Chapter 14

Agents used in Cardiac Arrhythmias
Cardiac arrhythmia

- Approximately 50% of post-myocardial infarction fatalities result from ventricular tachycardia (VT) or ventricular fibrillation (VF). These fatal arrhythmias arise from mechanical dysfunction and ischemic events interacting within a disordered electrophysiological situation.
Definition of arrhythmia

• Arrhythmias and disrhythmias are the same thing. Cardiac arrhythmia is an abnormality of the heart rhythm.
  
  – Bradycardia – heart rate slow (<60 beats/min)
  – Tachycardia – heart rate fast (>100 beats/min)
Categories of arrhythmias

Arrhythmias

↑ sinus bradycardia

↑ Bradycardia

↓ A-V block

↓ Tachycardia

atrial-, supraventricular -, ventricular~
Cardiac Electrophysiology

• To understand the action and classification of the antiarrhythmic drugs, it is first necessary to understand the ionic movements that underlie the cardiac membrane potential.

• The voltage change of the membrane potential is associated with the changes of ions across membrane, ie Na⁺, K⁺, and Ca²⁺
Membrane Potential of Cardiac Cell

There are two membrane potentials: resting potential and action potential.

- The resting potential maintains approximately -80 to -90 mV
- The action potential may be elevated to +10 to +20 mV
A typical AP of ventricular muscle cell can be divided into 5 phases

- **Phase 0**: rapid depolarisation
  - inflow of Na$^+$
- **Phase 1**: partial repolarization
  - inward Na$^+$ current deactivated, outflow of K$^+$
- **Phase 2**: plateau
  - slow inward calcium current
- **Phase 3**: rapid repolarisation
  - calcium current inactivates, K$^+$ outflow
- **Phase 4**: pacemaker potential/diastole
  - Na$^+$ outflow and K$^+$ inflow by Na-KATPase
  - Autorhythmic cell: Na$^+$ inflow to reach threshold potential
Fast and slow response

In view of characteristics of depolarization, cardiac action potentials are classified into slow and fast responses.

- The action potential of normal atrial, ventricular cell and His-Purkinje fibers is typical fast response.
- Action potentials of SA and AV notes exemplify slow response under normal condition.
Fast responses

- The fast response is characterized by a rapid phase 0 depolarization and a marked negative resting potential (-80 to -90 mV).
- The depolarization of fast response is due to the rapid and intense inward flow of Na\(^+\) through voltage gated Na\(^+\) channels.
Slow responses

- The slow response is characterized by a slow rising phase 0 and a less negative resting potential in the range of -40 to -70 mV.
- The phase 0 depolarization of slow response cardiac cell is elicited by the inward current of Ca$^{2+}$ through L-type calcium channel.
The heart has the physiological properties:

- Automaticity
- Conductivity
- Excitability
- Contractility

The former three are concerned with electrophysiology; the last with hemodynamics.
Automaticity

- It is the ability of a cardiac cell to reach threshold potential and generate impulses spontaneously.
- The changes of automaticity are associated with
  - resting membrane potential
  - threshold potential
  - steep slope of phase 4
Conductivity

- It is the ability of an action potential to spread to the cardiac cell.

- It is associated with
  - maximum velocity (Vmax) of depolarization of phase 0
  - resting membrane potential
Excitability

• Cardiac cell has the responsibility to an impulse resulting in depolarization.

• There are factors associated with excitability
  – a. APD (action potential duration) is a total time from Phase 0 to Phase 4
  – b. ERP (effective refractory period) is a period in APD in which no normal action potential can be elicited.
  – c. ARP (absolute refractory period) is a period in APD during which no local excitability can be elicited.
  – APD > ERP > ARP
How to treat arrhythmias

• Current antiarrhythmic drugs directly or indirectly affect Na, K and Ca fluxes across the membranes, thereby altering the automaticity, conductivity and excitability of cardiac cells.
  – Blockade of sodium channel
  – Blockade of calcium channel
  – Potassium channel
  – $\beta$ receptor blockade
Blockade of sodium channel

• Na\(^+\) inward current is responsible for the phase 0 depolarization of fast response cardiac cells including atrial, ventricular myocardial and His-Purkinje.

• Blockade of Na channel results in
  – Reduction of automaticity of fast response cells
  – Reduction of conduction velocity
  – Prolong the ERP and APD.

