# Agents Used in Cardiac Arrhythmias

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# Cardiac Arrhythmias

- Cardiac arrhythmias are a common problem in clinical practice.
- They may be due to drugs or electrolyte imbalance, and may follow myocardial infarction.
- Rhythms that are too rapid, too slow, or asynchronous can reduce cardiac output, and cause heart failure.
- Some arrhythmias can precipitate more serious or even lethal rhythm disturbances, such as ventricular fibrillations.
- In such patients, antiarrhythmic drugs may be life-saving.

# Cardiac Arrhythmias

- **On the other hand, the antiarrhythmic drugs are dangerous in that they can precipitate lethal arrhythmias in some patients.**

# Electrophysiology of Normal Cardiac Rhythm

- **The electrical impulse that triggers a normal cardiac contraction originates at regular intervals in the sinoatrial (SA) node usually at a frequency of 60 - 100 bpm.**
- **This impulse spreads rapidly through the atria and enters the atrioventricular (AV) node, which is normally the only conduction pathway between the atria and ventricles.**
- **The impulse then propagates down the His-Purkinje system and invades all parts of the ventricles, beginning with the endocardial surface near the apex and ending with the epicardial surface at the base of the heart.**

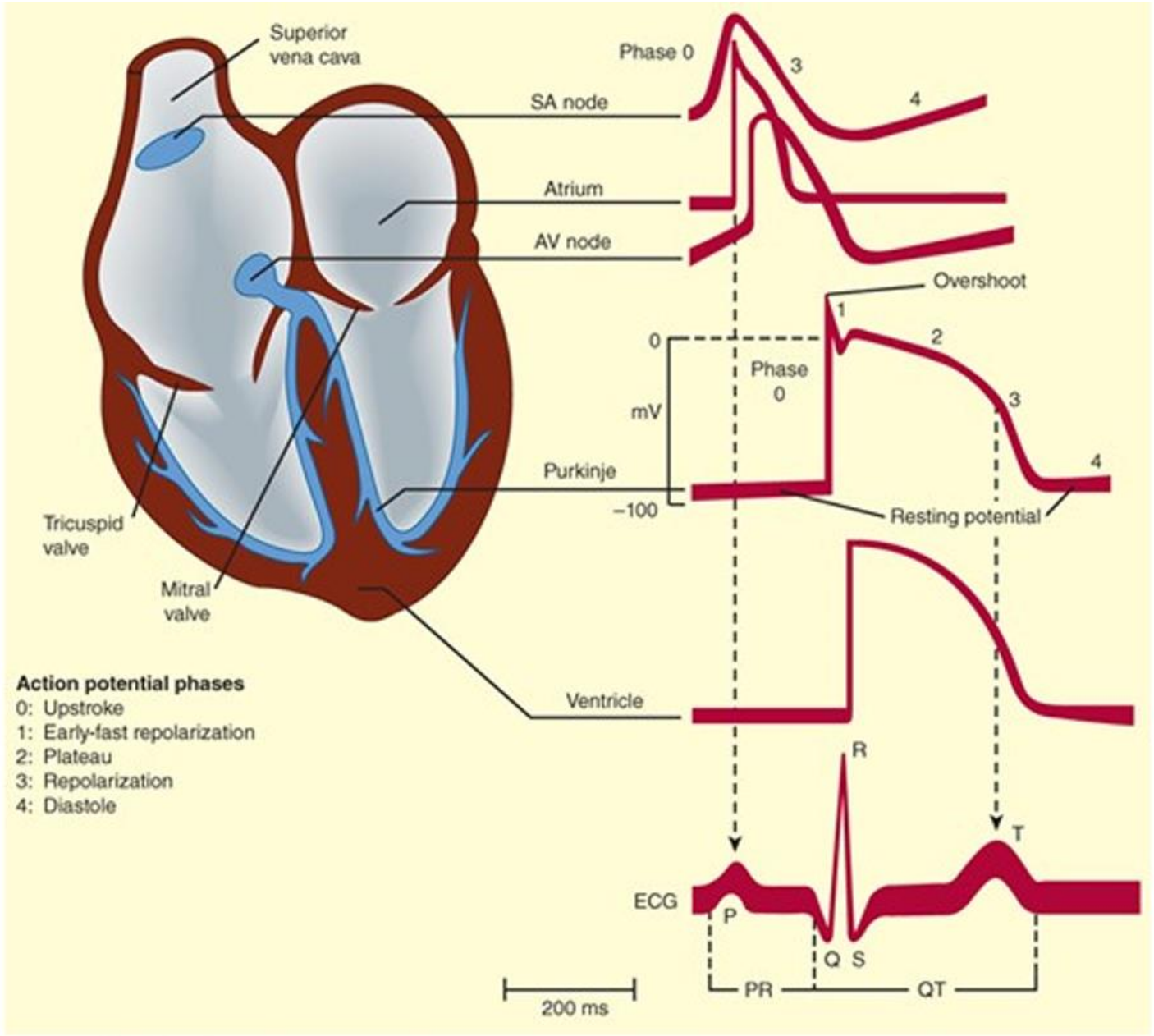





**FIGURE 14–1**
**Schematic representation of the heart and normal cardiac electrical activity (intracellular recordings from areas indicated and electrocardiogram [ECG]). Sinoatrial (SA) node, atrioventricular (AV) node, and Purkinje cells display pacemaker activity (phase 4 depolarization). The ECG is the body surface manifestation of the depolarization and repolarization waves of the heart.**
**The P wave is generated by atrial depolarization, the QRS by ventricular muscle depolarization, and the T wave by ventricular repolarization.**
**Thus, the PR interval is a measure of conduction time from atrium to ventricle and the QRS duration indicates the time required for all of the ventricular cells to be activated (the intraventricular conduction time). The QT interval reflects the duration of the ventricular action potential.**

