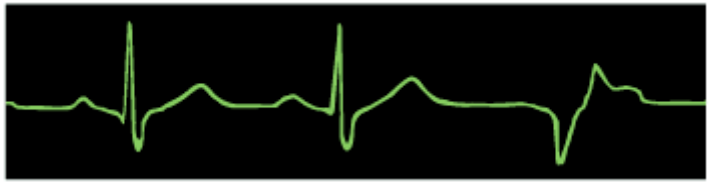
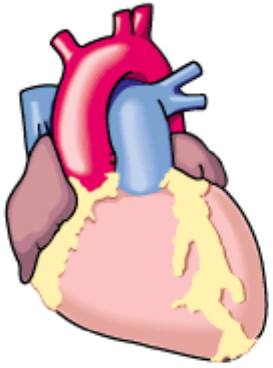
Antiarrhythmic Drugs

Or

Doing Drugs for Your Heartbeat





Background

- Recall: to function efficiently, heart needs to contract sequentially (atria, then ventricles) and in synchronicity
- Relaxation must occur between contractions (not true for other types of muscle [exhibit tetany → contract and hold contraction for certain length of time])
- Coordination of heartbeat is a result of a complex, coordinated sequence of changes in membrane potentials and electrical discharges in various heart tissues

Arrhythmia

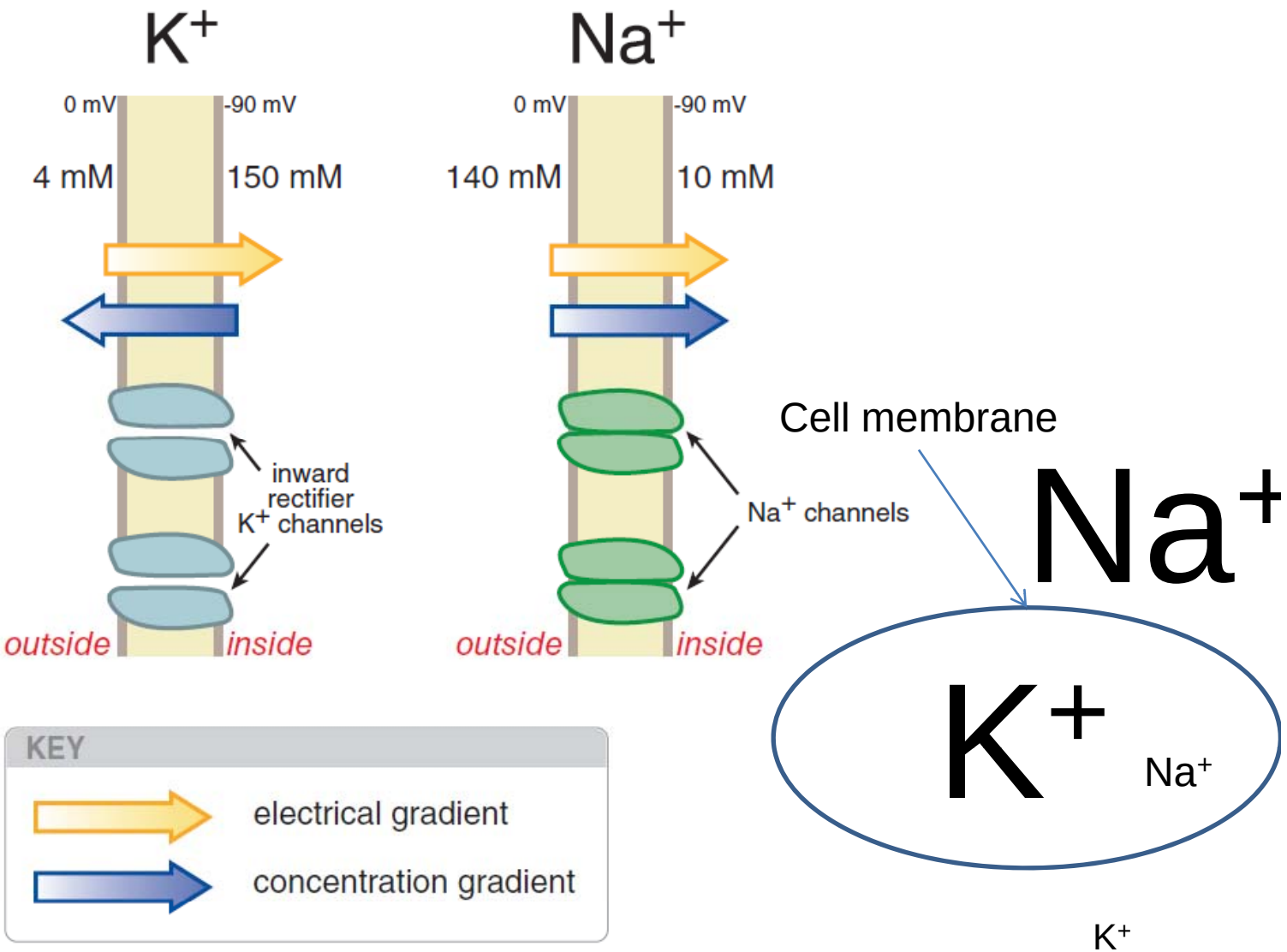
Heart condition where disturbances in

- Pacemaker impulse formation
- Contraction impulse conduction
- Combination of the two

An arrhythmia is by definition a perturbation of the normal sequence of impulse initiation and propagation.

