Antiarrhythmic Drugs
Part I

Arrhythmias are abnormalities of cardiac rhythm.
Their effect on heart function is variable.

- benign
- symptomatic
- life threatening

- Know the currently available antiarrhythmic drugs.
- Know the arrhythmia terminology.
- Understand the mechanisms by which arrhythmias can arise.

- Drug names and classification schemes.
- Arrhythmia terminology.
- Mechanisms of arrhythmia:
  - ectopic pacemakers, triggered activity
  - block, re-entry ... abnormal impulse conduction
Arrhythmias
Dysfunctions in current flow that cause abnormalities in impulse formation and conductance in the myocardium

1. Heart beats too slow (Sinus Bradycardia)
2. Heart beats too fast (Sinus or Ventricular Tachycardia, Atrial Flutter, Atrial or Ventricular Premature Depolarization)
3. Heart responds to impulses not originating from SA node
4. Heart responds to impulses traveling along accessory pathways that cause deviant depolarizations (A-V reentry, Wolff-Parkinson White syndrome)
Arrhythmias: Terms and Terminology

- **Sinus rhythm**: generated by SA node
- **Bradycardia**: heart rate <60 beats per minute
- **Tachycardia**: heart rate >100 beats per minute
- **Ventricular Tachycardia**: arising in ventricles, life threatening
- **Monomorphic**: “one shape”
- **Polymorphic**: “many shapes”, V tachycardia+ torsades de pointes
- **Supraventricular**: above the ventricles (i.e. in atria)
- **Atrial flutter**: rapid, regular beating of atria
- **Fibrillation**: very rapid, irregular beating
- **Atrial fibrillation**
- **Ventricular fibrillation**
- **Block**: failure of conduction
Mechanisms of Arrhythmia

- abnormal impulse initiation (ectopic pacemaker)
- abnormal impulse conduction
- simultaneous operation of both abnormalities (initiation and conduction)
- abnormal automaticity (ectopic pacemaker, spontaneous AP generation, arises somewhere else)
- triggered activity (caused by afterdepolarizations, normal AP)
- abnormal automaticity (ectopic pacemaker, Purkinje fibers have intrinsic pacemaker activity)
  - dysfunction of SA node, escape rhythm
  - depolarized resting potential
  - appearance of pacemaker current
- triggered activity (caused by afterdepolarizations,)
  - early afterdepolarizations (EADs)
  - delayed afterdepolarizations (DADs)
Pharmacology of Antiarrhythmic Drugs

- Cardiac Action Potential
- Mechanisms of Tachycardias
- Antiarrhythmic effects of Action Potential
- Antiarrhythmic effects on arrhythmias
- Classification of antiarrhythmic drugs
- Proarrhythmic effects

Dan M Roden  
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ELECTROPHYSIOLOGY: Antiarrhythmic drugs: from mechanisms to clinical practice
Cardiac Action Potential

**Depolarization phase**
- phase 0
- rapid sodium channels open allowing positively charged ions into the cells
- voltage dependent, opening when transmembrane potential reaches threshold
- speed of depolarization determines conduction velocity (slope phase 0)

**Repolarization phase**
- phase 1-3
- outward flow of positive ions (K) returns action potential to negative baseline state
- rapid phase 1 is interrupted by plateau phase (2) mediated by slow Ca channels
- influx positive ions prolongs action potential

**Resting phase**
- leakage of ions across cell membrane results in gradual in transmembrane potential
- cell depolarizes after threshold is reached

- SA and AV nodes lack rapid Na⁺ channels
- depend on slow Ca²⁺ channels
- speed of depolarization (phase 0), determines conduction velocity, impulses conducted slowly
Mechanisms of Tachycardias: Automaticity

Automaticity

- Occur in atria, AV junction or ventricles
- Account for less than 10% of tachycardias
- Warm-up and warm-down periods
- Metabolic cause: ischemia, hypoxemia, hypokalemia, hypomagnesemia, acid/base disorders, high sympathetic tone
Mechanisms of Tachycardias: **Triggered Activity**

**Triggered Activity**
- Originating from afterpolarizations
- Early afterpolarizations occur during phase 2 or 3
- Delayed afterpolarizations occur during phase 4
- Can engage rapid Na⁺ channel and initiate Action Potential
Mechanisms of Tachycardias: EAD

