Lecture-4- د.رياض الموسوي

Antiarrhythmic

In contrast to skeletal muscle, which contracts only when it receives a stimulus, the heart contains specialized cells that exhibit automaticity; that is, they can intrinsically generate rhythmic action potentials in the absence of external stimuli. These pacemakers cells differ from other myocardial cells in showing a slow, spontaneous depolarization during diastole (Phase 4), caused by an inward positive current carried by sodium- and calcium-ion flows. This depolarization is fastest in the sinoatrial (SA) node (the normal initiation site of the action potential), and it decreases throughout the normal conduction pathway through the atrioventricular (AV) node to the bundle of His and the Purkinje system. Dysfunction of impulse generation or conduction at any of a number of sites in the heart can cause an abnormality in cardiac rhythm.

Introduction to the Arrhythmias

The arrhythmias are conceptually simple dysfunctions cause abnormalities in impulse formation and conduction in the myocardium. However, in the clinic, arrhythmias present as a complex family of disorders that show a variety of symptoms. For example, cardiac arrhythmias may cause the heart to beat too slowly (bradycardia) or to beat too rapidly (tachycardia), and to beat regularly (sinus tachycardia or sinus bradycardia) or irregularly (atrial fibrillation). The heart cavity from which the arrhythmia originates gives the name to the arrhythmia atrial tachycardia for a rapid arrhythmia originating in the atria. Impulses originating from sites other than the SA node, or impulses traveling along accessory (extra) pathways that lead to deviant depolarizations (AV reentry, Wolff-Parkinson-White syndrome), may also trigger arrhythmias. To make sense of this large group of disorders, it is useful to organize the arrhythmias into groups according to the anatomic site of the abnormality the atria, the AV node, or the ventricles.

Causes of arrhythmias:-

Most arrhythmias arise either from aberrations in impulse generation (abnormal automaticity) or from a defect in impulse conduction.

Abnormal automaticity: The SA node shows the fastest rate of Phase 4 depolarization and, therefore, exhibits a higher rate of discharge than that occurring in other pacemaker cells exhibiting automaticity. Thus, the SA node normally sets the pace of contraction for the myocardium, and latent pacemakers are depolarized by impulses coming from the SA node. However, if cardiac sites other than the SA node show enhanced automaticity, they may generate competing stimuli, and arrhythmias may arise. Abnormal automaticity may also occur if the myocardial cells are damaged (for example, by hypoxia or potassium imbalance). These cells may remain partially depolarized during diastole and, therefore, can reach the firing threshold earlier than normal cells. Abnormal automatic discharges may thus be induced. **Effect of drugs on automaticity:** Most of the antiarrhythmic agents suppress automaticity by blocking either Na+ or Ca2+ channels to reduce the ratio of these ions to K+. This decreases the slope of Phase 4 (diastolic) depolarization and/or raises the threshold of discharge to a less negative voltage. Such drugs cause the frequency of discharge to

decrease an effect that is more pronounced in cells with ectopic pacemaker activity than in normal cells.

Abnormalities in impulse conduction: Impulses from higher pacemaker centers are normally conducted down pathways that bifurcate to activate the entire ventricular surface. A phenomenon called reen trycan occur if a unidirectional block caused by myocardial injury or a prolonged refractory period results in an abnormal conduction pathway. Reentry is the most common cause of arrhythmias, and it can occur at any level of the cardiac conduction system. For example, consider a single Purkinje fiber with two conduction pathways to ventricular muscle. An impulse normally travels down both limbs of the conduction path. However, if myocardial injury results in a unidirectional block, the impulse may only be conducted down Pathway 1. If the block in Pathway 2 is in the forward direction only, the impulse may travel in a retrograde fashion through Pathway 2 and reenter the point of bifurcation. This short-circuit pathway results in re-excitation of the ventricular muscle, causing premature contraction or sustained ventricular arrhythmia.

Effects of drugs on conduction abnormalities: Antiarrhythmic agents prevent reentry by slowing conduction and/or increasing the refractory period, thereby converting a unidirectional block into a bidirectional block.