# Electrophysiology of Normal Cardiac Rhythm

- **In the SA node phase 4 is due to the funny current ($I_f$) which produces spontaneous, gradual depolarization due to slow influx of sodium ions and a decrease in potassium permeability, making the inside of the cell less negative (- 40 mV) which triggers phase 0.**
- **The situation is similar in the AV node.**
- **In the His-Purkinje system, phase 4 depolarization is not stable but gradual depolarization due to slow inward leak of sodium which makes the membrane potential less negative towards the threshold for excitation. This triggers the next action potential.**

# Electrophysiology of Normal Cardiac Rhythm

- **The upstroke (phase 0) of the action potential is due to the inward sodium current ($I_{Na}$).**
- **The maximum upstroke velocity of the action potential is very fast and very brief, and is followed by inactivation of these channels.**
- **This inactivation contributes to the early repolarization phase of the action potential (phase 1).**
- **In some cardiac myocytes, phase 1 is also due to a brief increase in potassium permeability due to the activity of channels generating fast and slow transient outward currents.**

# Electrophysiology of Normal Cardiac Rhythm

- Sustained depolarization during the plateau (phase 2) is due primarily to the activity of calcium channels.
- Cardiac calcium channels activate and inactivate in a manner similar to sodium channels, but in the case of the most common type of calcium channels (the L type), the transition occur more slowly and at more positive potentials.
- After activation, these channels eventually inactivate decreasing the permeability to calcium, and the permeability to potassium begins to increase, leading to final repolarization (phase 3) of the action potential.

# Mechanisms of Cardiac Arrhythmias

**Factors that can precipitate or exacerbate arrhythmias:**

- **Ischemia, hypoxia, acidosis or alkalosis, electrolyte abnormalities, excessive catecholamine exposure, autonomic influences, drug toxicity (digitalis or antiarrhythmic drugs), overstretching of cardiac fibers, and the presence of scarred or diseased tissue.**
- **However, all arrhythmias result from disturbances in impulse formation and/or disturbances in impulse conduction.**

# Mechanisms of Cardiac Arrhythmias

## Disturbances of Impulse Formation:

- **Pacemaker activity is regulated by both sympathetic and parasympathetic nervous system**
- **Therefore, factors that antagonize or enhance these effects can alter normal impulse formation, producing either bradycardia or tachycardia.**

# Mechanisms of Cardiac Arrhythmias

- **Under certain circumstances, abnormal activity can be generated by latent pacemakers in cells that show slow phase 4 depolarization (Purkinje cells).**
- **Abnormalities in impulse formation can also be the result of afterdepolarizations (Figure 14-5).**

# Mechanisms of Cardiac Arrhythmias

- These can be either early afterdepolarizations (EADs), which occur during phase 3 of the action potential, or delayed afterdepolarizations (DADs), which occur during phase 4.
- EADs are usually triggered by factors that prolong action potential duration.
- When this prolongation occurs in ventricular cells, there is often a corresponding increase in the QT interval of the ECG.

# Mechanisms of Cardiac Arrhythmias

- **A number of drugs can produce drug-induced long QT (LQT) syndrome, which is typically due to block of rapidly activating delayed rectifier potassium channels.**
- **Many forms of LQT syndrome are exacerbated by factors that prolong action potential duration, including hypokalemia and slow heart rates.**

