UNIT 2 ANTI-ARRHYTHMIC DRUGS, PACEMAKERS, DEFIBRILLATORS

Structure

2.0 OBJECTIVES

After reading this unit, you should be able to:

- describe the classification of antiarrhythmic drugs;
- understand and describe the mechanism of action of different classes of antiarrhythmic drugs;
- understand and describe the indications, mechanism faction and methods of implementation of cardiac pace maker; and
- understand the usefulness of action of defibrillator.

2.1 INTRODUCTION

Antiarrhythmic drugs (AADs) are classified according to whether they exert blocking actions predominantly on sodium, potassium, calcium channels or beta-adrenoceptors. Vaughan Williams classification is widely known and provides a useful framework in which to consider antiarrhythmic drugs. A more realistic view of antiarrhythmic agents is provided by the "Sicilian gambit" approach to drug classification which is based on pharmacological site of action.

2.2 CLASSIFICATION OF ANTI ARRHYTHMIC DRUGS

Vaughan Williams Classification

Class I drugs: Predominantly block the fast sodium channel. They, in turn, arc divided into three subgroups.

Class IA. Drugs that reduce V max (rate of rise of action potential upstroke [phase 0]) and prolong action potential duration: quinidine, procainamide, disopyrarnide.

Class IB. Drugs that do not reduce V max and that shorten action potential duration: mexiletine, phenytoin, and lidocaine.

Classic IC : Drug that reduce V max, primarily slow conduction, and can prolong refractoriness minimally: flecainide, propafenone, and moricizine.

Class II drugs: Drugs that block beta-adrenergic receptors and include propranolol, timolol, metoprolol, and others.

Class III drugs: Drugs that predominantly block potassium channels and prolong repolarization. They include sotalol, amiodarone, bretylium.

Class IV drugs: Drugs that predominantly block the slow calcium channel and include verapamil, diltiazem.

Unclassified: Adenosine, digoxin, magnesium.

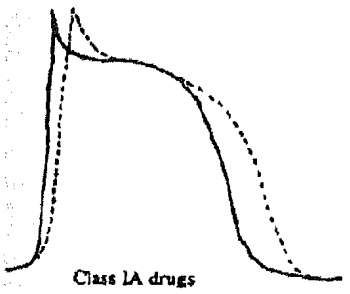


Fig. (1a): Class IA drugs

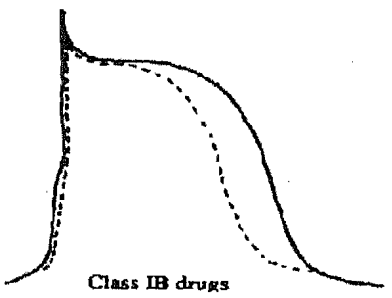
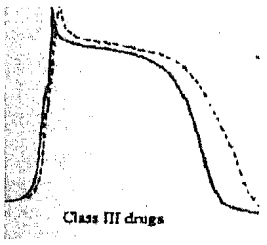


Fig. (1b): Class IB Drugs

Fig. (1c): Class IC drugs

Fig. (1d): Class II & IV Drugs



Rg. (1e): Class III Drugs

Fig. 2.1: Antiarrhythmic Drugs: Effects on Cardiac Action Potential

Use-dependence: Some drugs exert greater inhibitory effects on the upstroke of the action potential at more rapid rates of stimulation and after longer periods of, stimulation, a characteristic called *use-dependence.* With increased time spent in diastole (slower rate), a greater proportion of receptors become drug free, and the drug exerts less effect. Class IB agents demonstrate use dependent block of fast sodium channel.

Reverse Use-dependence: Some drugs exert greater effects at slow rates than at fast rates, a property known as *reverse use-dependence.* This is particularly true for drugs that lengthen repolarization. The QT interval becomes prolonged more at slow than fast rates.

Arrhythmia Suppression — Mechanisms

All arrhythmias occur due to changes in cellular action potential. AADs exert their effect by altering ion channels and re-changing the shape of action potential. Cardiac arrhythmias are caused by either abnormal automaticity, triggered activity or re-entry. Most antiarrhythmic agents in therapeutic doses depress the automatic firing rate of spontaneously discharging ectopic sites while minimally affecting the discharge rate of the normal sinus node. Slow-channel blockers like verapamil, beta-blockers like propranolol, and some antiarrhythmic agents like amiodarone also depress spontaneous discharge of the normal sinus node, whereas drugs that exert vagolytic effects, such as disopyramide or quinidine, can increase the sinus discharge rate. Drugs can also suppress early or

delayed afterdepolarizations and eliminate triggered arrhythmias due to these mechanisms. Re-entry depends on presence of unidirectional block and ciitical interrelationship between refractoriness and conduction velocity. AADs that depress conduction can transform the unidirectional block to bidirectional block and thus terminate re-entry or prevent it from occurring by creating an area of complete block in the reentrant pathway.

Drug Metabolites

Drug metabolites may alter the effects of the parent compound by exerting similar actions, competing with the parent compound, or mediating drug toxicity. Quinidine has at least four active metabolites but none with a potency exceeding the parent drug. About 50 per cent of procainamide is metabolized to NAPA. Only the parent drug blocks cardiac sodium channels and slows impulse propagation in the His-Purkinje system. NAPA prolongs repolarization and is a less effective antiarrhythmic drug but competes with procainamide for renotubular secretory sites and can increase the parent drug's elimination half-life. Lidocaine's metabolite can compete with lidocaine for sodium channels and partially reverse block produced by lidocaine.

