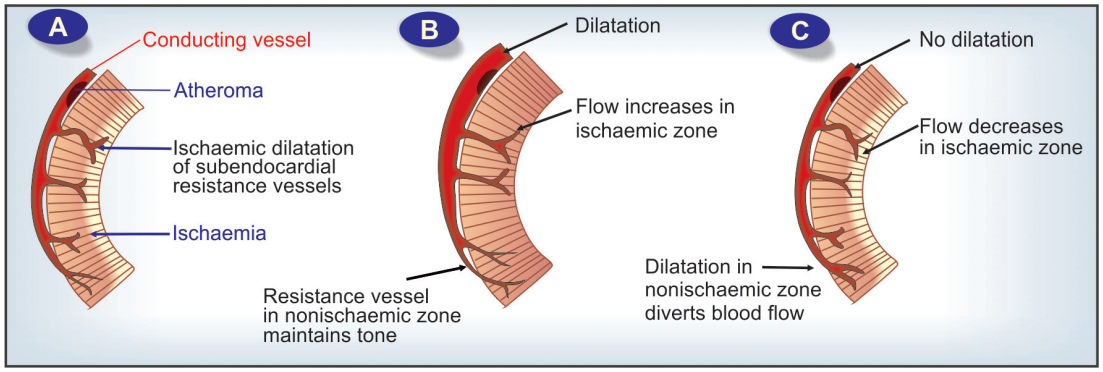



**Fig. 39.5:** Diagrammatic representation of coronary haemodynamics. A—in classical angina, B — Selective nitrate action on conducting vessels, which along with ischaemic dilatation of resistance vessels, increases flow to the subendocardial region → relief of angina. C—Dipyridamole action on all resistance vessels increases blood flow to nonischaemic zone to the detriment of ischaemic zone → coronary steal

are—gastric burning, dizziness, fatigue and muscle cramps. Reversible parkinsonism has been reported in the elderly.

Trimetazidine has also been advocated for visual disturbances, tinnitus, Méniére's disease, dizziness, etc., but conclusive evidence of efficacy in these conditions is lacking. For ischaemic heart disease, it has been widely used in France, Spain, some other European countries and India, but not in the UK or USA. It is mostly an add on medication to conventional therapy in angina and post-MI patients.

*Dose:* 20 mg TDS.

FLAVEDON, CARVIDON, TRIVEDON 20 mg tabs, 35 mg modified release tab.

**3. Ranolazine** This novel antianginal drug primarily acts by inhibiting a late $Na^+$ current (late $I_{Na}$) in the myocardium which indirectly facilitates $Ca^{2+}$ entry through $Na^+/Ca^{2+}$ exchanger. Reduction in $Ca^{2+}$ overload in the myocardium during ischaemia decreases contractility and has a cardioprotective effect. Sparing of fatty acid oxidation during ischaemia in favour of more $O_2$ efficient carbohydrate oxidation by inhibiting LC3KAT has also been demonstrated. This was earlier believed to be the main mechanism of antianginal action of ranolazine, but is now considered secondary. Ranolazine has no effect on HR and BP, but prolongs exercise duration in angina patient.

The efficacy of ranolazine in decreasing frequency of anginal attacks and in prolonging exercise duration has been demonstrated both as monotherapy as well as when added to conventional drugs in multicentric randomized trials: MARISA (monotherapy assessment of ranolazine in stable angina, 2004), CARISA (Combination assessment of ranolazine in stable angina, 2004), ERICA (Efficacy of ranolazine in chronic angina, 2005). In the MERLIN-TIMI36 (2007) trial on non ST-elevation acute coronary syndrome patients, ranolazine use was associated with a lower rate of ventricular arrhythmias. Incidence of AF was also decreased. However, ranolazine prolongs Q-T interval, and should not be used along with other Q-T prolonging drugs (class I and III antiarrhythmics, and other drugs listed on p. 528).

Oral absorption of ranolazine is slow taking 4–6 hours with a bioavailability of 30–50%. It is metabolized in liver mainly by CYP3A4 and excreted in urine, with an average t½ of 7 hours. Side effects reported are dizziness, weakness, constipation, postural hypotension, headache and dyspepsia. It should not be given to patients taking CYP3A4 inhibitors.

*Dose:* 0.5–1.0 g BD as SR tab; RANOZEX, RANK, CARTINEX, REVULANT, RANOLAZ 0.5 g SR tab.

**4. Ivabradine** This 'pure' heart rate lowering antianginal drug has been introduced recently as an alternative to β blockers. The only significant action of ivabradine is blockade of cardiac pacemaker (sino-atrial) cell 'f' channels, which are *'funny'* cation channels that open during early part of slow diastolic (phase 4) depolarization. The resulting inward current ($I_f$) determines the slope of phase 4 depolarization. Selective blockade of $I_f$ current by ivabradine results in heart rate reduction without any other electro-physiological or negative inotropic or negative lucitropic (slowing of myocardial relaxation) effect. Heart rate reduction decreases cardiac $O_2$ demand and prolongation of diastole tends to improve myocardial perfusion ($O_2$ supply). Accordingly, in clinical trials, ivabradine has been found to improve exercise tolerance in stable angina and reduce angina frequency.

Ivabradine is well absorbed orally, 40% bioavailable due to first pass metabolism; degraded by CYP3A4 and excreted in urine with a t½ of 2 hours. Apart from excess bradycardia, the most important adverse effect is visual disturbance. Extrasystoles, prolongation of P-R interval, headache, dizziness and nausea are the other problems. It should not be used if heart rate is <60/min, in sick sinus and in AF. Concurrent use of drugs which prolong Q-T or which inhibit CYP3A4 is contraindicated.

Ivabradine is indicated in chronic stable angina in patients with sinus rhythm who are intolerant to β blockers or when the latter are contraindicated. It can also be used in inappropriate sinus tachycardia.

*Dose*: Initially 5 mg BD, increase if needed to 7.5 mg BD, Elderly 2.5 mg BD.

IVABRAD, BRADIA 5, 7.5 mg tab.

**5. Oxyphedrine** This drug is claimed to improve myocardial metabolism so that heart can sustain hypoxia better. Though used in angina and MI for over 3 decades, its efficacy and status in coronary artery disease is not defined. It can diminish or alter taste sensation.

*Dose:* 8–24 mg TDS oral, 4–8 mg i.v. OD-BD; ILDAMEN 8, 24 mg tab., 4 mg/2 ml inj.

## DRUGS FOR PERIPHERAL VASCULAR DISEASES

Peripheral vascular diseases (PVDs) are either primarily occlusive (Buerger's disease with intermittent claudication of legs), or mainly vasospastic (Raynaud's phenomenon with episodic blanching ± cyanosis of fingers followed by hyperaemia), or both as in arteriosclerotic/diabetic vascular insufficiency, ischaemic leg ulcers, frost bite, gangrene, cerebrovascular inadequacy, etc. Increased cardiovascular risk is associated with all PVDs. Measures that reduce cardiovascular risk (smoking cessation, BP normalization, antiplatelet drugs, diabetes control, statins, weight management, exercise training) have solutary effect on PVDs as well. In addition, vasodilators and some other drugs have been used.

**1. Cyclandelate** It is a papaverine like general smooth muscle relaxant which increases cutaneous, skeletal muscle and cranial blood flow in normal individuals. However, efficacy in PVDs is not different from placebo. Side effects are flushing, palpitation and headache.
*Dose:* 200–400 mg TDS; CYCLOSPASMOL, CYCLASYN 200, 400 mg tab/cap.

**2. Xanthinol nicotinate (Nicotinyl xanthinate)** It is a compound of xanthine and nicotinic acid, both of which are vasodilators. It increases blood flow in many vascular beds and has been promoted for cerebrovascular disorders and PVDs, but therapeutic benefits are insignificant.
*Dose:* 300–600 mg TDS oral; 300 mg by i.m. or slow i.v. injection; COMPLAMINA 150 mg tab, 500 mg retard tab, 300 mg/2 ml inj.

**3. Pentoxiphylline (Oxpentifylline)** An analogue of theophylline and a weak phosphodiesterase (PDE) inhibitor, it has been shown to increase blood flow in ischaemic areas by reducing whole blood viscosity and by improving flexibility of RBCs. The *rheological* (dealing with property of flow) action rather than vasodilatation is said to be responsible for improving passage of blood through microcirculation. Thus, the 'steal' phenomenon is not likely. Oral doses do not affect heart rate, t.p.r. or BP.

Pentoxiphylline is usually well tolerated: side effects are nausea, vomiting, dyspepsia and bloating which can be minimized by taking the drug after meals.
*Dose:* 400 mg BD–TDS; TRENTAL-400, FLEXITAL 400 mg SR tab, 300 mg/15 ml for slow i.v. injection.

Pentoxiphylline is mainly used in intermittent claudication (calf pain on walking) due to occlusive vascular disease (Buerger's disease); walking distance is increased. Other conditions claimed to be improved are: trophic leg ulcers, transient ischaemic attacks (TIAs), nonhaemorrhagic stroke, and chronic cerebrovascular insufficiency. However, overall benefits are modest and restricted to a fraction of patients.

**4. Cilostazole** This is a PDE-3 inhibitor (like the inodilator inamrinone, p.524) which increases intracellular cAMP in platelets and vascular smooth muscle resulting in antiaggregatory and vasodilator effects. In clinical trials it has increased walking distance in patients with intermittent claudication and appears to be more effective than pentoxiphylline. Since long-term oral milrinone therapy for heart failure has increased cardiac mortality and has been discontinued, concern is expressed about long-term safety of cilostazole. However, no increase in cardiovascular mortality has so far been observed with cilostazole, but a warning has been issued not to use cilostazole in patients with heart failure. It is also not to be used in patients who have pain even at rest, or in those with tissue necrosis.