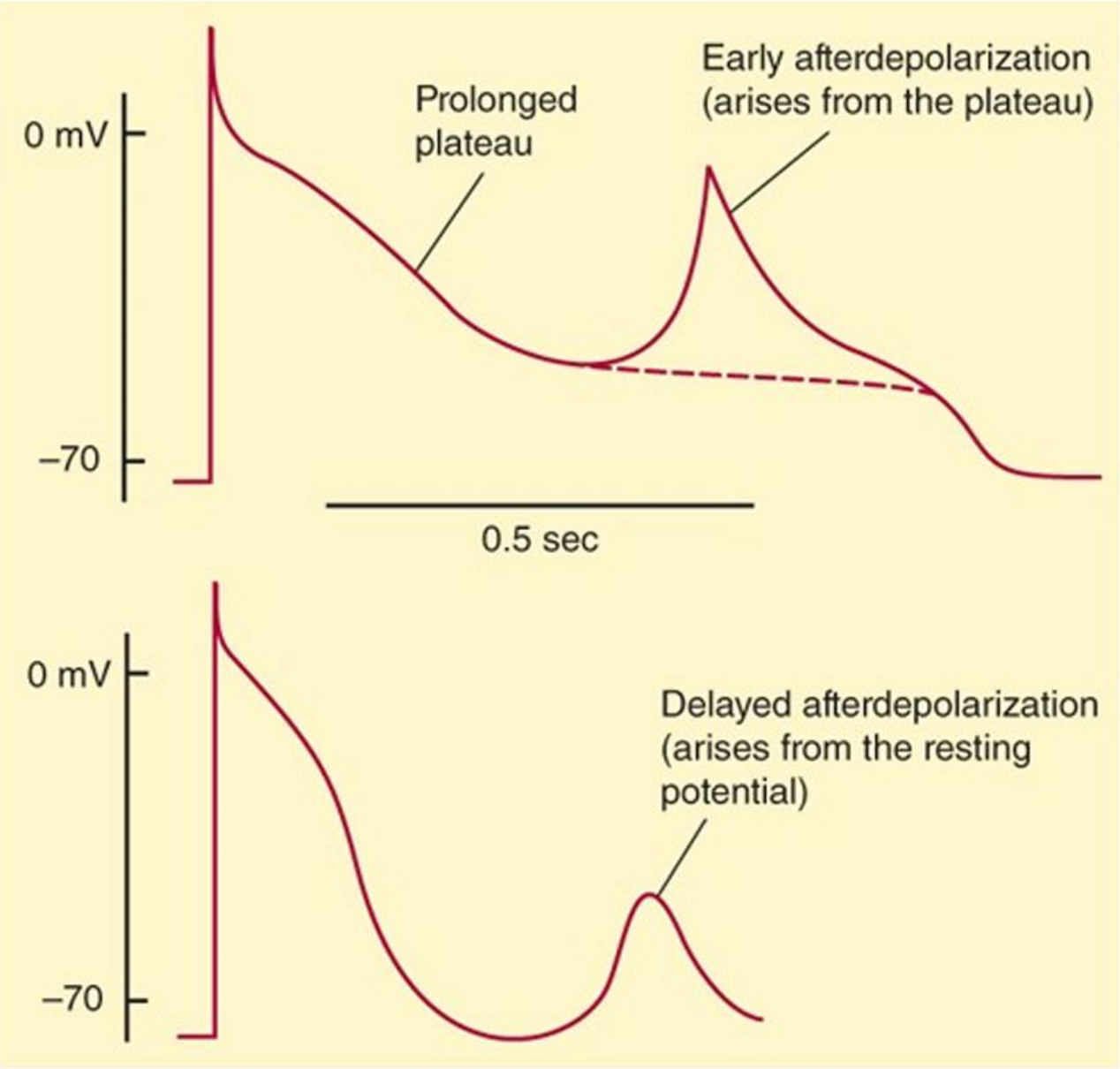





**FIGURE 14–5**

**Two forms of abnormal activity, early (top) and delayed afterdepolarizations (bottom). In both cases, abnormal depolarizations arise during or after a normally evoked action porential.**

**They are therefore often referred to as “triggered” automaticity; that is, they require a normal action potential for their initiation.**

# Mechanisms of Cardiac Arrhythmias

- **DADs, on the other hand, often occur when there is an excess accumulation of intracellular calcium, especially at fast heart rates.**
- **They are thought to be responsible for arrhythmias associated with digitalis toxicity, excess catecholamine stimulation, and myocardial ischemia.**

# Mechanisms of Cardiac Arrhythmias

## Disturbances of Impulse Conduction:

A. The most common form of conduction disturbance affects the AV node, causing various degrees of heart block.

- The result can be a simple slowing of impulse propagation through the AV node, which is reflected by an increase in the PR interval of the ECG.
- At the extreme, the result can be complete heart block, where no impulses are conducted from the atria to the ventricles.

# Mechanisms of Cardiac Arrhythmias

- **In this situation, ventricular activity must be generated by a latent pacemaker, such as a Purkinje cell, or by an artificial pacemaker.**
- **Because the AV node is typically under the tonic influence of the parasympathetic nervous system, which slows conduction, AV block can sometimes be relieved by antimuscarinic agents like atropine.**

# Mechanisms of Cardiac Arrhythmias

B. A serious form of conduction abnormality involves reentry (also known as “circus movement”).

- In this situation, one impulse fails to dissipate, and reenters and excites areas of the heart more than once.
- The path of the reentering impulse may be confined to very small areas, such as tissue within or near the AV node or where a Purkinje fiber makes contact with the ventricular wall (Figure 14-6), or it may involve large portions of the atria or ventricles.

