Part 2
Antiarrhythmic Drugs
**Abnormal pacemaker, rhythm and AV coordination of heart beats.**

all arrhythmias result from

(1) disturbances in impulse formation,

(2) disturbances in impulse conduction,

(3) both.
A. Electrophysiological basis of arrhythmias

1. Normal cardiac electrophysiology

- **Excitability:** ability to produce action potentials
  - maximal diastolic potentials (MDP)
  - threshold levels
- **Automaticity:** pacemaker
  - phase 4 slope
- **Conductivity:** ability to conduct impulse
  - conduction pathways,
  - phase 0 amplitude
Fast response cell

Action potential and ion transport
Action potential and ion transport

Na\(^+\) current

Ca\(^{2+}\) current
- L-type
- T-type

Transient outward current
- \(I_{TO1}\)
  - (4-AP-sensitive)
- \(I_{TO2}\)
  - (Ca\(^{2+}\)-activated)

Delayed rectifiers (\(I_K\))
- \(I_{Ks}\)
- \(I_{Kr}\)
- \(I_{Kur}\)

Inward rectifier, \(I_{K1}\)

Pacemaker current, \(I_f\)
  - (..., see above)

Na\(^+\)-Ca\(^{2+}\) exchange

Na\(^+\), K\(^+\)-ATPase

Fast response cell
Action potential Duration (APD) and effective refractory period (ERP)
A. Electrophysiological basis of arrhythmias

2. Slow and fast response cells

- slow response cells: pacemaker cells
- fast response cells: conduction and contraction cells

<table>
<thead>
<tr>
<th></th>
<th>Fast response</th>
<th>Slow response</th>
</tr>
</thead>
<tbody>
<tr>
<td>phase 4 potential</td>
<td>− 90 mV</td>
<td>− 70 mV</td>
</tr>
<tr>
<td>depolarization</td>
<td>Na(^+), 120 mV, 1-2 ms</td>
<td>Ca(^{2+}), 70 mV, 7 ms</td>
</tr>
<tr>
<td>automaticity</td>
<td>low (0.02 V/s)</td>
<td>high (0.1 V/s)</td>
</tr>
<tr>
<td>conduction</td>
<td>fast (200-1000 V/s)</td>
<td>slow (10 V/s)</td>
</tr>
<tr>
<td>effects</td>
<td>conduction</td>
<td>pacemaker</td>
</tr>
</tbody>
</table>
Action potentials of slow and fast response cells

Slow response

Fast response
Slow response pacemakers in sinoatrial (SA) node and atrioventricular (AV) node
Impulse generation and conduction in the heart
A. Electrophysiological basis of arrhythmias

3. Abnormal generation of impulse

(1) Augmented automaticity

- Augmented automaticity in the myocardial cells other than the sinoatrial node cells will produce arrhythmias

- Maximal diastolic potential (MDP) in phase 4: ischemia, digitalis, sympathetic excitation, imbalance of electrolytes

- Fast spontaneous depolarization in phase 4: fast response cells → slow response cells
a. increased phase 4 slope

b. decreased MDP

c. decreased threshold levels

d. Slow response cells
- A. increased phase 4 slope
- B. decreased threshold levels
- C. decreased MDP levels in phase 4

*fast response cells*
(2) Afterdepolarization and triggered activity

- **early afterdepolarization (EAD, 早后除极):**
  - phases 2, 3;
  - $\text{Ca}^{2+}$ inward flow increases
  - induced by drugs, plasma $\text{K}^+$ ↓

- **delayed afterdepolarization (DAD, 迟后除极):**
  - phase 4;
  - $\text{Ca}^{2+}$ inward flow leads to transient $\text{Na}^+$ inward flow
  - induced by digitalis intoxication, plasma $\text{Ca}^{2+}$↑, $\text{K}^+$ ↓
A. early afterdepolarization (EAD)
B. delayed afterdepolarization (DAD)
实验性早期后除极，A 图中左侧为发生在平台期的早期后除极，右侧为发生在复极3 相时的早期后除极；B 图为在第一个早期后除极后出现的一连串的异常兴奋。

