Cardiovascular system

Pharmacology – Lecture 1
Antiarrhythmic Drugs

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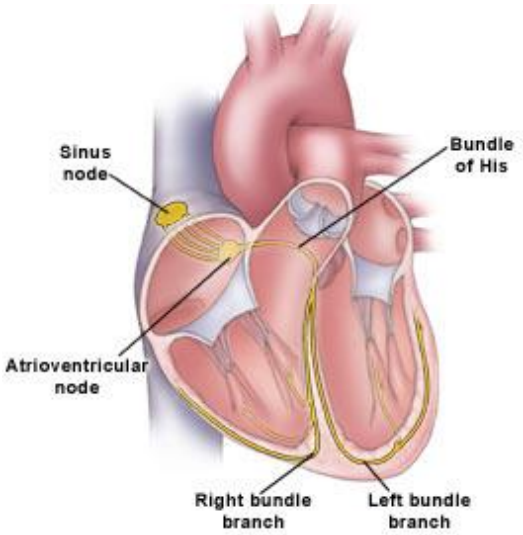
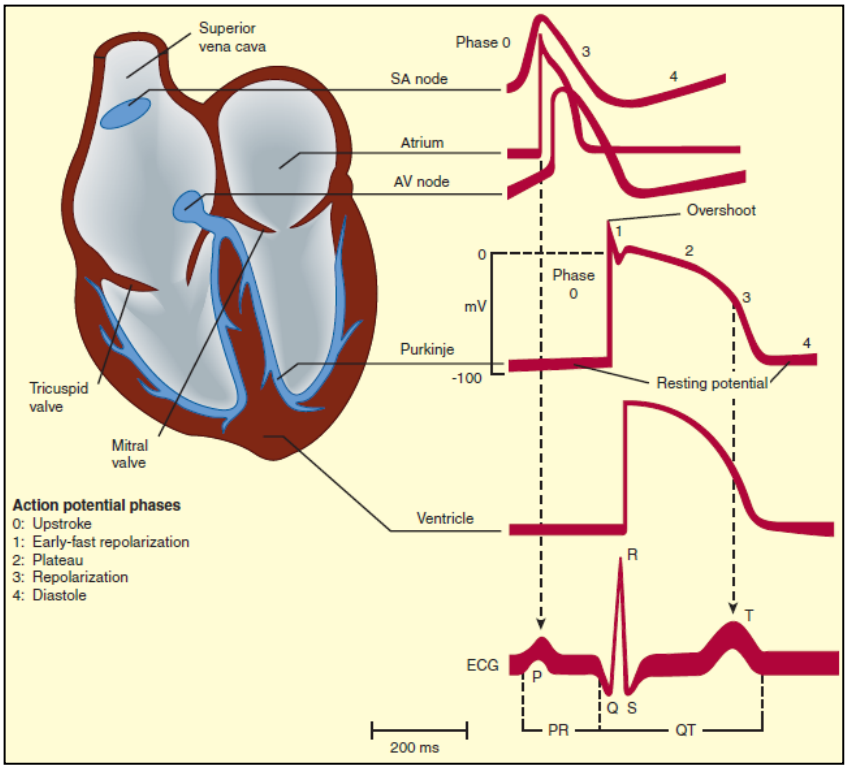
Overview

- The heart contains specialized cells that exhibit automaticity.
- They intrinsically generate rhythmic action potentials in the absence of external stimuli.
- These "pacemaker" 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 ions. 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.

Electrophysiology of Normal Cardiac Rhythm

1. Electrical impulse generates in the SA node
2. Spread rapidly thought the atria and enters the AV node
3. Conduction is delayed at the AV node
4. Impulse propagate over His-Purkinje system and invade the ventricles