Results in rate and/or timing of contraction of heart muscle that is insufficient to maintain normal cardiac output (CO)

To understand how antiarrhythmic drugs work, need to understand electrophysiology of normal contraction of heart



Electrical and chemical gradients for K^+ and for Na^+ in a resting cardiac cell. Inward rectifier K^+ channels are open (left), allowing K^+ ions to move across the membrane and the transmembrane potential to approach *E*K. In contrast, Na^+ does not enter the cell despite a large net driving force because Na^+ channel proteins are in the closed conformation (right) in resting cells.

Resting membrane potential

Nernst equation

$$E_x = -(RT/FZx)\ \ln([x]_i/[x]_o)$$

Zx: valence of the ion
T: absolute temperature
R: gas constant
F: is Faraday's constant
$[x]_o$: extracellular concentration of the ion
$[x]_i$: the intracellular concentration

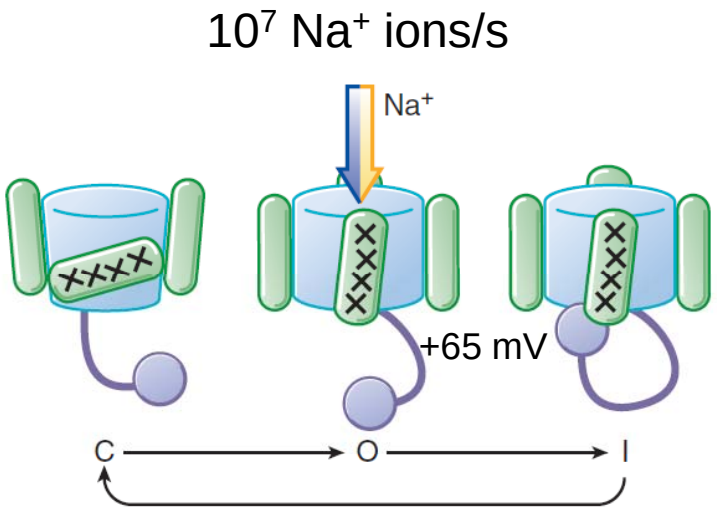
Calculation:
$[K]_o$ = 4 mM
$[K]_i$ = 150 mM

The calculated K+ equilibrium potential *E*K is –96 mV.
(Close to the resting potential.)

If:
$[K]_o$ = 10 mM (renal failure, cardiac ischemia can induce)
$[K]_i$ = 150 mM

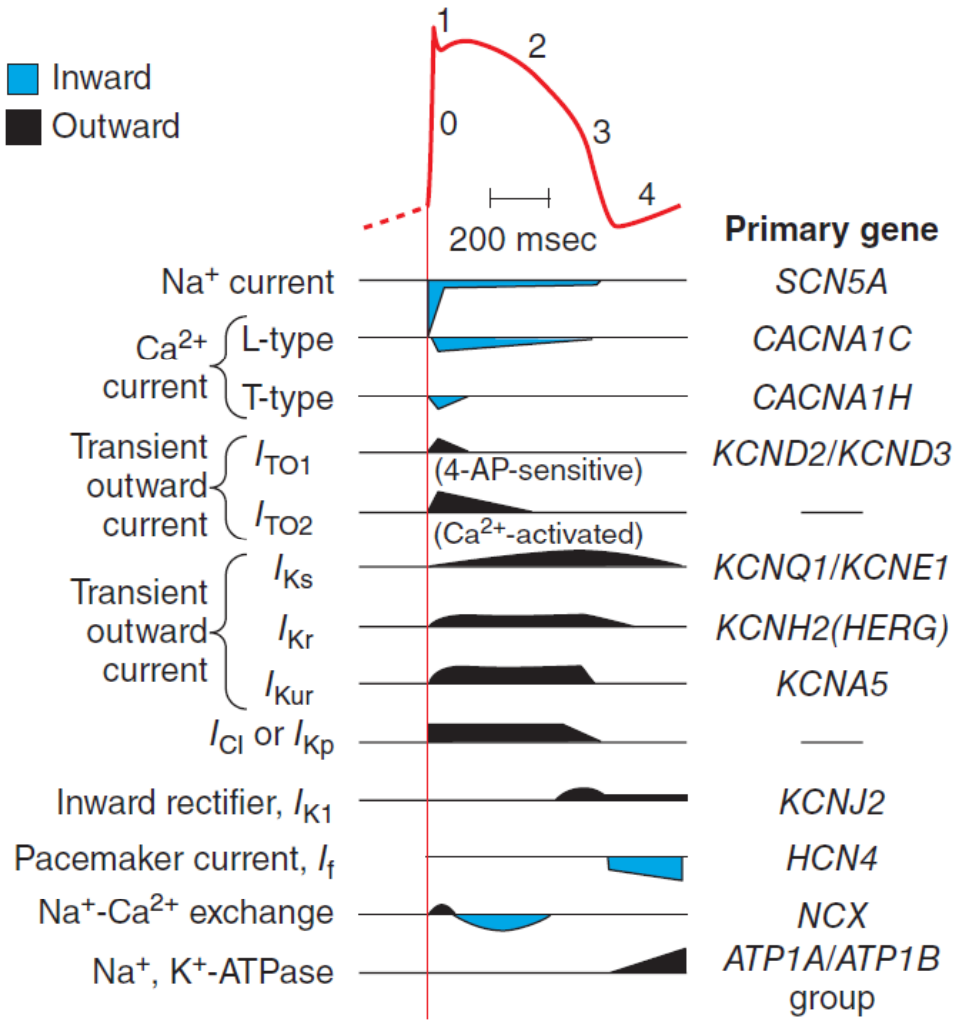
The calculated K+ equilibrium potential *E*K is –70 mV.