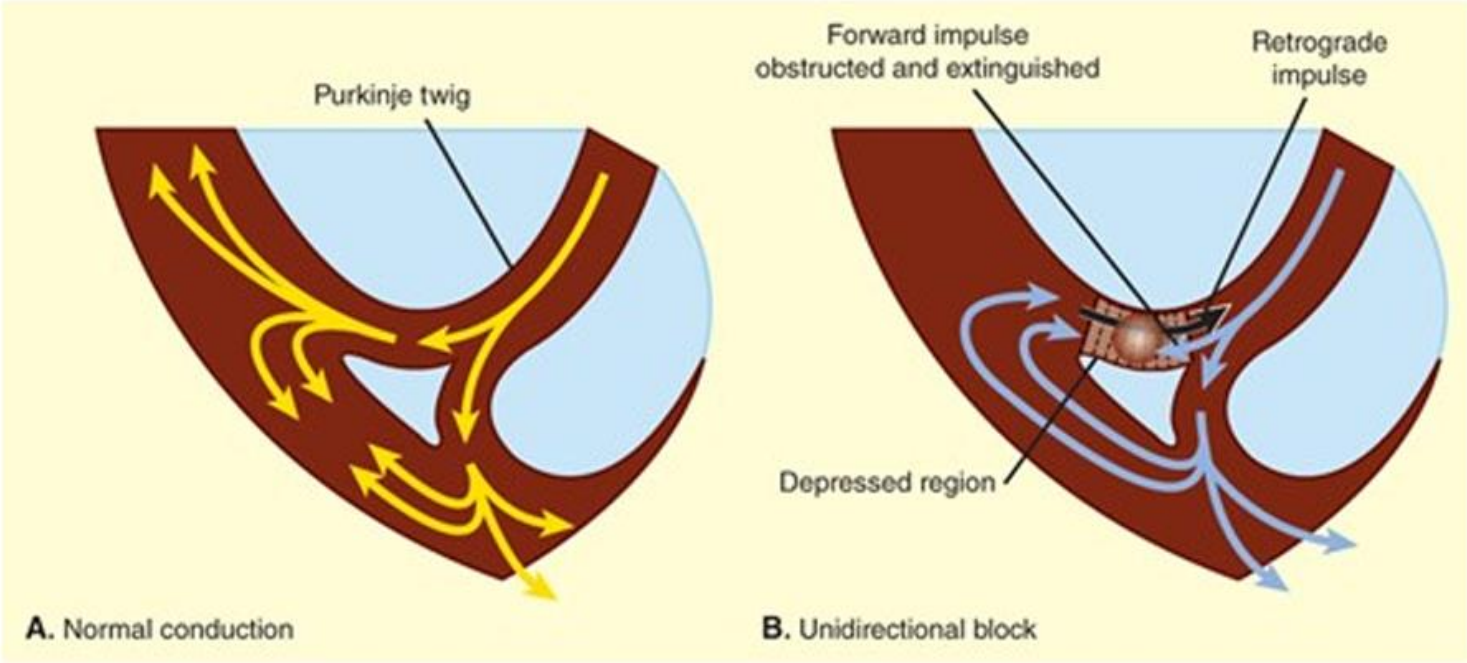





**FIGURE 14–6**

**Schematic diagram of a reentry circuit that might occur in small bifurcating branches of the Purkinje system where they enter the ventricular wall.**

**A: Normally, electrical excitation branches around the circuit, it is transmitted to the ventricular branches, and becomes extinguished at the other end of the circuit due to collision of impulses.**

**B: An area of unidirectional block develops in one of the branches, preventing anterograde impulse transmission at the site of block, but the retrograde impulse may be propagated through the site of block if the impulse finds excitable tissue; that is, the refractory period is shorter than the conduction time. This impulse can re-excite tissue it had previously passed through, and a reentry arrhythmia is established.**

# Mechanisms of Cardiac Arrhythmias

- **Some forms of reentry are strictly anatomically determined.**
- **For example, in Wolff-Parkinson-White syndrome, the reentry circuit consists of atrial tissue, the AV node, ventricular tissue, and an accessory AV connection (bundle of Kent, a bypass tract).**
- **Depending on how many round trips through the pathway a reentrant impulse makes before dying out, the arrhythmia may be manifest as one or a few extra beats or as a sustained tachycardia.**

