B.Pharm. Semester-V

Subject Name: Pharmacology-II

Subject Code: BP502TP

Sarswati Institute of Pharmaceutical Sciences

CARDIAC ELECTROPHYSIOLOGY

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

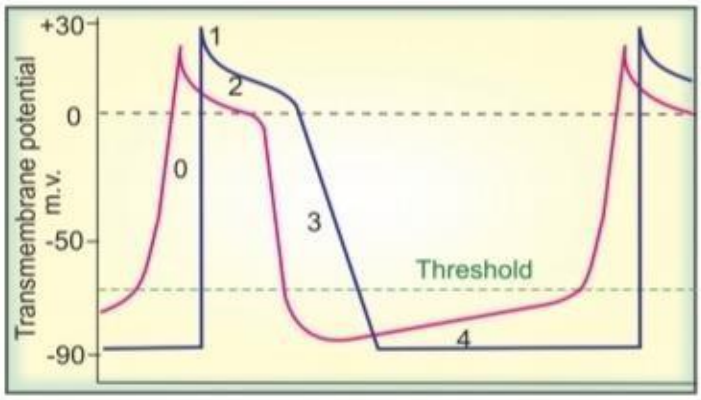


Fig. VIII.1: Transmembrane potential of automatic (red) and nonautomatic (purple) myocardial fibres recorded through intracellular electrodes

1. Impulse generation

   Electrophysiologically, two types of myocardial fibres can be distinguished

   (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 Ca2+ ions flow in and bring about contraction relatively rapid repolarization (phase3) 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).

   (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. Normally, the SA node has the steepest phase4 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. 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 (voltagedependent 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 (Ca2+ 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.

3. Excitability

This property of a fibre is defined by the strength of stimulus required toelicit 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 Ca2+ 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.