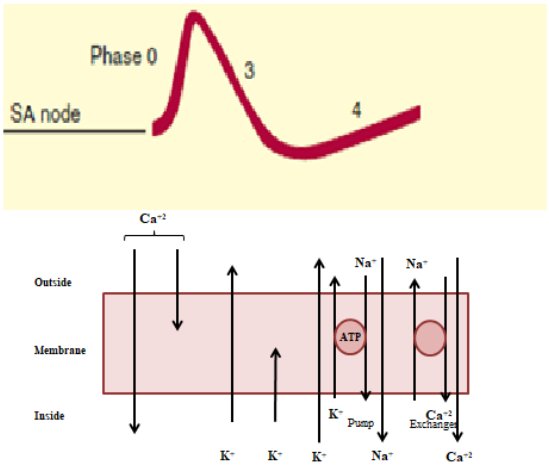




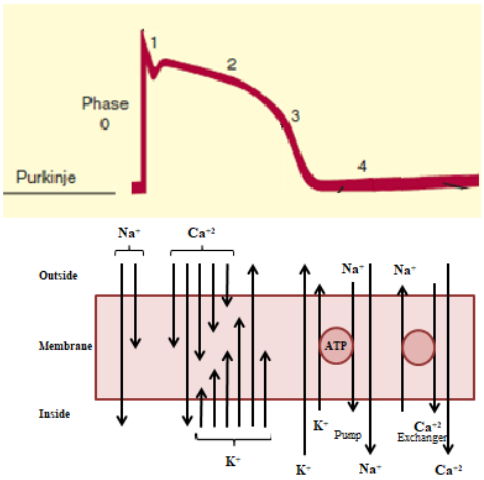
Arrhythmias

- Arrhythmias consist of cardiac depolarizations that deviate from the normal rhythm in one or more aspects:
  1. site of origin of the impulse, its rate or regularity,
  2. its conduction.

SA node

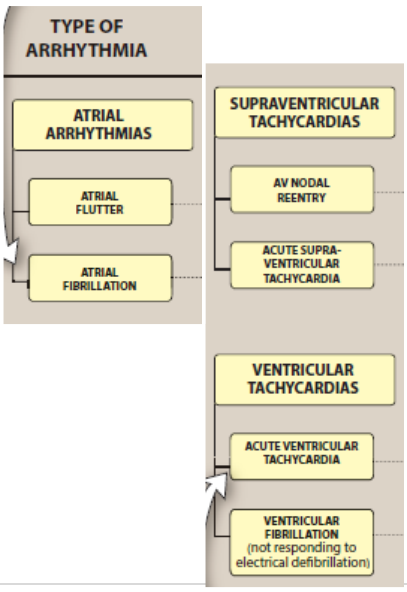


Purkinje



Introduction to The Arrhythmias

- Dysfunctions cause abnormalities in **impulse formation** and **conduction** in the myocardium.
- In the clinical setting, arrhythmias present as a <u>complex family of disorders with a variety of symptoms</u>.
- 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:
  1. the atria,
  2. the AV node, or
  3. the ventricles.



Causes of arrhythmias

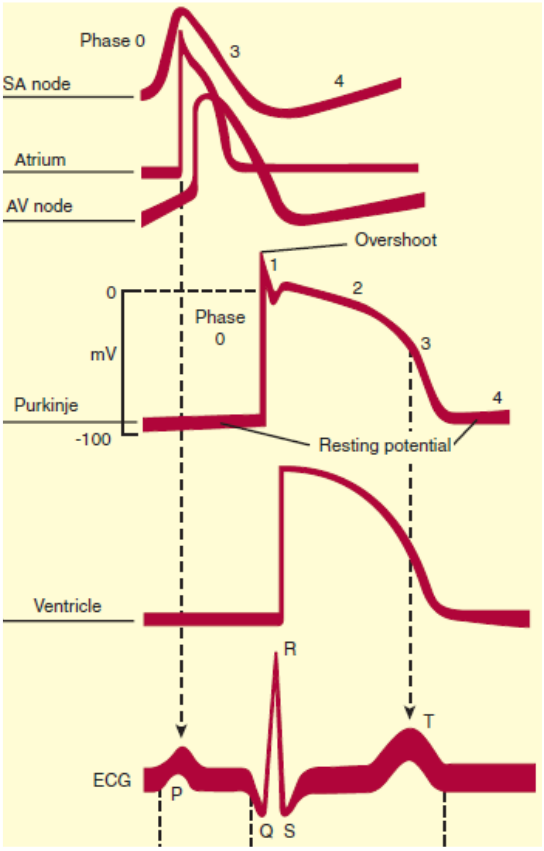
- Cardiac arrhythmias are a common problem in clinical practice, occurring in up to:

1. 25% of patients treated with **digitalis**,
2. 50% of **anesthetized** patients,
3. and over 80% of patients with **acute myocardial infarction**

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

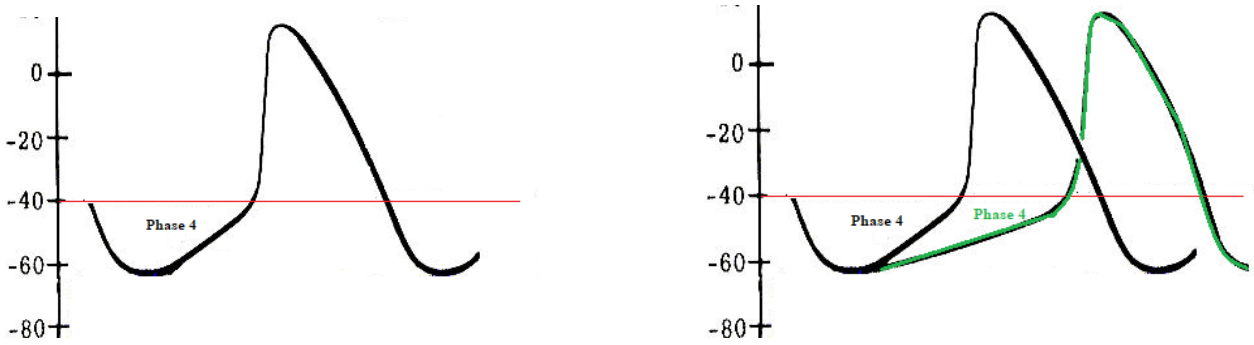
1. Abnormal automaticity:

- 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.
- If cardiac sites other than the SA node show enhanced automaticity, they may generate competing stimuli, and arrhythmias may arise.
- Most of the antiarrhythmic agents suppress automaticity by blocking either Na+ or Ca2+ channels to reduce the ratio of these ions to K+.

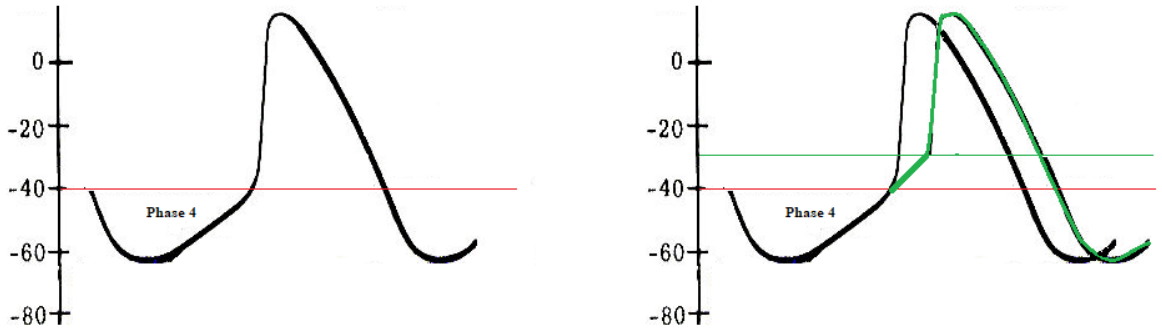


- This **decreases the slope of phase 4** (diastolic) depolarization and/or **raises the threshold of discharge to a less negative voltage**.
- Antiarrhythmic drugs cause the frequency of discharge to decrease. This effect is more pronounced in cells with **ectopic** pacemaker activity than in normal cells.