Early Afterdepolarizations

• When outward currents are inhibited or inward currents are enhanced
• Under circumstances that prolong duration of action potential
  Hypokalemia, hypomagnesia, antiarrhythmic drugs
• Proposed mechanism for Torsades de Pointes

Factors increasing EAD
• Autonomic increased sympathetic tone
  Increased catecholamines
  Decreased parasympathetic
• Metabolic
  Hypoxia
  Acidosis
• Electrolytes
  Cesium
  Hypokalemia

Heart Rate
  Brachycardia

Drugs
  Solatol
  N-acetylprocainamide
  Quinidine
Mechanisms of Tachycardias: DAD

Delayed Afterdepolarizations
Accumulation of calcium and activation of non-specific cation channel

Factors increasing DAD
- Tachycardia
- Cardiac glycosides
- Hypokalemia
- Hyperkalemia
- Catecholamines
- Stress
- Exercise
Mechanisms of Tachycardias: Reentry

- Most clinically significant tachyarrhythmias
- Two parallel conducting pathways connected proximally by conducting tissue
- Prolonged refractory in one pathway
- Slowed conduction in the other pathway
- Initiating event (premature contraction)
- Most ventricular arrhythmias are reentrant in mechanism
- Conditions for increased automaticity are temporary, substrate for reentrant arrhythmias tend to be permanent
- Fibrosis
- Tachycardia zone (time from end of refractory period of shorter-refractory period of longer-refractory period)
- Treating reentry involves narrowing or abolishing the tachycardia zone

Re-entry circuit stimulation can cause
- tachycardia (anatomical disorder, refractory period) and
- fibrillation (functional disorder)
Mechanisms of Tachycardias: Reentry
Wolff-Parkinson-White syndrome, premature beat

- premature beat occurs - accessory pathway may still be refractory from the proceeding of AP
- retrodirection - reentry - AV-tachycardia
Antiarrhythmics: Effect on Action Potential

- Alter ion channel in cardiac cell membrane
- Change shape of cation potential
- Fibrosis
- Affect 3 electrophysiological properties of cardiac tissue
  Conduction Velocity
  Effective Refractory Period
  Automaticity
AfterDepolarizations

**Early afterdepolarizations (EADs)**
Occur before completion of phase 3
Re-activation of Ca\(^{2+}\) channels when action potential is prolonged
Can cause torsades de pointes (polymorphic V-tah)

**Delayed afterdepolarizations (DADs)**
Occur after completion of phase 3
Spontaneous release of Ca\(^{2+}\) from SR activates inward Na\(^{+}\)-Ca\(^{2+}\) exchange current
Antiarrhythmics: Effect on Cardiac Arrhythmias

- Automatic arrhythmias
  metabolic abnormalities with changes in phase 4
- Antiarrhythmic drugs ineffective (Ca\(^2+\) channel and be blockers can be effective)
- Triggered activity
- Antiarrhythmic drugs cause of EAD
- Antiarrhythmic drugs directly affect the mechanism responsible for re-entrant tachycardias
- Functioning reentrant circuit requires
  one pathway with slowed conduction
  one pathway with prolonged refractory period
- Antiarrhythmic drugs alter properties of the re-entrant circuit
Antiarrhythmic Drugs currently in use
Vaughan Williams classification

Class I: Na\(^+\) channel blockers (slow conduction velocity)
  \(I_a\): intermediate unblocking rate
    Prolong action potential, blocks \(I_{K1}\)
    procainamide, quinidine, disopyramide
  \(I_b\): fast unblocking rate
    Shorten action potential
    lidocaine, mexiletine, tocainide
  \(I_c\): slow unblocking rate
    Little effect on action potential duration
    moricizine, flecainide, propafenone

Class II: \(\beta\) adrenergic receptor blockers (blunt sympathetic effects)
  propranolol, sotabola

Class III: K\(^+\) channel blockers (increase refractory periods, prolong AP, delayed Na\(^+\) channel inactivation)
  bretylium, amiodarone, dofetilide, ibutilide, sotalol

Class IV: Ca\(^{2+}\) channel blockers (affect primarily SA and AV nodes)
  verapamil, diltiazem

Class V: Cl\(^-\) channel blockers
Antiarrhythmic Drugs currently in use
Vaughan Williams unclassified