实验性迟发后除极，注意开始时只为阈值下除极，当迟发后除极振幅逐渐增大达到阈值时，便引起了激动，并产生一连串的触发活动。
4. Abnormal conduction of impulse

(1) Simple conduction block

- slow and small depolarization in phase 0, reduced MDP level in phase 4
  - MDP ↓ in ischemia, inflammation, metabolic disorders;
  - Usually occurred in atrioventricular regions
A. Electrophysiological basis of arrhythmias

- **(2) Reentrant reexcitation (reentry, 折返)**
- **Circuits** (环路) (especially in enlarged ventricles)
- (Wolff-Parkinson-White syndrome)
- **Unidirectional (one-way) block** (单向阻滞)
- (myocardial injury)
- **Slow conduction** (传导减慢)
- **Heterogeneity in ERP** (ERP不均一)
Reentrant reexcitation (reentry)
Reentry formation
Abnormal conduction pathway of Wolff-Parkinson-White syndrome
B. Electrophysiological effects and classification of antiarrhythmic drugs

- 1. Electrophysiological effects of antiarrhythmic drugs
  - (1) Reducing abnormal automaticity
    - decreasing phase 4 slope
    - increasing threshold levels
    - increasing MDP levels in phase 4
    - increasing action potential duration (APD)
- **A.** decreasing phase 4 slope
- **B.** increasing threshold levels
- **C.** increasing MDP levels in phase 4
- **D.** increasing action potential duration (APD)

*fast response cells*
b. decreasing phase 4 slope

A

100 毫秒

B

Slow response cells

c. increasing threshold levels; d. increasing MDP
B. Electrophysiological effects and classification of antiarrhythmic drugs

- **class IV drugs** decrease automaticity of slow response cells
- **class I drugs** decrease automaticity of fast response cells
- **class II drugs** decrease the augmented automaticity caused by sympathetic excitation
B. Electrophysiological effects and classification of antiarrhythmic drugs

- (2) inhibiting afterdepolarization and triggered activity
  - **EAD**: repolarization ↑ (class IB), inward current ↓ (class I, IV)
  - **DAD**: class IV, I
  - **Sympathetic excitation or digitalis**: class II
B. Electrophysiological effects and classification of antiarrhythmic drugs

- (3) Modulating conduction
- Accelerating conduction
- Abolishing reentry
  - one-way block $\rightarrow$ two-way block
  - abolishing one-way block
浦肯野纤维末梢正常冲动传导，单向阻滞、折返及药物对单向阻滞的影响

A

浦肯野纤维A支

B

normal

C

one-way block

reentry

D

two-way block

abolishing block
B. Electrophysiological effects and classification of antiarrhythmic drugs

- (4) Modulating effective refractory period (ERP)
  - prolonged ERP
  - prolonged ERP/APD
  - homogeneity of ERP
Reducing membrane responsiveness

Increasing APD and ERP

25% of Na$^+$ channels recovered from inactivation

- no drug
- drug
## 2. Classification of antiarrhythmic drugs

<table>
<thead>
<tr>
<th>Classification of Drug</th>
<th>Mechanism of Action</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>IA</td>
<td>Na(^+) channel blocker</td>
<td>Slows Phase 0 depolarization</td>
</tr>
<tr>
<td>IB</td>
<td>Na(^+) channel blocker</td>
<td>Shortens Phase 3 repolarization</td>
</tr>
<tr>
<td>IC</td>
<td>Na(^+) channel blocker</td>
<td>Markedly slows Phase 0 depolarization</td>
</tr>
<tr>
<td>II</td>
<td>(\beta) Adrenoreceptor blocker</td>
<td>Suppresses Phase 4 depolarization</td>
</tr>
<tr>
<td>III</td>
<td>K(^+) channel blocker</td>
<td>Prolongs Phase 3 repolarization</td>
</tr>
<tr>
<td>IV</td>
<td>Ca(^{++}) channel blocker</td>
<td>Shortens action potential</td>
</tr>
</tbody>
</table>

Prolongation of action potential duration (APD)
(1) Class I

(Na\(^+\) channel blockers)

Class IA (moderate Na\(^+\) channel blockers):
- moderately block Na\(^+\) channels,
- conduction ↓,
- APD and ERP ↑