decreases the slope of phase 4

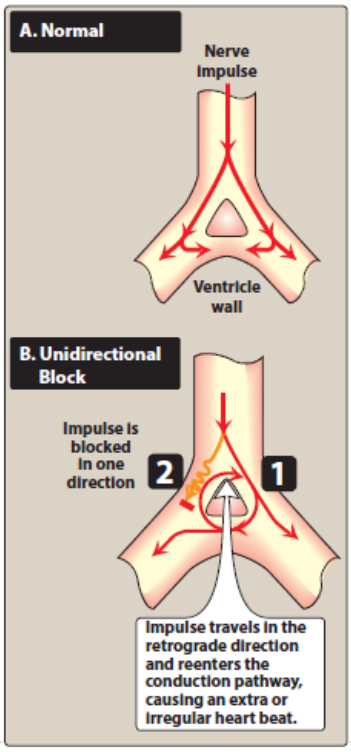


raises the threshold of discharge to a less negative voltage



2. 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 **reentry** can 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.
- This short-circuit pathway results in reexcitation of the ventricular muscle, causing **premature contraction** or **sustained ventricular arrhythmia**.
- Antiarrhythmic agents prevent reentry by slowing conduction (class I drugs) and/or increasing the refractory period (class III drugs), thereby converting a unidirectional block into a bidirectional block.



Treatment

- **Non-pharmacological**

1. Catheter ablation
2. Implantable cardioverter-defibrillator

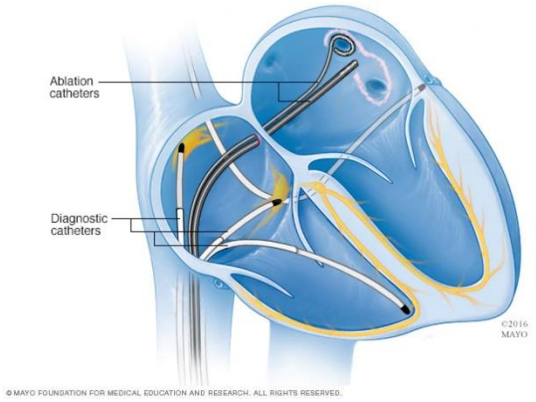
- **Pharmacological**

1. Na+ channel blockers
2. Beta blockers
3. K+ channel blockers
4. Ca++ channel blockers
5. Others

Non-pharmacological

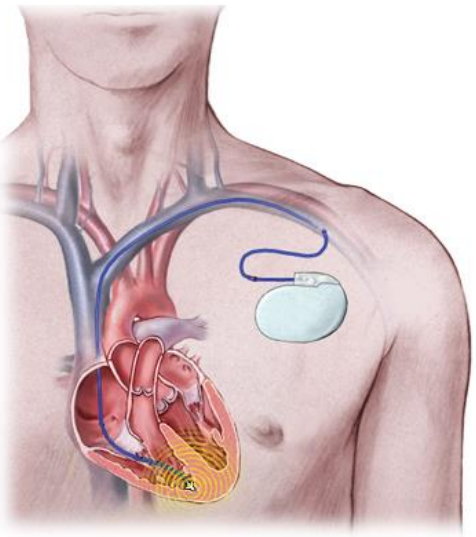
1. **Radiofrequency catheter ablation** or extreme cold, **cryoablation.**

- Mapping of reentrant pathways and ablation can be carried out by means of catheters threaded into the heart from peripheral arteries and veins



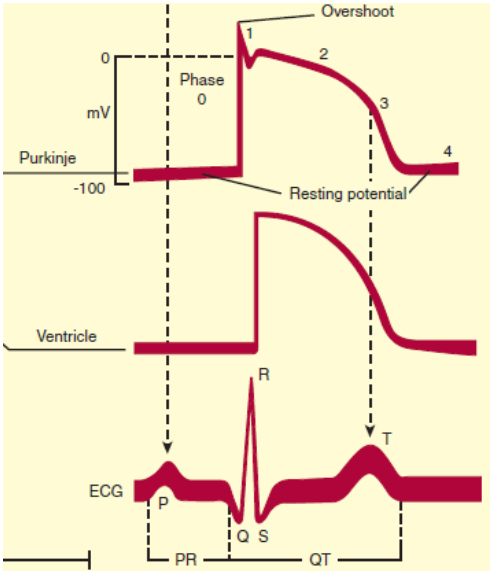
2. **Implantable cardioverter-defibrillator (ICD):**

- A device that can automatically detect and treat potentially fatal arrhythmias such as ventricular fibrillation.
- ICDs are now widely used in patients who have been resuscitated from such arrhythmias, and several trials have shown that ICD treatment reduces mortality in patients with coronary artery disease who have an ejection fraction ≤ 30% and in patients with class II or III heart failure and no prior history of arrhythmias.