Little direct effect on SA and AV nodal cells.
Blockade of calcium channel

- L-type calcium channels are slowly activated and inactivated in slow response cardiac cells including SA, AV nodal cells.
- Blockade of Ca channel results in
  - Reduction of automaticity of SA and AV nodal cells
  - Reduction of conduction velocity
  - Prolong the ERP and APD.
Potassium channel

- K channels are involved in the inward K current during the repolarization, and the formation of resting potential.
- Blockade of K channel results in
  - Prolong the ERP and APD, prolong ERP absolutely
- Increase of K outflow results in
  - Increase conduction velocity by increase of the maximum resting potential
β receptor blockade

• Decrease the steep slope of phase 0
  – Reduction of automaticity
• Decrease the steep slope of phase 1
  – Reduction of conduction velocity
Classification of Antiarrhythmic Drugs

- The standard classification of antiarrhythmic drugs was developed by Singh and Vaughan Williams based upon the drug's electrophysiological mechanisms of action
- Singh-Vaughan Williams Classification
Vaughan Williams classification of antiarrhythmic drugs

- **Class I: sodium channels blockers**
  - Ia-moderate phase 0 depression: quinidine, procainamide
  - Ib- minimal phase 0 depression: lidocaine, phenytoin
  - Ic-marked phase 0 depression: flecainide, propafenone

- **Class II: β -adrenoceptor antagonists**
  - Propranolol, atenolol

- **Class III: prolong action potential and refractory period**
  - Amiodarone, sotalol

- **Class IV: Calcium channel antagonists**
  - Verapamil, diltiazem

- **Others: adenosine**
Ia – Quinidine

- An alkaloid isolated from the bark of the South American cinchona tree, is the d-isomer of quinine, an antimalarial drug.
- In 1918, Dr Walter Frey identified the antiarrhythmic effects of quinidine and thereafter, it was extensively used to treat arrhythmias, especially atrial fibrillation.
Ia – Quinidine

Mechanisms of action

• Membrane stabilizing effects:
  – Moderate Na, K, Ca blockade

• Anticholinergic activity
  – Increase sinus rate
  – Increase the conduction of AV node

• α receptor blockade
  – Decrease of BP
Quinidine – Effects on cardiac electrophysiology

- Depress the automaticity of fast response cells
  - decrease the slope of phase 4 depolarisation and shift the threshold voltage towards zero (due to blockade of fast Na$^+$ channels)

- Effects on conduction
  - Slow conduction of fast response cells by moderately depress phase 0 of the cardiac AP
  - Increase the conduction of AV node by anticholinergic activity

- Prolong APD and ERP
Quinidine – Clinical uses

• Used mainly to treat atrial flutter and atrial fibrillation
  – Pre-digitalized

• Supraventricular arrhythmias, life-threatening ventricular arrhythmias, but may increase the mortality when overdose
Quinidine may cause the enhanced AV node conduction due to its anticholinergic effects and result in an increase in ventricular rate. Therefore, it usually needs to be pre-digitalized because digoxin pretreatment slows AV conduction.
Adverse effects

Narrow safety margin

- **Cardiovascular effects**
  - Hypotension, even quinidine syncope: results from the alpha-receptor blockade.
  - Arrhythmias, even torsade de points
  - Conduction block, even heart failure

- **Cinchonism: gastrointestinal and central nervous system effects**
Cinchonism

- Cinchonism: It is described by the symptoms caused by toxicity of quinidine or quinine et al, the alkaloids extracted from cinchona, which include 3 major symptoms: gastrointestinal disturbance like vomiting, nausea, diarrhea; visual and aural disturbances as diplopia, photophobia, altered-color, hearing loss, tinnitus; and central nervous system effects like headache, confusion, psychosis.
Ia – procainamide

• Pharmacologically similar to quinidine
• No M, α receptor blockade effects
• Used to treat atrial and ventricular arrhythmias
• The acetylated metabolite of procainamide may cause lupus-like syndrome, which is unique among all antiarrhythmics.
Lidocaine

- Lidocaine is a local anesthetic agent and also is an antiarrhythmic drug.