Phenytoin  Na\(^+\) channel blocker, fast unblocking rate (Ib?)
Digitalis  Vagal (parasympathetic) stimulation
Adenosine  Endogenous substance. G\(_{i}\)-coupled receptor.
Magnesium  Blocks Ca\(^{2+}\) channels

Other classifications of antiarrhythmic drugs
  e.g. “Sicilian Gambit”
### Antiarrhythmic Drugs: Clinical Generalization

<table>
<thead>
<tr>
<th>Vaughan-Williams Class</th>
<th>Location of Activity</th>
<th>General Level of Efficacy</th>
<th>End-Organ Toxicity</th>
<th>Potential for Proarrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class IA</td>
<td>A, V</td>
<td>2+</td>
<td>3+</td>
<td>2+</td>
</tr>
<tr>
<td>Class IB</td>
<td>V</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>Class IC</td>
<td>A, V</td>
<td>3+</td>
<td>1+</td>
<td>3+</td>
</tr>
<tr>
<td>Class II</td>
<td>AVN, V</td>
<td>1+</td>
<td>1+</td>
<td>0</td>
</tr>
<tr>
<td>Class III</td>
<td>A, V</td>
<td>2+</td>
<td>1+</td>
<td>2+</td>
</tr>
<tr>
<td></td>
<td>(amio 4+)</td>
<td>(amio 4+)</td>
<td>(amio 1+)</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>AVN</td>
<td>1+</td>
<td>1+</td>
<td>0</td>
</tr>
</tbody>
</table>

A = atrium; amio = amiodarone; AVN = atrioventricular node; V = ventricle.
Antiarrhythmic Drug Actions: Slowing down Automaticity

**Beta blockers:** alinidine
Reduce $I_f$ current

**Na$^+$ channel blockers** (fast response tissues)
Ca$^{2+}$ channel blockers (slow response tissues)

**K$^+$ channel blockers**

**adenosine**
activates $I_{K_{ACl}}$ in atria and SA node
Action by muscarinic or adenosine receptors
$G_{ai}$ or $G_{bh}$ activates $I_{K_{Ch}}$
Antiarrhythmic Drug Actions: Preventing early ADP

Shorten AP duration
Artificial pacemaker
Pacing at higher rate (shortens AP)
isoproterenol

Preventing EADs triggered beats
Mg\(^{2+}\) (Ca\(^{2+}\) channel block?)
Beta blockers – reduce Ca\(^{2+}\) activity
Antiarrhythmic Drug Actions: Preventing delayed ADP

Verapamil reduces intracellular Ca\textsuperscript{2+} loading

Preventing triggered beats arising from DADs
Na\textsuperscript{+} channel blockers
Antiarrhythmic Drug Actions: Prolongation of Refractoriness

Prolonging refractoriness (fast response tissues)
re-entry e.g. fibrillation
**Na⁺ channel** blockers

Prolonging refractoriness in fast response tissues
re-entry e.g. fibrillation
**K⁺ channel** block or delayed Na⁺ channel inactivation
**Cl⁻ channel block**
Antiarrhythmic Drugs: **Class I** kinetics

- Do not bind tonically, constantly binding and unbinding from Na⁺ channel
- Blockade occurs only when bound to Na⁺ channel at time it is open
- Bind to already open channel
- Must bind, stay bound until channel reopens
- Effect of drug dependant on rate at which binds and unbinds from Na⁺ channel
- the slower the binding kinetics, the greater the effect on conduction velocity
- **Class IB**: rapid binding kinetics
- **Class IC**: slow binding kinetics
Antiarrhythmic Drugs: kinetics

Class IA
• Intermediate binding kinetics
• moderately slow conduction
• intermediate K blocking
• moderately prolonged action potential

Class IB
• Rapid binding kinetics
• minimally slow conduction
• No K blocking
• shorted action potential

Class IC
• Slow binding kinetics
• markedly slow conduction
• minimal K blocking
• minimally prolonged action potential

Class III
• no Na blocking
• no effect on conduction velocity
• marked K blocking
• prolonged action potential
Arrhythmogenic Actions: \textbf{Na}^+ channel blockers

\begin{itemize}
  \item Na$^+$ channel block
  \begin{itemize}
    \item Slowed conduction
      \begin{itemize}
        \item Promotes re-entry
          \begin{itemize}
            \item Ventricular tachycardia
          \end{itemize}
        \item Decreases atrial flutter rate
          \begin{itemize}
            \item Paradoxical increase in ventricular rate
          \end{itemize}
      \end{itemize}
  \end{itemize}
\end{itemize}

especially drugs with slow unblocking rate: \textbf{flecainide, propafenone} (class Ic)
Arrhythmogenic Actions