The most common side effect is headache. Others are palpitation, dizziness, nausea, vomiting, weakness and increase in ventricular ectopics or nonsustained VT. Cilostazole is extensively metabolized by CYP3A4 and CYP2C19 into active and inactive metabolites, together having elimination t½ of ~ 12 hours. It should not be administered along with inhibitors of CYP3A4 and CYP2C19, which increase its toxicity.

Cilostazole is indicated for intermittent claudication in patients with no rest pain or heart failure.
*Dose*: 100 mg BD, 30 min before or 2 hour after food. PLETOZ, CILODOC, STILOZ 50, 100 mg tabs.

*Comment* Apart from the above drugs, β adrenergic agonists like isoxsuprine, CCBs like nifedipine and α blockers like prazosin, phenoxybenzamine have been used in PVDs. However, no vasodilator can overcome organic obstruction. Because ischaemia itself is the most potent vasodilator stimulus in skeletal muscle and cerebral beds, vasodilators can even divert the blood to nonischaemic areas (steal phenomenon). They obviously are more useful when vasospasm is wholely or partly involved, e.g. in Raynaud's phenomenon. $PGI_2$ has been employed in severe cases with rest pain (p. 190).

## DRUG THERAPY IN MYOCARDIAL INFARCTION

According to severity, the acute coronary syndromes may be graded into:

- *Unstable angina (UA):* Vascular obstruction is incomplete, myocardial necrosis is absent—biochemical markers of ischaemia (*see* p. 632) do not appear in blood, and ST segment is not elevated in ECG.
- *Non ST segment elevation myocardial infarction (NSTEMI):* Vascular obstruction is incomplete, but is attended by relatively smaller area of myocardial necrosis; biochemical markers appear in blood, but ST segment is not elevated.
- *ST segment elevation myocardial infarction (STEMI):* Vascular obstruction is complete, larger area of myocardium is necrosed, biochemical markers are prominent and ST segment in ECG is elevated.

However, UA and NSTEMI may progress to STEMI.

Myocardial infarction (MI) is ischaemic necrosis of a portion of the myocardium due to sudden occlusion of a branch of coronary artery. An acute thrombus at the site of atherosclerotic obstruction is the usual cause. About ¼ patients die before therapy can be instituted. The remaining are best treated in specialized coronary care units with continuous monitoring of the haemodynamic parameters, biochemical markers and ECG to guide the selection of drugs and dosage. Those who receive such facility can be greatly benefitted by drug therapy, which according to individual needs is directed to:

1. *Pain, anxiety and apprehension* After pain is not relieved by 3 doses of GTN given 5 min apart, an opioid analgesic (morphine/pethidine) or diazepam is administered parenterally.

2. *Oxygenation* By $O_2$ inhalation and assisted respiration, if needed.

3. *Maintenance of blood volume, tissue perfusion and microcirculation* Slow i.v. infusion of saline/low molecular weight dextran (avoid volume overload).

4. *Correction of acidosis* Acidosis occurs due to lactic acid production; can be corrected by i.v. sod. bicarbonate infusion.

5. *Prevention and treatment of arrhythmias* Prophylactic i.v. infusion of a β blocker (unless contraindicated) as soon as the MI patient is seen and its continuation orally for a few days has been shown to reduce the incidence of arrhythmias and mortality. β blockers used early in evolving MI can reduce the infarct size (myocardial salvage) and subsequent complications.

Tachyarrhythmias may be treated with i.v. lidocaine, procainamide or amiodarone. Routine prophylactic lidocaine infusion is not recommended now. Bradycardia and heart block may be managed with atropine or electrical pacing.

6. *Pump failure* The objective is to increase c.o. and/or decrease filling pressure without unduly increasing cardiac work or lowering BP. Drugs used for this purpose are:

(a) *Furosemide*: indicated if pulmonary wedge pressure is > 20 mm Hg. It decreases cardiac preload.

(b) *Vasodilators*: venous or combined dilator is selected according to the monitored haemodynamic parameters. Drugs like GTN (i.v.), or nitroprusside have been mainly used.

(c) *Inotropic agents*: dopamine or dobutamine i.v. infusion (rarely digoxin if AF present) may be needed to augment the pumping action of heart and tide over the crisis.

7. *Prevention of thrombus extension, embolism, venous thrombosis* Aspirin (162–325 mg) should be given for chewing and swallowing as soon as MI is suspected (if not already being taken on a regular basis). This is continued at 80–160 mg/day. Anticoagulants (heparin followed by oral anticoagulants) are used primarily to prevent deep vein thrombosis (increased risk due to bed rest) and pulmonary/systemic arterial embolism. Its value in checking coronary artery thrombus extension is uncertain. Any benefit is short-term; anticoagulants are not prescribed on long-term basis now (*see* Ch. 44).

8. *Thrombolysis and reperfusion* Fibrinolytic agents, i.e. plasminogen activators—streptokinase/urokinase/alteplase to achieve reperfusion of

the infarcted area (*see* Ch. 44). Unless thrombolysis can be started within 1–2 hours of MI symptom onset, primary percutaneous coronary intervention (PCI) with stenting is now the preferred revascularization procedure, wherever available.

9. *Prevention of remodeling and subsequent CHF* ACE inhibitors/ARBs are of proven efficacy and afford long-term survival benefit (*see* Ch. 36).

10. *Prevention of future attacks*

(a) Platelet inhibitors—aspirin or clopidogrel given on long-term basis are routinely prescribed (*see* Ch. 44).

(b) β blockers—reduce risk of reinfarction, CHF and mortality. All patients not having any contraindication are put on a β blocker for at least 2 years.

(c) Control of hyperlipidaemia—dietary substitution with unsaturated fats, hypolipidemic drugs especially statins (*see* Ch. 45).

## ☞ PROBLEM DIRECTED STUDY

**39.1** A 55-year-old man presented with complaints of tightness and discomfort over middle part of chest felt episodically, particularly after walking briskly or climbing stairs or during sex. This is relieved within 5–10 minutes of rest. One or two episodes occur practically every day. He is a past smoker who quit smoking 5 years back when he was diagnosed to have chronic obstructive pulmonary disease (COPD), for which he regularly takes 2 inhalations of Ipratropium Br. 3 times a day and 2 puffs of salbutamol inhalation whenever he feels out of breath. The pulse was 90/min and BP 124/82 mm Hg. The resting ECG was normal, but stress test was positive. A diagnosis of exertional angina was made and he was prescribed—Tab glyceryl trinitrate 0.5 mg to be put under the tongue as soon as he begins to feel the chest discomfort, as well as before undertaking any physical exertion.

(a) Should he be prescribed another drug to be taken on a regular basis to prevent episodes of angina? If so, which drugs can be given to him and which cannot be given?

(b) Should additional medication be given to prevent long-term complications and improve survival?

(see Appendix-1 for solution)

# Chapter 40 Antihypertensive Drugs

These are drugs used to lower BP in hypertension.

Hypertension is a very common disorder, particularly past middle age. It is not a disease in itself, but is an important risk factor for cardiovascular mortality and morbidity. The cutoff manometric reading between normotensives and hypertensives is arbitrary. For practical purposes 'hypertension' could be that level of BP at or above which long-term antihypertensive treatment will reduce cardiovascular mortality. The JNC 7* (2003) and WHO-ISH@ guidelines (2003) have defined it to be 140 mm Hg systolic and 90 mm Hg diastolic, though risk appears to increase even above 120/80 mm Hg. Epidemiological studies have confirmed that higher the pressure (systolic or diastolic or both) greater is the risk of cardiovascular disease.

Majority of cases are of essential (primary) hypertension, i.e. the cause is not known. Sympathetic and renin-angiotensin systems (RAS) may or may not be overactive, but they do contribute to the tone of blood vessels and c.o. in hypertensives, as they do in normotensives. Many antihypertensive drugs interfere with these regulatory systems at one level or the other. Antihypertensive drugs, by chronically lowering BP, may reset the barostat to function at a lower level of BP.

Antihypertensive drug therapy has been remarkably improved in the last 60 years. Different classes of drugs have received prominence with passage of time in this period. Before 1950 hardly any effective and tolerated antihypertensive was available. *Veratrum* and *Sod. thiocyanate* could lower BP, but were toxic and difficult to use. The *ganglion blockers* developed in the 1950s were effective, but inconvenient. *Reserpine* was a breakthrough, but produced mental depression. The therapeutic potential of *hydralazine* could not be tapped fully because of marked side effects when it was used alone. *Guanethidine* introduced in 1961 was an improvement on ganglion blockers. The antihypertensives of the 1960–70s were *methyldopa,* β *blockers*, *thiazide* and *high ceiling diuretics* and *clonidine*. The status of β blockers and diuretics was consolidated in the 1970s and selective $\alpha_1$ blocker *prazosin* broke new grounds. The antihypertensives of the 1980–90s are angiotensin II converting enzyme *(ACE) inhibitors* and *calcium channel blockers*. Angiotensin receptor blockers (*losartan,* etc.) were added soon after, and the direct renin inhibitor *aliskiren* is the latest drug. With the development of many types of drugs, delineation of their long-term benefits and complications, and understanding of the principles on which to combine them, hypertension can now be controlled in most cases with minimum discomfort.

## CLASSIFICATION

1. *Diuretics*
   *Thiazides:* Hydrochlorothiazide, Chlorthalidone, Indapamide
   *High ceiling:* Furosemide, etc.
   *$K^+$ Sparing:* Spironolactone, Amiloride
2. *ACE inhibitors*
   Captopril, Enalapril, Lisinopril, Perindopril, Ramipril, Fosinopril, etc.
3. *Angiotensin ($AT_1$ receptor) blockers*
   Losartan, Candesartan, Irbesartan, Valsartan, Telmisartan
4. *Direct renin inhibitor*
   Aliskiren
5. *Calcium channel blockers*
   Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine, etc.
6. β *Adrenergic blockers*
   Propranolol, Metoprolol, Atenolol, etc.

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* JNC 7—The seventh report of Joint National Committee (of USA) on prevention, detection, evaluation and treatment of high blood pressure.