Role of voltage-dependent sodium channels



From neighboring myocytes through gap junctions depolarization is coming, reaches the threshold potential, opens the sodium channels

Voltage-dependent conformational changes determine current flow through Na+ channels. At hyperpolarized potentials, the channel is in a closed conformation, and no current can flow (left). As depolarization begins, the voltage sensor (indicated here as ++++) moves, thus altering channel conformation and opening the pore, allowing conduction (middle). As depolarization is maintained, an intracellular particle blocks current flow, making the channel non-conducting in this inactivated state (right).



I_{kr} inhibition prolongs AP and causes arrhythmia! In drug development it should be avoided.

Entering Ca^{2+} induces CICR

hERG (the **h**uman ***Ether-à-go-go-*** **R**elated **G**ene) now KCNH2 codes protein $K_V11.1$

Restoration of ion balance (electrogenic): Na^+/K^+ ATPase (3 Na^+ out while 2 K^+ in)

- Multiple types of Ca^{2+} current, transient outward current I_{TO}, and delayed rectifier I_K have been identified. Each represents a different channel protein, usually associated with ancillary (function-modifying) subunits. 4-AP is a widely used in vitro blocker of K+ channels. I_{TO2} may be a Cl^- current in some species. Components of I_K have been separated on the basis of how rapidly they activate: slowly (I_{Ks}), rapidly (I_{Kr}), or ultrarapidly (I_{Kur}). The voltage-activated, time-independent current may be carried by Cl^- (I_{Cl}) or K_+ (I_{Kp}, *p* for plateau).

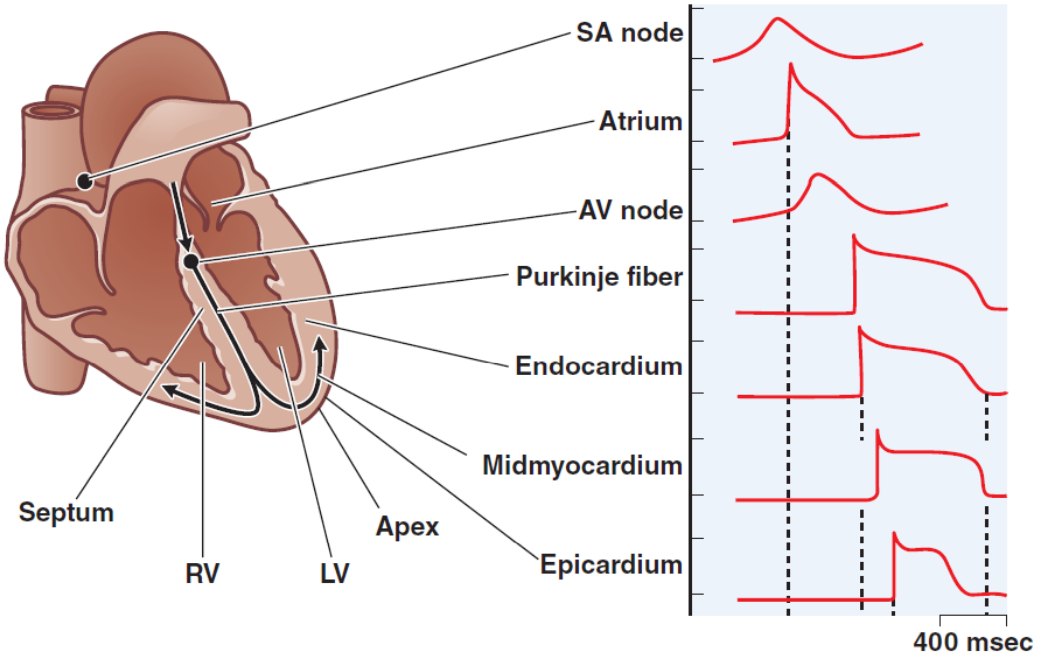
Genetic arrhythmia diseases

- Long QT Syndrome (LQTS)
  - mutations in the cardiac Na^+ channel gene SCN5A, prolonging AP and QT interval
  - *This late Na^+ current block is performed by certain antiarrhythmics (mexiletine, flecainide) and ranolazine (new type antianginal drug)*
- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)
  - mutations in the RyR2 gene encoding an intracellular Ca^{2+} release channel → DAD-dependent arrhythmia (flecainide, propafenone can mimic this)