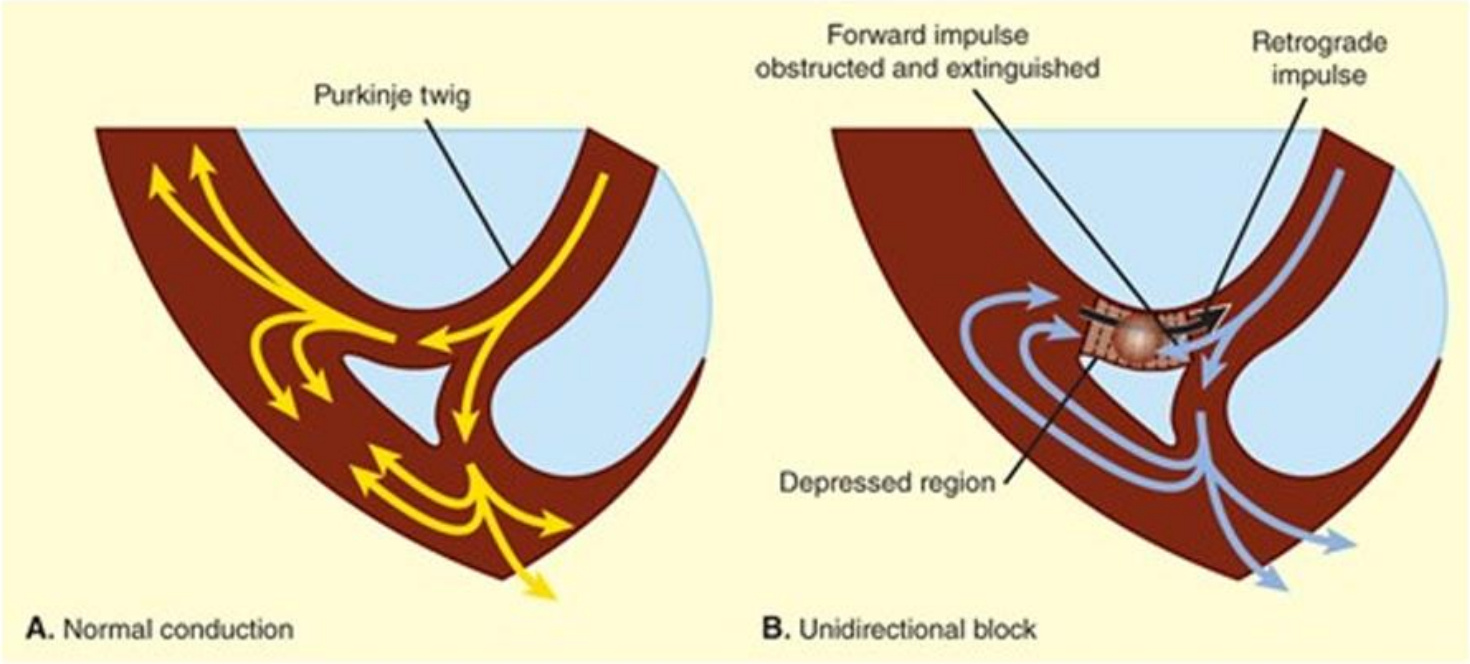
# Mechanisms of Cardiac Arrhythmias

- **Circulating impulses can also give off “daughter impulses” that can spread to the rest of the heart.**
- **In cases such as atrial or ventricular fibrillation, multiple reentry circuits may meander through the heart in apparently random paths, resulting in the loss of synchronized contraction.**

# Mechanisms of Cardiac Arrhythmias

- **How can reentry occur? There are three key elements:**

1. **First, there is an obstacle (anatomic or physiologic) to homogeneous impulse conduction, thus establishing a circuit around which the reentrant wave front can propagate.**
2. **The second element is unidirectional block at some point in the circuit. That is, something has occurred such that an impulse reaching the site initially encounters refractory tissue.**



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# Mechanisms of Cardiac Arrhythmias

3. **Finally, conduction time around the circuit must be long enough so that by the time the impulse returns to the site after traveling around the obstacle, the tissue is no longer refractory.**

- **In other words, conduction time around the circuit must exceed the effective refractory period duration in the area of unidirectional block.**

# Classification of Antiarrhythmic Drugs

| Class | Description | Drugs |
|---|---|---|
| Class 1 | Sodium Channel-Blocking Drugs | |
| | Subgroup 1A | Procainamide, quinidine, disopyramide |
| | Subgroup 1B | Lidocaine, mexiletine |
| | Subgroup 1C | Flecainide, propafenone |
| Class 2 | β-Adrenergic blockers | Propranolol, esmolol, sotalol, nadolol, .. |
| Class 3 | Drugs the prolong the effective refractory period by prolonging the action potential | Amiodarone, dronedarone, sotalol, dofetilide, ibutilide |
| Class 4 | Calcium-channel blocking drugs | Verapamil, diltiazem |
| Unclassified | Various mechanisms | Adenosine, Ivabradine, Ranolazine, Vernakalant, Magnesium, Potassium |

# Sodium Channel-Blocking Drugs (Class 1)

## Subgroup 1A:

## Procainamide:

- It slows the upstroke of the action potential by blocking sodium channels, thus, slowing conduction, and prolonging the QRS duration in the ECG.
- It has direct depressant actions on SA and AV nodes, which may be counter-balanced to a small extent by drug-induced vagal block.
- It has ganglion-blocking properties, which reduces peripheral vascular resistance and may cause hypotension.

# Sodium Channel-Blocking Drugs (Class 1)

## Adverse reactions:

1. **Excessive action potential prolongation, QT-interval prolongation, and induction of torsades de pointes arrhythmia and syncope.**
2. **Excessive slowing of conduction and development of new arrhythmias.**
3. **A lupus erythematosus-like syndrome consisting of arthralgia and arthritis (in one third of patients). Some patients may also have pleuritis and pericarditis; but rarely affecting the kidney.**

# Sodium Channel-Blocking Drugs (Class 1)

## Therapeutic Uses:

- **It is effective against most atrial and ventricular arrhythmias**
- **It is the drug of second and third choice (after lidocaine and or amiodarone) in most coronary care units for the treatment of sustained ventricular arrhythmias associated with acute myocardial infarction.**

# Sodium Channel-Blocking Drugs (Class 1)

## Subgroup 1B:

## Lidocaine:

- **It is a rapid sodium channel blocker during phase 0 and phase 2, leading to decreased ventricular excitability.**
- **Its binding is use-dependent, thus, the higher is the heart rate the more is the sodium channel blockade.**

# Sodium Channel-Blocking Drugs (Class 1)

## Therapeutic uses:

- **It is used via intravenous infusion.**
- **Ventricular tachycardia and ventricular fibrillation following acute myocardial infarction, cardiac surgery, and cardiac catheterization.**