Pharmacogenetics

Genetically determined metabolic pathways account for many of the differences in patient's responses to some drugs. The genetically determined activity of hepatic N-acetyltransferase regulates the development of antinuclear antibodies and development of the lupus syndrome in response to procainamide. Slow acetylator phenotypes appear more prone to develop lupus than do rapid acetylators. Quinidine in low doses can inhibit hepatic P450 enzyme and thereby alter concentrations of the drugs and metabolites given in combination that are affected by the enzyme, such as propafenone or flecainide. Cimetidine and ranitidine also affect drug metabolism, probably by inhibiting hepatic P450-metabolizing enzymes. Drugs such as rifampin, phenobarbital, and phenytoin induce synthesis of larger amounts of cytochrome P450, leading to lower concentrations of parent drugs that are extensively metabolized, whereas erythromycin and grapefruit juice inhibit enzyme activity, leading to accumulation of the parent coinpound. Cisapride, an agent to improve gastric motility, by itself does not cause QT prolongation but when given with an inhibitor of cytochrome P450 (such as erythromycin), can lead to QT prolongation and torsades de pointes.

Side Effects

Proarrhythmia: Drug-induced or drug-aggravated cardiac arrhythmias constitute a major clinical problem. Proarrhythmia can be manifested as an increase in frequency of a pre-existing arrhythmia, sustaining of a previously nonsustained arrhythmia (even making it incessant), or development of arrhythmias the patient has not previously experienced, Electrophysiological mechanisms relate to prolongation of repolarization, development of early afterdepolarizations to cause torsades de pointes, and alterations in re-entry pathways to initiate or sustain ventricular tachyarrhythrnias. Proarrhythmic events occur in 5 to 10 per cent of patients. The more commonly known proarrhythmic events occur within several days of beginning drug therapy or changing dosage and are represented by such developments as incessant ventricular tachycardia (VT), long QT syndrome, and torsades de pointes.

Torsades de pointes (twisting around a point) is a distinctive type of polymorphic VT associated with QT prolongation (Fig.2.2). Class IA and Class III drugs prolong action potential duration, increasing QT interval, cause pause-dependent early after-depolarizations leading to VT. Digitoxicity is associated with enhanced delayed after-depolarizations leading to polymorphic VT that is not pause dependent. Bradyarrhythmias are a form of proarrhythmia occurring due to

excessive suppression of sinoatrial and atrioventricular nodes (beta-blockers, calcium channel blockers, digoxin toxicity) or block in distal His-Purkinje system (Class IA, IC, Class III drugs). Treatment of the condition is by stopping the offending drug and instituting temporary pacing. AADs can worsen hemodynamics by depressing ventricular function or by causing hypotension. In CAST study, compared to controls, flecainide caused four times more mortality in post-myocardial infarct patients with reduced left ventricular function and complex ventricular ectopy.

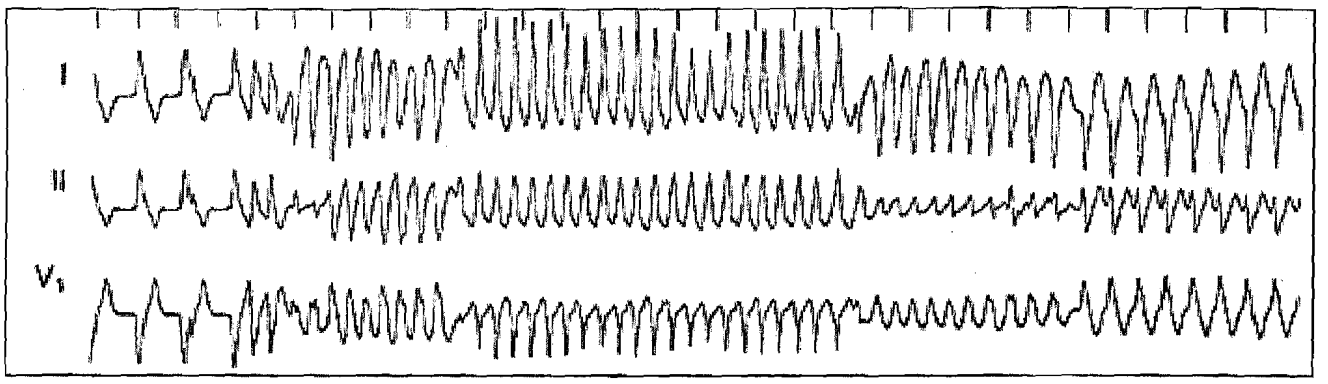


Fig. 2.2: Torsades de Pointes

Class IA Drugs

Act by blocking rapid sodium channel. They are moderately effective in treating most types of arrhythmias.They also cause significant side effects—on end organs as well as proarrhythmia.

Table 2.1: Clinical Pharmacology of Class IA Drugs

	Quinidine	Procainamide	Disopyramide
GI absorption	80- 90 per cent	70-90 per cent	80-90 per cent
Elimination	liver	metabolized to NAPA in liver excreted by kidneys	60 per cent renal, 40 per cent liver
Half life	5-8 hours	3-5 hours	8-9 hours
Dose	300-600 mg qid (sulfate)	15 mg/Kg IV, 1-6 mg/mn then 1-6 mg/min IV oral 500-1250 mg qid	100-200 mg qid

Table 2.2: Adverse Effects of Class IA Drugs

	General Toxicity	Proarrhythmia (Torsades)
Quinidine	Diarrhoea, cinchonism (tinnitus,visual disturbances), rash, anemia, thrombocytopenia	+ +
Procainamide	Lupus, nausea, diarrhoea, agranulocytosis, hypotension(IV)	+ +
Disopyramide	Reduced ventricular contractility, urinary retention, dry mouth and eyes (strong anticholinergic effect).	+ +

Class IB Drugs

These drugs are moderately useful in treating ventricular arrhythmias. In contrast to other Class I drugs, these agents have a low incidence of side effects.