Drugs used in congestive heart failure

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

CARDIAC GLYCOSIDES

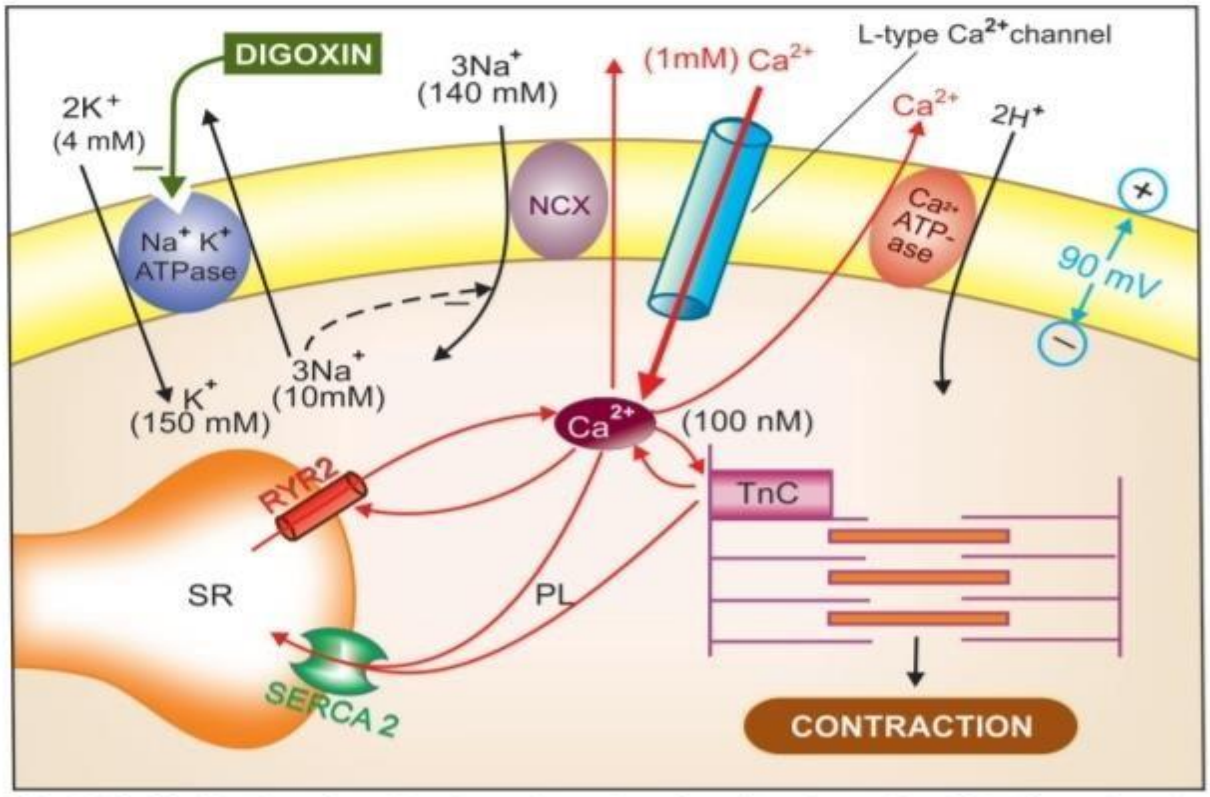


Fig. 37.3: Mechanism of positive inotropic action of cardiac glycosides. SR—Sarcoplasmic reticulum; TnC—Troponin C; NCX—Na^+-Ca^{2+} exchanger; RyR2—Ryanodine receptor calcium channel 2; PL—Phospholamban; SERCA2—Sarcoplasmic-endoplasmic reticulum calcium ATPase 2.

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.

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

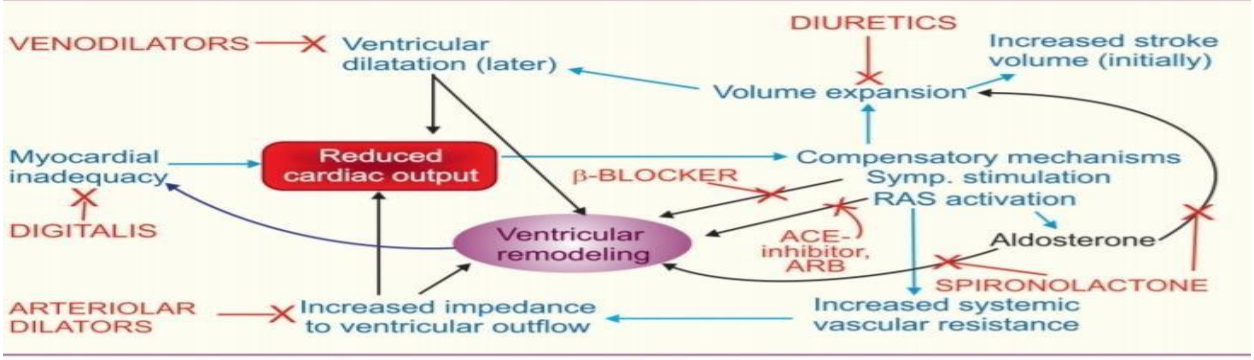
• The resting membrane potential (RMP) is progressively decreased (to less negative values) with increasing doses. Excitability is enhanced at low doses but depressed at toxic doses because Na+ channels are inactivated.

• 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—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. 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.

Mechanism of action



ig. 37.5: The vicious cycle in CHF: compensatory mechanisms evoked in response to reduced cardiac outpu hemselves perpetuate failure and contribute to remodeling responsible for disease progression. The paramete which is improved by different therapeutic measures is indicated

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. Inhibition of this cation pump results in progressive accumulation of Na+ intracellularly. This indirectly results in intracellular Ca2+ accumulation. During depolarization Ca2+ ions enter the cell driven by the steep Ca2+ gradient (>1 mM extracellular to < 100 nM cytosolic during diastole) through voltage sensitive L type Ca2+ channels. This triggers release of larger amount of Ca2+ stored in sarcoplasmic reticulum (SR) through Ryanodine calcium channel 2 (RYR2) → cytosolic Ca2+ 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 Ca2+ back into the SR. A fraction (equal to that which entered from outside during depolarization) is extruded mainly by 3Na+/1Ca2+ exchange transporter (NCX-antiporter) and to a lesser extent by sarcolemmal Ca2+ pump (Ca2+ ATPase). During phase 3 of AP, membrane Na+K+ATPase moves 3 intracellular Na+ ions for 2 extracellularK+ 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 Ca2+. The excess Ca2+ remaining in cytosol is taken up into SR which progressively get loaded with more Ca2+ → subsequent calcium transients are augmented. The relationship of cytosolic [Na+] and [Ca2+] is such that a small percentage increase in Na+ concentration leads to a large percentage increase in Ca2+ concentration. Moreover, raised cytosolic Ca2+ induces greater entry of Ca2+ through voltage sensitive Ca2+ 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, Ca2+ 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 Ca2+ loading of SR results in spontaneous cycles of Ca2+ release and uptake producing oscillatory after-depolarizations and after-contractions. Since both therapeutic and toxic effects of digitalis are due to myocardial Ca2+ 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.