Antiarrhythmic drugs:-

I. Class I Antiarrhythmic Drugs:-

The antiarrhythmic drugs can be classified according to their predominant effects on the action potential . Although this classification is convenient, it is not entirely clear-cut, because many of the drugs have actions relating to more than one class or may have active metabolites with a different class of action. Class I antiarrhythmic drugs act by blocking voltage-sensitive sodium channels via the same mechanism as local anesthetics. The decreased rate of entry of sodium slows the rate of rise of Phase 0 of the action potential. [Note: At therapeutic doses, these drugs have little effect on the resting, fully polarized membrane because of their higher affinity for the active and inactive channels rather than for the resting channel.] Class I antiarrhythmic drugs, therefore, generally cause a decrease in excitability and conduction velocity. The use of sodium channel blockers has been declining continuously due to their possible pro-arrhythmic effects, particularly in patients with reduced left ventricular function and ischemic heart disease.

A. Use-dependence

Class I drugs bind more rapidly to open or inactivated sodium channels than to channels that are fully repolarized following recovery from the previous depolarization cycle. Therefore, these drugs show a greater degree of blockade in tissues that are frequently depolarizing (for example, during tachycardia, when the sodium channels open often). This property is called use dependence (or state-dependence), and it enables these drugs to block cells that are discharging at an abnormally high frequency without interfering with the normal, low-frequency beating of the heart. The Class I drugs have been subdivided into three groups according to their effect on the duration of the action potential. Class IA agents slow the rate of rise of the action potential (thus slowing conduction), prolong the action potential, and increase the ventricular effective refractory period. They have an intermediate speed of association with activated/inactivated sodium-channels and an

intermediate rate of dissociation from resting channels. Prolongation of duration of the action potential and increased ventricular effective period are due to concomitant Class III activity. Class IB drugs have little effect on the rate of depolarization; rather, they decrease the duration of the action potential by shortening repolarization. They rapidly interact with sodium channels. Class IC agents markedly depress the rate of rise of the membrane action potential. Therefore, they cause marked slowing of conduction but have little effect on the duration of the membrane action potential or the ventricular effective refractory period. They bind slowly to sodium channels.

B. Arrhythmias

Inhibition of potassium channels (Class III activity) widens the action potential, leading to a prolonged QT interval on the electrocardiogram. Such an effect is associated with increased risk of developing life-threatening ventricular tachyarrhythmias (torsades de pointes). The most common cause of QT prolongation is drug-induced, although it may also be genetic. QT prolongation is not only seen with Class III antiarrhythmics. Drugs such as *cisapride, grepafloxacin, terfenadine,* and *astemizole* were withdrawn from the market because of severe and fatal arrhythmias. *Erythromycin, clarithromycin, pentamidine, moxifloxacin, levofloxacin, imipramine, desipramine, amitriptyline, doxepin, thioridazine, mesoridazine, haloperidol, risperidone, ziprasidone,* and *quetiapine* are some of the drugs known to prolong the QT interval. Caution should be exerted when combining several drugs with effects on the QT interval (for example, *quinidine* with *levofloxacin*) or when giving these drugs combined with azole antifungals (*fluconazole* and *itraconazole*). The latter are known to inhibit drug metabolism, leading to large increases in plasma drug concentrations.

C. Quinidine

Quinidine is the prototype Class IA drug. Because of its concomitant Class III activity, it can actually precipitate arrhythmias such as polymorphic ventricular tachycardia (torsades de pointes), which can degenerate into ventricular fibrillation. Because of the toxic potential of *quinidine*, calcium antagonists, such as *amiodarone* and *verapamil*, are increasingly replacing this drug in clinical use.

Mechanism of action: *Quinidine* binds to open and inactivated sodium channels and prevents sodium influx, thus slowing the rapid upstroke during Phase 0. It also decreases the slope of Phase 4 spontaneous depolarization and inhibits potassium channels.

Therapeutic uses: *Quinidine* is used in the treatment of a wide variety of arrhythmias, including atrial, AV-junctional, and ventricular tachyarrhythmias. *Quinidine* is used to maintain sinus rhythm after direct-current cardioversion of atrial flutter or fibrillation and to prevent frequent ventricular tachycardia.

Pharmacokinetics: *Quinidine sulfate* is rapidly and almost completely absorbed after oral administration. It undergoes extensive metabolism by the hepatic cytochrome P450 enzymes, forming active metabolites.

Adverse effects: A potential adverse effect of *quinidine* (or of any antiarrhythmic drug) is development of arrhythmia (torsades de pointes). *Quinidine* may cause SA and AV block or asystole. At toxic levels, the drug may induce ventricular tachycardia. Cardiotoxic effects are exacerbated by hyperkalemia. Nausea, vomiting, and diarrhea are commonly observed. Large doses of *quinidine* may induce the symptoms of cinchonism (for example, blurred vision, tinnitus, headache, disorientation, and psychosis). The drug has a mild α-adrenergic blocking action as

well as an *atropine*-like effect. *Quinidine* can increase the steady-state concentration of *digoxin* by displacement of *digoxin* from tissue-binding sites (minor effect) and by decreasing *digoxin* renal clearance (major effect).

