Antiarrhythmic Drugs

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Reference

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Electrophysiology of Normal Cardiac Rhythm

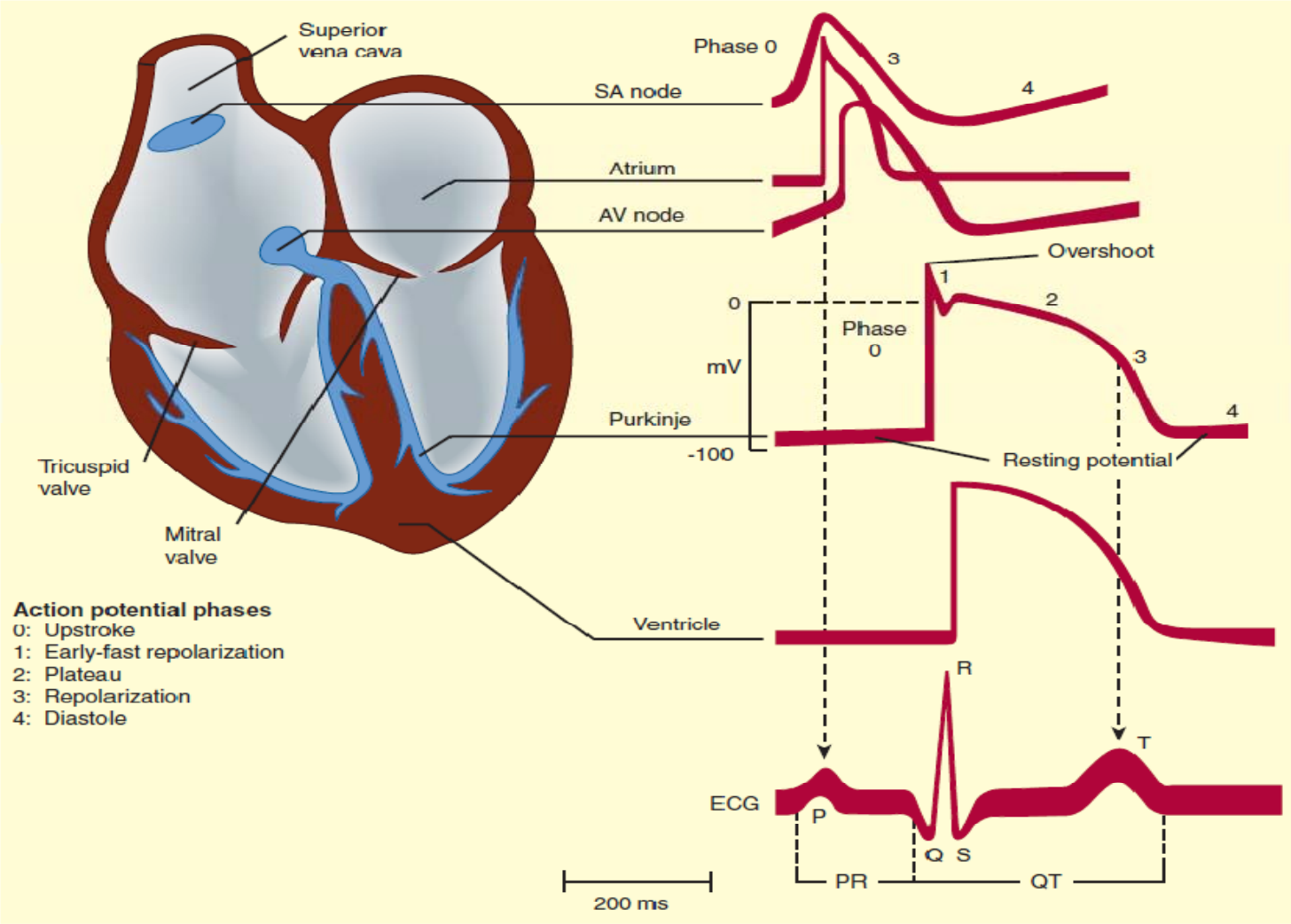


FIGURE 14–1 Schematic representation of the heart and normal cardiac electrical activity (intracellular recordings from areas indicated and ECG). Sinoatrial (SA) node, atrioventricular (AV) node, and Purkinje cells display pacemaker activity (phase 4 depolarization). The ECG is the body surface manifestation 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 (ie, the intraventricular conduction time). The QT interval reflects the duration of the ventricular action potential.

The Cardiac Action Potential

- When sodium channels open, the very large influx of Na^+ accounts for phase 0 depolarization of the action potential.
- This intense sodium current is very brief because of inactivation of the sodium channels.

The Cardiac Action Potential

- **The action potential plateau (phases 1 and 2) reflects the turning off of most of the sodium current, the waxing and waning of calcium current, and the slow development of a repolarizing potassium current.**

The Cardiac Action Potential

- **Final repolarization (phase 3) of the action potential results from completion of sodium and calcium channel inactivation and the growth of potassium permeability.**
- **The major potassium currents involved in phase 3 repolarization include a rapidly activating potassium current (I_{Kr}) and a slowly activating potassium current (I_{Ks}).**

The Cardiac Action Potential

- **These two potassium currents are sometimes discussed together as "I_K".**
- **Extracellular potassium concentration and inward rectifier K^+ channel function are the major factors determining the membrane potential of the resting cardiac cell.**