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.

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.

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.

(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.

β-Adrenergic blockers

Extensive studies over the past 30 years have established the utility of β1 blockers (mainly metoprolol, bisoprolol, nebivolol) and the nonselective β + selective α1 blocker carvedilol in mild to moderate CHF treated with ACE inhibitor ± diuretic, digitalis.

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.

Sympathomimetic inotropic drugs

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 β1 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.

Phosphodiesterase 3 inhibitors

Theophylline is a phosphodiesterase inhibitor that is nonselective 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 vesselsand bronchial smooth muscles. Amrinone increases myocardial cAMP and transmembrane influx of Ca2+. 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.

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.

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 (AT1 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.

7. β+ α Adrenergic Blockers Labetalol, Carvedilol

8. αAdrenergic blockers Prazosin, Terazosin, Doxazosin Phentolamine, Phenoxybenzamine

9. Central sympatholytics Clonidine, Methyldopa

10. Vasodilators

Arteriolar: Hydralazine, Minoxidil, Diazoxide

Arteriolar+venous: Sodium nitroprusside

DIURETICS

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.

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.

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.

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.

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. 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

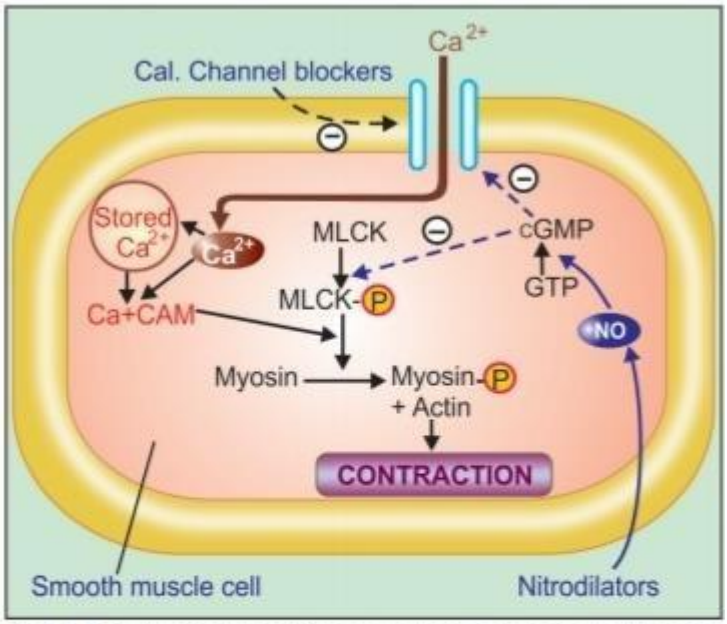


Fig. 39.3: Mechanism of vascular smooth muscle relaxant action of nitrodilators like glyceryl trinitrate and calcium channel blockers; (- - - →) Inhibition
CAM—Calmodulin; NO—Nitric oxide; MLCK—Myosin light chain kinase; MLCK-P—Phosphorylated MLCK; GTP—Guanosine triphosphate; cGMP—Cyclic guanosine monophosphate

Calcium channel blockers (CCBs) are another class of first line antihypertensive drugs. 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.

β-ADRENERGIC BLOCKERS

They are mild antihypertensives; do not significantly lower BP in normotensives. Used alone they suffice in 30–40% patients—mostly stageI 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 β2 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 β1 selective blockers and in those with ISA.

β+α ADRENERGIC BLOCKERS

Labetalol 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 α1 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 is prototype selective α1 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.

CENTRAL SYMPATHOLYTICS

Clonidine is an imidazoline derivative having complex actions. Clonidine is a partial agonist with high affinity and high intrinsic activity at α2 receptors, especially α2A subtype in brainstem. The major haemodynamic effects result from stimulation of α2A 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 α2 action), this is not manifest at clinically used doses. Clonidine is a moderately potent antihypertensive.