@ WHO-ISH—World Health Organization and International Society of Hypertension.

7. β + α *Adrenergic blockers*
   Labetalol, Carvedilol
8. α *Adrenergic blockers*
   Prazosin, Terazosin, Doxazosin
   Phentolamine, Phenoxybenzamine
9. *Central sympatholytics*
   Clonidine, Methyldopa
10. *Vasodilators*
   *Arteriolar:* Hydralazine, Minoxidil, Diazoxide
   *Arteriolar + venous:* Sodium nitroprusside

Adrenergic neurone blockers (Reserpine, Guanethidine, etc.) and ganglion blockers (Pentolinium, etc.) are only of historical importance, though reserpine is still marketed.

## DIURETICS

Diuretics have been the standard antihypertensive drugs over the past 4 decades, though they do not lower BP in normotensives. Their pharmacology is described in Ch. 41.

**Thiazides** (hydrochlorothiazide, chlorthalidone) These are the diuretic of choice for uncomplicated hypertension; have similar efficacy and are dose to dose equivalent. All megatrials have been carried out with these two only. Chlorthalidone is longer acting (~ 48 hours) than hydrochlorothiazide (< 24 hours) and may have better round-the-clock action. Indapamide (*see* later) is also mainly used as antihypertensive, and is equally effective. There is little experience with other members of the thiazide class, and they should not be considered interchangeable with hydrochlorothiazide/chlorthalidone as antihypertensive. The proposed mechanism of antihypertensive action is:

1. Initially, the diuresis reduces plasma and e.c.f. volume by 5–15%, and this decreases c.o.
2. Subsequently, compensatory mechanisms operate to almost regain $Na^+$ balance and plasma volume; c.o. is restored, but the fall in BP is maintained by a slowly developing reduction in t.p.r.
3. The reduction in t.p.r. is most probably an indirect consequence of a small (~5%) persisting $Na^+$ and volume deficit. Decrease in intracellular $Na^+$ concentration in the vascular smooth muscle may reduce stiffness of vessel wall, increase their compliance and dampen responsiveness to constrictor stimuli (NA, Ang II). Similar effects are produced by salt restriction; antihypertensive action of diuretics is lost when salt intake is high. A mild slowly developing vasodilator action of thiazides due to opening of smooth muscle $K^+_{ATP}$ channels and hyperpolarization has been proposed, but does not appear to be real.

The fall in BP develops gradually over 2–4 weeks. During long-term treatment with thiazides, the heart rate and c.o. remain unaffected, while t.p.r. is reduced despite compensatory increase in plasma renin activity, which confirms persisting $Na^+$ deficit. Thiazides have no effect on capacitance vessels, sympathetic reflexes are not impaired: postural hypotension is rare. Thiazides are mild antihypertensives, average fall in mean arterial pressure is ~10 mm Hg. They are effective by themselves in ~ 30% cases (mostly low grade hypertension) but they potentiate all other antihypertensives (except DHPs) and prevent development of tolerance to these drugs by not allowing expansion of plasma volume. Thus, in combination, they are useful in any grade of hypertension. They are more effective in the elderly and maximal antihypertensive efficacy is reached at 25 mg/day dose, though higher doses produce greater diuresis. Their antihypertensive action is attenuated by NSAIDs.

**High ceiling diuretics** Furosemide, the prototype of this class, is a strong diuretic, but the antihypertensive efficacy does not parallel diuretic potency. Furosemide is a weaker antihypertensive than thiazides: fall in BP is entirely dependent on reduction in plasma volume and c.o. The explanation to this paradox may lie in its brief duration of action. The natriuretic action lasting only 4–6 hr after the conventional morning dose is followed by compensatory increase in proximal tubular reabsorption of $Na^+$. The $Na^+$ deficient state in vascular smooth muscle may not be maintained round-the-clock. The t.p.r. and vascular responsiveness are not reduced. Moreover, the

high ceiling diuretics are more liable to cause fluid and electrolyte imbalance, weakness and other side effects. They are indicated in hypertension only when it is complicated by:

(a) Chronic renal failure: thiazides are ineffective, both as diuretic and as antihypertensive.
(b) Coexisting refractory CHF.
(c) Resistance to combination regimens containing a thiazide, or marked fluid retention due to use of potent vasodilators.

### *Desirable properties of thiazide diuretics as antihypertensives are:*

1. Once a day dosing and flat dose-response curve permitting simple standardized regimens.
2. No fluid retention, no tolerance.
3. Low incidence of postural hypotension and relative freedom from side effects, especially CNS, compared to sympatholytics.
4. Effective in isolated systolic hypertension (ISH).
5. Lessened risk of hip fracture in the elderly due to hypocalciuric action of thiazides.
6. Low cost.

### *Current status of diuretics as antihypertensives*

The popularity of diuretics as antihypertensive has had ups and downs. In the 1960–70s they were almost routinely prescribed alone or in combination, to nearly all hypertensive patients. The usual dose used was hydrochlorothiazide/chlorthalidone 50 mg/day. Soon a number of drawbacks were highlighted:

- Hypokalaemia—muscle pain, fatigue and loss of energy.
- Erectile dysfunction in males.
- Carbohydrate intolerance: due to inhibition of insulin release (probably secondary to $K^+$ depletion which interferes with conversion of proinsulin to insulin), precipitation of diabetes.
- Dyslipidemia: rise in total and LDL cholesterol and triglycerides with lowering of HDL. This could increase atherogenic risk, but no direct evidence has been obtained.
- Hyperuricaemia: by inhibiting urate excretion—increased incidence of gout.
- Increased incidence of sudden cardiac death: attributed to episodes of *torsades de pointes* and ischaemic ventricular fibrillation precipitated by hypokalaemia.

Consequently, prescribing of diuretics fell. Over the past 25 years thiazides have been used at lower doses (12.5–25 mg/day hydrochlorothiazide or equivalent) alone and in combination with a $K^+$ sparing diuretic.

The multiple risk factor intervention trial (1982), the Medical research council trial (1987, 1992), the systolic hypertension in the elderly programme (SHEP, 1991) and a case control study (1994) demonstrated that increased incidence of death associated with thiazide use in the elderly was dose-dependent, and that 25 mg/day yielded the best benefit-risk ratio. Favourable results obtained with ≤ 25 mg/day in the above and subsequent studies, including ALLHAT (2002) and a meta-analysis (2003) have reinstated thiazide diuretics as the first choice antihypertensive.

Findings with low dose thiazide therapy are:

- Though serum $K^+$ falls a little, significant hypokalaemia does not occur.
- Continuous ECG recording studies have failed to document increased incidence of arrhythmias during low-dose thiazide therapy.
- Impairment of glucose tolerance or increase in serum cholesterol or hyperuricaemia over long-term are minimal.
- Whereas earlier data had failed to document reduction in the incidence of MI with thiazides, analysis of recent trials has found them to reduce fatal and nonfatal MI by 27–44%. The incidence of stroke is reduced by 31–49%. Overall mortality and morbidity is reduced in long-term trials.
- Though not as effective as ACE inhibitors in reversing left ventricular hypertrophy, some recent trials in mild to moderate hypertension have found thiazides to reduce left ventricular mass.

The JNC 7 recommends instituting low-dose (12.5–25 mg) thiazide therapy, preferably with added $K^+$ sparing diuretic, as a first choice treatment of essential hypertension, especially in the elderly. Higher doses are neither more effective nor safe. If the low dose (25 mg/day) fails to reduce BP to desired level, another antihypertensive should be added, rather than increasing

dose of the diuretic. However, in the treatment of severe hypertension when potent vasodilators/sympatholytics have induced fluid retention, higher dose of thiazide or a loop diuretic may be appropriate. Not withstanding the above, there are subsets of patients in whom other antihypertensives are more suitable. Some patients complain impairment of quality of life with diuretics.

*Indapamide* It is a mild diuretic, chemically related to chlorthalidone; reduces BP at doses which cause little diuresis. Electrolyte disturbances and $K^+$ loss are minimal at antihypertensive doses. It probably has additional vasodilator action exerted through alteration of ionic fluxes across vascular smooth muscle cell.

Indapamide is well absorbed orally, has an elimination t½ of 16 hr. Single daily dose (2.5 mg) is enough.

LORVAS, NATRILIX 2.5 mg tab, NATRILIX-SR 1.5 mg SR tab

It is well tolerated: side effects are minor g.i. symptoms and fatigue. Hypokalaemia is infrequent.

**Potassium sparing diuretics** Spironolactone, eplerenone and amiloride but not triamterene themselves lower BP slightly. However, they are used only in conjunction with a thiazide diuretic to prevent $K^+$ loss and to augment the antihypertensive action. Spironolactone is not favoured because of its hormonal side effects (gynaecomastia, impotence, menstrual irregularities). This problem has been offset in the newer aldosterone antagonist eplerenone, and it is increasingly used.

With the recent appreciation of the role of aldosterone in promoting hypertension related ventricular and vascular hypertrophy and renal fibrosis, it is considered that aldosterone antagonists will attenuate these complications. As such, there is resurgence in their use, especially in refractory hypertension.

Hyperkalemia should be watched when $K^+$ sparing diuretics are used with ACE inhibitors/ARBs.

## ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS

The ACE inhibitors are one of the first choice drugs in all grades of essential as well as renovascular hypertension (except those with bilateral renal artery stenosis). Most patients require relatively lower doses (enalapril 2.5–10 mg/day or equivalent) which are well tolerated. Used alone they control hypertension in ~50% patients, and addition of a diuretic/β blocker extends efficacy to ~90%. Because of supraadditive synergism, only a low dose of diuretic (12.5 mg of hydrochlorothiazide, rarely 25 mg) needs to be added. The pharmacology and use of ACE inhibitors in hypertension are described in Ch. 36. Of particular mention are their renal blood flow improving action, their potential to retard diabetic nephropathy and their capacity to regress left ventricular/vascular hypertrophy. They are the most appropriate antihypertensives in patients with diabetes, nephropathy (even nondiabetic), left ventricular hypertrophy, CHF, angina and post MI cases. Several large prospective studies including AIRE (1993), HOPE (2000), ALLHAT (2002) have confirmed the antihypertensive and cardioprotective effects of ACE inhibitors. They appear to be more effective in younger (< 55 year) hypertensives than in the elderly. Dry persistent cough is the most common side effect requiring discontinuation of ACE inhibitors.