Table 2.3: Clinical Pharmacology of Class IB Drugs

	Lidocaine	Mexelitine	Phenytoin
GI absorption	—	>90 per cent	variable
protein' binding	70 per cent	70 per cent	90 per cent
Elimination	Liver	Liver	Liver
Half-life	1-4 hours	8-16 hours	24 hours
Dosage	1-4 mg/kg IV, then 1-4 mg/min	150-200 mg tid	10 mg/kg IV oral:300-500 mg/day

Table 2.4: Common Adverse Effects of Class IB Drugs

	General Toxicity	Proarrhythmia
Lidocaine	CNS (slurred speech,paresthesia,seizures)	+
Mexiletine	Nausea, CNS (tremors, ataxia)	+
Phenytoin	Ataxia, nystagmus, anemia, hypersensitivity reactions	+

Class IC Drugs

These drugs are very effective in treating both atrial and ventricular tachycardias and gene ally cause only mild end-organ toxicity. CAST study revealed the significant proarrhythmic potential of these drugs in patients with ventricular dysfunction.

Table 2.5: Clinical Pharmacology of Class IC Drugs

	Flecainide	Propafenone	Moricizine
GI Absorption	>90 per cent	>90 per cent	>90 per cent
Protein binding	40 per cent	90 per cent	>90 per cent
Elimination 30 per cent renal	70 per cent liver	Liver	Liver
Half-life	12-24 hours	6-7 hours	3-12 hours
Dosage	100-200 mg bid	150-300 mg tid	200-300 mg tld

Table 2.6: Adverse Effects of Class IC Drugs

	General Toxicity	Proarrhythmia
Flecainide	Visual disturbances, nausea, ventricular dysfunction	+ + +
Propafenone	Nausea, dizziness, ataxia, ventricular dysfunction	+ + +
Moricizine	Dizziness, headache, nausea	+ +

Class II Drugs: Beta-Blocking Agents

These agents act by blunting the arrhythmogenic actions of catecholamines. They significantly reduce the incidence of sudden cardiac arrest by preventing cardiac tachyarrhythmias.Since adrcncrgic stimulation is most profound normally in the sinoatrial and atrioventricular nodes, these structures are most affected by beta-blockers. This results in slowing of heart rate and conduction delay across atrioventricular node.These agents have a profound effect on ischemic myocardium and have been shown to reduce risk of ventricular fibrillation during ischemia.

Table 2.7: Clinical Pharmacology of Beta-Blocking Drugs						
Drug	β_1 selective	ISA	Class I	Vasodilator	Lipid soluble	Half life (hours)
Atenolol	+ +	0	0	0	Weak	6-9
Carvedilol	0	0	+ +	+	Moderate	7-10
Esmolol	+ +	0	0	+	Weak	9 mins
Labetolol	0	+	0	+	Weak	3-4
Metoprolol	+ +	0	0	0	Moderate	3-4
Propranolol	0	0	+ +	0	High	3-4

Adverse Effects of β-blockers

As a direct consequence of adrenergic blockade, these agents can cause brady cardia, myocardial depression, bronchoconstriction, claudication, Raynaud's phenomenon, fatigue, mental depression. In diabetes mellitus, these drugs can mask symptoms of hypoglycemia. Drugs with β_1 selectivity avoid bronchospasin, claudication, Raynaud's phenomenon. Drugs with low lipid solubility help in preventing CNS side effects.

Class III Drugs

These drugs prolong the duration of cardiac action potential by blocking potassium channels and increase refractory periods of conduction tissues.

Table 2.8: Clinical Pharmacology of Class III drugs				
	GI absorption	Elimination	Half-life	Dosage
Amiodarone	30-40 per cent	Hepatic	30-106 days	800-1600 mg/d for 7-14 days, then 100-400 mg/day
Bretylium	—	Renal	9-10 hours	5 mg/kg IV, 1-2 mg/min IV infusion
Sotalol	>90 per cent	Renal	12 hours	160-320 mg/ day oral
Ibutilide	—	Renal	2-12 hours	10 mg IV infusion in 10 mins

Amiodarone: Displays activity of all four classes of antiarrhythmic agents, with major effect of homogeneous prolongation of the action potential.

Indications: It is a broad spectrum antiarrhythmic dmg. It is effective for any type of tachyarrhythmia.It is moderately effective in converting atrial flutter and atrial fibrillation to sinus rhythm. It is effective for paroxysmal supraventricular tachycardias (SVT) — including accessory pathway mediated tachycardia and AV nodal re-entrant tachycardia. It is one of the most effective agents developed for treatment of VT and ventricular fibrillation. Patients who have an internal cardioverter-defibiillator (ICD) receive fewer shocks if they are treated with amiodarone compared with other conventional drugs.

Adverse Effects: Has high incidence of side effects ranging from minor to life-threatening. Mild gastsointestinal (GI) side effects are common *(25* per cent) with high dose loading phase but uncommon with maintenance dose. Pulmonary toxicity is the most serious adverse reaction, mechanism may be

related to hypersensitivity. Acute amiodarone induced pneumonitis (2-5 per cent incidence) and chronic interstitial fibrosis can occur. At maintenance doses less than 300 mg/d, pulmonary toxicity is uncommon. Although asymptomatic elevations of liver enzymes are found in most patients, the drug is not stopped unless values exceed two or three times normal in a patient with initially abnormal values. Neurological dysfunction, photosensitivity (perhaps minimized by sunscreens), bluish skin discoloration and hyperthyroidism (1 to 2 per cent) or hypothyroidism (2 to 4 per cent) can occur.

Drug Interactions: When given concoinitantly with amiodarone, the doses of warfarin, digoxin, and other antiarrhythmic drugs should be reduced by one third to one half.

Bretylium Tosylate

This drug is approved for parenteral use only in patients with life-threatening ventricular tachyarrhythmias. Bretylium is selectively concentrated in sympathetic ganglia and their postganglionic adrenergic nerve terminals. After initially causing norepinephrine release, bretylium *prevents* norepinephrine release by depressing sympathetic nerve terminal excitability resulting in chemical sympathectomy-like state. After an initial increase in blood pressure, the drug can cause significant hypotension by blocking the efferent limb of the baroreceptor reflex. Bretylium has been effective in trealing patients with drug-resistant recurrent ventricular tachyarrhythmias and in treating victims of out-of-hospital VF.