Methyldopa is 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 α2 agonist) formed in the brain from methyldopa acts on central α2 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 response 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.

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.

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.

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.

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.

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 arteriosclerotic 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 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 torecurrent 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. Wall tension = intraventricular pressure × ventricular radius Thus, reduction in ventricular radius decreases the tension that must be generated in the ventricular wall—hence decreased O2 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.

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

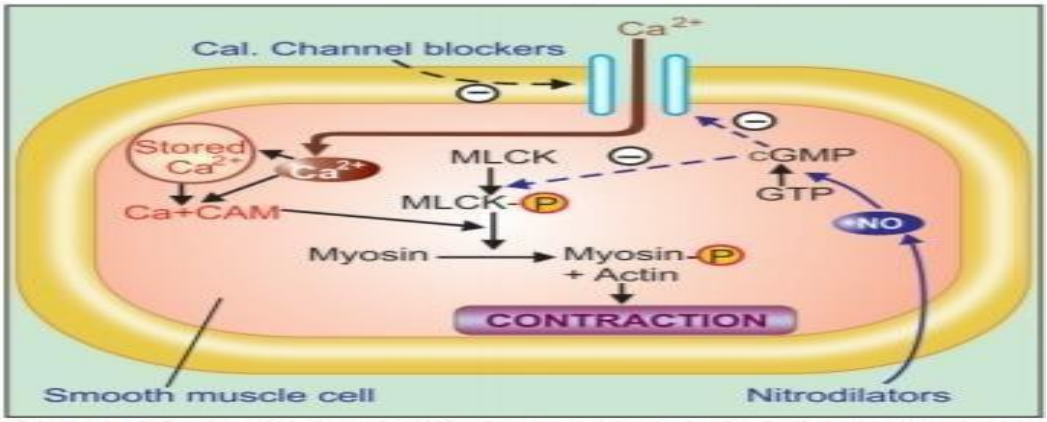


Fig. 39.3: Mechanism of vascular smooth muscle relaxant action of nitrodilators like glyceryl trinitrate and calcium channel blockers; (- - - →) Inhibition
CAM—Calmodulin; NO—Nitric oxide; MLCK—Myosin light chain kinase; MLCK-P—Phosphorylated MLCK; GTP—Guanosine triphosphate; cGMP—Cyclic guanosine monophosphate

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. 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 Ca2+ entry—contributing to relaxation.

USES

1. Angina pectoris
2. Acute coronary syndromes (ACS)
3. Myocardial infarction (MI)
4. CHF and acute LVF 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.

Anti-arrhythmic drugs

Abnormal automaticity or impaired conduction or both underlie cardiac arrhythmias. 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). 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 Ca2+ 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.

classification

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 Amiodarone, Dronedarone (prolong repolarization and ERP) 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.
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 τrecovery 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.

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 Ca2+ channels. Quinidine decreases the availability of Na+ channels as well as delays their reactivation.

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 antiarrhythmic 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.

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 HisPurkinje 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.

CLASS II

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

Propranolol

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.

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 Ca2+ channels, has noncompetitive β adrenergic blocking property and alters thyroid function. Thus amiodarone is a multichannel blocker with some additional activities.

CLASS IV

The primary action of this class of drugs is to inhibit Ca2+ mediated slow channel inward current. Verapamil of the many Ca2+ channel blockers, verapamil has the most prominent cardiac electrophysiological action (Table 38.1). It blocks L type Ca2+ 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 Ca2+ 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.

Anti-hyperlipidemic drugs

CLASSIFICATION

1. HMG-CoA reductase inhibitors (Statins):
   Lovastatin, Simvastatin, Pravastatin, Atorvastatin, Rosuvastatin, Pitavastatin
2. Bile acid sequestrants (Resins):
   Cholestyramine, Colestipol
3. Lipoprotein lipase activators (PPAR α activators, Fibrates):
   Clofibrate, Gemfibrozil, Bezafibrate, Fenofibrate.
4. Lipolysis and triglyceride synthesis inhibitor:
   Nicotinic acid.
5. Sterol absorption inhibitor:
   Ezetimibe.