## ANGIOTENSIN RECEPTOR BLOCKERS

The pharmacology of *losartan* and other ARBs is described on p. 506. In a dose of 50 mg/day losartan is an effective antihypertensive. Action manifests early and progresses to peak at 2–4 weeks. Addition of 12.5 mg/day hydrochlorothiazide further enhances the fall in BP. The newer ARBs—valsartan, candesartan, irbesartan and telmisartan have been shown to be as effective antihypertensives as ACE inhibitors, while losartan may be somewhat weaker than high doses of ACE inhibitors. ARBs are remarkably free of side effects. Because they do not increase kinin levels, the ACE inhibitor related cough is not encountered. Angioedema, urticaria and taste disturbance are also rare. Though effects of ACE inhibitors and ARBs are not identical, the latter have all the metabolic and prognostic advantages of ACE inhibitors.

Several interventional endpoint reduction trials like LIFE (2002), VALUE (outcomes in hypertensive patients with valsartan or amlodipine, 2004), SCOPE (study on cognition and prognosis in the elderly; stroke prevention with candesartan in elderly with isolated systolic hypertension, 2004), JLIGHT (Japanese losartan therapy intended for global renal protection in hypertensive patients, 2004) have attested to the favourable effects of ARBs on morbidity and mortality in hypertensive patients.

As antihypertensive, use of ARBs has outstripped that of ACE inhibitors. The value of combining ARBs with ACE inhibitors is discussed on p. 507.

### DIRECT RENIN INHIBITORS

*Aliskiren* the only available member of the latest class of RAS inhibitors which act by blocking catalytic activity of renin and inhibiting production of Ang I and Ang II. It is described in Ch. 36. Aliskiren is an equally effective antihypertensive as ACE inhibitors and ARBs, but experience with it so far is limited. However, no remarkable features have emerged and presently it is a second line antihypertensive which may be employed when the more established ACE inhibitors or ARBs cannot be used, or to supplement them.



## CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (CCBs) are another class of first line antihypertensive drugs. Their pharmacology is described in Ch. 39. All 3 subgroups of CCBs, *viz.* dihydropyridines (DHPs, e.g. amlodipine), phenylalkylamine (verapamil) and benzothiazepine (diltiazem) are equally efficacious antihypertensives. They lower BP by decreasing peripheral resistance without compromising c.o. Despite vasodilatation, fluid retention is insignificant.

Ankle edema that occurs in some patients is due to increased hydrostatic pressure across capillaries of the dependent parts as a result of reflex constriction of post capillary vessels in these vascular beds.

The onset of antihypertensive action is quick. With the availability of long acting preparations, most agents can be administered once a day. Monotherapy with CCBs is effective in ~ 50% hypertensives; their action is independent of patient's renin status, and they may improve arterial compliance. Other advantages of CCBs are:

1. Do not compromise haemodynamics: no impairment of physical work capacity.
2. No sedation or other CNS effects; cerebral perfusion is maintained.
3. Not contraindicated in asthma, angina (especially variant) and PVD patients: may benefit these conditions.
4. Do not impair renal perfusion.
5. Do not affect male sexual function.
6. No deleterious effect on plasma lipid profile, uric acid level and electrolyte balance.
7. Shown to have no/minimal effect on quality of life.
8. No adverse foetal effects; can be used during pregnancy (but can weaken uterine contractions during labour).

In the past few years large amount of data from controlled trials (HINT, TRENT, SPRINT I, II) and metaanalysis has consistently indicated increased mortality/reinfarction in patients treated with standard nifedipine (or other short-acting DHP) formulations. This increase in mortality is dose-related. Worsening of unstable angina and CHF has also been noted. The CCBs do not decrease venous return. DHPs may even increase it and jeopardise haemodynamics in patients with diastolic dysfunction. DHPs (especially short-acting) also tend to increase HR and c.o. by invoking reflex sympathetic stimulation. The increased mortality among coronary heart disease patients has been attributed to repeated surges of adrenergic discharge and marked swings of BP attending each dose of rapidly acting DHP. However, this risk cannot be extrapolated to verapamil/diltiazem as broughtout by DAVIT I, II and other controlled studies, as well as to slow acting DHPs (amlodipine type) including nifedipine GITS (gastrointestinal therapeutic system).

The Systolic hypertension in Europe (Syst-EUR) trial has shown that nitrendipine (long-acting DHP) reduces cardiovascular morbidity and mortality in elderly hypertensives. The Hypertension optimal treatment (HOT), and Sweedish trial in old patients with hypertension-2 (STOP-2) studies have also found CCBs equi-effective as diuretics/β blockers/ACE inhibitors in reducing cardiovascular/total mortality. No excess mortality with the use of amlodipine in post MI and acute coronary syndrome patients has been noted in the ALLHAT (2002) study. On the other hand, CCBs do not afford survival benefit in post MI patients as β blockers, ACE inhibitors or low dose thiazides do. CCBs are also not as effective in suppressing left ventricular hypertrophy (a major risk factor in ischaemic heart disease) as ACE inhibitors.

The JNC 7 have considered CCBs to be less suitable for monotherapy in hypertensives with no other risk factors, because they appear to afford

less prognostic benefits than thiazides, β blockers and ACE inhibitors/ARBs. However, some recent large trials including ASCOT-BPLA (2005) and ACCOMPLISH (2008) have testified to superior efficacy of amlodipine both as monotherapy and when combined with an ACE inhibitor for reducing cardiovascular events in high risk hypertensive patients. Thus, CCBs continue to be used as one of the first line monotherapy options because of their high efficacy and excellent tolerability. They are preferred in the elderly hypertensive. Also there is convincing evidence of their stroke preventing potential (syst EUR, ALLHAT studies). The long-acting DHPs are next to ACE inhibitors in reducing albuminuria and slowing disease progression in hypertensive/diabetic nephropathy. They are the most useful antihypertensives in cyclosporine induced hypertension in renal transplant recipients.

Use of rapid acting oral nifedipine for urgent BP lowering in hypertensive emergencies is out moded. In fact, there is currently no therapeutic indication for rapid and short-acting oral DHPs in hypertension.

Other concerns in the use of CCBs as antihypertensive are:

(i) The negative inotropic/dromotropic action of verapamil/diltiazem may worsen CHF and cardiac conduction defects (DHPs are less likely to do so).
(ii) By their smooth muscle relaxant action, the DHPs can worsen gastroesophageal reflux.
(iii) CCBs (especially DHPs) may accentuate bladder voiding difficulty in elderly males.

## β-ADRENERGIC BLOCKERS

The pharmacology and mechanism of antihypertensive action of β blockers is described in Ch. 10. They are mild antihypertensives; do not significantly lower BP in normotensives. Used alone they suffice in 30–40% patients—mostly stage I cases. Additional BP lowering may be obtained when combined with other drugs.

The hypotensive response to β blockers develops over 1–3 weeks and is then well sustained. Despite short and differing plasma half lives, the antihypertensive action of most β blockers is maintained over 24 hr with a single daily dose.

All β blockers, irrespective of associated properties, exert similar antihypertensive effect. Drugs with intrinsic sympathomimetic activity (ISA) cause less/no reduction of HR and c.o. but lower vascular resistance by $\beta_2$ agonism. Nebivolol reduces t.p.r. by generating NO. The nonselective β blockers slightly reduce renal blood flow and g.f.r., but this is minimal in the $\beta_1$ selective blockers and in those with ISA.

There are several contraindications to β blockers, including cardiac, pulmonary and peripheral vascular disease. The nonselective β blockers have an unfavourable effect on lipid profile (raise triglyceride level and LDL/HDL ratio). They have also fared less well on quality of life parameters like decreased work capacity, fatigue, loss of libido and subtle cognitive effects (forgetfulness, low drive), nightmares and increased incidence of antidepressant use. Many of these drawbacks are minimized in the $\beta_1$ selective agents and in those which penetrate brain poorly. Patient's acceptability of a $\beta_1$ selective hydrophilic drug like atenolol is better than that of propranolol. However, some recent studies have pointed out that atenolol monotherapy may be less effective in preventing hypertension related stroke and coronary artery disease.

Because of absence of postural hypotension, bowel alteration, salt and water retention; a low incidence of side effects, and once a day regimen, β blockers retain their place among the first choice drugs recommended by JNC 7 and WHO-ISH, especially for relatively young non-obese hypertensives, those prone to psychological stress or those with ischaemic heart disease. β blockers and ACE inhibitors are the most effective drugs for preventing sudden cardiac death in post-infarction patients. However, they are less effective for primary prophylaxis of MI and for preventing left ventricular hypertrophy. All cause mortality has been lowered in long-term trials by β blockers. Hypertensives with stable heart failure should be

treated with one of the selected β blockers (metoprolol/bisoprolol/carvedilol/nebivolol) along with an ACE inhibitor/ARB (CIBIS, 1999; MERIT-HF, 1999, COPERNICUS, 2002 studies). Barring the above subsets of patients with compelling indications and suitability criteria, β blockers are now less commonly selected as the initial antihypertensive. β blockers are considered less effective and less suitable for the older hypertensive. The LIFE (2002) and ALLHAT (2002) trials have found β blockers to be inferior to low-dose thiazide or ACE inhibitor/ARB (losartan) or a combination of these in preventing stroke, as well as in diabetic patients. As monotherapy, ACE inhibitors/ARBs and CCBs appear to compromise quality of life less than β blockers. Rebound hypertension has occurred on sudden discontinuation of β blockers; myocardial ischaemia may be aggravated and angina or MI may be precipitated.