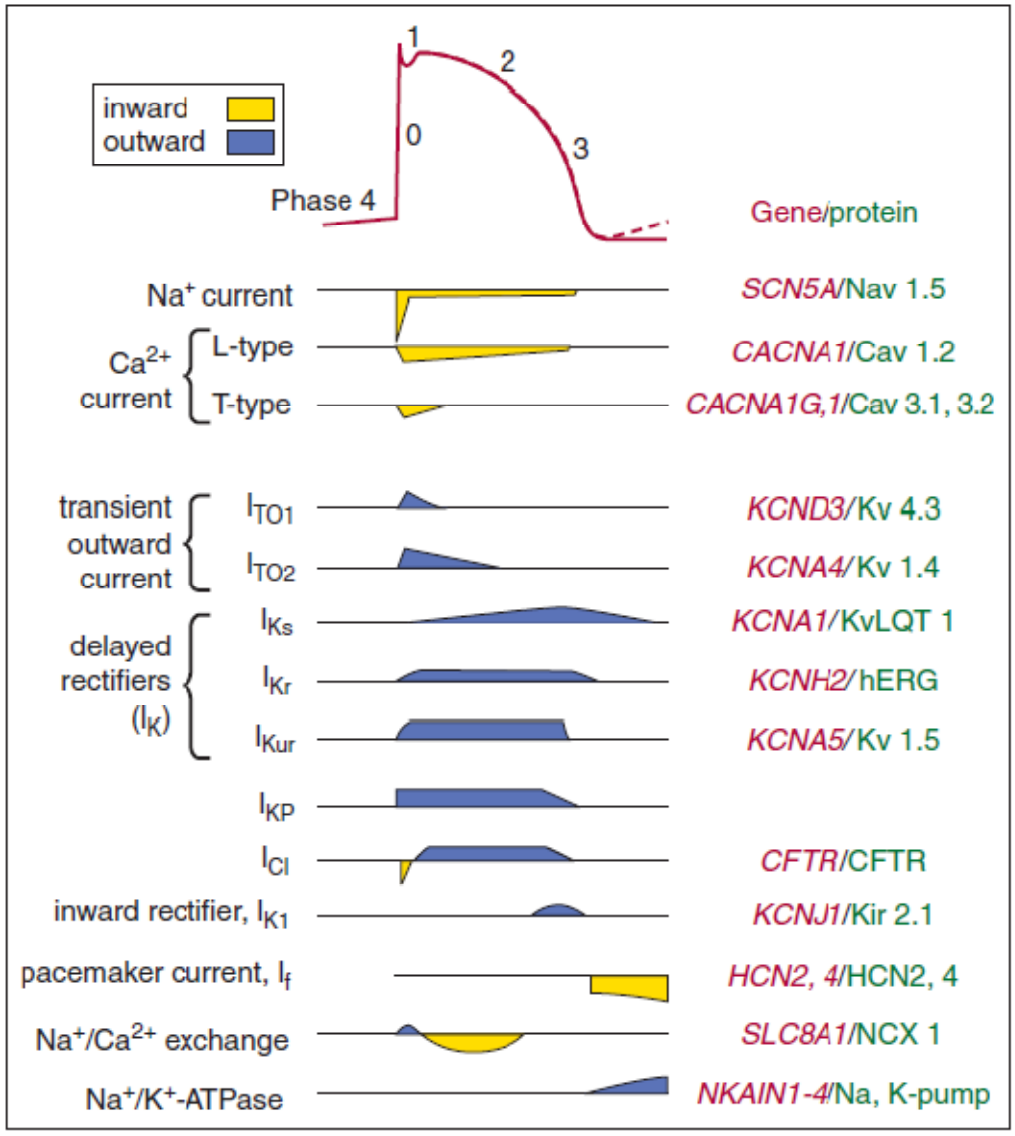


FIGURE 14–2 Schematic diagram of the ion permeability changes and transport processes that occur during an action potential and the diastolic period following it. Yellow indicates inward (depolarizing) membrane currents; blue indicates outward (repolarizing) membrane currents. Multiple subtypes of potassium and calcium currents, with different sensitivities to blocking drugs, have been identified. The right side of the figure lists the genes and proteins responsible for each type of channel or transporter.

The Cardiac Action Potential

- **In pacemaker cells (whether normal or ectopic), spontaneous depolarization (the pacemaker potential) occurs during diastole (phase 4).**
- **This depolarization results from a gradual increase of depolarizing current through special hyper-polarization-activated ion channels (I_f) in SA node cells.**

The Cardiac Action Potential

- **I_f is an inward current activated by hyper-polarization.**
- **The hyper-polarization-activated channel in the sinus node activity is regulated by cAMP, and co-localizes with the β_2-adrenergic receptor. [β_1]??**
- **This association may play a role in the autonomic regulation of heart rate.**

Effects of K^+

- **The effects of changes in serum potassium on cardiac action potential duration, pacemaker rate, and arrhythmias may look paradoxical if we consider only potassium electrochemical gradient.**

Effects of K^+

Hypokalemia:

1. **Prolongs AP duration → increased risk of early- and delayed- afterdepolarizations.**
2. **Increases pacemaker rate.**
3. **Increases pacemaker arrhythmogenesis, especially in the presence of digitalis.**
4. **Increases arrhythmogenicity of antiarrhythmic drugs (accentuated action potential prolongation and tendency to cause torsades de pointes).**

- **Effects more on ectopic pacemakers than SA node.**

Effects of K^+

Hyperkalemia:

1. **Reduces AP duration.**
2. **Slows conduction.**
3. **Decreases pacemaker rate.**
4. **Decreases pacemaker arrhythmogenesis.**

- **Thus, both insufficient and excess potassium is potentially arrhythmogenic.**
- **Therefore, potassium therapy is directed toward normalizing potassium gradients and pools in the body.**

Mechanisms of Cardiac Arrhythmias

Factors that precipitate or exacerbate arrhythmias:

1. **Hypoxia or Ischemia.**
2. **Acidosis or alkalosis.**
3. **Electrolyte abnormalities.**
4. **Excessive catecholamine exposure.**
5. **Other autonomic influences.**
6. **Overstretching of cardiac fibers.**
7. **Scarred or diseased tissue.**
8. **Drug toxicity: Digitalis and antiarrhythmic drugs.**