- quinidine
- procainamide
- **Class IB (mild Na\(^+\) channel blockers):**
  - mildly block Na\(^+\) channels,
  - not markedly inhibit conduction,
  - K\(^+\) outward flow ↑,
  - shorten repolarization

- **lidocaine** 利多卡因
- **phenytoin** 苯妥英
- **Class IC** *(decided Na\(^+\) channel blockers)*:
  - markedly block Na\(^+\) channels,
  - depolarization velocity in phase 0 ↓
  - conduction ↓
  - no marked effect on repolarization

- **propafenone** 普罗帕酮
- **flecainide** 氟卡尼
B. Electrophysiological effects and classification of antiarrhythmic drugs

- (2) Class II
  - β adrenoceptor blockers
  - propranolol 普萘洛尔
(3) Class III
Prologation of APD
($K^+$ channel blocker; prolongation of repolarization)

- amiodarone 胺碘酮,
- sotalol 索他洛尔
Group IV drugs slow phase 4 spontaneous depolarization and slow conduction in tissues dependent on calcium currents, such as AV node.

(4) Class IV
Ca\(^{2+}\) channel blockers

verapamil 维拉帕米

Verapamil, diltiazem and nifedipine block open or inactivated calcium channels.
### B. Electrophysiological effects and classification of antiarrhythmic drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Action Sites</th>
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<tbody>
<tr>
<td>Class I (Na(^+) channel blockers)</td>
<td>SV, V*</td>
</tr>
<tr>
<td>IA</td>
<td>SV, V*</td>
</tr>
<tr>
<td>IB</td>
<td>V</td>
</tr>
<tr>
<td>IC</td>
<td>SV, V*</td>
</tr>
<tr>
<td>Class II (β receptor blockers)</td>
<td>SV*, V</td>
</tr>
<tr>
<td>Class III (prolongation of APD)</td>
<td>SV, V</td>
</tr>
<tr>
<td>Class IV (Ca(^{2+}) channel blockers)</td>
<td>SV*, V</td>
</tr>
</tbody>
</table>

* primary action sites
C. Antiarrhythmic drugs

- **Class I drugs: Na\(^+\) channel blockers**
- Class IA drugs

**Quinidine**

![Chemical structure of Quinidine](image)
C. Antiarrhythmic drugs

1. Pharmacological effects

- Na$^+$ channel block
- muscarinic / $\alpha$ receptor block

(1) Automaticity:
- depolarization slope in phase 4 $\downarrow$
- abnormal automaticity $\downarrow$

(2) Conduction $\downarrow$: direct action, one-way $\rightarrow$ two-way block
- atrioventricular conduction $\uparrow$ because of M receptor block

(3) ERP and APD: ERP $\uparrow$, APD $\uparrow$, ERP/APD $\uparrow$

(4) Other effects: hypotension: $\alpha$ receptor block
C. Antiarrhythmic drugs

2. Clinical uses

(1) Atrial fibrillation and flutter, pre- and post-cardioversion
- conversion to sinus rhythm (pretreated with digitalis)
- maintaining sinus rhythm

(2) Other arrhythmias
- ventricular and supraventricular arrhythmias
C. Antiarrhythmic drugs

3. Adverse effects

- (1) Extracardiac effects: GI reactions (diarrhoea, etc)
- hypotension,
- Chichonism,
- allergy

- (2) Cardiac toxicity: prolonged QRS and QT intervals,
- paradoxical ventricular tachycardia,
- quinidine syncope

- (3) Arterial embolism: after cardioversion
4. **Drug interactions**

- **(1) Hepatic enzyme inducers** (barbiturates, phenytoin, *etc.*): increase the metabolism of quinidine

- **(2) Hepatic enzyme inhibitors** (cimitidine, verapamil, *etc.*): decrease the metabolism of quinidine

- **(3) Other drugs**
  - nitroglycerine: postural hypotension
  - digoxin: reducing the dose of digoxin
Agents that stimulate metabolism of quinidine
Phenytoin
Rifampin
Barbiturates

Quinidine $\rightarrow$ Inactive metabolite

Quinidine $\rightarrow$ Metabolite

Agent that inhibits metabolism of quinidine
Cimetidine
**C. Antiarrhythmic drugs**

**Procainamide**

\[
\text{H}_2\text{N} - \text{C} - \text{NHCH}_2\text{CH}_2\text{N(C}_2\text{H}_5)_2
\]

Effects and uses are similar to quinidine, but weak to atrial fibrillation and flutter.