### β+α ADRENERGIC BLOCKERS

**Labetalol** (*see* Ch. 10). It is a combined α and β blocker; reduces t.p.r. and acts faster than pure β blockers. It has been used i.v. for rapid BP reduction in hyperadrenergic states, cheese reaction, clonidine withdrawal, eclampsia, etc. Oral labetalol therapy is restricted to moderately severe hypertension not responding to a pure β blocker, because side effects of both α blocker and β blocker occur with it.

**Carvedilol** This nonselective β + weak selective $\alpha_1$ blocker produces vasodilatation and has additional antioxidant/free radical scavenging properties. Whether these ancilliary properties confer any superiority is not known. Carvedilol is a frequently selected drug for long-term treatment of CHF, and is approved as an antihypertensive as well. Side effects are similar to labetalol; liver enzymes may rise in some.

## α-ADRENERGIC BLOCKERS

### Prazosin (*see* Ch. 10)

This prototype selective $\alpha_1$ antagonist dilates both resistance and capacitance vessels; effect on the former predominating. The haemodynamic effects, *viz* reduction in t.p.r. and mean BP accompanied by minor decrease in venous return and c.o. are similar to that produced by a direct acting vasodilator. However, unlike hydralazine, there is little reflex cardiac stimulation and renin release during long-term therapy. Tachycardia does not compensate for the fall in BP, because release inhibitory $\alpha_2$ (presynaptic) receptors are not blocked: autoregulation of NA release remains intact. It probably decreases central sympathetic tone also.

Renal blood flow and g.f.r. are maintained but fluid retention may attend fall in B.P. Cardiovascular reflexes are not appreciably impaired during chronic therapy, but postural hypotension and fainting may occur in the beginning—called 'first dose effect', and with dose increments. This disappears with continued therapy, but may persist in the elderly. For this reason, prazosin is always started at low dose (0.5 mg) given at bedtime and gradually increased with twice daily administration till an adequate response is produced (max. dose 10 mg BD). An oral dose produces peak fall in BP after 4–5 hours and the effect lasts for nearly 12 hours, though plasma t½ is only 3 hours. This may be due to generation of active metabolites.

Other advantages of prazosin are:

- Does not impair carbohydrate metabolism; suitable for diabetics, but not if neuropathy is present, because postural hypotension is accentuated.
- Has a small but favourable effect on lipid profile: lowers LDL cholesterol and triglycerides, increases HDL.
- Affords symptomatic improvement in coexisting benign prostatic hypertrophy.

MINIPRESS XL: Prazosin GITS 2.5 mg, 5 mg tabs.; PRAZOPRESS 1, 2 mg tabs.

*Adverse effects* Prazosin is generally well tolerated at low doses. Apart from postural hypotension related symptoms (particularly in the beginning), other side effects are headache, drowsiness, dry mouth, weakness, palpitation, nasal blockade, blurred vision and rash. Ejaculation may be impaired in males: especially with higher doses. Fluid retention attending prazosin monotherapy may precipitate CHF.

*Use* Prazosin is a moderately potent antihypertensive, but is not used as a first line drug because fluid retention and tolerance gradually develops

with monotherapy—necessitating dose increase—more side effects and risk of CHF. It may be added to a diuretic + β blocker in those not achieving target BP.

**Terazosin, Doxazosin** These are long-acting congeners of prazosin with similar properties but suitable for once daily dosing (*see* p. 142). In the ALLHAT (2002) study doxazosin monotherapy has doubled the incidence of CHF; but this can occur with any $\alpha_1$ blocker. A higher incidence of stroke relative to patients receiving a thiazide diuretic was also noted. Their status in hypertension is similar to that of prazosin.

### Nonselective α blockers (Phentolamine, Phenoxybenzamine)

The nonselective α blockers have been disappointing for routine treatment of hypertension, because fall in t.p.r. is compensated by increased HR and c.o. They block both $\alpha_1$ and $\alpha_2$ receptors—NA release is accentuated. They are reserved for special situations like pheochromocytoma, clonidine withdrawal, cheese reaction, etc., where circulating CAs are responsible for the rise in BP.

## CENTRAL SYMPATHOLYTICS

**Clonidine** It is an imidazoline derivative having complex actions. Clonidine is a partial agonist with high affinity and high intrinsic activity at $\alpha_2$ receptors, especially $\alpha_{2A}$ subtype in brainstem. The major haemodynamic effects result from stimulation of $\alpha_{2A}$ receptors present mainly postjunctionally in medulla (vasomotor centre). This decreases sympathetic out flow → fall in BP and bradycardia. Enhanced vagal tone contributes to bradycardia. Plasma NA declines. Though clonidine is capable of reducing NA release from peripheral adrenergic nerve endings (release inhibitory prejunctional $\alpha_2$ action), this is not manifest at clinically used doses. Clonidine is a moderately potent antihypertensive.

Clonidine also activates *Imidazoline receptors* which are distinct from $\alpha_2$ receptors and are present in the brain as well as periphery. Activation of medullary imidazoline receptors also causes decreased sympathetic outflow and fall in BP.

Rapid i.v. injection of clonidine raises BP transiently due to activation of peripheral postsynaptic vasoconstrictor $\alpha_{2B}$ receptors at the high concentrations so attained. Oral doses producing lower plasma clonidine levels cause only fall in BP, because clonidine has lower intrinsic activity on $\alpha_{2B}$ receptors which predominate in vascular smooth muscle. Probably for the same reason clonidine exhibits the therapeutic window phenomenon: optimum lowering of BP occurs between blood levels of 0.2–2.0 ng/ml. At higher concentrations fall in BP is less marked.

On chronic administration of clonidine decrease in c.o. contributes more to the fall in BP than decrease in t.p.r. Cardiovascular reflexes are affected little. Decreased sympathetic flow to the kidney results in reduced renin release. Plasma lipid levels are not altered.

*Pharmacokinetics* Clonidine is well absorbed orally; peak occurs in 2–4 hours; 1/2 to 2/3 of an oral dose is excreted unchanged in urine, the rest as metabolites. Plasma t½ is 8–12 hours. Effect of a single dose lasts for 6–24 hours.

*Dose:* Start with 100 µg OD or BD, max. 300 µg TDS, orally or i.m.

CATAPRES 150 µg tab, ARKAMIN 100 µg tab.

*Adverse effects* Side effects with clonidine are relatively common.

- Sedation, mental depression, disturbed sleep; dryness of mouth, nose and eyes (secretion is decreased by central action), constipation (antisecretory effect on the intestines).
- Impotence, salt and water retention, bradycardia.
- Postural hypotension occurs, but is mostly asymptomatic.
- Alarming rise in BP, in excess of pretreatment level, with tachycardia, restlessness, anxiety, sweating, headache, nausea and vomiting occur in some patients when doses of clonidine are missed for 1–2 days. The syndrome is very similar to that seen in pheochromocytoma: plasma catecholamine (CA) concentration is increased. This is due to:
  (a) Sudden removal of central sympathetic inhibition resulting in release of large quantities of stored CAs.
  (b) Supersensitivity of peripheral adrenergic structures to CAs that develops due to chronic reduction of sympathetic tone during clonidine therapy.

A combination of α blocker with a β blocker, or a potent vasodilator (nitroprusside) or clonidine itself can be used to treat the syndrome.

*Interactions* Tricyclic antidepressants and chlorpromazine abolish the antihypertensive action of clonidine, probably by blocking α receptors on which clonidine acts.

*Use* Clonidine was a popular antihypertensive in the late 1960s and 1970s, but frequent side effects, risk of withdrawal hypertension and development of tolerance have relegated it to a 3rd or 4th choice drug. There is no data on prognostic benefits, if any, of clonidine. At present, it is occasionally used in combination with a diuretic.

### Other indications

1. Opioid withdrawal: Opioid and $\alpha_2$ adrenergic systems converge on the same effectors in many systems; both activate the Gi regulatory protein. Clonidine suppresses sympathetic overactivity of opioid withdrawal syndrome and reduces craving to some extent.

   Clonidine has also facilitated alcohol withdrawal and smoking cessation.
2. Clonidine has analgesic activity. It has been used to substitute morphine for intrathecal/epidural surgical and postoperative analgesia.
3. Clonidine attenuates vasomotor symptoms of menopausal syndrome.
4. Clonidine has been used to control loose motions due to diabetic neuropathy. It may be acting by $\alpha_2$ receptor mediated enhancement of salt absorption in gut mucosa.

**Methyldopa** This α-methyl analogue of dopa, the precursor of dopamine (DA) and NA is one of the first rationally designed antihypertensives. The α methyl-NA (a selective $\alpha_2$ agonist) formed in the brain from methyldopa acts on central $\alpha_2$ receptors to decrease efferent sympathetic activity. Because methyldopa decreases t.p.r. more than HR or c.o., it may be acting on a different population of neurones in the vasomotor centre than clonidine. In large doses, methyldopa inhibits the enzyme dopa decarboxylase in brain and periphery → reduces NA synthesis and forms the *false transmitter* methyl-NA in periphery as well. These mechanisms were considered to be responsible for the antihypertensive effect; but it was demonstrated that neither responses to stimulation of sympathetic nerves nor their NA content was reduced at clinically used antihypertensive doses. Moreover, α methyl NA is as potent vasoconstrictor as NA. The primary central site of action of methyldopa has been confirmed.

Methyldopa is a moderate efficacy antihypertensive. Circulating levels of NA and renin tend to fall due to reduction in sympathetic tone. Inhibition of postural reflexes is mild.

*Pharmacokinetics* Though methyldopa is transported actively by intestinal amino acid carrier, less than 1/3 of an oral dose is absorbed. It is partly metabolized and partly excreted unchanged in urine. Antihypertensive effect develops over 4–6 hours and lasts for 12–24 hours.

*Dose:* 0.25–0.5 g BD–QID oral.

EMDOPA, ALPHADOPA 250 mg tab.