Adverse Effects:

Hypotension, most prominently orthostatic but also supine, appears to be the most significant side effect and can be prevented with tricyclic drugs such as protriptyline.

Sotalol

Both *d*- and I-isomers have similar effects on prolonging repolarization, whereas the I-isomer is responsible for virtually all the beta-blocking activity. Effective in treating ventricular tachyarrhythmias, sotalol is also useful to prevent recurrence of a wide variety of SVTs, including atrial flutter and fibrillation, atrial tachycardia, AV node re-entry, and AV re-entry. Sotalol has been shown to be superior to liclocaine for acute termination of sustained VT and is useful in patients with arrhythmogenic right ventricular dysplasia. It may decrease the frequency of ICD discharges and reduce the defibrillation threshold.

Adverse Effects:

Proarrhythmia is the most serious adverse effect—torsades de pointes occurs in about 2.5 per cent.

Ibutilide

It is useful in acutely terminating episodes of atrial flutter and fibrillation. It should not be used in patients with frequent, short paroxysms of atrial fibrillation because it merely terminates episodes and is not useful for prevention.

Adverse Effects:

The most significant adverse effect of ibutilide is torsades de pointes, which occurs in approximately two per cent of patients given the drug.

Class IV Drugs: Calcium-channel Blocking Agents

Many calcium-channel blocking agents are available, but only two drugs- verapamil and diltiazem- are approved for treatment of cardiac tachyarrhythmias.

Clinical Pharmacology of Verapamil and Diltiazem

After an oral dose, more than 90 per cent of verapamil is absorbed but bioavailability is reduced to 20 per cent to 35 per cent by first-pass hepatic metabolism. About 90 per cent of the drug is protein bound.Elimination half-life is 5-12 hours.

Diltiazem is also well absorbed after oral administration and is 40 per cent bioavailable after first-pass metabolism. It is 70 per cent to 80 per cent protein bound. It is metabolized in liver and elimination half life is 3.5 hours.

Both the drugs are available for intravenous administration, used in treatment of emergent SVTs.

Dosage

Usual oral dose of verapamil is 240-360 mg/day given every eight hours. Diltiazcm is given every 6-8 hours to a daily dose of 120-360mg. Various long-acting preparations are available for veraparnil and diltiazem. The most commonly used IV dose of verapamil is 10 mg infused over I to 2 minutes while cardiac rhythm and blood pressure are monitored. The initial effect may be maintained by a continuous infusion of the drug at a rate of 0.005 mg/kg/min. Diltiazem is given intravenously at a dose of 0.25 mg/kg as a bolus over 2 minutes, followed if necessary by infusion at 10mg/hr.

Electrophysiologic Effects

These drugs block the slow calcium-channel and reduce the plateau height of the action potential. Veraparnil and diltiazem suppress electrical activity in the normal sinus and AV nodes in concentrations that do not suppress action potentials of fast-channel-dependent cells. Verapamil does not exert a significant direct effect on atrial or ventricular refractoriness or on anterograde or retrog ade properties of accessory pathways. However, reflex sympathetic stimulation may increase the ventricular response over the accessory pathway during atrial fibrillation in patients with the Wolff-Parkinson-White (WPW) syndrome. Even though verapamil terminates a left septal fascicular VT, hemodynarnic collapse can occur if intravenous verapamil is given to patients with the more common forms of VT.

Adverse Effects

Verapamil has negative inotropic effect and can precipitate congestive heart failure in patients with impaired ventricular function.Both drugs can cause constipation, nausea, bradyarrhythmias (seen with pre-existent sinoatrial or atrioventricular nodal disease), hypotension.

Unclassified Drugs

Digoxin, adenosine and magnesium are often used for treating cardiac arrhythmias; as these agents do not fit into Vaughan-Williams classification, they are discussed separately.

Digoxin

Digoxin preparations have been available for clinical use since 1700s. Digoxin is well absorbed orally, is excreted by kidneys and has an elimination half-life of 1.7 days. It increase parasympathetic tone and has greatest effect on sinoatrial (SA) and atrioventricular (AV) nodes. Apart from antiarrhythmic effect, it increases intracellular calcium during myocardial contraction, increasing contractility.

Digoxin is well tolerated but toxicity can be a serious clinical problem with gastrointestinal (nausea, vomiting, anorexia, diarrhea, cramps), neurological disturbances (visual, delirium) and significant arrhythmias which are potentially life-threatening. Digoxin toxicity is enhanced by low potassium levels. For refractory ventricular arrhythmias occurring due to high digoxin levels, cardioversion is better avoided; correcting hypokalemia, administering phenytoin or lidocaine and when available using digoxin-specific antibodies is effective.

Adenosine

It is a naturally occurring nucleoside that has a profound but very short-lasting depressive effect on SA node and AV node, approved for acute treatment of SVT. Adenosine is removed from the vascular space by vascular endothelium and the formed blood elements which result in very rapid clearance of adenosine from the circulation. Elimination half-life is 1 to 6 seconds.

Dosage: To terminate tachycardia, a bolus of adenosine is rapidly injected intravenously into a central vein (if possible) at doses of 6 to 12 mg. Pediatric dosing should be 0.1 to 0.3 mg/kg. Transient sinus slowing or AV node block results.

Adverse Effects

Transient side effects occur in almost 40 per cent of patients with SVT given adenosine and are most commonly flushing, dyspnea, and chest pressure. These symptoms are fleeting, lasting less than one minute, and are well tolerated. Ventricular ectopics, transient sinus bradycardia, sinus arrest, and AV block are common when an SVT abruptly terminates. Atrial fibrillation(AF) is occasionally observed (12 per cent) and is problematic in patients with WPW syndrome when the accessory pathway conducts antegradely rapidly.