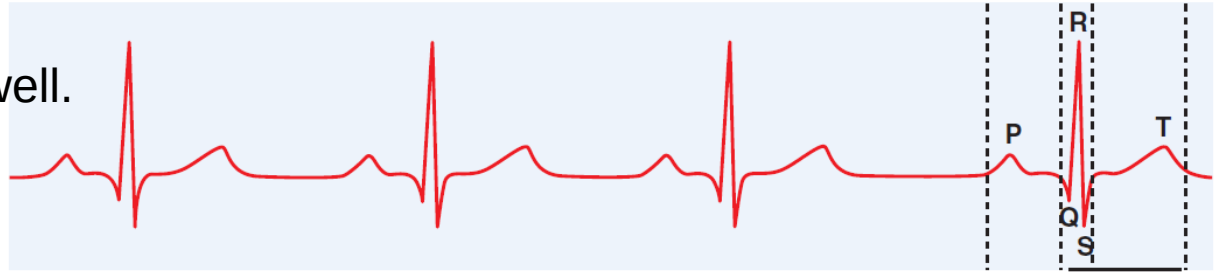
Action Potential Heterogeneity

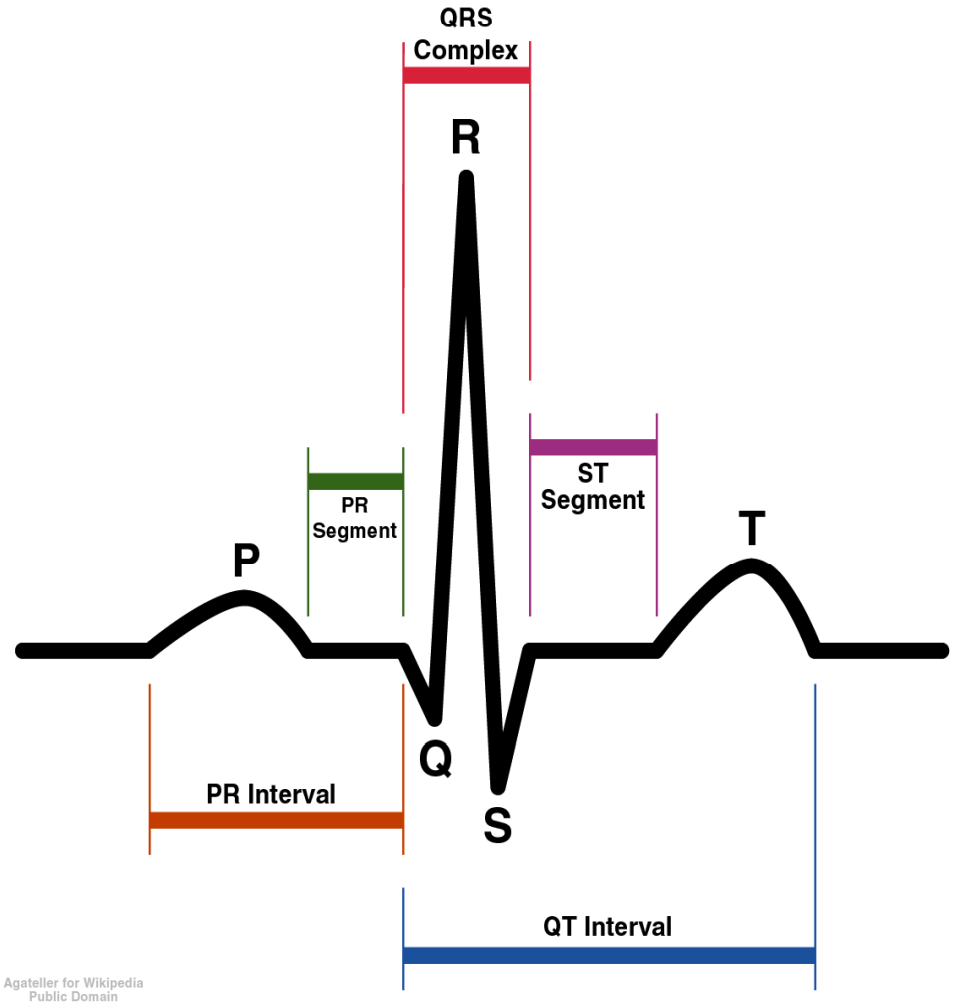
Channel content is varying

- Chambers to chambers
- Apicobasal direction
- T-type Ca^{2+} channels (mibefradil)
- Cl^- channels
- K_{ATP} channels



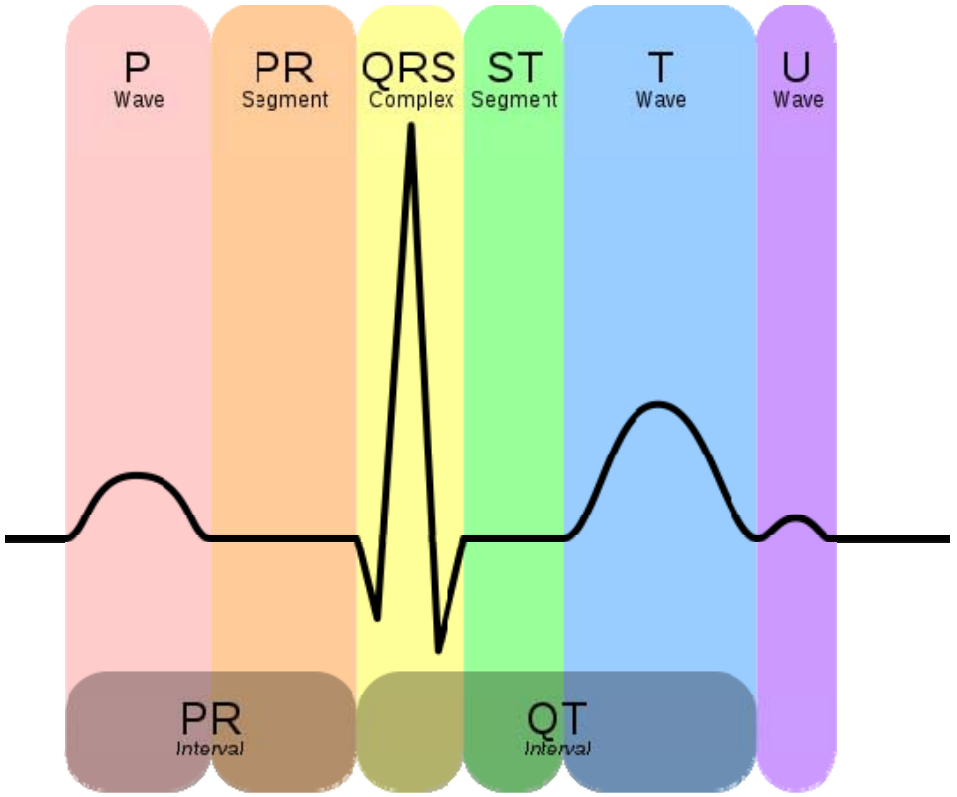
Problem can be the beat-to-beat variation as well.