*Adverse effects* Sedation, lethargy and reduced mental capacity are common side effects. Cognitive impairment may develop. Dryness of mouth, nasal stuffiness, headache, fluid retention, weight gain, impotence are the other side effects. Postural hypotension is generally mild.

Positive Coomb's test occurs in 1/6 patients, few develop haemolytic anaemia. Fever, rash, hepatitis, 'flu' like illness, thrombocytopenia and rarely lupus syndrome occur.

Rebound hypertension on sudden withdrawal of methyldopa is mild and less common.

*Interactions* Tricyclic antidepressants reverse its action by blocking its active transport into the adrenergic neurones.

*Use* Methyldopa was a widely used antihypertensive, especially in combination with a diuretic. However, it is infrequently used now, except to treat hypertension during pregnancy wherein it has a long track record of safety, both for the mother as well as the foetus.

## VASODILATORS

**Hydralazine/Dihydralazine** Introduced in the 1950s, it is a directly acting arteriolar vasodilator with little action on venous capacitance vessels; reduces t.p.r. and causes greater decrease in diastolic than in systolic BP. Reflex compensatory mechanisms are evoked which cause tachycardia, increase in c.o. and renin release → increased aldosterone → $Na^+$ and water retention. The disproportionate cardiac stimulation appears to involve direct augmentation of NA release and myocardial contractility as well. Thus, a hyperdynamic circulatory state is induced—angina may be precipitated due to increased cardiac work as well as steal phenomenon. There is no reduction in renal blood flow despite fall in BP. However, fluid retention and edema may occur by the above mechanism. Tolerance to the hypotensive action develops unless diuretics or β blockers or both are given together to block the compensatory mechanisms.

The mechanism of vascular smooth muscle relaxant action of hydralazine is not clearly known. Interference with $Ca^{2+}$ release, opening of certain $K^+$ channels and/or NO generation may be involved.

*Pharmacokinetics* Hydralazine is well absorbed orally, and is subjected to first pass metabolism in liver. The chief metabolic pathway is acetylation which exhibits a bimodal distribution in the population: there are slow and fast acetylators. Bioavailability is higher in slow acetylators, but these patients are more prone to develop the lupus syndrome.

Hydralazine is completely metabolized both in liver and plasma; the metabolites are excreted in urine, t½ 1–2 hours. However, hypotensive effect lasts longer (12 hours), probably because of its persistence in the vessel wall.

*Dose*: 25–50 mg OD–TDS; NEPRESOL 25 mg tab.

*Adverse effects* are frequent and mainly due to vasodilatation.

- Facial flushing, conjunctival injection, throbbing headache, dizziness, palpitation, nasal stuffiness, fluid retention, edema, CHF.
- Angina and MI may be precipitated in patients with coronary artery disease.
- Postural hypotension is not prominent because of little action on veins: venous return and c.o. are not reduced.
- Paresthesias, tremor, muscle cramps, rarely peripheral neuritis.
- Lupus erythematosus or rheumatoid arthritis like symptoms develop on prolonged use of doses above 100 mg/day. This is more common in women and in slow acetylators.

*Use* Hydralazine is now used as a second line alternative only in combination with a diuretic and/or β blocker for patients not achieving target BP with first line drugs. It is one of the preferred antihypertensives during pregnancy, especially preeclampsia, because of decades of safety record. Parenterally, it is occasionally employed in hypertensive emergencies. Hydralazine is contraindicated in older patients and in those with ischaemic heart disease.

The arteriolar dilator action of hydralazine can be employed in the management of CHF particularly in combination with isosorbide dinitrate (*see* p. 522).

**Minoxidil** It is a powerful vasodilator, the pattern of action resembling hydralazine, i.e. direct relaxation of arteriolar smooth muscle with little effect on venous capacitance. Marked vasodilatation elicits strong compensatory reflexes: increased renin release and proximal tubular $Na^+$ reabsorption → marked $Na^+$ and water retention → edema and CHF may occur. Reflex sympathetic activity causes palpitation and increased c.o. To offset these, it has to be used along with a loop diuretic and a β blocker.

Minoxidil is a prodrug—converted to an active metabolite (by sulfate conjugation) which is an opener of ATP operated $K^+$ channels; acts by hyperpolarizing smooth muscle.

Minoxidil is indicated only rarely in severe or life-threatening hypertension.

*Use in alopecia* Oral minoxidil increases growth of body hair. Applied topically (2% twice daily) it promotes hair growth in *male pattern baldness* and *alopecia areata*. The response is slow (takes 2–6 months) and incomplete, but upto 60% subjects derive some benefit, albeit for short periods. Baldness recurs when therapy is discontinued. The mechanism of increased hair growth is not known; may involve:

(a) Opening of $K^+$ channels and enhanced microcirculation around hair follicles.

(b) Direct stimulation of resting hair follicles.

(c) Alteration of androgen effect on genetically programmed hair follicles.

Local irritation, itching and burning sensation are frequent. Dermatological reaction and systemic side effects (headache, dizziness, palpitation) occur in 1–3% cases.

MINTOP, GROMANE 2% scalp lotion, MULTIGAIN 2% topical solution and metered spray, MANEXIL 5% gel; apply twice a day.

**Diazoxide** This $K^+$ channel opener arteriolar dilator was used in the past for rapid reduction of BP in hypertensive emergencies. Administered by rapid i.v. injection it can be employed in place of nitroprusside, when regulated i.v. infusion or close monitoring is not possible.

**Sodium nitroprusside** It is a rapidly (within seconds) and consistently acting vasodilator; has brief duration of action (2–5 min) so that vascular tone can be titrated with the rate of i.v. infusion. It relaxes both resistance and capacitance vessels: reduces t.p.r. as well as c.o. (by decreasing venous return). Myocardial work is reduced—ischaemia is not accentuated, as occurs with selective arteriolar dilators (hydralazine). Little reflex tachycardia is produced in supine posture. Plasma renin is increased.

In patients with heart failure and ventricular dilatation, nitroprusside improves ventricular function and c.o. mainly by reducing aortic impedance (afterload), but also by lowering atrial filling pressure (preload).

Endothelial cells, RBCs (and may be other cells) split nitroprusside to generate NO which

relaxes vascular smooth muscle. This occurs both enzymatically and nonenzymatically. The enzymes involved are different from those that produce NO from glyceryl trinitrate. Nonenzymatically it is converted to NO (and CN) by glutathione. This may be responsible for the different pattern of vasodilator action compared to nitrates, as well as for the fact that no nitrate like tolerance develops to nitroprusside action.

Nitroprusside has gained popularity in the management of hypertensive emergencies; 50 mg is added to a 500 ml bottle of saline/glucose solution. The infusion is started at 0.02 mg/min and titrated upward with the response: 0.1–0.3 mg/min is often needed. It decomposes at alkaline pH and on exposure to light: the infusion bottle should be covered with black paper.

Nitroprusside is split to release cyanide. The latter is converted in liver to thiocyanate which is excreted slowly. If larger doses are infused for more than 1–2 days, excess thiocyanate may accumulate and produce toxicity, including psychosis.

Side effects mainly due to vasodilatation are—palpitation, nervousness, vomiting, perspiration, pain in abdomen, weakness, disorientation, and lactic acidosis (caused by the released cyanide).

Nitroprusside has also been used to produce controlled hypotension, in refractory CHF (*see* p. 522), pump failure accompanying MI and in acute mitral regurgitation.

SONIDE, PRUSIDE, NIPRESS 50 mg in 5 ml inj.

### ADRENERGIC NEURONE BLOCKERS

**Reserpine** It is an alkaloid from the roots of *Rauwolfia serpentina* (sarpgandha) indigenous to India which has been used in 'Ayurvedic' medicine for centuries. The pure alkaloid was isolated in 1955 and later found to act by causing CA and 5-HT depletion. It was a popular antihypertensive of the late 1950s and early 1960s, but is now used only as a pharmacological tool.

Reserpine acts at the membrane of intraneuronal vesicles which store monoamines (NA, DA, 5-HT) and irreversibly inhibits the vesicular monoamine transporter (VMAT2). The monoamines are gradually depleted and degraded by MAO. The effects last long after the drug is eliminated (hit and run drug) because tissue CA stores are restored only gradually.

Higher doses deplete CAs and 5-HT in the brain as well; cause sedation and mental depression. Antipsychotic effect (mild) and extrapyramidal symptoms are produced due to DA depletion.

SERPASIL 0.25 mg tab; 1 mg/ml inj.

**Guanethidine** It is a polar guanidine compound which is taken up into the adrenergic nerve endings by active amine transport, and has three important facets of action:

(a) Displaces NA from storage granules stoichiometrically.
(b) Inhibits nerve impulse coupled release of NA.
(c) Engages and blocks NA uptake mechanism at the axonal membrane.

Guanethidine has gone out of use now due to marked side effects.

## TREATMENT OF HYPERTENSION

The aim of antihypertensive therapy is to prevent morbidity and mortality associated with persistently raised BP by lowering it to an acceptable level, with minimum inconvenience to the patient. Both systolic and diastolic BP predict the likelihood of target organ damage (TOD) and complications such as:

(a) Cerebrovascular disease, transient ischaemic attacks, stroke, encephalopathy.
(b) Hypertensive heart disease—left ventricular hypertrophy, CHF.
(c) Coronary artery disease (CAD), angina, myocardial infarction, sudden cardiac death.
(d) Arteriosclerotic peripheral vascular disease, retinopathy.
(e) Dissecting aneurysm of aorta.
(f) Glomerulopathy, renal failure.

Patients who have already suffered some TOD have greater risk of further organ damage and death at any level of raised BP, than those without TOD.