Mechanisms of Cardiac Arrhythmias

Disturbances in cardiac rhythm result from:

1. **Disturbances in impulse formation.**
2. **Disturbances in impulse conduction.**
3. **Disturbances in both.**

Disturbances in impulse formation

- **The interval between depolarizations of a pacemaker cell is the sum of the duration of the action potential and the duration of the diastolic interval.**
- **Shortening of either duration results in an increase in pacemaker rate.**
- **The diastolic interval, is determined primarily by the slope of phase 4 depolarization (pacemaker potential).**

Disturbances in impulse formation

1. **Vagal discharge and β-receptor-blocking drugs slow normal pacemaker rate by reducing the phase 4 slope (acetylcholine also makes the maximum diastolic potential more negative).**

Disturbances in impulse formation

- **Acceleration of pacemaker discharge may be produced by increased phase 4 depolarization slope, which can be caused by hypokalemia, β-adrenoceptor stimulation, positive chronotropic drugs, fiber stretch, acidosis, and partial depolarization by currents of injury, which especially affects Purkinje fibers latent pacemakers.**

Disturbances in impulse formation

2. **Afterdepolarizations are transient depolarizations that interrupt phase 3 (early afterdepolarizations, EADs) or phase 4 (delayed afterdepolarizations, DADs).**

- **EADs are usually exacerbated at slow heart rates and are thought to contribute to the development of long QT-related arrhythmias.**

Disturbances in impulse formation

- **DADs, on the other hand, often occur when intracellular calcium is increased.**
- **They are exacerbated by fast heart rates and are thought to be responsible for some arrhythmias related to digitalis excess, to catecholamines, and to myocardial ischemia.**

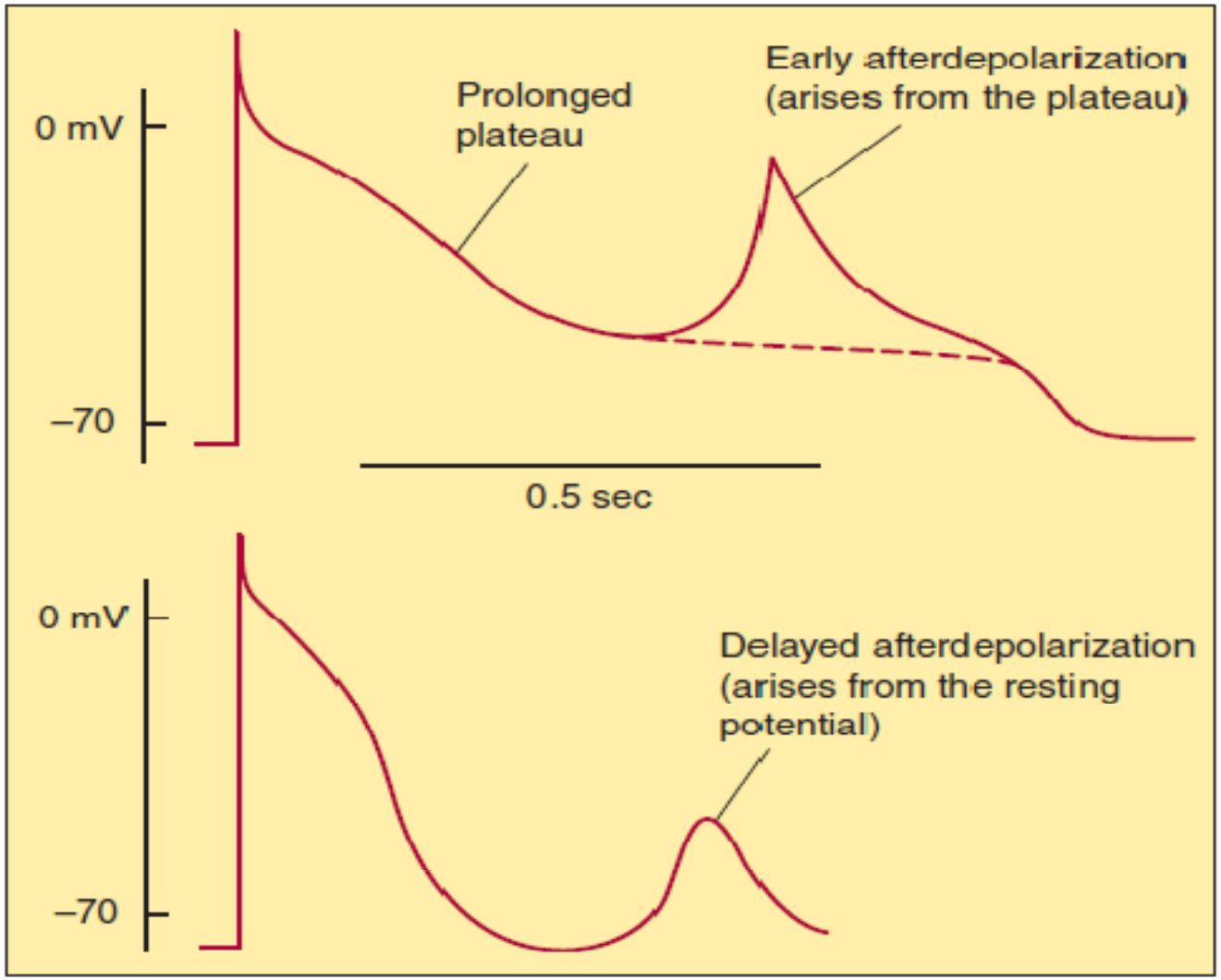
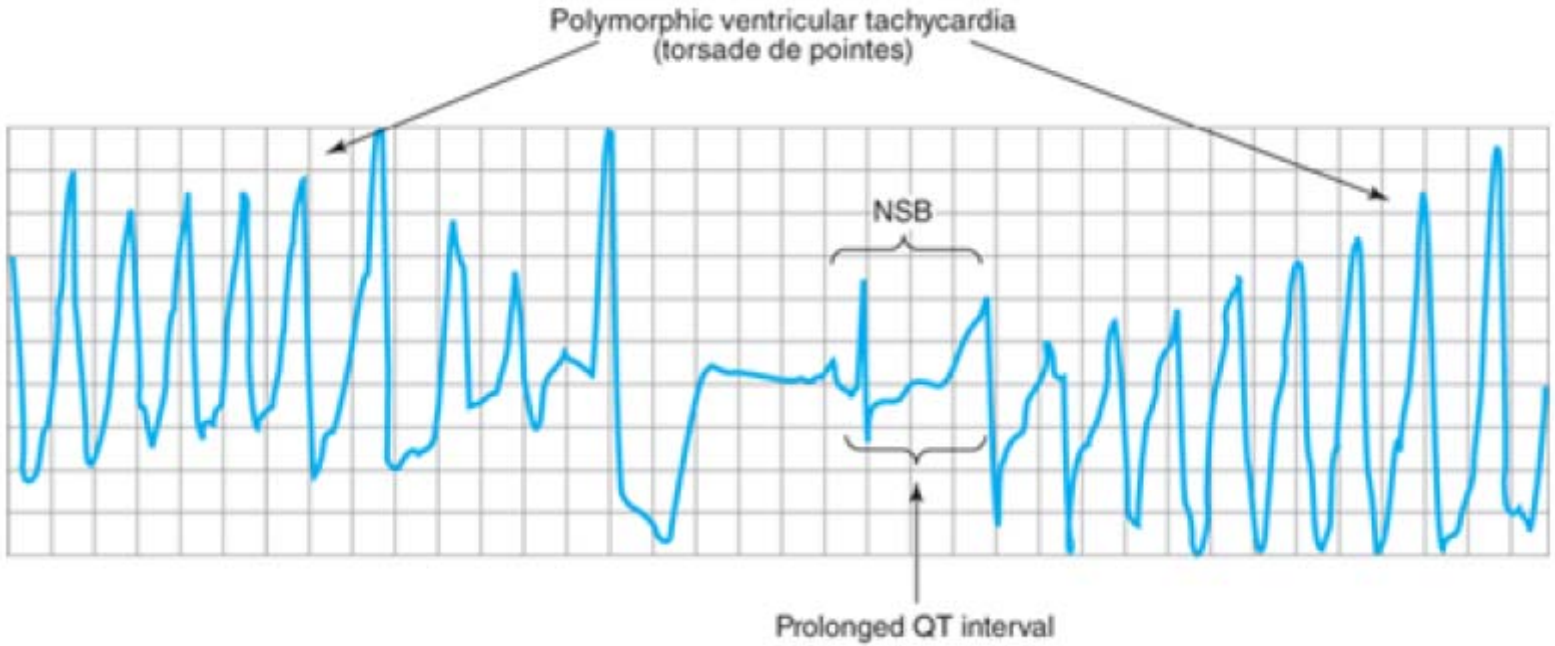