# Sodium Channel-Blocking Drugs (Class 1)

**Contraindications:**

1. **Patients with Wolf-Parkinson-White syndrome because it preferentially blocks the normal conduction pathway, leading to increased conduction through the accessory pathway and potentially causing ventricular fibrillation.**
2. **Patients with severe heart block because it further depresses the His-Purkinje conduction system, potentially leading to complete heart block and asystole.**

# Sodium Channel-Blocking Drugs (Class 1)

**Adverse reactions:**

1. **Hypotension, cardiovascular collapse, bradycardia, cardiac arrest**
2. **Light-headedness, unconsciousness**
3. **Convulsions**
4. **Respiratory depression**
5. **Tennitus, visual disturbances, and vomiting.**

- **Mexiletine is an orally active analogue of lidocaine.**

# Sodium Channel-Blocking Drugs (Class 1)

**Subgroup 1C:**

**Flecainide:**

- **It is a potent blocker of sodium and potassium channels with slow unblocking kinetics.**
- **(although it does block certain potassium channels, it does not prolong the action potential or the QT interval.)**
- **It suppresses premature ventricular contractions.**
- **It has no antimuscarinic effects.**

# Sodium Channel-Blocking Drugs (Class 1)

## Adverse Effects:

- It may cause severe exacerbation of arrhythmia in patients with preexisting ventricular tachyarrhythmias and those with a previous myocardial infarction and ventricular ectopy.
- It may increase mortality rate.

## Therapeutic uses:

1. It is used for patients with normal hearts who have supraventricular arrhythmias but not as first line.

# Sodium Channel-Blocking Drugs (Class 1)

**Propafenone:**

- It possesses weak β-blocking activity.
- It does not prolong the action potential.
- Its sodium channel-blocking kinetics are similar to those of flecainide.
- It is used primarily for supraventricular arrhythmias.
- The most common adverse effects are a metallic taste and constip ation.
- Arrhythmia exacerbation can also occur.

# β-Adrenergic-Blocking Drugs (Class 2)

## Actions in the electrical activity of the heart:

1. **Negative chronotropic effect → bradycardia.**
2. **Slowing of AV nodal conduction and prolonging its refractory period, and prolong PR interval.**

- **They are effective in both supraventricular and ventricular arrhythmias.**

# β-Adrenergic-Blocking Drugs (Class 2)

- They improve survival following myocardial infarction due to suppression of arrhythmias.
- By increasing the AV nodal refractory period, they slow ventricular response rates in atrial flutter and fibrillation.
- They also reduce ventricular ectopic beats, those precipitated by catecholamines.

# β-Adrenergic-Blocking Drugs (Class 2)

- **Esmolol is particularly useful against acute perioperative arrhythmias because it has a short duration of action and can be given parenterally.**
- **The non-selective β-blockers (propranolol, nadolol) are more effective subgroup of β-blockers for prevention and treatment of cardiac arrhythmias.**

# β-Adrenergic-Blocking Drugs (Class 2)

## Adverse reactions:

1. **Sinus bradycardia**
2. **Depression of myocardial contractility, leading to heart failure**
3. **They can mask the early adrenergic warning symptoms of hypoglycemia (tachycardia, sweating and anxiety), and may delay recovery from hypoglycemia, therefore, it is not advisable to use the non-selective agents in insulin-dependent diabetics.**
4. **Fatigue, depression, exercise intolerance and sexual dysfunction**

# β-Adrenergic-Blocking Drugs (Class 2)

5. **A small increase in body weight and triglycerides and a decrease in HDL. These effects are not seen with vasodilating β blockers (labetalol and carvedilol).**
6. **Acute withdrawal leads to sudden onset of tachycardia and exacerbation of ischemic symptoms. This is due to upregulation of β-receptors. This can be prevented by gradual tapering of dose rather than abrupt discontinuation of the drug.**

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

- **These drugs prolong action potential duration, by blocking potassium channels in phase 3 of the cardiac cycle, which increases the effective refractory period.**

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

**Amiodarone:**

- **Used orally or intravenously to treat ventricular arrhythmias, as well as supraventricular arrhythmias such as atrial fibrillation.**
- **It has a broad spectrum of adverse effects.**
- **Dronedarone, an analog that lacks iodine atoms, used for the treatment of atrial flutter and fibrillation.**

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

## Cardiovascular Effects:

- It markedly prolongs the action potential duration (and the QT interval on the ECG) by blockade of multiple potassium channels, including the rapid component of the delayed rectifier potassium current ($I_{Kr}$), as well as ATP-sensitive potassium channels ($K_{ATP}$) and the inward rectifier potassium channel ($I_{K1}$).
- It also affects the slow component of the delayed rectifier ($I_{Ks}$) and ultra-rapid delayed rectifier ($I_{Kur}$).

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

- It blocks inactivated sodium channels.
- It blocks calcium channels.
- It blocks α- and β-adrenergic receptors.
- Consequences of these actions include slowing of the heart rate and AV node conduction.