Agateller for Wikipedia
Public Domain

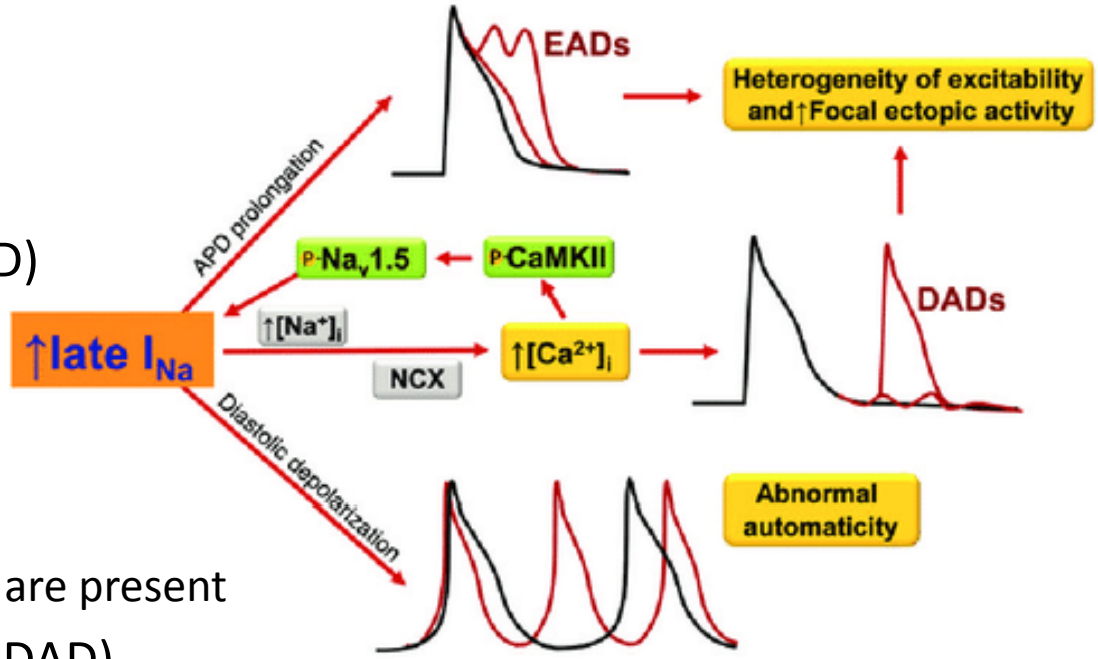
60-100 ms

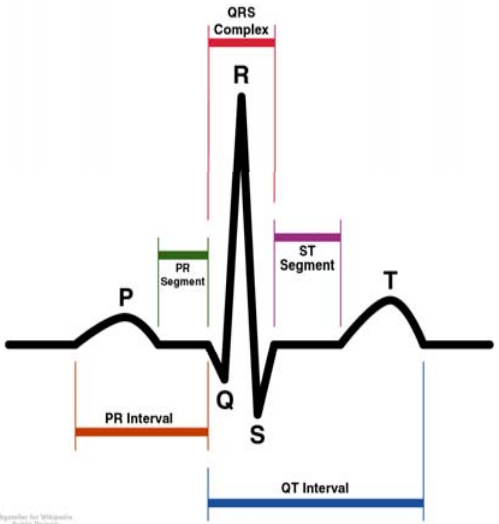


120-200 ms

Basic arrhythmia formation mechanisms

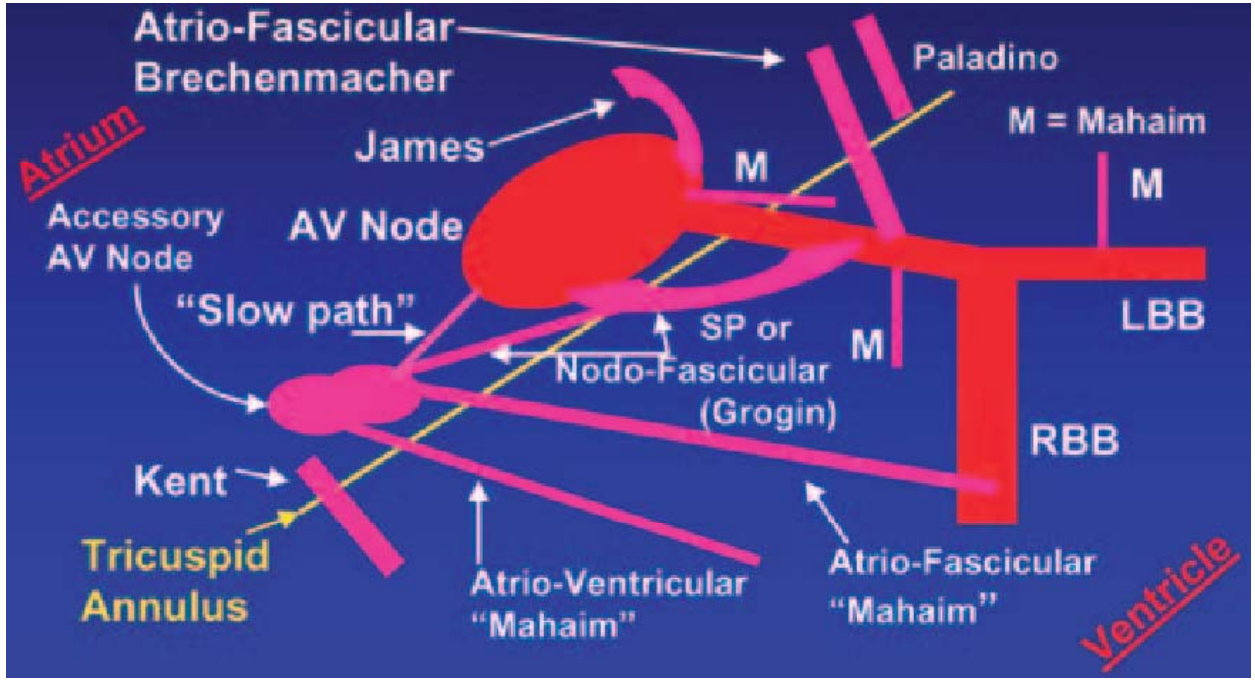
- Faulty impulse initiations
  - Triggered automaticities
    - Early afterdepolarizations (EAD)
      - underlying heart rate is slow
      - extracellular K^+ is low
      - certain drugs that prolong action potential duration (antiarrhythmics and others) are present
    - Delayed afterdepolarizations (DAD)