Beta blockers
Verapamil
Diltiazem

Digitalis (vagotonic effect)

Sinus bradycardia
AV block

- Digitalis
  - inhibition of Na⁺-K⁺ ATPase
  - Ca²⁺ loading in SR and mitochondria
  - spontaneous Ca²⁺ release into cytoplasm
  - activation of Na⁺-Ca²⁺ exchanger
  - Inward current
  - DAD

Triggered activity
  - tachycardia
Class Ia drugs (intermediate unblocking rate)

**Quinidine**
used for atrial flutter, fibrillation -> sinus rhythm; prevention of ventricular tachycardia, fibrillation

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**Na\(^+\) channel block**
- Increased threshold
- Decreased automaticity

**K\(^+\) channel block**
- Slows conduction
- Delayed recovery from inactivation
- Increased Refractory period

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**Alpha-adrenergic blocker**
- Vasodilation
- Hypotension

**vagolytic**
- AV node conduction
- AV node refractoriness

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2-8% of patients

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EADs
Torsades de pointes

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Faster ventricular rate in atrial flutter

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Sinus tachycardia
**Class Ia drugs (intermediate unblocking rate)**

**procainamide**
used for acute treatment of most tachyarrhythmias. Chronic treatment has problems with side-effects (e.g. lupus).

**disopyramide**
used for atrial flutter, fibrillation -> sinus rhythm; prevention of ventricular tachycardia, fibrillation
Anticholinergic side-effects, negative inotropy (reduced contractility)

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**Na$^+$ channel block**
- ↓ threshold
- ↓ automaticity
- ↑ threshold
- Delayed recovery from inactivation
- ↓ conduction
- Prolonged action potential
- EADs
- Torsades de pointes

**K$^+$ channel block**
- ↑ Refractory period
- Prolonged action potential
Class Ib drugs (fast unblocking rate)

**lidocaine**
Used for acute intravenous therapy of ventricular arrhythmias (not effective for atrial arrhythmias)

**mexiletine**
Uses and electrophysiology similar to lidocaine. Chronic oral use.

**tocainide**
Uses and electrophysiology similar to lidocaine. Chronic oral use.
Serious side-effects: bone marrow aplasia; pulmonary fibrosis

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**Na⁺ channel block**
(eespecially inactivated state)

- ↑ threshold
- ↓ Phase 4 slope
- ↓ automaticity

- ↑ $I_{K1}$
- ↓ Repolarizes & depolarized Purkinje fibers
- ↓ Increased conduction velocity
- ↓ Suppress re-entry
Class Ic drugs (slow unblocking rate)

**moricizine**
Chronic treatment of ventricular arrhythmias (not post-MI)

- Na$^+$ channel block
  - slow unblocking rate
    - Slows conduction at normal heart rates
      - Promotes re-entry
        - Increased mortality in post-myocardial infarction patients
Class Ic drugs (slow unblocking rate)

**flecainide**
Atrial fibrillation, flutter -> sinus rhythm
Prolongs action potential in atrium at fast rates, Suppresses re-entry
Not used in post-MI patients because of increased mortality

**Slow Na\(^+\) channel unblocking rate promotes re-entry**

- Block of late-opening Na\(^+\) channels in phase 2
- Shortens action potential in Purkinje cells
- Promotes re-entry?
  - disparity

- blocks \(I_{Kr}\)
- Lengthens action potential in ventricle
Class Ic drugs: (slow unblocking rate)

**propafenone**

Atrial fibrillation -> sinus rhythm
S-(+)-enantiomer: beta-blocker (some patients), Slows AV and conduction, Sinus bradycardia

![Diagram of propafenone effects](image)

- **Na⁺ channel block**
  - slow unblocking rate
  - Slows conduction at normal heart rates
  - Promotes re-entry
  - Can increase re-entrant ventricular tachycardia

- **Blocks I_{to}, I_{Kr}**
  - Prolongs action potential
  - Suppresses re-entry
Control ventricular response to atrial fibrillation or flutter