Magnesium

The most well established use of parenteral magnesium as an antiarrhythmic agent is in therapy of torsades de pointes. The precise mechanism by which it ameliorates arrhythmias is unclear but it has an important influence on sodium-potassium pump in the cell membrane and changes the action potential. Apart from being drug of first choice for emergency treatment of torsades, it also has a place in treating arrhythmias due to digoxin toxicity, multifocal atrial tachycardia and in preventing arrhythmias after cardiac surgery.

Dosage: 8-16mEq (I-2g) of magnesium sulphate can be infused rapidly over several. minutes.

Toxicity: Is exacerbated in renal failure. Manifestations include ECG changes (increased PR interval and QRS duration), loss of deep tendon reflexes and respiratory paralysis.

Table 2.9: Relative Efficacy of Antiarrhythmic Drugs for Tachyarrhythmias

Atrial Tachycardia	AV Node-dependent Tachycardias	Ventricular Tachycardia
Class IA	Class IA	Class II
Sotalol	Digoxin	Class IB
Class IC	Class II	Class IA
Amiodarone	Class IV	Class IC
	Sotalol Class IC Amiodarone Adenosine	Sotalol Amiodarone

Table 2.10: Drugs of Choice for Atrial and Ventricular Tachyarrhythmias			
With Underlying Heart Disease		No Underlying Heart Disease	
Atrial Arrhythmias	Ventricular Arrhythmias	Atrial Arrhythmias	Ventricular Arrhythmias
Class IC	Class II	Sotalol	Amiodarone
Sotalol	Class IB	Amiodarone	Sotalol
Class IA	Sotalol Class IC Class IA Amiodarone	Class IA	Class IA

Table 2.11: Major Drug Interactions of Antiarrhythmic Drugs		
Drug	Levels or Effect Increased	Levels or Effect Decreased
Class IA		
Quinidine	Amiodarone Anticholinegics Warfarin Digoxin	Phenobarbital Phenytoin Rifampicin
Procainamide	Amiodarone Cimetidine	Ethanol
Disopyramide		Phenobarbital Phenytoin Rifampicin
Class IB		
Lidocaine	Propranolol Metoprolol	Phenobarbital
Mexelitine	Isoniazid Chloramphenicol Theophylline Lidocaine	Phenytoin Phenobarbital Rifampicin
Phenytoin	Sulfonamides Amiodarone Isoniazid	Theophylline
Class IC		
Flecainide	Amiodarone Quinidine Digoxin Propranolol	
Propafenone	Quinidine Digoxin Metoprolol Theophylline Warfarin	Phenobarbital Phenytoin Rifampicin

Drug	Levels or Effect Increased	Levels or Effect Decreased
Class III Amiodarone	Warfarin Digoxin Class I drugs Beta-blockers Calcium blockers	
Sotalol	Class IA drugs Beta-blockers	
Ibutilide	Class IA drugs	

Check Your Progress 1

I) How many classes of drugs are there in the Vaughan Williams classifications?

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2) What is meant by the term pro arrhythmia?

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3) How often does pro arrhythmia occur?

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4) What are the more common types of pro arrhythmias?

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5) What are some of the side effects of disopyramide?

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6) What is the route of elimination of Amiodarone?

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7) Mention some of the organs affected bny amiodarone toxicity.

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8) What are some of the important drug interactions with Amiodarone?

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9) What types of arrhythmias is Ibutilide used in?

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10) What are some of the adverse effects of Verapamil and Diltiazem?

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2.3 CARDIAC PACEMAKERS

Cardiac pacemakers are used to treat a heart that beats loo slowly. Sometimes the natural pacemaker of the heart becomes diseased and does not keep the heart beating regularly. The average heart rate is 60 to **100** beats per minute. The normal heart can occasionally beat as slowly as **40** times a minute while resting and as fast as 200 times a minule while exercising. However there can be symptoms of weakness, dizziness and fainting when the heart beats to slowly. The heart may always be slow or the may be episodic pauses in the heartbeat that may lead to symptoms. Occasionally an EPS study may be needed to determine the need for a pacemaker.

How do pacemakers work?

Pacemakers consist of two major parts: the generator, and the leads.

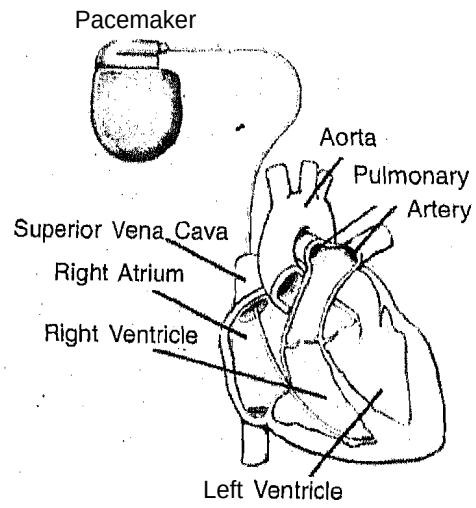

Fig. 2.3: Functions of Pacemakers

The generator is essentially a tiny, hermetically sealed computer – along with a battery to run it – housed in a titanium container. Most modern pacemaker generators are roughly the size of a 50 per cent piece, and approximately three times as thick. The battery life of most pacemaker generators today is 5-8 years.

The lead is a flexible insulated electrical wire. One end is attached to the generator and the other end is passed through a vein into the heart. Most pacemakers today use two leads – one placed in the right atiium, and the other in the right ventricle.

How it works: The pacemaker leads detect the heart's own electrical activity (in the right atrium and right ventricle), and transmit that information to the pacemaker generator. The generator – which, again, is a computer – analyzes the heart's electrical signals, and uses that information to decide whether, when, and where to pace. If the heart rate becomes too slow, the generator transmits a tiny electrical signal to the heart, thus stimulating the heart muscle to contract (This is called pacing).