      - Myocardial ischemia
      - Adrenergic stress
      - Digitalis intoxication
      - CPVT
- Faulty impulse conduction
  - Accessory bundles
  - Re-entry mechanism





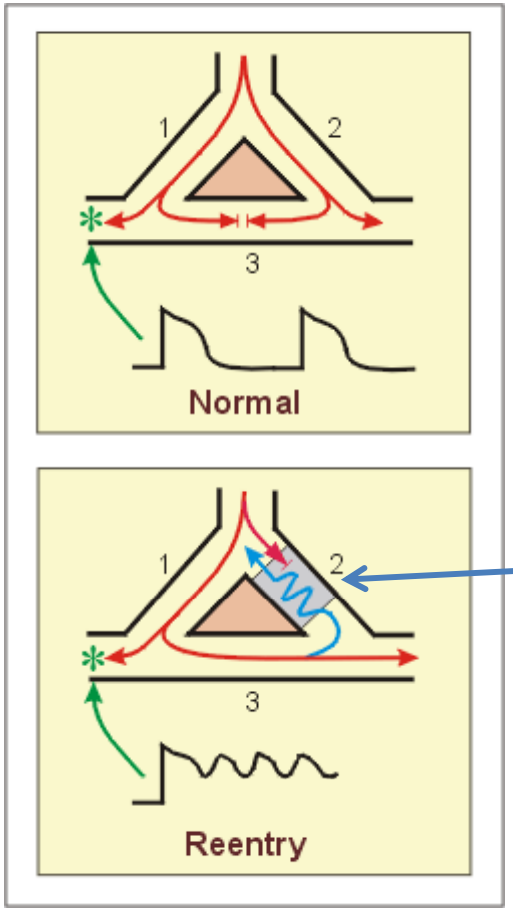
Accessory bundles

- Kent-Paladino bundle (Albert Kent, Giovanni Paladino („muscle fibers” around AV valves 1876))
- James
- Mahaim
- Grogin



Anatomical basis of WPW (Wolf-Parkinson-White) Syndrome

Re-entry mechanism



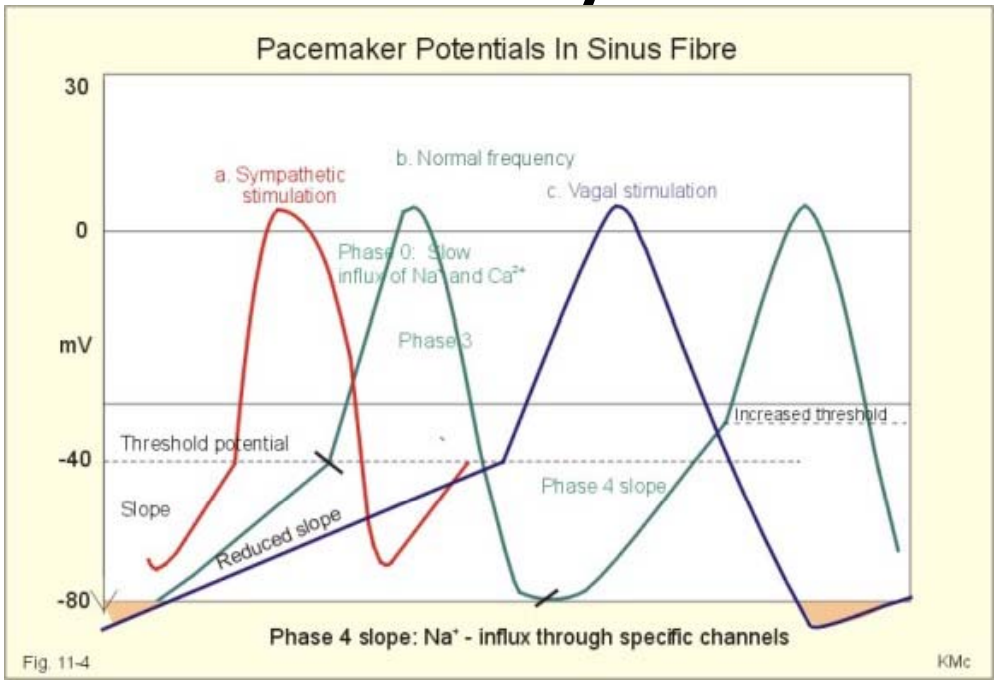
Condition of existance:
Unidirectional block