The JNC 7 (2003) has reclassified BP readings as:

| BP classification | BP (mm Hg) Systolic | | Diastolic |
|---|---|---|---|
| 1. Normal | <120 | and | <80 |
| 2. Prehypertension | 120–139 | or | 80–89 |
| 3. Hypertension Stage I | 140–159 | or | 90–99 |
| 4. Hypertension Stage II | ≥ 160 | or | ≥ 100 |

Since the risk of complications depends not only on the level of BP, but also on other risk factors (*see* box) and existing TOD, these have

also to be considered in deciding when to start drug therapy, as well as in selection of drugs and in devising therapeutic regimens.

**Cardiovascular risk factors**

1. Age > 55 years (men), > 65 years (women)
2. Family h/o premature CV disease
3. Smoking
4. Dyslipidemia (↑LDL, ↓HDL, ↑TG)
5. Diabetes mellitus
6. Hypertension
7. Obesity (BMI ≥ 30)
8. Microalbuminuria or g.f.r. < 60 ml/min

The JNC7 have also identified compelling indications (*see* box) which may mandate use of specific antihypertensive drugs even in patients with BP values in the 'prehypertension' range. Moreover, presence of compelling indications may suggest fixing a lower target BP value to be attained by drug therapy.

**Compelling indications for use of antihypertensive drugs**

1. Heart failure
2. High coronary artery disease (CAD) risk
3. H/o MI in the past
4. H/o stroke in the past
5. Diabetes
6. Chronic renal disease

Beneficial effects of lowering BP has been established in all patients having BP above 140/90 mm Hg, and even in the 120–139 (systolic) or 80–89 mm Hg (diastolic) range in those with compelling indications or cardiovascular risk factors; e.g. in diabetics, lowering diastolic BP to 80 mmHg was found to reduce cardiovascular events more than reducing it upto 90 mm Hg.

Data from several large studies has shown that effective use of antihypertensive drugs reduces occurrence of stroke by 30–50%, heart failure by 40–50% and coronary artery disease (CAD) by ~15%.

If the cause of hypertension can be identified (hormonal, vascular abnormality, tumour, renal disease, drugs) all efforts should be made to remove it. Nonpharmacological measures (life style modification—diet, $Na^+$ restriction, aerobic activity or exercise, weight reduction, moderation in alcohol intake, mental relaxation, etc.) should be tried first and concurrently with drugs. The level to which BP should be lowered is uncertain. A value of < 140 systolic and < 90 mmHg diastolic is considered adequate response, because it clearly reduces morbidity and mortality, though risk reduction may continue upto 120/80 mm Hg in terms of CAD, heart failure, stroke, etc. When significant cardiovascular and/or renal damage has already occurred, lowering BP to normotensive level may not be tolerated: edema, CHF, angina, rise in blood urea and syncope may be precipitated. Therefore, reduce BP gradually and only to the level tolerated.

The Swedish trial in old patients with hypertension-2 (STOP-2, 1999) conducted over 5 years in 6614 hypertensives aged 70–84 years showed that conventional therapy with diuretic and/or β blockers is as effective in reducing BP and risk of major cardiovascular events as are ACE inhibitors or CCBs. The ALLHAT (2002) study comparing chlorthalidone, lisinopril and amlodipine has also found no difference in the primary outcomes of death and MI. The results convey that efficacywise there is little to choose among the 4 classes of drugs; choice of initial drug has to be guided by associated features/contraindications and acceptable side effects in individual patients.

With the recognition of 4 groups of first choice antihypertensive drugs *viz.* diuretics, ACE inhibitor/ARBs, CCBs and β blockers, as well as their evaluation in large randomized trials, a *'stepped care'* approach (initially using a single drug and progressively adding 1–3 more drugs, as required, from different groups), is recommended by most experts and therapeutic guidelines. The drug for initial therapy is selected on the basis of compelling indications (if present), suitability criteria taking into consideration the age, life style issues, risk factors, concomitant medical conditions, tolerability in respect of the individual patient and cost of different drugs. For each class of antihypertensive drugs, certain patients can be identified who are best suited to be treated with it, and those in whom it should be avoided (*see* box).

The general principles of antihypertensive therapy enunciated in JNC7, WHO-ISH and

**Selection of first line antihypertensive drugs**

| *Compelling indications* | *Suitable for* | *To be avoided in* |
|---|---|---|
| | **Diuretics** | |
| 1. Heart failure<br>2. High CAD risk<br>3. Recurrent stroke prevention<br>4. Diabetes | 1. Older patients<br>2. Isolated systolic hypertension<br>3. Obese with volume overload<br>4. Low cost therapy | 1. Gout or family history of gout<br>2. Abnormal lipid profile<br>3. Pregnancy induced hypertension |
| | **ACE inhibitors/Ang II receptor blockers** | |
| 1. Heart failure<br>2. Post-MI<br>3. High CAD risk<br>4. Diabetes<br>5. Chronic kidney disease<br>6. Recurrent stroke prevention | 1. Relatively young patients<br>2. Patients with left ventricular hypertrophy<br>3. Gout, PVD, dyslipidemic patients | 1. Bilateral renal artery stenosis or that in single kidney<br>2. Pregnancy<br>3. Hyperkalaemia<br>4. Preexisting dry cough (ACE inhibitor) |
| | **β Adrenergic blockers** | |
| | | (especially applicable to nonselective β blockers) |
| 1. Stable heart failure<br>2. Post-MI<br>3. High CAD risk | 1. Coexisting anxiety or tachycardia<br>2. Relatively young patient<br>3. Migraine patients<br>4. Low cost therapy | 1. Asthma, COPD<br>2. Bradycardia, conduction defects<br>3. Decompensated heart failure<br>4. PVD<br>5. Abnormal lipid profile |
| | **Calcium channel blockers** | |
| 1. Recurrent stroke prevention | 1. Older with poor arterial wall compliance<br>2. Isolated systolic hypertension<br>3. Asthma/COPD patients<br>4. Raynaud's (and other PVD) patients<br>5. Pregnant hypertensive<br>6. Diabetics | 1. Myocardial inadequacy, CHF<br>2. Conduction defects, sick sinus<br>3. Receiving β blockers } Verapamil and diltiazem<br>4. Ischaemic heart disease; post MI cases<br>5. Males with prostate enlargement<br>6. Gastroesophageal reflux } DHPs |

British Hypertension Society* (BHS) 2004, guidelines may be summarized as:

1. Except for stage II hypertension, start with a single most appropriate drug, which for majority of patients is a thiazide. However, an ACE inhibitor/ARB or CCB or in some cases β blocker may also be considered. Many experts now opine that β blockers should no longer be regarded as first choice drugs, except for patients with compelling indications or suitability features.
2. The BHS (2004) recommended following the **A B C D** rule (**A**—ACE inhibitor/ARB; **B**—β blocker; **C**—CCB, **D**—diuretic). While A and (in some cases) B are preferred in younger patients (<55 years), C and D are preferred in the older (> 55 years) for the **step I** or monotherapy.
3. Initiate therapy at low dose; if needed increase dose moderately. Thiazide dose should be 12.5–25 mg/day hydrochlorothiazide or chlorthalidone.
4. If only partial response is obtained, add a drug from another complimentary class or change to low dose combination (antihypertensive action of the components adds up, while side effects being different, do not).

* Williams B: British Hypertension Society. Guidelines for management of hypertension: report of the 4th working party of the British Hypertension Society. J Hum Hypertens. **2004;** *18(3):* 139-185.

5. If no response, change to a drug from another class, or low dose combination from other classes.
6. In case of side effect to the initially chosen drug, either substitute with drug of another class or reduce dose and add a drug from another class.
7. Majority of stage II hypertensives are started on a 2 drug combination; one of which usually is a thiazide diuretic.

With the above approach 50–70% stage I hypertensives can be successfully treated, at least initially, with monodrug therapy. A simple regimen with once or twice daily drug dosing is most likely to be complied with. Because most stage I and some stage II hypertension patients are asymptomatic, a drug which makes them symptomatic (one or the other side effect) is not likely to be accepted for prolonged periods. Effect of the drug on quality of life measured by sense of wellbeing, energy level, mental acuity, drive, libido, sleep, life satisfaction, etc. is an important criterion in drug selection.

**Combination therapy** Though JNC 7, WHO-ISH and BHS guidelines emphasise on single drug therapy, the addition of a second (and third or even fourth) drug is also highlighted when monotherapy fails. In practice, a large majority of hypertensives ultimately require 2 or more drugs. In the HOT study 70% patients who achieved target BP were being treated with 2 drugs.

Since BP is kept up by several interrelated factors, an attempt to block one of them tends to increase compensatory activity of the others. It is rational in such cases to combine drugs with different mechanisms of action or different patterns of haemodynamic effects:

(a) Drugs which increase plasma renin activity—diuretics, vasodilators, CCBs, ACE inhibitors may be combined with drugs which lower plasma renin activity—β blockers, clonidine, methyldopa.

(b) All sympathetic inhibitors (except β blockers) and vasodilators, except CCBs, cause fluid retention leading to tolerance. Addition of a diuretic checks fluid retention and development of tolerance.

(c) Hydralazine and DHPs cause tachycardia which is counteracted by β blockers, while the initial increase in t.p.r. caused by non-selective β blockers is counteracted by the vasodilator.

(d) ACE inhibitors/ARBs are particularly synergistic with diuretics; this combination is very good for patients with associated CHF or left ventricular hypertrophy.

(e) In **step 2** when two drugs are to be used, the BHS recommend combining one out of *A* or *B* with one out of *C* or *D*.

(f) Use of combined formulation improves compliance and usually lowers cost.

(g) In the **step 3** (when two drugs are inadequate in achieving target BP lowering), triple drug regimen is prescribed. Both *C* and *D* are combined with *A* or *B*, whereby large majority of patients are adequately controlled.

(h) Patients who fail to reach the goal BP despite being adherent to full doses of an appropriate 3 drug (including a diuretic) regimen, have been labelled by JNC7 as 'resistant hypertension'. In them even 4 drug therapy **step 4** may have to be given to achieve the target BP. However, the patient must be reevaluated and factors like non-compliance, pseudotolerance, need for a loop diuretic, drug interactions, secondary hypertension, etc. must be first excluded. All four first line drugs are used together, or an $\alpha_1$ blocker is included with 3 first line drugs. Eplerenone also is being used as the 4th drug now. Hydralazine or clonidine are rarely included.