FIGURE 14–5 Two forms of abnormal activity, early (**top**) and delayed afterdepolarizations (**bottom**). In both cases, abnormal depolarizations arise during or after a normally evoked action potential. They are therefore often referred to as "triggered" automaticity; that is, they require a normal action potential for their initiation.

Disturbances in impulse formation

3. **The polymorphic ventricular tachycardia known as torsades de pointes is associated with prolongation of the QT interval, syncope, and sudden death.**

- **This represents prolongation of the action potential of some ventricular cells.**
- **The effect can be attributed to either increased inward current (gain of function) or decreased outward current (loss of function) during the plateau of the AP.**



Electrocardiogram from a patient with the long QT syndrome during two episodes of torsades de pointes. The polymorphic ventricular tachycardia is seen at the start of this tracing and spontaneously halts at the middle of the panel. A single normal sinus beat (NSB) with an extremely prolonged QT interval follows, succeeded immediately by another episode of ventricular tachycardia of the torsades type. The usual symptoms include dizziness or transient loss of consciousness. (Reproduced, with permission, from *Basic and Clinical Pharmacology*, 10th edition, McGraw-Hill, 2007. Copyright © The McGraw-Hill Companies, Inc.)

Disturbances in impulse formation

- **Loss-of-function mutations in potassium channel genes produce decreases in outward repolarizing current and can cause LQT.**
- **Gain-of-function mutations in the sodium channel gene or calcium channel gene cause increases in inward plateau current and also cause LQT.**

Disturbances in impulse formation

- **The potassium channel I_{kr} is blocked or modified by many drugs (quinidine, sotalol) or electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia) that also produce torsades de pointes.**
- **It is likely that torsades de pointes originates from triggered upstrokes arising from early after-depolarizations.**

Disturbances in impulse formation

- **Thus, therapy is directed at correcting hypokalemia, eliminating triggered upstrokes (by using β blockers or magnesium), or shortening the action potential (by increasing heart rate with isoproterenol or pacing), or all of these.**

Disturbances in impulse formation

4. **Short QT syndrome may be linked to gain-of-function mutations in some potassium channel genes.**
5. **Catecholaminergic polymorphic ventricular tachycardia, a disease that is characterized by stress or emotion-induced syncope, can be caused by genetic mutations in two different proteins in the sarcoplasmic reticulum that control intracellular calcium homeostasis.**

Disturbances of Impulse Conduction

- **Severe depression of conduction may result in block (AV- block or bundle-branch block)**
- **Partial AV block is reversed by atropine because parasympathetic control of AV conduction is significant.**