Reduce heart rate

\( I_{Ca,L} \) decreases AV conduction and AV refractoriness

\( Ca^{2+} \) overload suppresses DADs, reducing triggered activity

Suppress AV re-entry & Control ventricular response to atrial fibrillation or flutter

Class II drugs (beta-blockers)

propranolol, esmolol (sotalol)
Class III drugs: $K^+$ blockers (action potential prolongation)

**sotalol**
- Used for ventricular tachyarrhythmias, atrial fibrillation, flutter

- Blocks $I_{Kr}$
- Prolongs action potential
  - Prolongs refractory period
  - Suppresses re-entry
  - EADs
    - Can cause torsades de pointes
Class III drugs: \(K^+\) blockers (action potential prolongation)

**amiodarone**
Ventricular tachycardia, fibrillation, Atrial fibrillation -> sinus rhythm
Serious side-effect with chronic use: pulmonary fibrosis

**bretylium**
Used for ventricular fibrillation
Blocks \(K^+\) channels and suppress re-entry
Blocks norepinephrine re-uptake which causes transient hypertension and leads to hypotension

Electrical coupling

Conduction velocity

Blocks \(Na^+\) channels

Blocks \(I_{Ca}\)

AV conduction

Blocks \(I_{Ks}, I_{to}, I_{K1}\)

Prolongs action potential

Torsades de pointes is rare
Class III drugs: $K^+$ blockers (action potential prolongation)

**Dofetilide**
Atrial fibrillation $\rightarrow$ sinus rhythm

- Selective $I_{Kr}$ blocker
- 1-3% of patients
- Suppress re-entry
- Torsades de pointes
- No other side-effects

**Ibutilide**
Atrial fibrillation or flutter $\rightarrow$ sinus rhythm

- Delays $Na^+$ channel inactivation
- Blocks $I_{Kr}$
- Prolongs action potential
- 6% of patients
- Suppress re-entry
- Torsades de pointes
**Class IV drugs: Ca$^{2+}$ blockers**

**verapamil, diltiazem**  
Used for: AV re-entrant arrhythmias  
Controlling ventricular response to atrial fibrillation or flutter

**verapamil**  
Decreases Ca$^{2+}$ overload, which suppress DADs

- **Threshold in SA node**  
- **AV conduction**  
- **Heart rate**  
  (Opposed by baroreflex)  
- **AV refractoriness**
**Digitalis glycosides**
Used for: AV re-entrant arrhythmias
Controlling ventricular response to atrial fibrillation or flutter
Alternative to Ca\(^{2+}\) channel blockers or beta-blockers in heart failure

**Phenytoin**
Used for suppression of ventricular arrhythmias
Na\(^{+}\) channel blocker

Other Antiarrhythmics

- Inhibit Na\(^{+}\)-K\(^{+}\) ATPase
- \(\text{Ca}^{2+}\) loading in SR and mitochondria
- DADs
Adenosine
Used for: AV re-entrant arrhythmias
DAD-induced ventricular tachycardia

Activation of $G_i$
$I_{K,ACh}$
$I_f$
$cAMP$
$I_{Ca,L}$
Heart rate
AV conduction
AV refractoriness
Ca$^{2+}$ loading
DADs

Magnesium
Used for: prevention of torsades de pointes
Possibly by suppression of EADs by blocking Ca$^{2+}$ channels

Other Antiarrythmics
Non-pharmaceutical Antiarrhythmic Interventions

DC cardioversion: ‘paddles’
Implanted cardioverter/defibrillator
Ablation of accessory pathway
ectopic pacemaker
anatomically defined site of re-entry
Antiarrhythmics: summary

• **Class I (Na\(^+\) blockers)** drugs suppress tachyarrhythmias but can promote re-entry.

• **Class II (beta blockers)** and **Class IV (Ca\(^{2+}\) blockers)** drugs suppress AV nodal re-entrant arrhythmias, ventricular response to atrial tachyarrhythmias and DAD-induced triggered activity, but can cause bradycardia and AV block.

• **Class III (K\(^+\) blockers)** drugs suppress re-entry, but most can cause torsades de pointes.

• **Digitalis glycosides** can cause DAD-induced triggered activity.

• **Adenosine** suppresses AV nodal re-entrant arrhythmias and DAD-induced triggered activity.

• **Mg\(^{2+}\)** suppresses torsades de pointes.