HMG-CoA reductase inhibitors (Statins)

Introduced in the 1980s, this class of compounds are the most efficacious and best tolerated hypolipidaemic drugs. They competitively inhibit conversion of 3-Hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) to mevalonate (rate limiting step in CH synthesis) by the enzyme HMG-CoA reductase. Therapeutic doses reduce CH synthesis by 20–50%. This results in compensatory increase in LDL receptor expression on liver cells → increased receptor mediated uptake and catabolism of IDL and LDL. Over long-term, feedback induction of HMG-CoA reductase tends to increase CH synthesis, but a steady-state is finally attained with a dosedependent lowering of LDL-CH levels.

A dose-dependent effect is seen with all statins. With lovastatin a mean reduction of LDL-CH by 25% at 20 mg/day, 32% at 40 mg/day and 40% at 80 mg/day has been measured. Atorvastatin is more potent; the corresponding figures of LDLCH reduction are 33% at 10 mg/day, 40% at 20 mg/day, 45% at 40 mg/day and 50–55% at 80 mg/day. A concurrent fall by 10–30% in plasma TG level, probably due to reduction of VLDL occurs. A modest rise in HDL-CH by 5–15% is also noted. Simultaneous use of bile salt sequestrant augments the LDL lowering effect upto 60% and addition of nicotinic acid to this combination may boost the effect to 70% reduction in LDL-CH. Statins are effective in secondary hypercholesterolaemias also. The more efficacious statins (simvastatin, atorvastatin, rosuvastatin) given at their higher doses effectively reduce TGs (by 25% to 35%) when they are moderately raised, but not when they are markedly raised.

Atorvastatin

This newer and most popular statin is more potent and appears to have the highest LDL-CH lowering efficacy at maximal daily dose of 80 mg. At this dose a greater reduction in TGs is noted

if the same was raised at baseline. Atorvastatin has a much longer plasma t½ of 18– 24 hr than other statins, and has additional antioxidant property.

Lovastatin

It is the first clinically used statin; is lipophilic and given orally in the precursor lactone form. Absorption is incomplete and first pass metabolism is extensive. Metabolites are excreted mainly in bile. The t½ is short (1–4 hours).

Pravastatin

It is hydrophilic and given in the active form. At low doses it is equipotent to lovastatin, but at higher dose (40 mg/day), CH lowering effect is less. It can be employed when reduction of LDL-CH by < 25% is contemplated. An additional action of decrease in plasma fibrinogen level has been observed. The t½ is 1–3 hours.

Bile acid sequestrants (Resins)- Cholestyramine and Colestipol

These are basic ion exchange resins supplied in the chloride form. They are neither digested nor absorbed in the gut: bind bile acids in the intestine interrupting their enterohepatic circulation. Faecal excretion of bile salts and CH (which is absorbed with the help of bile salts) is increased. This indirectly leads to enhanced hepatic metabolism of CH to bile acids. More LDL receptors are expressed on liver cells: clearance of plasma IDL, LDL and indirectly that of VLDL is increased. Resins have been shown to retard atherosclerosis, but are not popular clinically because they are unpalatable, inconvenient, have to be taken in large doses, cause flatulence and other g.i. symptoms, interfere with absorption of many drugs and have poor patient acceptability.

LIPOPROTEIN-LIPASE ACTIVATORS (Fibrates) - bezafibrate, fenofibrate

The fibrates (isobutyric acid derivatives) primarily activate lipoprotein lipase which is a key enzyme in the degradation of VLDL resulting in lowering of circulating TGs. This effect is exerted through peroxisome proliferator-activated receptor α (PPARα) that is a gene transcription regulating receptor expressed in liver, fat and muscles. Activation of PPARα enhances lipoprotein lipase synthesis and fatty acid oxidation. PPARα may also mediate enhanced LDL receptor expression in liver seen particularly with second generation fibrates like bezafibrate, fenofibrate. Fibrates decrease hepatic TG synthesis as well. A peripheral effect reducing circulating free fatty acids has also been shown. Drugs in this class primarily lower TG levels by 20–50%, generally accompanied by 10–15% decrease in LDL-CH and a 10–15% increase in HDL-CH. In some patients with hypertriglyceridaemia LDL-CH may rise, partly because of inability of LDL receptor to clear the excess number of LDL particles generated by enhanced VLDL catabolism. The increase in HDL-CH is at least in part due to transfer of surface lipid components from catabolized VLDL to HDL, and partly due to increased production of HDL apoproteins (apo A-I, apo A-II) by liver. Gemfibrozil also appears to reduce VLDL secretion by liver.