Pacemakers that have two leads not only keep the heart rate from dropping too low, they can also maintain the optimal coordination between the atria and the ventricles (by pacing the atrium and the ventiicle in sequence).

Thus, pacemakers do not take over the work of the heart – the heart still does its own beating – but instead, pacemakers merely help to regulate the timing of the heart beat.

Pacemaker Naming Code

The NASPE/BPEG generic (NPG) code is a pacemaker naming convention originally developed in 1974 that uses a 3-5 letter code to describe the main features of an artificial pacemaker. Each of the five positions signifies a particular aspects of pacemaker functionality. Using this scheme, a designation of VATOO would describe, for example, a pacemaker that sensed the atria and paced the ventricles in a triggered mode with no rate response or multisite pacing.

Position	I	II	III	IV	V
Category	Chamber(s) Paced	Chamber(s) Sensed	Response to Sensing	Rate Response	Multisite Pacing
Code	O = none, A=atrium, V=ventricle and D = dual (A + V)	O = none, A=atrium, V = ventricle and D = dual (A + V)	O = none, = trlggered, I = inhibited and D=dual (T+I)	O = none, R = rate modulation	O = none, A = atrium V = ventricle and D=dual (A + V)
Manufacturer's designation only	S = Single (A or V)	S = Single (A or V)			

Advancements in Pacemaker Function

When first invented, pacemakers controlled only the rate at which the heart's two largest chambers, the ventricles, beat.

Many advancements have been made to enhance the control of the pacemaker once implanted, Many of these enhancements have been made possible by the transition to microprocessor controlled pacemakers. Pacemakers that control not only the ventricles but the atria as well have become common. Pacemakers that

control both the atria and ventricles are called dual-chamber pacemakers. Timing the contractions of the atria to precede that of the ventricles improves the pumping efficiency of the heart and can be useful in congestive heart failure.

Implantation and **Follow-up** of Pacemakers

Pacemaker implantation today is minimally invasive surgery. It is done under local anesthesia, and generally takes less than 45 minutes.

After the area under the patient's collarbone is numbed, a small incision is made (usually about three inches long,) and a "pocket" is fashioned in the tissue overlying the muscle. The leads are inserted through a vein near the site of the pocket, and advanced into the heart using fluoroscopy (X-rays) for guidance. The leads are then attached to the generator, the generator is placed in the pocket, and the incision is closed.

Once a pacemaker is implanted, it is important to program it. Pacemakers today are extremely flexible devices, and can vary their function according to the precise needs of the patient. But to do this, the doctor needs to program the devices.

As noted, pacemaker generators are essentially tiny computers, and like any computer, before they can be optimally useful their software needs to be "tweaked" to suit the individual user. Pacemakers can be programmed non-invasively, with a handheld device that communicates with the pacemaker through the skin. The programming can be repeated as often as necessary if the patient's underlying heart rhythm problem changes.

What happens after the pacemaker is implanted?

Once the incision completely heals (which takes about 2-4 weeks,) the patient can largely return to a completely normal life. In fact, since pacemakers alleviate the symptoms of bradycardia, many patients find they are able to do even more after a pacemaker is implanted.

Periodic pacemaker checks are necessary, to measure the function of the device and the amount of energy left in the battery. The "scheduled maintenance" for pacemakers generally consists of periodic telephone follow-up (every month or two,) and usually yearly visits to the doctor's office. The telephone follow-up is a simple procedure consisting of placing a special "trans-telephonic follow-up device" over the pacemaker, and transmitting data over the telephone.

When the battery begins to get low, the doctor schedules an elective pacemaker replacement. This procedure is similar to the implantation procedure, except that usually the pacemaker leads do not need to be replaced. Under local anesthesia, the incision is opened, the generator is detached from the leads and thrown away, a new generator is attached, and the incision is then closed. (This is not merely a "battery change," though doctors sometimes call it that. No batteries are changed; instead, the entire old generator is discarded and a brand new one is placed).

Pacemaker problems can rarely occur long after the implantation procedure. These "late" complications include generator failure (extremely rare), and lead failure (less rare). Lead failure can occur if the pacemaker is traumatized somehow, such as from the wear and tear of movement. (The most common cause of such trauma is the habit some people have of "twiddling" with their pacemaker). Manufacturers are required to report device failures to the FDA. Which will order companies to issue either "advisories" or recalls if a particular model seems prone to failure.

Following the suggested maintenance schedule usually ineans that pacemaker will be detected before they become serious.

However, it is important for patients to be aware of the symptoms of bradycardia, symptoms that might indicate a pacemaker malfunction. Once again, these symptoms include weakness, easy fatigability, lightheadedness, dizziness, or loss of consciousness. Patients experiencing any of these symptoms should notify their doctor. A simple telephone check of the pacemaker is usually enough to rule out a pacemaker problem.

What devices can interfere with pacemakers?

Home appliances do not inteifere with pacemakers, and should not cause any concern whatsoever. (This includes microwave ovens, despite the signs you still see posted in some restaurants).

Arc welding equipment and other devices that generate powerful magnetic fields– medical devices and heavy duty industrial motors —can inhibit the function of pacemakers.

Cellular telephones, if held in close proximity to the pacemaker (which may happen if the phone is kept in a breast pocket) can potentially affect the function of a pacemaker. As long as the phone is kept six or more inches from the pacemaker there should not be a problem.

MRI scanners can interrupt the pacing function of pacemakers, and under some circumstances may be dangerous to the pacemaker and the patient. Many problems with MRI can be circumvented by taking special care during the procedure and limiting the MRI scan appropriately. Patients with pacemakers should discuss the risks and benefits of MRI scanning with their doctors.

Radiation therapy for cancers can dainage the circuits of a pacemaker, and the pacemaker needs to be shielded from the radiation field.