D. Procainamide

Actions: This Class IA drug, a derivative of the local anesthetic *procaine*, shows actions similar to those of *quinidine*.

Pharmacokinetics: *Procainamide* is well-absorbed following oral administration. [Note: The intravenous route is rarely used, because hypotension occurs if the drug is infused too rapidly.] *Procainamide* has a relatively short half-life of 2 to 3 hours. A portion of the drug is acetylated in the liver to N-acetylprocainamide (NAPA), which has little effect on the maximum polarization of Purkinje fibers but prolongs the duration of the action potential. Thus, NAPA has properties of a Class III drug. NAPA is eliminated via the kidney, and dosages of *procainamide* may need to be adjusted in patients with renal failure.

Adverse effects: With chronic use, *procainamide* causes a high incidence of side effects, including a reversible lupus erythematosus like syndrome that develops in 25 to 30 percent of patients. Toxic concentrations of *procainamide* may cause asystole or induction of ventricular arrhythmias. Central nervous system (CNS) side effects include depression, hallucination, and psychosis. With this drug, gastrointestinal intolerance is less frequent than with *quinidine*.

E. Disopyramide

Actions: This Class IA drug shows actions similar to those of *quinidine*. *Disopyramide* produces a negative inotropic effect that is greater than the weak effect exerted by *quinidine* and *procainamide*, and unlike the latter drugs, *disopyramide* causes peripheral vasoconstriction. The drug may produce a clinically important decrease in myocardial contractility in patients with preexisting impairment of left ventricular function. *Disopyramide* is used in the treatment of ventricular arrhythmias as an alternative to *procainamide* or *quinidine*. Like *procainamide* and *quinidine*, it also has Class III activity.

Pharmacokinetics: Approximately half of the orally ingested drug is excreted unchanged by the kidneys. Approximately 30 percent of the drug is converted by the liver to the less active mono-N-dealkylated metabolite.

Adverse effects: *Disopyramide* shows effects of anticholinergic activity (for example, dry mouth, urinary retention, blurred vision, and constipation).

F. Lidocaine

Lidocaine is a Class IB drug. The Class IB agents rapidly associate and dissociate from sodium channels. Thus, the actions of Class IB agents are manifested when the cardiac cell is depolarized or firing rapidly. Class IB drugs are particularly useful in treating ventricular arrhythmias. *Lidocaine* was the drug of choice for emergency treatment of cardiac arrhythmias.

Actions: *Lidocaine*, a local anesthetic, shortens Phase 3 repolarization and decreases the duration of the action potential

Therapeutic uses: *Lidocaine* is useful in treating ventricular arrhythmias arising during myocardial ischemia, such as that experienced during a myocardial infarction. The drug does not markedly slow conduction and, thus, has little effect on atrial or AV junction arrhythmias.

Pharmacokinetics: *Lidocaine* is given intravenously because of extensive first-pass transformation by the liver, which precludes oral administration. The drug is dealkylated and eliminated almost entirely by the liver; consequently, dosage adjustment may be necessary in patients with liver dysfunction or those taking drugs that lower hepatic blood flow, such as *propranolol*.

Adverse effects: *Lidocaine* has a fairly wide toxic-to-therapeutic ratio. It shows little impairment of left ventricular function and has no negative inotropic effect. CNS effects include drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsions. Cardiac arrhythmias may also occur.

G. Mexiletine and tocainide

These Class IB drugs have actions similar to those of *lidocaine*, and they can be administered orally. *Mexiletine* is used for chronic treatment of ventricular arrhythmias associated with previous myocardial infarction. *Tocainide* is used for treatment of ventricular tachyarrhythmia. *Tocainide* has pulmonary toxicity, which may lead to pulmonary fibrosis.

H. Flecainide

Flecainide is a Class IC drug. These drugs slowly dissociate from resting sodium channels, and they show prominent effects even at normal heart rates. They are approved for refractory ventricular arrhythmias and for the prevention of paroxysmal atrial fibrillation/flutter associated with disabling symptoms and paroxysmal supraventricular tachycardia. However, recent data have cast serious doubts on the safety of the Class IC drugs.