Pharmacological treatment

Antiarrhythmic drugs



- Antiarrhythmic drugs can **modify** impulse generation and conduction to prevent arrhythmias from occurring or to reduce symptoms associated with arrhythmias.
- Unfortunately, many of the antiarrhythmic agents are known to have dangerous **proarrhythmic** actions—that is, to cause arrhythmias.
- Inhibition of potassium (K+) channels (typically thought of as class III activity) **widens** the action potential and can, thus, **prolong the QT interval**.
- If prolongation is excessive, these drugs increase the risk of developing life-threatening ventricular tachyarrhythmias (**torsades de pointes**).
- The most common cause of QT prolongation is drug-induced, although other conditions (for example, ischemia and hypokalemia) and genetic profiles may contribute.
- QT prolongation is not only seen with class III antiarrhythmics. Drugs such as *cisapride* and *terfenadine* were withdrawn from the market because of severe and fatal arrhythmias. Many drugs are known to prolong the QT interval, such as macrolide antibiotics and antipsychotics.
- Caution should be employed when combining drugs with additive effects on the QT interval or when giving QT-prolonging antiarrhythmic drugs with drugs known to inhibit their metabolism.
- As such, the benefit of antiarrhythmic drugs must always be compared to the potential for serious adverse effects or drug interactions.
- Implantable cardioverter defibrillators are becoming more widely used to manage ventricular arrhythmias.

Antiarrhythmic drugs

- 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 drugs have actions relating to more than one class or may have active metabolites with a different class of action.

CLASSIFICATION OF DRUG	MECHANISM OF ACTION	COMMENT
IA	Na^+ channel blocker	Slows Phase 0 depolarization in ventricular muscle fibers
IB	Na^+ channel blocker	Shortens Phase 3 repolarization in ventricular muscle fibers
IC	Na^+ channel blocker	Markedly slows Phase 0 depolarization in ventricular muscle fibers
II	β-Adrenoreceptor blocker	Inhibits Phase 4 depolarization in SA and AV nodes
III	K^+ channel blocker	Prolongs Phase 3 repolarization in ventricular muscle fibers
IV	Ca^{2+} channel blocker	Inhibits action potential in SA and AV nodes

CLASS I (Na^+-channel blockers)

Disopyramide (IA) NORPACE
Flecainide (IC) TAMBOCOR
Lidocaine (IB) XYLOCAINE
Mexiletine (IB) MEXITIL
Procainamide (IA) PRONESTYL
Propafenone (IC) RYTHMOL
Quinidine (IA) QUINIDEX, QUINAGLUTE

CLASS II (ß-adrenoreceptor blockers)

Atenolol TENORMIN
Esmolol BREVIBLOC
Metoprolol LOPRESSOR, TOPROL-XL

CLASS III (K^+ channel blockers)

Amiodarone CORDARONE, PACERONE
Dofetilide TIKOSYN
Dronedarone MULTAQ
Ibutilide CORVERT
Sotalol BETAPACE, SORINE

CLASS IV (Ca^{2+} channel blockers)

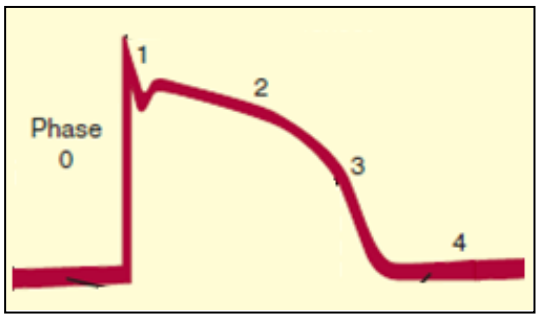
Diltiazem CARDIZEM, CARTIA XT
Verapamil CALAN, ISOPTIN SR, VERELAN