### Combinations to be avoided

1. An α or β adrenergic blocker with clonidine: apparent antagonism of clonidine action has been observed.
2. Hydralazine with a DHP or prazosin; because of similar pattern of haemodynamic action.

3. Verapamil or diltiazem with β blocker, because marked bradycardia, A-V block can occur.
4. Methyldopa with clonidine or any two drugs of the same class.

**Some antihypertensive combinations**

1. *Amlodipine 5 mg + Lisinopril 5 mg*—AMLOPRES-L, LISTRIL-AM
2. *Amlodipine 5 mg + Atenolol 50 mg*—AMCARD-AT, AMLOPIN-AT, AMLOPRES-AT
3. *Amlodipine 5 mg + Enalapril 5 mg*—AMACE, AMTAS-E
4. *Atenolol 25 mg or 50 mg + chlorthalidone 12.5 mg*—TENOCLOR, TENORIC
5. *Enalapril 10 mg + Hydrochlorothiazide 25 mg*—ENACE-D, VASONORM-H
6. *Ramipril 2.5 mg + Hydrochlorothiazide 12.5 mg*—CARDACE-H
7. *Losartan 50 mg + Hydrochlorothiazide 12.5 mg*—LOSAR-H, TOZAAR-H, LOSACAR-H
8. *Lisinopril 5 mg + Hydrochlorothiazide 12.5 mg*—LISTRIL PULS, LISORIL-HT
9. Losartan 50 mg + Ramipril 2.5 mg or 5 mg—TOZAAR-R, LAPIDO-R
10. Losartan 50 mg + Amlodipine 5 mg—AMCARD-LP, AMLOPRESS-Z, LOSACAR-A
11. Losartan 50 mg + Ramipril 2.5 mg + Hydrochlorothiazide 12.5 mg—LOSANORM-HR
12. Irbesartan 150 mg + Hydrochlorothiazide 12.5 mg—IROVEL-H, XARB-H.

When the BP has been well controlled for > 1 year, stepwise reduction in dose and/or withdrawal of one or more components of a combination may be attempted to workout a minimal regimen that will maintain the target BP. However, in most patients of essential hypertension, drug therapy is usually life-long.

**Hypertension in pregnancy** A sustained BP reading above 140/90 mm Hg during pregnancy has implications both for the mother and the foetus: reduction of BP clearly reduces risks. Two types of situations are possible:

(a) A woman with preexisting essential hypertension becomes pregnant.
(b) Pregnancy induced hypertension; as in toxaemia of pregnancy—preeclampsia.

Toxaemic hypertension is associated with a hyperadrenergic state, decrease in plasma volume (despite edema) and increase in vascular resistance.

In the first category the same therapy instituted before pregnancy may be continued. However, one of the 'safer' drugs listed below may be substituted if one of the 'drugs to be avoided' was being used.

### *Antihypertensives to be avoided during pregnancy*

*ACE inhibitors, ARBs*: Risk of foetal damage, growth retardation.
*Diuretics*: Tend to reduce blood volume—accentuate uteroplacental perfusion deficit (of toxaemia)—increase risk of foetal wastage, placental infarcts, miscarriage, stillbirth.
*Nonselective β blockers*: Propranolol has been implicated to cause low birth weight, decreased placental size, neonatal bradycardia and hypoglycaemia.
*Sod. nitroprusside*: Contraindicated in eclampsia.

### *Antihypertensives found safer during pregnancy*

Hydralazine
Methyldopa (a positive Coombs' test occurs, but has no adverse implication).
Dihydropyridine CCBs: if used, they should be discontinued before labour as they weaken uterine contractions.
Cardioselective β blockers and those with ISA, e.g. atenolol, metoprolol, pindolol, acebutolol: may be used if no other choice.
Prazosin and clonidine—provided that postural hypotension can be avoided.

## Hypertensive emergencies and urgencies

Systolic BP > 220 or diastolic BP > 120 mm Hg with evidence of active end organ damage is labelled '*hypertensive emergency*', while the same elevation of BP without overt signs of endorgan damage is termed '*hypertensive urgency*'. Severity and rate of progress of TOD determines the seriousness of the condition.

Controlled reduction of BP over minutes (in emergencies) or hours (in urgencies) is required to counter threat to organ function and life in:

1. Cerebrovascular accident (haemorrhage) or head injury with high BP.
2. Hypertensive encephalopathy.

3. Hypertensive acute LVF and pulmonary edema.
4. Unstable angina or MI with raised BP.
5. Dissecting aortic aneurysm.
6. Acute renal failure with raised BP.
7. Eclampsia.
8. Hypertensive episodes in pheochromocytoma, cheese reaction or clonidine withdrawal.

#### Oral therapy

Some rapidly acting oral hypotensive drugs have been used in hypertensive urgencies, but are now considered neither necessary nor safe.

*Nifedipine* (10 mg soft geletine cap.) orally or s.l. every 30 min was widely employed in urgencies. This practice has now been abandoned because it often causes abrupt fall in BP and precipitates MI or stroke, or may be fatal. Once the drug is ingested, rate and degree of fall in BP cannot be controlled, and adverse consequences outweigh any advantage.

*Captopril* (25 mg oral every 1–2 hours) was also used, but response is variable and it carries risk of excessive hypotension.

*Clonidine* (100 µg every 1–2 hours oral) acts mostly in 30–60 min, but produces sedation and rebound rise in BP on stopping the drug.

### Parenteral therapy

Parenteral (preferably i.v.) drugs with controllable action are used both in emergencies and in urgencies (less vigorously in the latter).

However, many experts consider that in the absence of end organ damage (urgencies), i.v. drugs are not necessary; slow reduction of BP with oral drugs is adequate and safer.

Mean BP should be lowered by no more than 25% over a period of minutes or a few hours and then gradually to not lower than 160/100 mm Hg. Drugs employed are:

1. *Sodium nitroprusside* (*see* p. 567) Because of predictable, instantaneous, titratable and balanced arteriovenous vasodilatory action which persists without tolerance till infused, nitroprusside (20–300 µg/min) is the drug of choice for most hypertensive emergencies. However, it is toxic in high dose and when used for longer period. GTN may be better choice when there is associated MI or LVF. In aortic dissection, nitroprusside may require concurrent esmolol infusion. Another limitation is that nitroprusside needs an infusion pump and constant monitoring.
2. *Glyceryl trinitrate* (*see* p. 543) Given by i.v. infusion (5–20 µg/min) GTN also acts within 2–5 min and has brief titratable action, but is a less potent hypotensive. Its predominant venodilator action makes it particularly suitable for lowering BP after cardiac surgery and in acute LVF, MI, unstable angina, but not in other conditions. Tolerance starts developing after 18–24 hours of continuous infusion.
3. *Hydralazine* (*see* p. 566) 10–20 mg i.m. or slow i.v. injection; acts in 20–30 min and keeps BP low for 4–8 hours, but is less predictable, and not a first line drug. It has been especially used in eclampsia. It causes tachycardia and should be avoided in patients with myocardial ischaemia or aortic dissection.
4. *Esmolol* (*see* p. 149) This β blocker given as 0.5 mg/kg bolus followed by slow i.v. injection (50–100 µg/kg/min) acts in 1–2 min; action lasts for 10–20 min. It is particularly useful when cardiac contractility and work is to be reduced, such as in aortic dissection. Nitroprusside is given concurrently, because the BP lowering action is weaker. It is a useful hypotensive and bradycardiac drug during and after anaesthesia. Excess bradycardia is to be guarded.
5. *Phentolamine* (*see* p. 141) This nonselective $\alpha_1 + \alpha_2$ blocker is the drug of choice for hyperadrenergic states, e.g. hypertensive episodes in pheochromocytoma, cheese reaction or clonidine withdrawal. Injected i.v. (5–10 mg) it acts in 2 min and action lasts 5–15 min. Tachycardia and myocardial ischaemia may complicate its use. A β blocker may be added.
6. *Labetalol* Injected i.v., it is an alternative to an α blocker + a β blocker combination for lowering BP in pheochromocytoma, etc. but has only weak α blocking action. It has been used to lower BP in MI, unstable angina, eclampsia as well. It is also good for patients with altered consciousness, because it does not cause sedation or increase intracranial pressure. Concomitant CHF or asthma preclude its use.

7. *Furosemide* (20–80 mg oral or i.v.) It may be given as an adjunct with any of the above drugs if there is volume overload (acute LVF, pulmonary edema, CHF) or cerebral edema (in encephalopathy), but should be avoided when patient may be hypovolemic due to pressure induced natriuresis (especially in eclampsia, pheochromocytoma).

*Fenoldopam* (depamine agonist), *nicardipine* and *clevidipine* (parenteral DHPs), *enalaprilat* (a parenteral ACE inhibitor) and *trimethaphan* (a ganglion blocker) are other drugs for hypertensive emergencies. They are occasionally used in other countries.

## ☞ PROBLEM DIRECTED STUDY

**40.1** A 70-year-old male presented with complaint of dull headache, giddiness, weakness and occasional breathlessness. He gave history of left sided paralytic stroke about 2 years back, from which he has recovered nearly completely, but is taking Aspirin 75 mg per day. The pulse was 66/min. The BP was found to range between 152–160 mm Hg systolic and 82–86 mm Hg diastolic, when measured on 3 occasions over one week. The ECG showed signs of left ventricular hypertrophy, but no ischaemia. Fundus examination revealed mild age related changes. Fasting blood sugar was 96 mg/dl; kidney function, liver function tests and lipid profile were within normal range. (a) Should he be prescribed antihypertensive medication? If so, whether one, or more than one, antihypertensive should be prescribed concurrently, and which drug/drugs will be more suitable for him?

(see Appendix-1 for solution)