Actions: *Flecainide* suppresses Phase 0 upstroke in Purkinje and myocardial fibers . This causes marked slowing of conduction in all cardiac tissue, with a minor effect on the duration of the action potential and refractoriness. Automaticity is reduced by an increase in the threshold potential rather than a decrease in the slope of Phase 4 depolarization.

Therapeutic uses: *Flecainide* is useful in treating refractory ventricular arrhythmias. It is particularly useful in suppressing premature ventricular contraction. *Flecainide* has a negative inotropic effect and can aggravate congestive heart failure.

Pharmacokinetics: *Flecainide* is absorbed orally, undergoes minimal biotransformation, and has a half-life of 16 to 20 hours.

Adverse effects: *Flecainide* can cause dizziness, blurred vision, headache, and nausea. Like other Class IC drugs, *flecainide* can aggravate preexisting arrhythmias or induce life-threatening ventricular tachycardia that is resistant to treatment.

I. Propafenone

This Class IC drug shows actions similar to those of *flecainide*. *Propafenone* , like *flecainide*, slows conduction in all cardiac tissues and is considered to be a broad-spectrum antiarrhythmic agent.

II. Class II Antiarrhythmic Drugs

Class II agents are B-adrenergic antagonists. These drugs diminish Phase 4 depolarization, thus depressing automaticity, prolonging AV conduction, and decreasing heart rate and contractility. Class II agents are useful in treating tachyarrhythmias caused by increased sympathetic activity. They are also used for atrial flutter and fibrillation and for AV-nodal reentrant tachycardia. [Note: In contrast to the sodium-channel blockers, Î²-blockers and Class III compounds, such as *sotalol* and *amiodarone*, are increasing in use.]

A. Propranolol

Propranolol reduces the incidence of sudden arrhythmic death after myocardial infarction (the most common cause of death in this group of patients). The mortality rate in the first year after a heart attack is significantly reduced by *propranolol*, partly because of its ability to prevent ventricular arrhythmias.

B. Metoprolol

Metoprolol is the B-adrenergic antagonist most widely used in the treatment of cardiac arrhythmias. Compared to propranolol, it reduces the risk of bronchospasm.

C. Esmolol

Esmolol is a very short-acting Î²-blocker used for intravenous administration in acute arrhythmias that occur during surgery or emergency situations.

III. Class III Antiarrhythmic Drugs

Class III agents block potassium channels and, thus, diminish the outward potassium current during repolarization of cardiac cells. These agents prolong the duration of the action potential without altering Phase 0 of depolarization or the resting membrane potential. Instead, they prolong the effective refractory period. All Class III drugs have the potential to induce arrhythmias.

A. Amiodarone

Actions: *Amiodarone*, containing iodine, is related structurally to thyroxine. It has complex effects, showing Class I, II, III, and IV actions. Its dominant effect is prolongation of the action potential duration and the refractory period. *Amiodarone* has antianginal as well as antiarrhythmic activity.

Therapeutic uses: *Amiodarone* is effective in the treatment of severe refractory supraventricular and ventricular tachyarrhythmias. Despite its side-effect profile, *amiodarone* is the most commonly employed antiarrhythmic.

Pharmacokinetics: *Amiodarone* is incompletely absorbed after oral administration. The drug is unusual in having a prolonged half-life of several weeks, and it distributes extensively in adipose issue. Full clinical effects may not be achieved until 6 weeks after initiation of treatment.

Adverse effects: *Amiodarone* shows a variety of toxic effects. After long-term use, more than half of patients receiving the drug show side effects that are severe enough to prompt its discontinuation. However, use of low doses reduces toxicity, while retaining clinical efficacy. Some of the more common effects include interstitial pulmonary fibrosis, gastrointestinal tract intolerance, tremor, ataxia, dizziness, hyper- or hypothyroidism, liver toxicity, photosensitivity, neuropathy, muscle weakness, and blue skin discoloration caused by iodine accumulation in the skin. As noted earlier, recent clinical trials have shown that *amiodarone* does not reduce the incidence of sudden death or prolong survival in patients with congestive heart failure.

B. Sotalol

Sotalol although a class III antiarrhythmic agent, also has potent nonselective B-blocker activity. It is well established that B-blockers reduce mortality associated with acute myocardial infarction.

Actions: *Sotalol* blocks a rapid outward potassium current, known as the delayed rectifier. This blockade prolongs both repolarization and duration of the action potential, thus lengthening the effective refractory period.