Clofibrate

It was a widely used hypolipidaemic drug, but later evidence showed that it does not prevent atherosclerosis, therefore has gone out of use.

Gemfibrozil

This fibric acid derivative effectively lowers plasma TG level by enhancing breakdown and suppressing hepatic synthesis of TGs. Besides high efficacy in type III hyperlipoproteinemia, gemfibrozil has shown action in subjects with raised blood CH in addition. In the 'Helsinki Heart Study' men without known CAD treated with gemfibrozil had a 34% reduction in fatal and nonfatal MI, though overall mortality was not affected. That these benefits extend to secondary prevention of coronary events in men with existing CAD and low HDL-CH, has been demonstrated in another trial. Additional actions to decrease the level of clotting factor VII-phospholipid complex and promotion of fibrinolysis have been observed, which may contribute to the antiatherosclerotic effect.

Bezafibrate

This second generation fibric acid derivative is an alternative to gemfibrozil in mixed hyperlipidaemias (type III, IV and V). Though it has also been indicated in hypercholesterolaemia (type II), it is inferior to statins and resins. Bezafibrate has not shown propensity to increase LDL-CH in hypertriglyceridaemic patients and appears to have greater LDL-CH lowering action than gemfibrozil. Circulating fibrinogen and glucose levels may decrease. The 5 year 'Bezafibrate Coronary Atherosclerosis Intervention Trial' (BECAIT) in young male postMI subjects showed an atherosclerosis slowing effect and reduction in coronary events. The Bezafibrate Infarction Prevention (BIP) registry has also noted reduction in coronary events in subjects with high TG and low HDL-CH levels.

Fenofibrate

Another 2nd generation prodrug fibric acid derivative which has greater HDL– CH raising and greater LDL-CH lowering action than other fibrates: may be more appropriate as an adjunctive drug in subjects with raised LDLCH levels in addition to raised TG levels. No rise in LDL-CH has been observed in patients with high TG levels.

LIPOLYSIS AND TRIGLYCERIDE SYNTHESIS INHIBITOR - Nicotinic Acid (Niacin)

It is a B group vitamin (see Ch. 67) which in much higher doses reduces plasma lipids. This action is unrelated to its vitamin activity and not present in nicotinamide. When nicotinic acid is given, TGs and VLDL decrease rapidly, followed by a modest fall in LDL-CH and total CH. A 20–50% reduction in plasma TGs and 15–25% reduction in CH levels has been recorded. Nicotinic acid is the most effective drug to raise HDL-CH, probably by decreasing rate of HDL destruction; a 20–35% increase is generally obtained. Relatively lower dose suffices to raise HDL–CH. It also reduces lipoprotein Lp (a), which is considered more atherogenic.

Nicotinic acid reduces production of VLDL in liver by inhibiting TG synthesis. Indirectly the VLDL degradation products IDL and LDL are also reduced. No direct effect on CH and bile acid

metabolism has been found. It inhibits intracellular lipolysis in adipose tissue and increases the activity of lipoprotein lipase that clears TGs.

Adverse effects -The large doses needed for hypolipidaemic action are poorly tolerated. Only about half of the patients are able to take the full doses. Nicotinic acid is a cutaneous vasodilator: marked flushing, heat and itching.

STEROL ABSORPTION INHIBITOR - Ezetimibe

It is a novel drug that acts by inhibiting intestinal absorption of cholesterol and phytosterols. It interferes with a specific CH transport protein NPC1L1 in the intestinal mucosa and reduces absorption of both dietary and biliary CH. There is compensatory increase in hepatic CH synthesis, but LDL-CH level is lowered by 15–20%. The enhanced CH synthesis can be blocked by statins, and the two drugs have synergistic LDL-CH lowering effect. Due to very poor aqueous solubility, ezetimibe is not absorbed as such. A fraction is absorbed after getting conjugated with glucuronic acid in the intestinal mucosa. This is secreted in bile and undergoes enterohepatic circulation to be mainly excreted in faeces. A plasma t½ of 22 hours has been calculated.