CARDIOVASCULAR DRUGS

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 or 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. They 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 the Na^+ and Ca^{2+} channels remain closed and the repolarizing K^+ current (I_K) develops slowly. The 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).

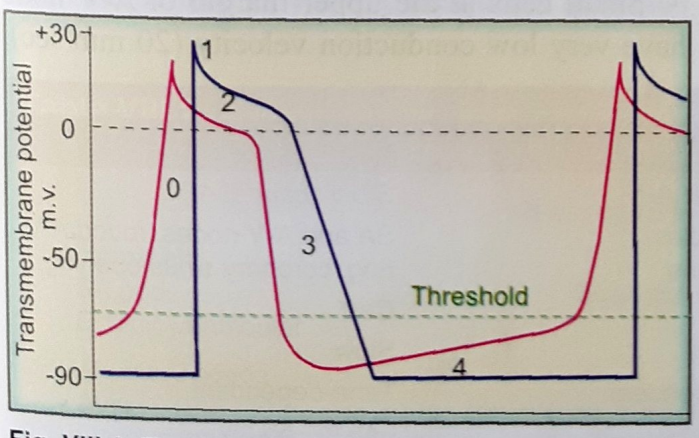


Fig. VIII.1: Transmembrane potential of automatic (red) and nonautomatic (purple) myocardial fibres recorded through intracellular electrodes

(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.

Normally, the SA node has the steepest phase-4 depolarization, undergoes self-excitation

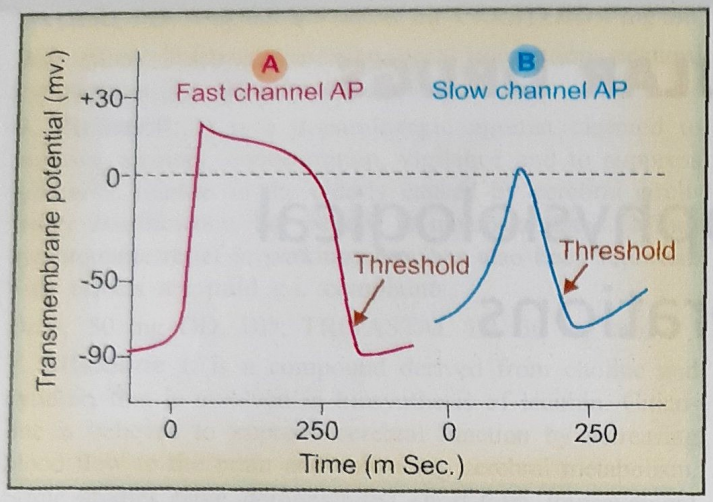


Fig. VIII.2: (A) Fast channel action potential (AP) in a Purkinje fibre, (B) Slow channel action potential in a SA node fibre

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.

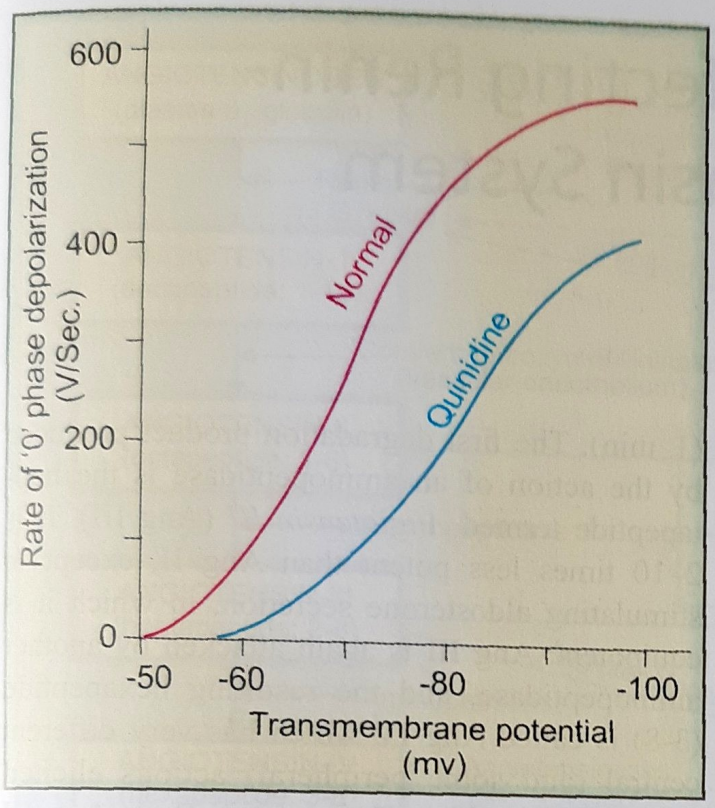
A drug which reduces the slope of 0 phase (at any given resting membrane potential) will shift the membrane responsiveness curve to the right and impede conduction. The reverse occurs with a drug that shifts the curve to the left. Membrane responsiveness curve can also be altered by disease.

Small cells at the upper margin of A-V node have very low conduction velocity (20 mm/sec).

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

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 –55 mV, the fibre becomes inexcitable, since all Na^+ channels are inactivated.

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. Another implication of voltage dependent recovery of Na^+ channel is that partially depolarized fibres recover more slowly, and ERP is prolonged. 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	Depressed	Enhanced
4. Contractility	Decreased (little effect on ventricle)	Increased