Induces GI reactions, hypotesion, allergy, occasionally **systemic erythematous lupus** (long-term use).
C. Antiarrhythmic drugs

- Class IB drugs

Lidocaine  利多卡因
C. Antiarrhythmic drugs

1. **ADME**

- Low bioavailability after oral administration
- Rapid elimination after *i.v.* injection
- Given by *i.v.* infusion (*i.v. gtt*)
C. Antiarrhythmic drugs

2. Pharmacological effects

(1) Automaticity: reducing spontaneous depolarization in phase 4 of Purkinje fibers

(2) Conduction:
- therapeutic dose: no remarkable effects
- larger doses, $K^+$ ↑, pH ↓: decrease
- $MDP \downarrow, K^+ \downarrow$: increase

(3) APD and ERP:
- $Na^+$ inward flow ↓ in phase 2
- $K^+$ outward flow ↑ in phase 3
- $ERP \downarrow, APD \downarrow, ERP/APD \uparrow$
C. Antiarrhythmic drugs

3. Clinical uses

- Ventricular arrhythmias:
  - acute myocardial infarction
  - intoxication of digitalis and other drugs

- Local anesthesia
C. Antiarrhythmic drugs

- 4. Adverse effects
  - (1) CNS depression
  - (2) Hypotension
  - (3) Arrhythmias: bradycardia, A-V block
C. Antiarrhythmic drugs

Phenytoin Sodium

苯妥英钠

Effects and uses are similar to lidocaine; an antiepileptic drug.

More effective on digitalis toxicity because of competition to Na⁺-K⁺-ATPase.
C. Antiarrhythmic drugs

- Class IC drugs

**Propafenone**

\[
\text{OCH}_2\text{CHCH}_2\text{NHCH}_2\text{CH}_2\text{CH}_3
\]

普罗帕酮
C. Antiarrhythmic drugs

1. **Pharmacological effects**
   - Reducing automaticity and conduction of fast response cells in atrium and *Purkinje* fibers

2. **Clinical uses**
   - Supraventricular and ventricular arrhythmias

3. **Adverse effects**
   - GI reactions, postural hypotension, arrhythmias
C. Antiarrhythmic drugs

**Flecainide**

\[
\text{CF}_3\text{CH}_2\text{O} \quad \text{OCH}_2\text{CF}_3
\]

\[
\text{HN} \quad \text{CH}_2 \quad \text{N}
\]

\[
\text{C} \quad \text{C} \quad \text{C}
\]
C. Antiarrhythmic drugs

1. Pharmacological effects
   - Similar to propafenone

2. Clinical uses
   - Supraventricular and ventricular arrhythmias, as a second choice

3. Adverse effects
   - CNS, arrhythmias, etc.
C. Antiarrhythmic drugs

- **Class II drugs:** \( \beta \) adrenoceptor blockers

**Propranolol** 普萘洛尔
C. Antiarrhythmic drugs

1. Pharmacological effects
   - Reducing sinus, atrial, ventricular automaticity
   - Reducing A-V and Purkinje fiber conduction
   - Prolonging A-V node ERP

2. Clinical uses
   - Supraventricular arrhythmias
   - Ventricular arrhythmias caused by exercise, emotion, ischemic heart diseases, anesthetics, digitalis, etc.

3. Adverse effects
   - Conduction block, bradycardia, contractility ↓, and many other reactions
C. Antiarrhythmic drugs

- **Class III drugs: Prolongation of APD**
  
  
  *(K⁺ channel blockers; prolongation of repolarization)*
C. Antiarrhythmic drugs

1. Pharmacological effects

(1) Cardiac electrophysiological effects
- $K^+, Na^+, Ca^{2+}$ channel block
- Prolonging repolarization: APD $\uparrow$, ERP $\uparrow$
- Reducing sinus and Purkinje fiber automaticity, and A-V and Purkinje fiber conduction