OTHER ANTIARRHYTHMIC DRUGS

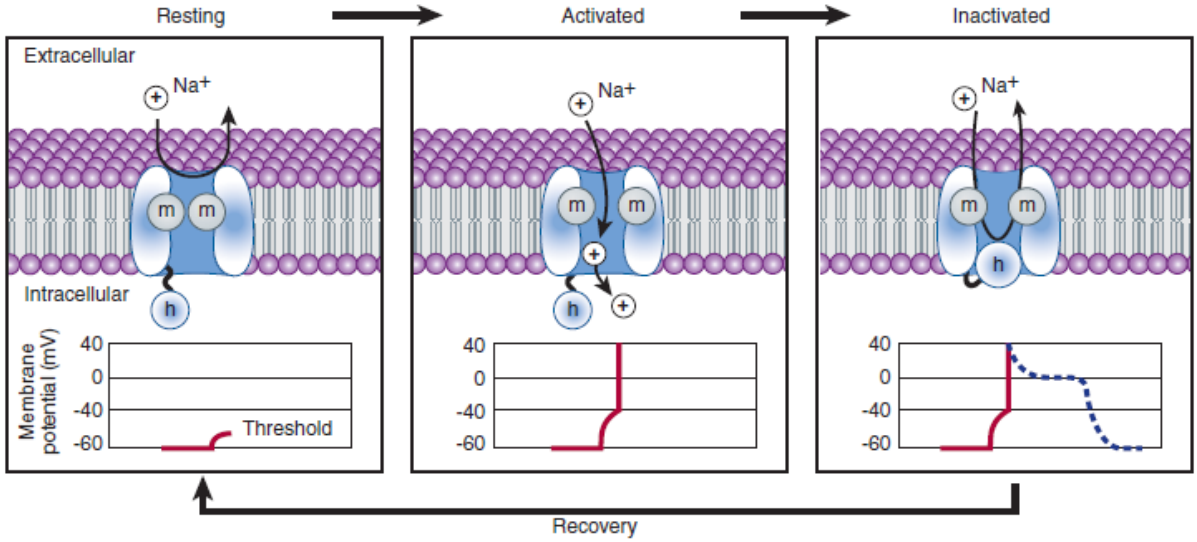
Adenosine ADENOCARD
Digoxin LANOXIN
Magnesium sulfate

CLASS I ANTIARRHYTHMIC DRUGS

- Class I antiarrhythmic drugs act by **blocking voltage-sensitive sodium (Na+) channels**.
- The use of sodium channel blockers has declined due to their proarrhythmic effects, particularly in patients with reduced left ventricular function and ischemic heart disease.



Use dependence



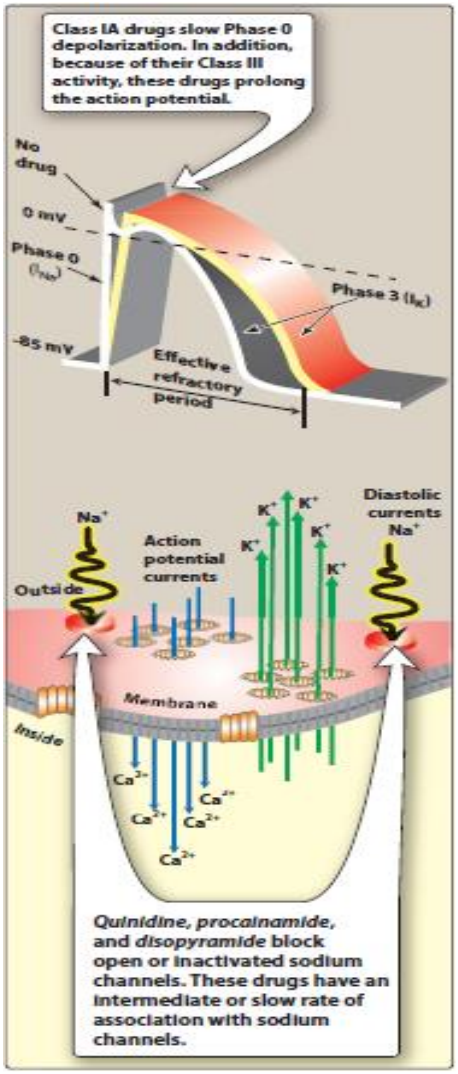
- Class I drugs bind more rapidly to **open or inactivated** sodium channels than to channels that are fully repolarized following recovery from the previous depolarization cycle.
- Therefore, these drugs show a greater degree of blockade in tissues that are **frequently depolarizing**.
- This property 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 ventricular action potential.