- Pharmacological effects
  - Minimal blockade of sodium channel
  - Increase of K outflow

- Cite of action
  - His-Purkinje system
Lidocaine - Effects on electrophysiology

• Suppresses the automaticity of Purkinje’s fibers more than that of other cardiac tissue.

• Change the velocity of conduction
  – Decreases the conduction of Purkinje’s fibers in the area of ischemia or infarction
  – Increases K outflow when the plasma K con decreases, so that increases conduction velocity by increase of the maximum resting potential
Lidocaine - Clinical Uses

Narrow spectrum antiarrhythmics, mainly used for ventricular arrhythmias

• First used to prevent and treat the ventricular arrhythmias caused by acute myocardial ischemia.

• Effective against the ventricular arrhythmias caused by digitalis toxicity

• Rarely used in supraventricular arrhythmias.
Ib- Phenytoin

• An antiepileptic drug and also an antiarrhythmic drug.
• Pharmacological effects are similar to lidocaine.
• Superior against digitalis-induced arrhythmias to lidocaine.
• Side effects in CNS and cardiovascular system (see antiepileptic drugs).
Class IC -- Propafenone

• Action of mechanism
  – Marked blockade of Na channels
  – Weak β-adrenoceptor antagonist properties

• Effects on electrophysiology
  – Decrease of automaticity
  – Slow conduction of AV node and His-Purkinje system
  – Prolong APD and ERP
  – Negative inotropic effects
Class IC -- Propafenone

- Clinical uses: broad spectrum antiarrhythmics
  - used to treat atrial, ventricular and supraventricular arrhythmias.

- Adverse effects
  - Metallic or bitter taste in the mouth
  - Headache, nausea
Class II drugs

Examples of class II drugs include the Beta Blockers - the "olol" drugs.

- Propranolol
- Acebutalol
- Atenolol
- Esmolol

The prototype is propranolol
Propranolol

• Mechanism of action
  – $\beta$-receptor blocking action in low dose and direct membrane stabilizing effects in large dose.

• Effects on electrophysiology
  – Decrease automaticity
  – Slow the conduction velocity of AV node
  – Prolong APD and ERP in SA, and AV node
  Negative inotropic and chronotropic effects
Propranolol - clinical uses

• First line drug to treat sinus tachycardia and supraventricular arrhythmias due to sympathetic activation

• Mainly used in supraventricular arrhythmias and ventricular arrhythmias induced by enhanced catecholamines, e.g. stress, excitation, sport, anesthesia, hyperthyroidism, pheochromocytoma
Class III drugs - amiodarone

- **Mechanisms of action**
  - Potassium channel blockade
  - Sodium, calcium channel blockade
  - α, β adrenoceptor blockade

- **Pharmacological effects**
  - Prolong APD and ERP
  - Decrease the automaticity
  - Decrease conduction velocity
  - Dilation of coronary artery and hypotension
Amiodarone - Clinical Uses

A broad spectrum antiarrhythmic drug.

- Useful for both supraventricular and ventricular tachyarrhythmias.
Amiodarone – adverse effects

- **Cardiovascular adverse effects**
  - Sinus bradycardia
  - Pro-arrhythmic effects (torsade de pointe)
  - Heart block

- **Thyroid abnormalities**
  - Amiodarone contains 37% iodine, so it affects the triiodothyronine (T3) and thyroxine (T4) metabolism. If long-term use, the thyroid function may be disturbed.

- **Others:** Corneal microdeposits, photosensitive rashes pulmonary toxicity
  - Pulmonary alveolar fibrosis is the most serious and can be fatal.
Class III drugs - sotalol

- Sotalol is a racemate drug combining d- and l-isoforms.
  - d-isoform is a potassium channel blocker
  - l-isoform is non-selective β-adrenoceptor antagonist
- Approved for treatment of atrial fibrillation and atrial flutter
Class IV drugs - Verapamil

- Mechanism of action
  - Inhibit L-type calcium channel

- Site of action
  - SA and AV nodal cells

- Pharmacological effects
  - Reduction of automaticity → terminate DADs.
  - Reduction of conduction velocity
  - Prolong the ERP and APD
Class IV drugs - Verapamil

• Clinical Uses
  – First line to treat reentrant paroxysmal supraventricular tachycardia.
  – Also used in atrial fibrillation or flutter, only protecting ventricular rate, not converting to sinus rhythm.
  – Rarely used for ventricular arrhythmias.