Disturbances of Impulse Conduction

- **Another abnormality of conduction is re-entry (circus movement), in which one impulse reenters and excites areas of the heart more than once**
- **The path of reentry may be confined to small areas (within or near the AV node), or it may involve a large area of atrial or ventricular walls.**

Disturbances of Impulse Conduction

- **Some forms of re-entry are anatomically determined such as the Wolf-Parkinson-White syndrome, where the entry circuit consists of :**

1. **Atrial tissue.**
2. **AV node.**
3. **Ventricular tissue.**
4. **Accessory AV conduction (bypass tract, bundle of kent).**

Disturbances of Impulse Conduction

- **In other cases (AF, or VF), multiple reentry circuits may meander through the heart in apparently random paths.**
- **The circulating impulse often gives off “daughter impulses” that can spread to the rest of the heart.**
- **Depending on how many round trips through the pathway the impulse makes before dying out, the arrhythmia may manifest as one or few extra beats or as a sustained tachyarrhythmia.**

Disturbances of Impulse Conduction

In order for reentry to occur, 3 conditions must coexist:

1. **There must be an obstacle to homogeneous conduction – anatomic or physiologic – thus establishing a circuit around which the re-enterant wave front can propagate.**
2. **There must be unidirectional block at some point in the circuit, i.e. conduction must die out in one direction but continue in the opposite direction.**

Disturbances of Impulse Conduction

3. **Conduction time around the circuit must be long enough so that retrograde impulse does not enter refractory tissue as it travels around the obstacle (conduction time must exceed the ERP).**

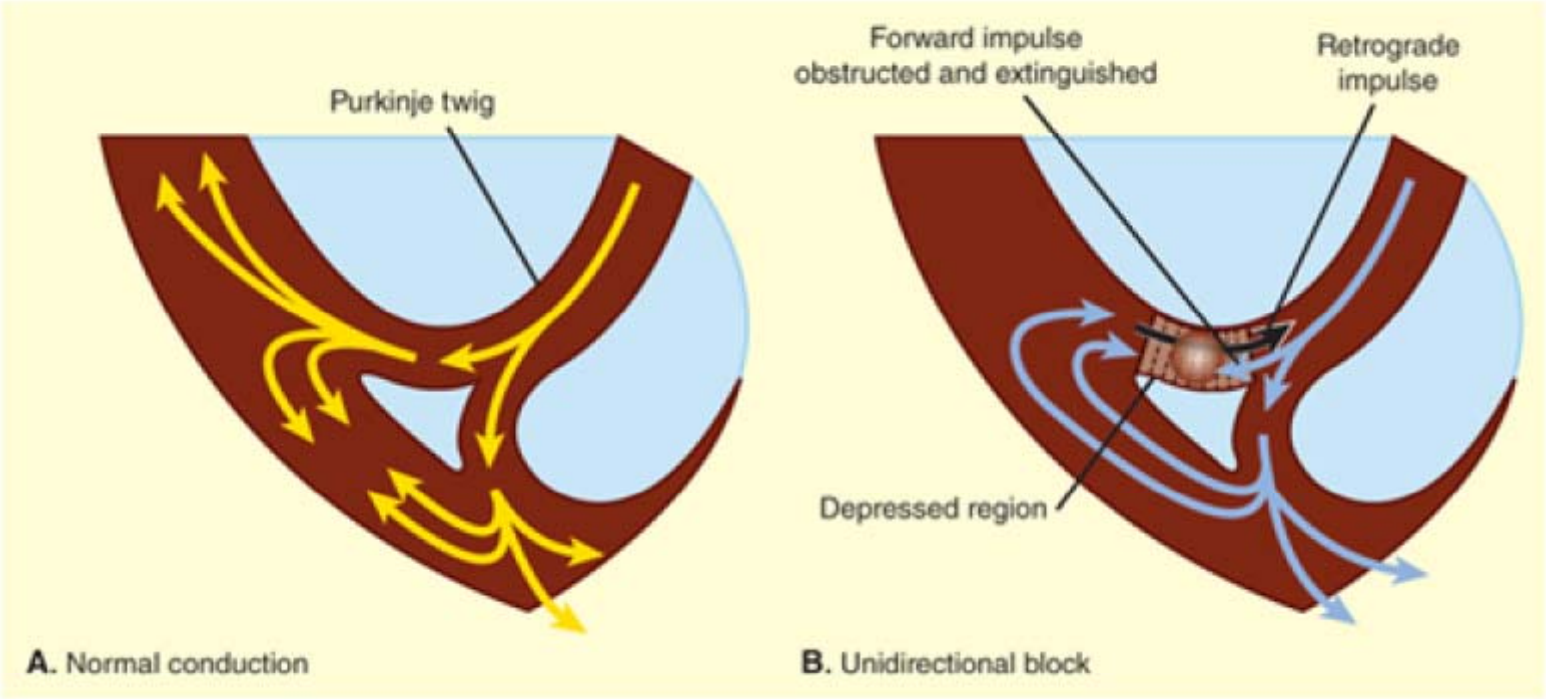


Figure 14-6: Schematic diagram of a reentry circuit that might occur in small bifurcating branches of the Purkinje system where they enter the ventricular wall.
A: Normally, electrical excitation branches around the circuit, is transmitted to the ventricular branches, and becomes extinguished at the 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 then reexcites tissue it had previously passed through, and a reentry arrhythmia is established.