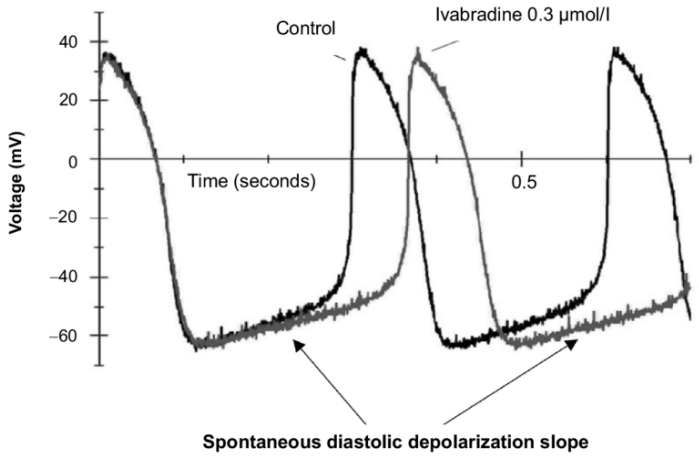
Treatment: 1. To restore the normal conduction.
2. To make it bidirectional.

Ca^{2+} channel blockers, β-blockers, adenosine can be effective

Enhanced automaticity

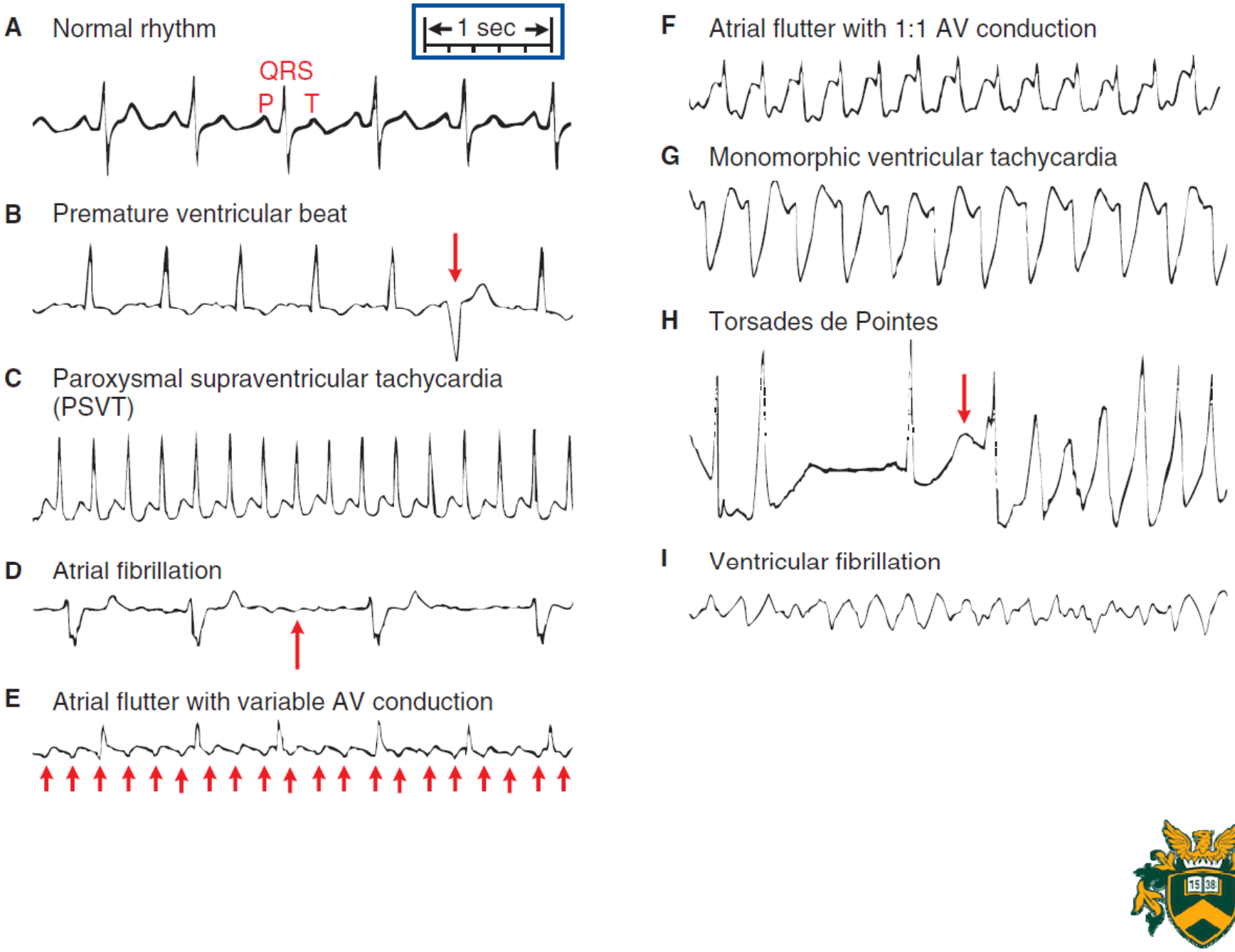
- Pacemaker cells defect
  - SA node
  - AV node
  - His-Purkinje system
- SDD slope (phase 4) increased (HR↑) by
  - β-adrenergic stimulation
  - Hypokalemia
  - Mechanical stretch
- SDD slope decreased by
  - Ach (vagal influence)