Class IA antiarrhythmic drugs: Quinidine, procainamide, and disopyramide

- *Quinidine* is the prototype class IA drug. Other agents in this class include *procainamide* and *disopyramide*.
- Because of their concomitant class III activity, they can precipitate arrhythmias that can progress to ventricular fibrillation.

Mechanism of action:

- *Quinidine* binds to open and inactivated sodium channels and **prevents sodium influx**, thus slowing the rapid upstroke during phase 0.
- It decreases the slope of phase 4 spontaneous depolarization, inhibits potassium channels, and blocks calcium channels.
- Because of these actions, it **slows conduction velocity** and **increases refractoriness**.
- *Quinidine* also has mild α-adrenergic blocking and anticholinergic actions.
- *Procainamide* and *disopyramide* have actions similar to those of *quinidine*.
- However, there is less anticholinergic activity associated with *procainamide* and more with *disopyramide*.
- Neither *procainamide* nor *disopyramide* has α-blocking activity.
- *Disopyramide* produces a negative inotropic effect that is greater than the weak effect exerted by *quinidine* and *procainamide*, and unlike the other drugs, it causes peripheral vasoconstriction.
- The drug may produce a clinically important decrease in myocardial contractility in patients with systolic heart failure.



Therapeutic uses:

- ***Quinidine*** is used in the treatment of a wide variety of arrhythmias, including atrial, AV junctional, and ventricular tachyarrhythmias.
- ***Procainamide*** is available in an intravenous formulation only and may be used to treat acute atrial and ventricular arrhythmias. However, electrical cardioversion or defibrillation and *amiodarone* have mostly replaced *procainamide* in clinical use.
- ***Disopyramide*** is used in the treatment of ventricular arrhythmias as an alternative to *procainamide* or *quinidine* and may also be used for maintenance of sinus rhythm in atrial fibrillation or flutter.

Pharmacokinetics:

1. ***Quinidine:***

- *Quinidine sulfate or gluconate* is rapidly and almost completely absorbed after oral administration.
- It undergoes extensive metabolism primarily by the hepatic cytochrome P450 3A4 (CYP3A4) isoenzyme, forming active metabolites.

2. ***Procainamide:***

- Has a relatively short duration of action of 2 to 3 hours.
- A portion of *procainamide* is acetylated in the liver to *N*-acetylprocainamide (**NAPA**), which prolongs the duration of the action potential.
- Thus, NAPA has properties and side effects 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.

3. ***Disopyramide:***

- Well absorbed after oral administration. It is metabolized in the liver to a less active metabolite and several inactive metabolites.
- *Disopyramide* is a substrate of CYP3A4. About half of the drug is excreted unchanged by the kidneys.

Adverse effects:

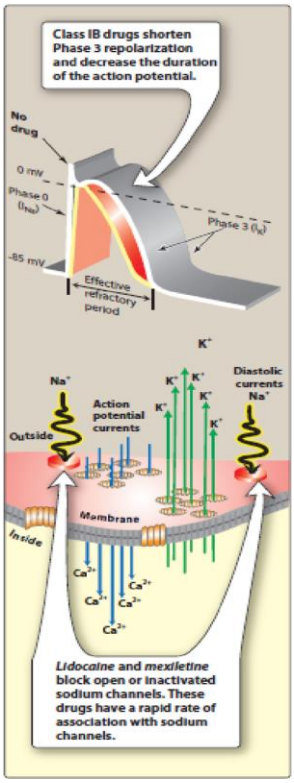
- Large doses of *quinidine* may induce the symptoms of cinchonism (for example, blurred vision, tinnitus, headache, disorientation, and psychosis).
- Drug interactions are common with *quinidine* since it is an inhibitor of both CYP2D6 and P-glycoprotein.
- Intravenous administration of *procainamide* may cause hypotension.
- *Disopyramide* has the most anticholinergic adverse effects of the class IA drugs (for example, dry mouth, urinary retention, blurred vision, and constipation).
- Both *quinidine* and *disopyramide* should be used with caution with potent inhibitors of CYP3A4.