Disturbances of Impulse Conduction

- **If conduction velocity is too slow, bidirectional block rather than unidirectional block occurs.**
- **If re-entry impulse is too weak, conduction may fail, or the impulse may arrive so late that it collides with the next regular impulse**
- **If conduction is too rapid, almost normal bidirectional conduction rather than unidirectional block will occur.**

Disturbances of Impulse Conduction

- **Even in the presence of unidirectional block, if the impulse travels around the obstacle too rapidly, it will reach tissue that is still refractory.**
- **Slowing of conduction may be due to depression of Na^+ current, depression of Ca^{2+} current (AV node) or both.**
- **Drugs that abolish re-entry work by further slowing depressed conduction (Block Na^+ and Ca^{2+} current) and causing bidirectional block.**

Disturbances of Impulse Conduction

Lengthening or shortening of RP may also make reentry less likely:

1. **The longer the RP in tissue near the site of block, the greater the chance that the tissue will still be refractory when reentry is attempted.**
2. **The shorter the RP in the depressed region, the less likely it is that unidirectional block will occur.**

Disturbances of Impulse Conduction

- **Thus, increased dispersion of refractoriness is one contributor to reentry, and drugs may suppress arrhythmias by reducing such dispersion.**

Antiarrhythmic Drugs

Classification:

1. **Class 1: Na^+ channel blockers.**

   1A: Intermediate interaction with and dissociation from the channel → prolong action potential duration.

   Quinidine, Procainamide, Disopyramide

   1B: Rapid interaction with and dissociation from the channel → shorten action potential duration

   Lidocaine, Tocainide, Mexiletine, Phenytoin

   1C: Slow interaction with and dissociation from the channel → minimal effect on action potential duration

   Flecainide, Propafenone, Moricizine

Antiarrhythmic Drugs

2. **Class 2: β-Adrenoceptor blockers**

   Reduce sinus rate, slow conduction through the AV node and prolongs its refractory period

   Propranolol, Atenolol, Esmolol

3. **Class 3: Drugs that prolong action potential duration.**

   Most of these drugs block the rapid component of the rectifier potassium current

   Amiodarone, Sotalol, Bretylium, Ibutilide, Dofetilide

Antiarrhythmic Drugs

4. **Class 4: Calcium channel blockers**

   Slow SA node rate and Prolong conduction time and refractory period of the AV node

   Verapamil, Diltiazem

5. **Unclassified:**

   Digoxin, Adenosine, Magnesium

Procainamide

Pharmacodynamics:

A. Cardiac Effects:

1. It slows the upstroke of the action potential, slows conduction, and prolongs QRS duration due to Na^+ channel block.
2. It has a direct depressant action on SA & AV nodes.

B. Extracardiac Effects:

- Ganglion-blocking properties → reduction of peripheral vascular resistance and hypotension, particularly with IV use or in the presence of left ventricular dysfunction.

Procainamide

Adverse (Toxic) Effects:

A. Cardiac:

1. Excessive action potential prolongation.
2. QT interval prolongation.
3. Induction of torsade de pointes arrhythmia and syncope.
4. Excessive slowing of conduction.
5. New arrhythmias.

Procainamide

B. **Extracardiac:**

1. **Lupus erythematosus – like syndrome: arthralgia, arthritis, pleuritis, pericarditis and parenchymal pulmonary disease, with rare renal impairment. Reversible.**

- **During long-term therapy, Increased ANA occur in almost all patients, but not all of them develop the syndrome (~ 1/3).**

2. **Nausea, diarrhea, rash, fever, hepatitis and agranulocytosis.**

Procainamide

Pharmacokinetics:

1. **Can be used orally, IV and IM**
2. **Metabolized by acetylation to NAPA (N-acetylprocainamide).**

- **NAPA has class III antiarrhythmic activity → torsades de pointes especially in patients with renal failure.**
- **Rapid vs Slow acetylators. Lupus syndrome is less common in rapid acetylators.**

3. **Partially eliminate by renal excretion.**
4. **t½ ~ 3-4 hours.**

Procainamide

3. **NAPA is eliminated by the kidneys, with longer half-life than procainamide.**
- **It is necessary to monitor the concentration of procainamide and NAPA especially in patients with circulatory or renal impairment.**

Procainamide

Therapeutic Uses:

1. **Effective against most atrial and ventricular arrhythmias, but long-term use should be avoided because of lupus syndrome.**
2. **Second or third choice after lidocaine and amiodarone for treatment of sustained ventricular arrhythmias associated with acute myocardial infarction.**

Disopyramide

Cardiac Effects:

- **The effects of disopyramide are very similar to those of procainamide.**
- **It has antimuscarinic effects. Therefore, a drug that slows AV conduction should be administered with disopyramide when treating atrial flutter or fibrillation.**
- **Indicated for the treatment of ventricular arrhythmias.**

Disopyramide

Toxicity:

1. **It has negative inotropic effect, and may precipitate heart failure, and thus, it is not used as a first-line antiarrhythmic agent. It should not be used in patients with heart failure.**
2. **Atropine-like effects: urinary retention especially in patients with prostatic hyperplasia), dry mouth, blurred vision, constipation, and worsening of preexisting glaucoma.**

Lidocaine

- **A local anesthetic, used only by the intravenous route.**

Cardiac Effects:

1. **Blocks sodium channels with rapid interaction kinetics.**
2. **It has greater effect on cells with long action potentials (Purkinje and ventricular cells), compared with atrial cells.**

Lidocaine

Toxic (Adverse) Effects:

A. **Cardiac:**

1. **Proarrhythmic effects, sinoatrial node arrest, worsening of impaired conduction and ventricular arrhythmias are uncommon.**
2. **Cardiac depression and hypotension at large doses in patients with heart failure.**

Lidocaine

B. Extracardiac:

- **Neurologic: paresthesias, tremors, nausea (central), lightheadedness, hearing disturbances, slurred speech and convulsions, especially in the elderly or with rapid bolus IV injection.**
- **Thes effects are dose-related and usually short-lived.**
- **Seizures respond to intravenous diazepam.**
- **Avoid plasma concentrations > 9 mcg/mL.**

Lidocaine

Pharmacokinetics:

- Extensive first-pass metabolism (BA ~ 3%), must be given parenterally.
- Determination of lidocaine plasma levels is of great value in adjusting the infusion rate.
- t½ ~ 1-2 hours.
- Some patients with MI or acute illness require higher infusion rates, because it is bound to α_1-acid glycoprotein (acute phase reactant) → making less free drug available to exert its pharmacologic effects.