(2) Vasodilatation
- Reducing peripheral resistance
- Reducing cardiac oxygen consumption
- Increasing coronary blood flow
C. Antiarrhythmic drugs

2. Clinical uses

- Supraventricular and ventricular arrhythmias

- Longer action duration \((t_{1/2}: 25 \pm 12 \text{ days})\),
  effects maintained for 4 – 6 weeks after withdrawal
C. Antiarrhythmic drugs

3. Adverse effects

(1) Arrhythmias
- Bradycardia, A-V block, prolonged Q-T intervals

(2) Iodine reactions
- Iodine allergy, hypo- and hyperthyroidism, iodine accumulation in cornea and skin

(3) Others
- Hypotension, tremor, interstitial pulmonary fibrosis, etc.
C. Antiarrhythmic drugs

*Sotalol* 索他洛尔

\[
\text{CH}_3\text{SO}_2\text{NH} - \text{C} - \text{CHCH}_2\text{NHCH(CH}_3\text{)}_2\text{OH}
\]
C. Antiarrhythmic drugs

Selectively blocks delayed rectifier K$^+$ currents

No-selective β receptor antagonist

Prolonging repolarization: APD ↑, ERP ↑

No remarkable effects on conduction

Used for supraventricular and ventricular arrhythmias, arrhythmias in acute myocardial infarction

Prolonged Q-T, dysfunction of sinus, cardiac failure
C. Antiarrhythmic drugs

Class IV drugs: $\text{Ca}^{2+}$ channel blockers

Verapamil

维拉帕米
C. Antiarrhythmic drugs

1. Pharmacological effects

(1) Antiarrhythmic effects:
- Reducing spontaneous depolarization in phase 4 and depolarization rate in phase 0 of slow response cells
- Reducing automaticity and conduction of sinus and atrial tissues
- Effective on abnormal pacemaker cells from fast response to slow response in cardiac injury (such as ischemia)

(2) Other effects: depressing cardiac contraction, vasodilatation
C. Antiarrhythmic drugs

2. Clinical uses

- **Supraventricular**: tachycardia, atrial arrhythmias
- **Ventricular**: myocardial ischemia, digitalis toxicity

3. Adverse effects

- Depressing cardiac electrophysiological function and contractility, hypotension, *etc.*
- Combined with class II drugs and quinidine:
  - potentiating cardiac depression
C. Antiarrhythmic drugs

- **Other antiarrhythmic drugs**
  - **Adenosine** 腺苷
    - Activating adenosine receptors and ACh-sensitive K$^+$ channels, prolonging ERP of A-V node, decreasing conduction and automaticity
    - Rapid elimination, $t_{1/2}$ 10 ~ 20 seconds, *i.v.* injection
    - Used for acute supraventricular tachycardia
    - Cardiac and respiration depression (*i.v.* injection)
**Drug choice**

- **Sinus tachycardia:** β blockers; verapamil
- **Atrial premature contraction:** β blockers; verapamil; class I drugs
- **Atrial flutter or fibrillation:**
  - **Cardioversion:** quinidine (+ digitalis)
- **Ventricular rate control:** β blockers, verapamil, digitalis
- **Paroxysmal supraventricular tachycardia:** verapamil;
  - digitalis, β blockers, adenosine, etc.
- **Ventricular premature contraction:** procainamide,
  - lidocaine, phenytoin, etc.
- **Ventricular fibrillation:** lidocaine, procainamide,
  - amiodarone, etc.
D. Proarrhythmic effects of antiarrhythmic drugs

- *All antiarrhythmic drugs have the proarrhythmic effects*
- 表现为：原有的心律失常加重
- 出现新的心律失常
- 严重者有：尖端扭转型室性心动过速
- 室颤
- 心脏停搏
- 对策：谨慎用药
- 控制病因
- 合理选择和应用
- 用药的个体化
D. Proarrhythmoc effects of antiarrhythmic drugs

- **Other drugs**
  - digitalis
  - ions (iv): $\text{Ca}^{2+}$, $\text{K}^{+}$
  - antimicrobials: amantadine, SMZ, TMP,
  - chloroquine, erythromycin
  - neuroleptics: haloperidol
  - antidepressants: imipramine, amitryline
  - antihistamines: terfenadine, cimitidine