Therapeutic uses: B-Blockers are used for long-term therapy to decrease the rate of sudden death following an acute myocardial infarction. B-Blockers have a modest ability to suppress ectopic beats and to reduce myocardial oxygen demand. They have strong antifibrillatory effects, particularly in the ischemic myocardium. *Sotalol* was

more effective in preventing recurrence of arrhythmia and in decreasing mortality than *imipramine, mexiletine, procainamide, propafenone*, and *quinidine* in patients with sustained ventricular tachycardia.

Adverse effects: This drug also has the lowest rate of acute or long-term adverse effects. As with all drugs that prolong the QT interval, the syndrome of torsade de pointes is a serious potential adverse effect, typically seen in three to four percent of patients.

C. Dofetilide

Dofetilide can be used as a first-line antiarrhythmic agent in patients with persistent atrial fibrillation and heart failure or in those with coronary artery disease with impaired left ventricular function. Because of the risk of proarrhythmia, *dofetilide* initiation is limited to the inpatient setting and is restricted to prescribers who have completed a specific manufacturer's training session. Along with *amiodarone* and B-blockers, *dofetilide* is the only antiarrhythmic drug that is recommended by experts for the treatment of atrial fibrillation in a wide range of patients. The half-life is 10 hours. Excretion is in the urine, with 80 percent as unchanged drug and 20 percent as inactive or minimally active metabolites.

IV. Class IV Antiarrhythmic Drugs

Class IV drugs are calcium-channel blockers . They decrease the inward current carried by calcium, resulting in a decreased rate of Phase 4 spontaneous depolarization. They also slow conduction in tissues that are dependent on calcium currents, such as the AV node Although voltage-sensitive calcium channels occur in many different tissues, the major effect of calcium-channel blockers is on vascular smooth muscle and the heart.

A. Verapamil and diltiazem

Verapamil shows greater action on the heart than on vascular smooth muscle, whereas *nifedipine*, a calcium-channel blocker used to treat hypertension, exerts a stronger effect on the vascular smooth muscle than on the heart. *Diltiazem* is intermediate in its actions.

Actions: Calcium enters cells by voltage-sensitive channels and by receptor-operated channels that are controlled by the binding of agonists, such as catecholamines, to membrane receptors. Calcium-channel blockers, such as *verapamil* and *diltiazem*, are more effective against the voltage-sensitive channels, causing a decrease in the slow inward current that triggers cardiac contraction. *Verapamil* and *diltiazem* bind only to open, depolarized channels, thus preventing repolarization until the drug dissociates from the channel. These drugs are therefore use-dependent; that is, they block most effectively when the heart is beating rapidly, because in a normally paced heart, the calcium channels have time to repolarize and the bound drug dissociates from the channel before the next conduction pulse. By decreasing the inward current carried by calcium, *verapamil* and *diltiazem* slow conduction and prolong the effective refractory period in tissues that are dependent on calcium currents, such as the AV node. These drugs are therefore effective in treating arrhythmias that must traverse calcium-dependent cardiac tissues.

Therapeutic uses: *Verapamil* and *diltiazem* are more effective against atrial than against ventricular arrhythmias. They are useful in treating reentrant supraventricular tachycardia and in reducing the ventricular rate in atrial flutter and fibrillation. In addition, these drugs are used to treat hypertension and angina.

Pharmacokinetics: *Verapamil* and *diltiazem* are absorbed after oral administration. *Verapamil* is extensively metabolized by the liver; thus, care should be taken when administering this drug to patients with hepatic dysfunction.

Adverse effects: *Verapamil* and *diltiazem* have negative inotropic properties and, therefore, may be contraindicated in patients with preexisting depressed cardiac function. Both drugs can also produce a decrease in blood pressure because of peripheral vasodilation an effect that is actually beneficial in treating hypertension.

VII. Other Antiarrhythmic Drugs

A. Digoxin

Digoxin shortens the refractory period in atrial and ventricular myocardial cells while prolonging the effective refractory period and diminishing conduction velocity in the AV node. *Digoxin* is used to control the ventricular response rate in atrial fibrillation and flutter. At toxic concentrations, *digoxin* causes ectopic ventricular beats that may result in ventricular tachycardia and fibrillation. [Note: This arrhythmia is usually treated with *lidocaine* or *phenytoin*.]

B. Adenosine

Adenosine is a naturally occurring nucleoside, but at high doses, the drug decreases conduction velocity, lengthens the refractory period, and decreases automaticity in the AV node. Intravenous *adenosine* is the drug of choice for abolishing acute supraventricular tachycardia. It has low toxicity but causes flushing, chest pain, and hypotension. *Adenosine* has an extremely short duration of action (approximately 15 seconds)