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

- **The broad spectrum of actions may account for its relatively high efficacy and its low incidence of torsades de pointes despite significant QT-interval prolongation.**
- **It causes peripheral vasodilation, primarily after intravenous administration and may be related to the action of the vehicle or α-adrenergic receptor blockade.**

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

## Adverse reactions:

1. **Symptomatic bradycardia and heart block in patients with preexisting sinus or AV node disease.**
2. **The drug accumulates in many tissues (10 - 50 times more than plasma) including the heart, lung, liver, and skin, and is concentrated in tears.**
3. **Dose-related pulmonary toxicity is the most important adverse effect. → fatal pulmonary fibrosis in 1% of patients.**

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

4. **Abnormal liver function tests and hypersensitivity hepatitis may develop during amiodarone treatment. Liver function tests should be monitored regularly.**
5. **Skin deposits result in a photo-dermatitis and a gray-blue skin discoloration in sun exposed areas and the malar regions.**
6. **Asymptomatic corneal micro-deposits occur in all patients treated with amiodarone after a few weeks of treatment.**

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

7. Halos may develop in the peripheral visual fields.
8. Rarely, an optic neuritis may progress to blindness.
9. It blocks the peripheral conversion of thyroxine (T4) to triiodothyronine (T3).
10. It is also a potential source of large amounts of inorganic iodine.

A. It may result in hypothyroidism or hyperthyroidism.
B. Type 1 amiodarone-induced thyrotoxicosis is due to excessive thyroxine production

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

C. **Type 2 amiodarone-induced thyroiditis is due to destructive thyroiditis.**

- **Treatment of each form of thyroditis is different: Type 1 is treated with thionamides while type 2 is treated with prednisolone.**
- **Thyroid function should be evaluated before starting treatment and should be monitored periodically.**

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

## Pharmacokinetics:

- Amiodarone bioavailability is 35 - 65%.
- It undergoes hepatic metabolism by CYP3A4, and the major metabolite, desethylamiodarone, is bioactive.
- The elimination half life is complex, with a rapid component of 3 - 10 days (50% of the drug) and a slower component of several weeks.
- After discontinuation of the drug, effects are maintained for 1 - 3 months.

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

- Measurable tissue levels may be observed up to 1 year after discontinuation.
- It has many important drug interactions, and all medications should be reviewed when the drug is initiated and when the dose is adjusted.
- It is a substrate for liver cytochrome CYP3A4, and its levels are increased by drugs that inhibit this enzyme.
- Drugs that induce CYP3A4, (rifampin), decrease amiodarone concentration.

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

- It inhibits several cytochrome P450 enzymes and may result in high levels of many drugs, including statins, digoxin, and warfarin.
- The dose of warfarin should be reduced by 1/3 - 1/2 following initiation of amiodarone, and prothrombin times should be closely monitored.

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

**Sotalol:**

- **Sotalol is a β-adrenergic receptor-blocker and prolongs the duration of the action potential (class 3).**
- **The drug is formulated as a racemic mixture of D- and L-sotalol.**
- **All the β-adrenergic–blocking activity resides in the L-isomer isomer while the D- and L-isomers share action potential prolonging effects.**
- **It is not cardio-selective.**

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

- **Sotalol antiarrhythmic effects involve ion channel blockade in addition to its β-blocking action.**
- **It is a potent inhibitor of the rapid component of the delayed rectifier potassium current ($I_{Kr}$). This blockade slows the efflux of potassium ions, which prolongs the cardiac action potential duration and the effective refractory period in the atrium and ventricle.**

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

## Cardiac adverse effect:

1. A dose-related incidence of torsades de pointes.
2. Patients with overt heart failure may experience further depression of left ventricular function.

## Therapeutic uses:

1. Life-threatening ventricular arrhythmias
2. Maintenance of sinus rhythm in patients with atrial fibrillation.
3. Treatment of supraventricular and ventricular arrhythmias in the pediatric age group.

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

**Dofetilide:**

- **It prolongs the action potential duration.**
- **This action is effected by a dose-dependent blockade of the rapid component of the delayed rectifier potassium current ($I_{Kr}$) which increases in hypokalemia.**
- **It does not block other potassium channels or the sodium and calcium channels; or adrenergic receptors.**

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

- It is 100% bioavailable.
- Verapamil increases peak plasma dofetilide concentration by increasing intestinal blood flow.
- Mainly eliminated by the kidney.
- Inhibitors of the renal cation secretion mechanisms prolong its half-life.
- QT prolongation and the risk of ventricular arrhythmias is concentration dependent, thus dosing should be according to creatinine clearance.