Lidocaine

Therapeutic Uses:

1. **It is the drug of choice for termination of ventricular tachycardia and prevention of ventricular fibrillation after cardioversion in the setting of acute ischemia (MI).**
- **Routine *prophylactic use* in this setting may increase total mortality, by increasing the incidence of asystole.**
2. **Digitalis-induced arrhythmias.**

Flecainide

- **Is a potent blocker of Na^+ and K^+ channels with slow unblocking kinetics. Despite that, it does not prolong the action potential duration or QT interval.**
- **Very effective in suppressing premature ventricular contractions but may cause exacerbations → increases mortality (in patients with preexisting ventricular tachyarrhythmias, and previous myocardial infarction and ventricular ectopy).**

Flecainide

- **Eliminated by hepatic metabolism and renal excretion**
- **t½ ~ 20 hours.**
- **Used for supraventricular arrhythmias in patients with normal hearts.**

Propafenone

- Its Na^+ channel blocking activity is similar to flecainide, and it does not prolong the action potential.
- It has weak β-blocking activity.
- Metabolized in the liver, t½ ~ 5-7 hours .
- Most common adverse effects are metallic taste and constipation; and arrhythmia exacerbation.
- Used primarily for supraventricular arrhythmias.

β-Adrenoceptor Blockers

Propranolol & others.

Uses:

1. **Supraventricular arrhythmias: AF, A. Flutter, paroxysmal supraventricular tachycardia.**
2. **Suppression of ventricular ectopic depolarization's (less than that by Na^+ channel blockers**

β-Adrenoceptor Blockers

3. **Wolff – Parkinson - White syndrome in combination with Na^+ channel blocker:**

   a. Quinidine increases refractory period of the accessory pathway

   b. Propranolol increases that of the AV node

Esmolol is used for intraoperative or acute arrhythmias, because it is short acting.

Amiodarone

Cardiac Effects:

1. It markedly prolongs the action potential duration and the QT interval by blockade of I_{kr} .
2. During chronic administration, I_{Ks} is also blocked.
3. It also significantly block inactivated Na^{+} channels
4. It has weak adrenergic and Ca^{2+} channel blocking actions, → slowing of heart and AV node conduction.

Amiodarone

Extracardiac Effects:

- Peripheral vasodilation, which is more prominent after IV administration (may be related to the vehicle).

Toxic (adverse) Effects:

A. Cardiac:

- Symptomatic bradycardia and heart block in patients with preexisting sinus or AV node disease.

Amiodarone

B. Extracardiac:

1. Dose- related pulmonary toxicity is the most important adverse effect: fatal pulmonary fibrosis may be seen in 1% of patients.
2. Abnormal liver function tests and hypersensitivity hepatitis. Need to monitor liver functions.
3. Skin deposites result is photodermatitis and a gray-blue skin discoloration in sun-exposed areas (malar regions).

Amiodarone

4. Asymptomatic corneal microdensities in almost all patients.
5. Halos develop in the peripheral visual fields of some patients, that does not require stopping of the drug.
6. Rarely, an optic neuritis may progress to blindness.

Amiodarone

7. It blocks the peripheral conversion of T_4 into T_3. It is also a potential source of large amounts of organic iodine. Thus, it may result in hypo- or hyperthyroidism. Thyroid function should be evaluated before initiating treatment and should be monitored periodically.
8. Amiodarone treatment should be re-evaluated with new side effects symptoms and with arrhythmia aggravation.

Amiodarone

Pharmacokinetics:

1. Bioavailability ~ 35-65%, with variable absorption.
2. It undergoes hepatic metabolism (CYP3A4), and the major metabolite desethylamiodarone is bioactive.
3. It accumulates in many tissues including the heart (10-50X plasma), lung, liver, skin, and is concentrated in tears.
4. Elimination t½ is complex:

   Initial ~ 3-10 days, Terminal ~ several weeks.

Amiodarone

- **Following discontinuation of the drug, effects are maintained for 1-3 months, and measurable tissue levels may be observed after 1 year.**

Amiodarone

Drug Interactions:

- **Tremendous. All other medications should be reviewed when the drug is initiated and when the dose is adjusted.**

1. **Its levels are increased by inhibitors of CYP3A4 – cimetidine, …**
2. **Its levels are reduced by inducers of CYP3A4 – Rifampin, ..**

Amiodarone

3. **It inhibits many 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 one third to one half following initiation of amiodarone, and prothrombin times should be closely monitored.**

Amiodarone

Therapeutic Uses:

Broad spectrum antiarrhythmic agent.

1. **Low doses (100-200 mg) maintain sinus rhythm in patients with atrial fibrillation.**
2. **Prevention of recurrent ventricular tachycardia (200-400 mg).**

- **Low incidence of torsade de pointes despite significant QT interval prolongation.**

Dronedarone

- **Dronedarone is a structural analog of amiodarone but without iodine atoms. It contains a methanesulfonyl group instead.**
- **This eliminates the action of the parent drug on thyroxine metabolism.**
- **No thyroid dysfunction or pulmonary toxicity has been reported in short-term studies.**
- **Liver toxicity has been reported.**

Dronedarone

- Like amiodarone, dronedarone has multichannel actions, including blocking I_{Kr}, I_{Ks}, I_{Ca}, and I_{Na}.
- It also has β-adrenergic-blocking action.
- The half-life is ~ 24 hours.
- Absorption increases two-fold to three-fold when taken with food.
- Elimination is primarily non-renal.
- It is both a substrate and an inhibitor of CY3A4.
- It restores sinus rhythm in < 15% of patients with atrial fibrillation.