Shock wave lithotripsy, used to break up kidney stones, can potentially damage pacemakers, espècially if they are implanted in the abdomen instead of under the collarbone. Pacemakers should be tested after lithotripsy to document that they are still functioning normally.

Methods of Pacing

External Pacing

External pacemakers can be used for initial stabilization of a patient, but implantation of a permanent internal pacemaker is usually required for most conditions. External cardiac pacing is typically performed by placing two pacing pads on the chest wall. Usually one pad is placed on the upper poi-tion of the *sternum,* while the other is placed along the left axilla, near the bottom of the rib cage. When an electrical impulse goes from one pad to the other, it will travel through the tissues between them and stimulate the muscles between them, including the cardiac muscle and the muscles of the chest wall. Electrically stimulating any muscle, including the heart muscle, will make it contract. The stimulation of the muscles of the chest wall will frequently make those muscles twitch at the same rate as the pacemaker is set.

Pacing the heart via external pacing pads should not be relied upon for an extended period of time, If the person is conscious, he or she may feel discomfort due to the frequent stimulation of the muscles of the chest wall. Also, stimulation of the chest wall muscles does not necessarily mean that the heart is being stimulated as well.

Temporary Internal Pacing

An alternative to external pacing is the temporary internal pacing wire. This is a wire that is placed under sterile conditions via a central line. The distal tip of the wire is placed into either the right atrium or right ventricle. The proximal tip of the wire is attached to the pacemaker generator, outside of the body. Temporary internal pacing is often used as a bridge to permanent pacemaker placement. Under certain conditions, a person may require temporary pacing but would not require permanent pacing. In this case, a temporary pacing wire may be the optimal treatment option.

Permanent Pacemaker Placement

Placement of a permanent pacemaker involves placement of one or more pacing wires within the chambers of the heart. One end of each wire is attached to the muscle of the heart. The other end is screwed into the pacemaker generator. The pacemaker generator is a hermetically sealed device containing a power source and the **computer** logic for the pacemaker.

Most commonly, the generator is placed below the subcutaneous fat of the chest wall, above the muscles and bones of the chest. However, the placement may vary on a case by case basis.

Another advancement in pacemaker technology is left ventricular pacing.' A pacemaker wire is placed on the outer surface of the left ventricle, with the goal of more physiological pacing than what is available in standard pacemakers. This extra wire is implanted to improve symptoms in patients with severe heart failure.

Devices with Pacemaker Function

Sometimes devices resembling pacemakers, called ICDs **(implantable cardioverter-defibrillators)**are implanted. These devices' are often used in the treatment of patients at risk for sudden cardiac death. An ICD has the ability to treat many types of heart rhythm disturbances by means of pacing, **cardioversion,** or **defibrillation.**

Check Your Progress 2

1) What are the two major parts of a pacemaker?

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2) What is meant by the terms OAVDI, in pacemaker technology?

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3) What is meant by temporary internal pacing?

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2.4 DEFIBRILLATORS

A defibrillator is an electronic device that is used to administer an electric shock to the heart as a treatment for life-threatening heart rhythm abnormalities. The defibrillator sends an electric shock of preset voltage to the heart through the chest wall attempting to restore the normal rhythm of the heart during ventricular fibrillation. These are three main types of devices used for defibrillation of the heart.

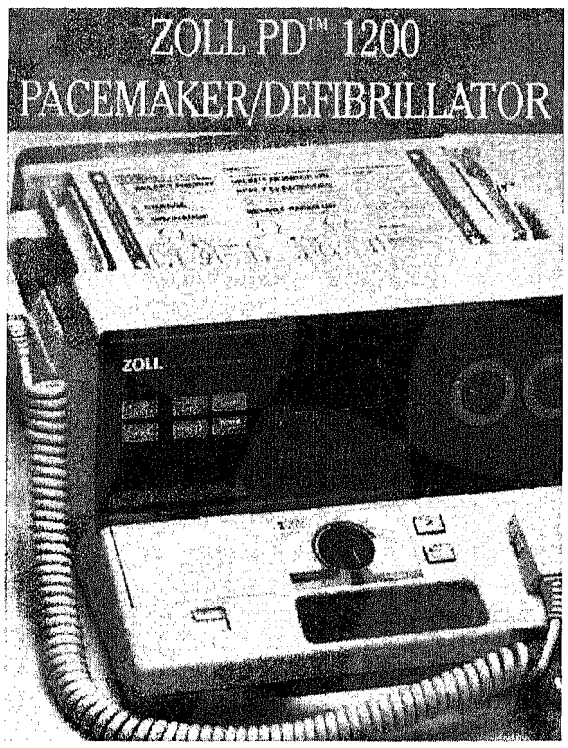

Fig. 2.4: Defibrillator

Design

The most well-known type of electrode is the traditional metal paddle with an insulated handle. This type must be held in place on the patient's skin while a shock or a series of shocks is delivered. Before the paddle is used, a gel must be applied to the patient's skin, in order to ensure a good connection and to minimize electrical impedance.

Anotlier type of resuscitation electrode is designed as an adhesive pad. When a patient has been admitted due to heart problems, and the physician or nurse has determined that lie or she is at risk of arrhythmia, they may apply adhesive electrodes to the patient in anticipation of any problems that may arise. These electrodes are left connected to a defibrillator. If defibrillation is required, the machine is charged, and the shock is delivered, without any need to apply any gel 'or to retrieve and place any paddles.

Both solid-gel and wet-gel adhesive electrodes are available. Solid-gel electrodes are more convenient, because there is no need to clean the patient's skin after removing the electrodes. However, the use of solid-gel electrodes presents a higher risk of burns during defibrillation, since wet-gel electrodes more evenly conduct electricity into the body.

Adhesive electrodes are designed to be used not only for defibrillation, but also for non-invasive pacing and electrical cardioversion.