Class IB antiarrhythmic drugs: Lidocaine and mexiletine

- 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.
- The class IB drugs *lidocaine* and *mexiletine* are useful in treating **ventricular arrhythmias**.

Mechanism of action:

1. Sodium channel blockade
2. shorten phase 3 repolarization
3. decrease the duration of the action potential.



Therapeutic uses:

A. Lidocaine:

1. Alternative of amiodarone in ventricular fibrillation or pulseless ventricular tachycardia (VT),
2. In combination with amiodarone for VT storm
3. Polymorphic VT

- The drug does not markedly slow conduction and, thus, has little effect on atrial or AV junction arrhythmias.

B. ***Mexiletine*** is used for chronic treatment of ventricular arrhythmias, often in **combination** with *amiodarone*.

Pharmacokinetics:

A. ***Lidocaine:***

- It is given intravenously because of extensive first-pass transformation by the liver, which precludes oral administration.
- The drug is dealkylated to two less active metabolites, primarily by CYP1A2 with a minor role by CYP3A4.
- *Lidocaine* should be monitored closely when given in combination with drugs affecting these CYP isoenzymes.
- As *lidocaine* is a high extraction drug, drugs that lower hepatic blood flow (β-blockers) may require *lidocaine* dose adjustment.

B. ***Mexiletine:***

- It is well absorbed after oral administration.
- It is metabolized in the liver primarily by CYP2D6 to inactive metabolites and excreted mainly via the biliary route.

Adverse effects:

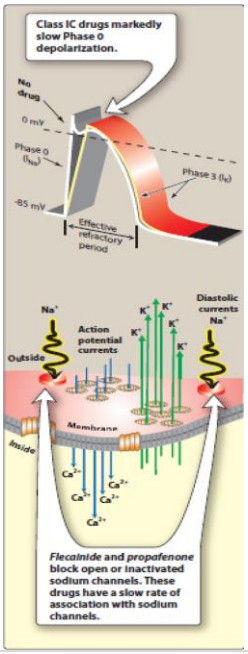
- ***Lidocaine*** has a fairly wide therapeutic index.
- It shows little impairment of left ventricular function and has **no** negative inotropic effect.
- Central nervous system (CNS) effects include **nystagmus** (early indicator of toxicity), drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsions, which often limit the duration of continuous infusions.
- ***Mexiletine*** has a narrow therapeutic index and caution should be used when administering the drug with inhibitors of CYP2D6.
- Nausea, vomiting, and dyspepsia are the most common adverse effects.

Class IC antiarrhythmic drugs: Flecainide and propafenone

- These drugs **slowly** dissociate from resting sodium channels and show prominent effects even at normal heart rates.
- Several studies have cast serious doubts on the safety of the class IC drugs, particularly in patients with structural heart disease.

Mechanism of action:

- *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 slope of phase 4 depolarization.
- *Flecainide* also blocks potassium channels leading to increased action potential duration, even more so than *propafenone*.
- *Propafenone*, like *flecainide*, slows conduction in all cardiac tissues but does not block potassium channels.



Pharmacokinetics:

A. ***Flecainide:***

- is absorbed orally and is metabolized by CYP2D6 to multiple metabolites.
- The parent drug and metabolites are mostly eliminated renally, and dosage adjustment may be requiredin renal disease.

B. ***Propafenone:***

- It is metabolized to active metabolites
- primarily via CYP2D6, and also by CYP1A2 and CYP3A4.
- The metabolites are excreted in the urine and the feces.

Adverse effects:

- *Flecainide* is generally well tolerated, with blurred vision, dizziness, and nausea occurring most frequently.
- *Propafenone* has a similar side effect profile, but it may also cause bronchospasm due to its β-blocking effects. It should be avoided in patients with asthma.
- *Propafenone* is also an inhibitor of P-glycoprotein.
- Both drugs should be used with caution with potent inhibitors of CYP2D6.