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

- **It is indicated for the maintenance and restoration of normal sinus rhythm in patients with atrial fibrillation.**
- **Treatment with dofetilide should be initiated in hospital after baseline measurement of the rate-corrected QT interval (QTc) and serum $K^+$, and $Mg^{2+}$.**
- **During loading, the QTc is measured before the second and subsequent doses; an increase in the QTc to ≥500 ms is an indication to reduce the dose or discontinue the drug.**

# Drugs the Prolong the Effective Refractory Period by Prolonging the Action Potential (Class 3)

**Relative contraindications:**

1. **A baseline QTc of greater than 450 ms (500 ms in the presence of an intraventricular conduction delay)**
2. **Bradycardia of less than 50 bpm**
3. **Hypokalemia**

# Calcium Channel-Blocking Drugs (Class 4)

- **Verapamil and diltiazem, but not the dihdropyridines, have antiarrhythmic effects.**

**Verapamil Cardiac Effects:**

- **It blocks both activated and inactivated L-type calcium channels.**
- **Thus, its effect is more marked in tissues that fire frequently, those that are less completely polarized at rest, and those in which activation depends exclusively on the calcium current, such as the SA and AV nodes.**

# Calcium Channel-Blocking Drugs (Class 4)

- **It prolongs AV nodal conduction time and its effective refractory period.**
- **It usually slows the SA node by its direct action, but its hypotensive action may occasionally result in a small reflex increase of SA rate.**
- **Verapamil can suppress both early and delayed after-depolarizations and may abolish slow responses arising in severely depolarized tissue.**

# Calcium Channel-Blocking Drugs (Class 4)

- A common error has been to administer intravenous verapamil to a patient with ventricular tachycardia misdiagnosed as supraventricular tachycardia.
- In this setting, hypotension and ventricular fibrillation can occur.
- It may precipitate heart failure.
- It can induce AV block when used in large doses or in patients with AV nodal disease.
- This block can be treated with atropine and β-receptor stimulants.
- May produce constipation, and peripheral edema.

# Calcium Channel-Blocking Drugs (Class 4)

## Therapeutic Use:

1. **Supraventricular tachycardia.**
2. **To reduce the ventricular rate in atrial fibrillation or flutter (rate control).**

- **It only rarely converts atrial flutter and fibrillation to sinus rhythm.**
- **It should be avoided in arrhythmias induced by digoxin because it increases digoxin concentration and enhances its AV block**

# Other Antiarrhthmic Agents

## Adenosine:

## Mechanism & Clinical Use:

- Adenosine is a nucleoside that occurs naturally throughout the body.
- Its half-life in the blood is less than 10 seconds.
- It activates $K^+$ efflux from the cell.
- It reduces $Ca^{++}$ influx into the cell.
- The results of these actions are marked hyperpolarization and suppression of calcium-dependent action potentials.

# Other Antiarrhthmic Agents

- **With a bolus dose, it directly inhibits AV nodal conduction and increases its refractory period but has lesser effects on the SA node.**
- **Adenosine is currently the drug of choice for prompt conversion of paroxysmal supraventricular tachycardia to sinus rhythm (high efficacy and very short duration of action).**
- **It is less effective in the presence of adenosine receptor blockers (theophylline or caffeine), and its effects are potentiated by adenosine uptake inhibitors such as dipyridamole.**

# Other Antiarrhthmic Agents

**Adverse reactions:**

- **Flushing in about 20% of patients and shortness of breath or chest burning (perhaps related to bronchospasm) in over 10%.**
- **Induction of very short lived high-grade AV block.**
- **Less common toxicities include headache, hypotension, nausea, and parasthesias.**

# Other Antiarrhthmic Agents

**Ivabradine:**

- **Ivabradine is a selective blocker of "funny" current ($I_f$) in the SA node and is useful for heart rate control.**
- **It slows pacemaker activity by decreasing diastolic depolarization of sinus node cells.**
- **It is an open channel blocker that shows use-dependent block.**
- **Unlike other heart rate-lowering agents such as β-blockers, it reduces heart rate without affecting myocardial contractility, ventricular repolarization, or intracardiac conduction.**

# Other Antiarrhthmic Agents

- At therapeutic concentrations, block of $I_f$ is not complete, and thus, the autonomic control of the SA node rate is retained.
- Elevated heart rate is an important determinant of the ischemic threshold in patients with coronary artery disease and a prognostic indicator in patients with congestive heart failure.
- It has antianginal and anti-ischemic effects in patients with coronary artery disease and chronic stable angina.

# Other Antiarrhthmic Agents

- **In patients with left ventricular dysfunction and heart rates greater than 70 bpm, it reduces mean heart rate.**
- **Inappropriate sinus tachycardia is an uncommon disorder characterized by multiple symptoms, including palpitations, dizziness, and orthostatic intolerance.**
- **Visual disturbances attributable to the block of the $I_f$ channels in the retina have been described.**

# Other Antiarrhthmic Agents

**Magnesium:**

- **Originally used for patients with digitalis-induced arrhythmias who were hypomagnesemic.**
- **It influences $Na^+/K^+$ATPase, sodium channels, certain potassium channels, and calcium channels.**
- **Magnesium therapy may be indicated in patients with torsades de pointes even if serum magnesium is normal.**

# Other Antiarrhthmic Agents

**Potassium:**

- **The effects of increasing serum potassium are:**

1. **A resting potential depolarizing action**
2. **A membrane potential stabilizing action, the latter caused by increased potassium permeability.**

- **Hypokalemia results in an increased risk of early and delayed after-depolarizations, and ectopic pacemaker activity, especially in the presence of digitalis.**

# Other Antiarrhthmic Agents

- **Hyperkalemia depresses ectopic pacemakers (severe hyperkalemia is required to suppress the SA node) and slows conduction.**
- **Because both insufficient and excess potassium are potentially arrhythmogenic, potassium therapy is directed toward normalizing potassium gradients and pools in the body.**