• Adverse effects
  – Bradycardia, hypotension
  – CHF, A-V block
  – Constipation
Others: Adenosine

- Not in Vaughan Williams class
- Purine nucleotide
- Activate adenosine receptor → activate K channel and block Ca channel
- $T_{1/2} < 2$ seconds, Given IV (rapid bolus) only
- Treat reentrant paroxysmal supraventricular tachycardia
Summary

• Current antiarrhythmic drugs directly or indirectly affect Na, K and Ca fluxes across the membranes, thereby altering the automaticity, conductivity and excitability of cardiac cells.

• Anti-arrhythmic drugs are classified into 4 classes, but not all drugs fit this classification

• The therapeutic index of antiarrhythmic drugs is particularly narrow and the application of these agents must be aware of the indications, contraindications, toxicities and pharmacological properties of each drug.
The therapeutic rationale for the use of quinidine or procainamide includes their ability to:

• A. Depress ectopic automaticity
• B. Enhance myocardial membrane responsiveness
• C. Decrease the effective refractory period
• D. A and B
Choose the best choice

In a patient who has had attacks of paroxysmal supraventricular tachycardia, an ideal drug is:

• A. quinidine
• B. procainamide
• C. lidocaine
• D. nifedipine
• E. verapamil
Choose the best choice

Which of the following agent is prefer to suppress the ventricular arrhythmia caused by myocardial ischemia:

- A. propranolol
- B. procainamide
- C. quinidine
- D. lidocaine
- E. verapamil
Choose the best choice

Patients with genetically low levels of N-acetyltransferase are more prone to develop a lupus-like syndrome with which of the following antiarrhythmic drugs?

- A. propranolol
- B. procainamide
- C. quinidine
- D. lidocaine
- E. verapamil
A 68-year-old female has AF, which is treated with an antiarrhythmic agent that blocks Na\(^+\) channels. On a recent office visit, she complained of recurrent attacks of feeling faint and of experiencing an episode of loss of consciousness. An EKG showed marked prolongation of the QT interval. Which drug she has used?

- A. propranolol
- B. procainamide
- C. quinidine
- D. lidocaine
- E. verapamil
Choose the best choice

Which of the following drugs can change the characters of action potential as moderate phase 0 depression; slow conduction and prolonging repolarization.

• A. propranolol
• B. procainamidex
• C. quinidine
• D. lidocaine
• E. verapamil
Choose the best choice

Which of the following drugs can change the characters of action potential as: mainly affecting phase 3 and prolonging repolarization

• A. propranolol
• B. amiodarone
• C. quinidine
• D. lidocaine
• E. verapamil
Choose the best choice

The effect of different antiarrhythmic agents is best understood by knowing their predominant actions on cardiac fibers. All of the following general statements are true except:

- A. Quinidine slows the rate of depolarization of cardiac action potentials and increases the refractory period
- B. β-receptor blocking drugs act by reducing the slope of the pacemaker
- C. Procainamide acts as a specific calcium antagonist
- D. Amiodarone prolongs the action potential and so prolongs the absolute refractory period
Choose the best choice

Which of the following drug is particularly effective in suppressing ventricular arrhythmias associated with digitalis toxicity:

• A. Lidocaine
• B. Quinidine
• C. Procainamide
• D. Phenytoin
• E. Amiodarone
Choose the best choice

Antiarrhythmic drug: may cause hypothyrosis or hyperthyroidism; approved for use only in the treatments of serious ventricular arrhythmias; also use for refractory supraventricular arrhythmias:

- A. propranolol
- B. tocainide
- C. adenosine
- D. amiodarone
- E. quinidine
Choose the best choice

False statement concerning use of calcium antagonists as antiarrhythmic drugs:

• A. Slows inward calcium current thereby decreasing the rate of spontaneous phase 4 depolarization in AV and SA nodal cells
• B. Slows conduction velocity through the A-V node and increases functional refractory period
• C. Hypotension may be a limiting side effect
• D. Verapamil, diltiazem, and nifedipine all exert equally effective antiarrhythmic actions
Questions

• Describe the classification and represent drugs of antiarrhythmic agents?
• Describe the characteristic of the represent antiarrhythmic drugs of every class when treating arrhythmias?