Dronedarone

- **Its use in AF is associated with increased risk of death, stroke, and heart failure.**
- **It increases mortality in acute decompensated or advanced (class IV) heart failure. The drug carries a “black box” warning.**

Sotalol

- **Sotalol has both β-adrenergic receptor-blocking (class 2) and action potential- prolonging (class 3) actions.**
- **It is well absorbed orally with bioavailability of nearly 100%.**
- **It is not metabolized in the liver and is not bound to plasma proteins.**
- **Excreted by the kidneys unchanged.**
- **Elimination half-life ~ 2 hours.**

Sotalol

- **Cardiac adverse effects are an extension of pharmacologic action:**

1. **Dose-related torsades de pointes in ~ 6% of patients at the highest recommended daily dose.**
2. **Patients with heart failure may experience further depression of left ventricular function.**

Sotalol

Therapeutic effects:

1. **Treatment of life-threatening ventricular arrhythmias.**
2. **Maintenance of sinus rhythm in patients with atrial fibrillation.**
3. **Supraventricular and ventricular arrhythmias in the pediatric age group.**
4. **It decreases the threshold for cardiac defibrillation.**

Ibutilide

- It slows cardiac repolarization by blockade of the rapid component (I_{Kr}) of the delayed rectifier potassium current, which leads to action potential prolongation.
- It is rapidly eliminated by hepatic metabolism.
- The elimination half-life ~ 6 hours.
- The metabolites are excreted by the kidney.

Ibutilide

- **Intravenous ibutilide is used for the acute conversion of atrial flutter and atrial fibrillation to normal sinus rhythm. The drug is more effective in atrial flutter than atrial fibrillation, with a mean time to termination of 20 minutes.**
- **The most important adverse effect is excessive QT-interval prolongation and torsades de pointes.**

Verapamil (& Diltiazem)

Cardiac Effects:

1. Block activated and inactivated L-type calcium channels.
2. Slow SA node rate.
3. Prolong conduction time and refractory period of the AV node.
4. Can suppress both early and delayed after depolarizations.

- Verapamil may antagonize slow responses arising in severely depolarized tissue.

Verapamil

Cardiac Toxicity:

Dose-related, usually avoidable.

1. **Hypotension and ventricular fibrillation if administered IV for patients with ventricular tachycardia misdiagnosed as supraventricular tachycardia.**
2. **Negative inotropic effect → heart failure in diseased heart.**
3. **AV block in patients with AV nodal disease . This effect may be treated with atropine or β-stimulants.**

Verapamil

4. **Sinus arrest in patients with sinus node disease.**

Therapeutic Uses:

1. **Supraventricular tachycardia.**
2. **To reduce ventricular rate in atrial fibrillation and flutter. It only rarely converts atrial flutter and fibrillation to sinus rhythm.**

Adenosine

It is an endogenous nucleoside.

Cardiac Effects:

1. **Activation of inward rectifier K^+ current.**
2. **Inhibition of Ca^{2+} current.**

   → marked hyperpolarization and suppression of calcium-dependant action potentials.
3. **When given as bolus doses, it inhibits AV nodal conduction and increases its refractory period, with a lesser effect on SA node.**

Adenosine

Therapeutic Use:

- **The drug of choice for prompt conversion of paroxysmal supraventricular tachycardia to sinus rhythm (effective in 90-95% of cases and has a short duration of action, t½ ~ 10 seconds). IV bolus.**
- **The effect is less in the presence of its receptor blockers – caffeine & theophylline.**
- **The effect is potentiated by adenosine uptake inhibitors such as dipyridamole.**

Adenosine

Toxic Effects:

1. **Flushing in 20% of patients**
2. **Shortness of breath and chest burning – bronchospasm – in 10% of patients**
3. **Short-lived high grade AV-block**
4. **Rarely AF.**
5. **Headache, hypotension, nausea & paresthesia.**

Ivabradine

- It is a selective blocker of I_f.
- It slows pacemaker activity by decreasing diastolic depolarization of sinus node cells.
- It reduces heart rate without affecting myocardial contractility, ventricular repolarization, or intracardiac conduction.
- At therapeutic doses, block of I_f is not complete, thus, autonomic control of the sinus node pacemaker rate is retained.

Ivabradine

- It has antianginal and anti-ischemic effects.
- It used as an effective alternative to β-blockers and calcium channel blockers to slow the heart rate in patients with inappropriate sinus tachycardia
- May produce visual disturbances due to block of the I_f channels in the retina (but the drug poorly cross the blood-brain-barrier).

Ranolazine

- It blocks the early I_{Na}, and late component of the Na^+ current I_{NaL}, ten-fold more so on the latter.
- It blocks the rapid component of the delayed rectifier K^+ current I_{Kr}.
- The blockade of both I_{NaL} and I_{Kr} results in opposing effects on the APD; the net effect depends on the relative contribution of each to the APD.

Ranolazine

- **It has antiarrhythmic properties in both atrial and ventricular arrhythmias.**
- **It prevents the induction of and may terminate atrial fibrillation.**
- **It is an antianginal agent.**

Magnesium (Sulfate)

- **The mechanism of antiarrhythmic effect is poorly understood.**
- **It influences Na^+/K^+- ATPase, sodium channels, certain potassium channels, and calcium channels.**
- **Used for patients with digitalis-induced arrhythmias who were hypomagnesemic.**

Magnesium

- **It is also effective in some patients with normal serum magnesium levels.**
- **It is also indicated in some patients with torsades de pointes even if serum magnesium is normal.**