External Defibrillators

External defibrillators are typically used in hospitals or ambulances, but are increasingly common outside the medical realm, as automated external defibrillators become safer and cheaper. There are a variety of technologies and form factors in use for external defibrillators, and recent progress in cardiac research has led to substantial improvements in the underlying technology.

Automated External Defibrillators (AEDs)

Small electronic devices that are placed in locations where people can quickly respond to sudden cardiac arrest. These locations range from private office buildings to public gathering areas such as ail-ports and hospitals.

Implantable Cardioverter—Defibrillator (ICDs)

Implanted devices similar to pacemakers that briefly passes an electric current through the heart. It includes a pulse generator and one or more leads that constantly monitors the heartbeat. It is a small computer that operates on a battery that takes signals from your heart to the ICD and then takes an electric current from the pulse generator to your heart.

Electrodes

The electrode is a key part of any defibrillation system. The proper selection and placement of electrodes can determine the effectiveness of the procedure.

Check Your Progress **3**

What is an automatic implanted cardiac defibrillator?

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Placement

Resuscitation electrodes are placed according to one of two schemes. The anterior-posterior scheme is the preferred scheme for long-term electrode placement. One electrode is placed over the left precordium (the lower part of the chest, in front of the heart). The other electrode is placed on the back, behind the heart in the region between the scapula. This placement is preferred because it is best for non-invasive pacing.

The anterior-apex scheme can be used when the anterior-posterior scheme is inconvenient or unnecessary. In this scheme, the anterior electrode is placed on the right, below the clavicle. The apex electrode is applied to the left side of the patient, just below and to the left of the pectoral muscle. This scheme works well for defibrillation and *cardioversion,* as well as for monitoring an ECG.

2.5 LET US SUM UP

In this unit you have learnt about the classification of antiarrhythmic drugs, understand and able to describe the mechanism of action of different classes of antiarrhythmic drugs. You have also learnt the indications, mechanism of function and methods of implementation of cardiac pace maker and usefulness of action of defibrillator.

2.6 ANSWERS TO CHECK YOUR PROGRESS

Check Your Progress 1

1) **Yaughan William Classification**

Class I drugs: predominantly block the fast sodium channel. They, in turn, are divided into three subgroups.

Class I A. Drugs that reduce Vmax (rate of rise of action potential upstroke [phase 0]) and prolong action potential duration: quinidine, procainamide, disopyramide

Class l B. Drugs that do not reduce Vmax and that shorten action potential duration: mexiletine, phenytoin, and lidocaine

Class 1C. Drugs that reduce vmax, primarily slow conduction, and can prolong refractoriness minimally: flecainide, propafenone, and moricizine

Class II drugs: Drugs that block beta-adrenergic receptors and include propranolol, timolol, metoprolol, and others.

Class III drugs: Drugs that predominantly block potassium channels and prolong repolarization. They include sotalol, amiodarone, bretylium

Class IV drugs: Drugs that predominantly block the slow calcium channel and include verapamil, diltiazem.

Unclassified: Adenosine, digoxin, magnesium.

2) This is drug-induced or drug-aggravated cardiac arrhythmias constitute a major clinical problem. Proarrhythmia can be manifested as an increase in frequency of' a preexisting arrhythmia, sustaining of a previously nonsustained arrhythmia (even making it incessant), or development of arrhythmias the patient has not previously experienced.

3) Proarrhythmic events occur in 5 to 10 per cent of patients.

4) The more commonly known proarrhythmic events occur within several days of beginning drug therapy or changing dosage and are represented by such developments as incessant ventricular tachycardia (VT), long QT syndrome, and torsades de pointes.

5) Reduced ventricular contractility, urinary retention dry mouth and eyes (strong anticholinergic effect).

6) Eliminated by the liver and so no dose reduction necessary in renal insuffiency.

7) Pulmonary toxicity is the most serious adverse reaction, mechanism may be related to hypersensitivity. Acute amiodarone induced pneuinonitis (2-5 per cent incidence) and chronic interstitial fibrosis can occur.

Hyperthyroidism (1 to 2 per cent) or hypothyroidism (2 to 4 per cent) can occur. Although asymptomatic elevations of liver enzymes are found in most patients, the drug is not stopped unless values exceed two or three times normal in a patient with initially abnormal values.

Neurological dysfunction

Photosensitivity (perhaps minimized by sunscreens), bluish skin discoloration

8) When given concomitantly with amiodarone, the doses of warfarin, digoxin, and other antiarrhythmic drugs should be reduced by one third to one half.

9) It is useful in acutely terminating episodes of atrial flutter and fibrillation.

10) Verapamil has negative inotropic effect and can precipitate congestive heart failure in patients with impaired ventricular function. Both drugs can cause constipation, nausea, bradyarrhythrnias (seen with preexistent sinoatrial or atrioventricular nodal disease), hypotension.

Check Your Progress 2

1) Pacemakers consist of two major parts: the generator and the leads.

2) O = none, A = atrium, V = ventricle, D = dual (A + V) and I = inhibited.

3) An alternative to external pacing is the temporary internal pacing wire. This is a wire that is placed under sterile conditions via a central line or vein. The distal tip of the wire is placed into either the right atrium or right ventricle. The proximal tip of the wire is attached to the pacemaker generator, outside of the body. Temporary internal pacing is often used as a bridge to pernlanent pacemaker placement. Under certain conditions, a person may require temporary pacing but would not require pernlanent pacing. In this case, a temporary pacing wire may be the optimal treatment option.

Check Your Progress 3

Sometimes devices resembling pacemakers, called ICDs **(implantable cardioverter-defibrillators)**are implanted. These devices are often used in the treatment of patients at risk for sudden cardiac death. An ICD has the ability to treat many types of heart rhythm disturbances by means of pacing, **cardioversion, or defibrillation.**

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