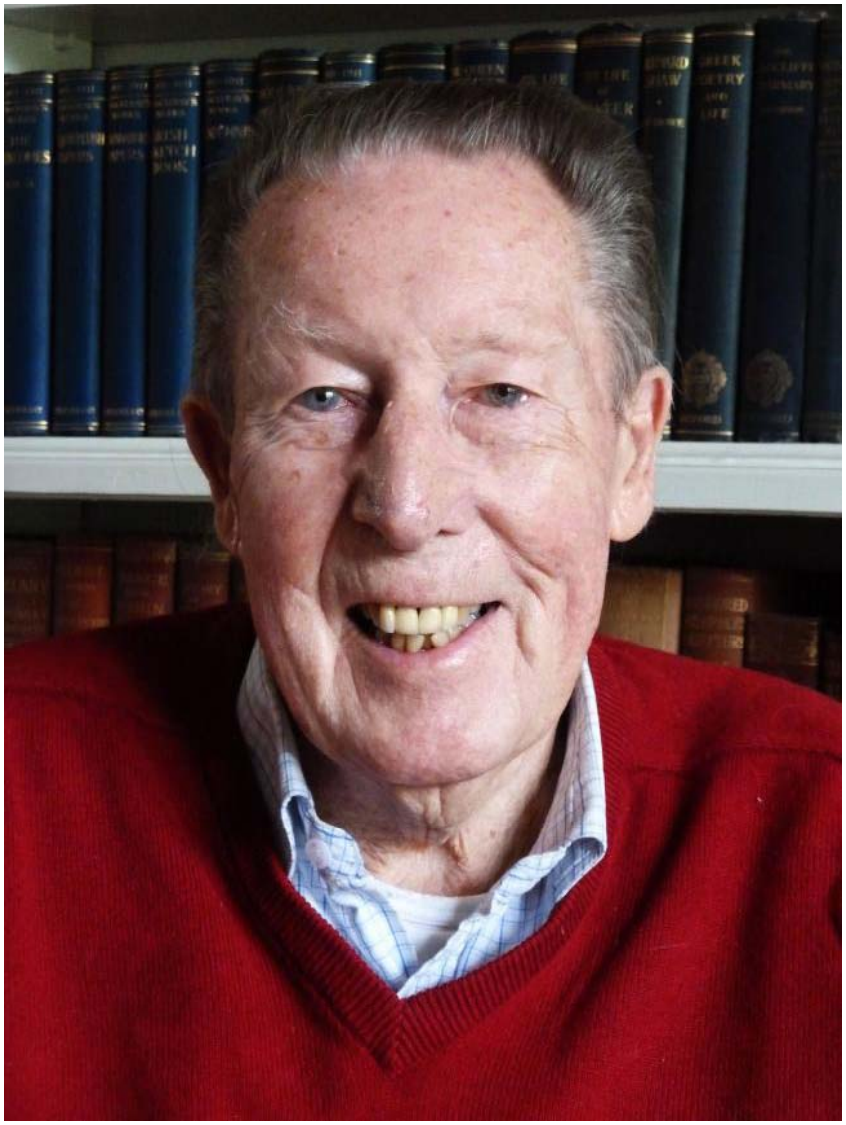


Four determinants of pacemaker discharge

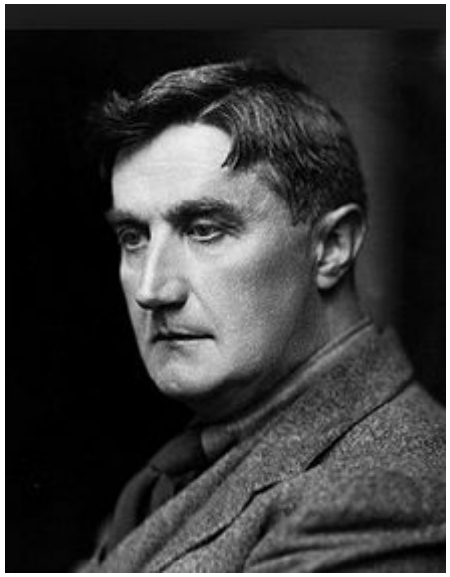
- 1. increase maximum diastolic potential (adenosine, Ach)
- 2. decrease phase 4 slope (β-blockers)
- 3. increase threshold potential (Na^+ and Ca^{2+} channel blockers)
- 4. increase action potential duration (blockade of cardiac K^+ channels)


A Normal rhythm
1 sec
QRS
P
T
B Premature ventricular beat
C Paroxysmal supraventricular tachycardia (PSVT)
D Atrial fibrillation
E Atrial flutter with variable AV conduction
F Atrial flutter with 1:1 AV conduction
G Monomorphic ventricular tachycardia
H Torsades de Pointes
I Ventricular fibrillation

Miles Vaughan Williams (1918-2016)



His father, an engineer working on the railways of India, was a cousin of the English composer Ralph Vaughan Williams.

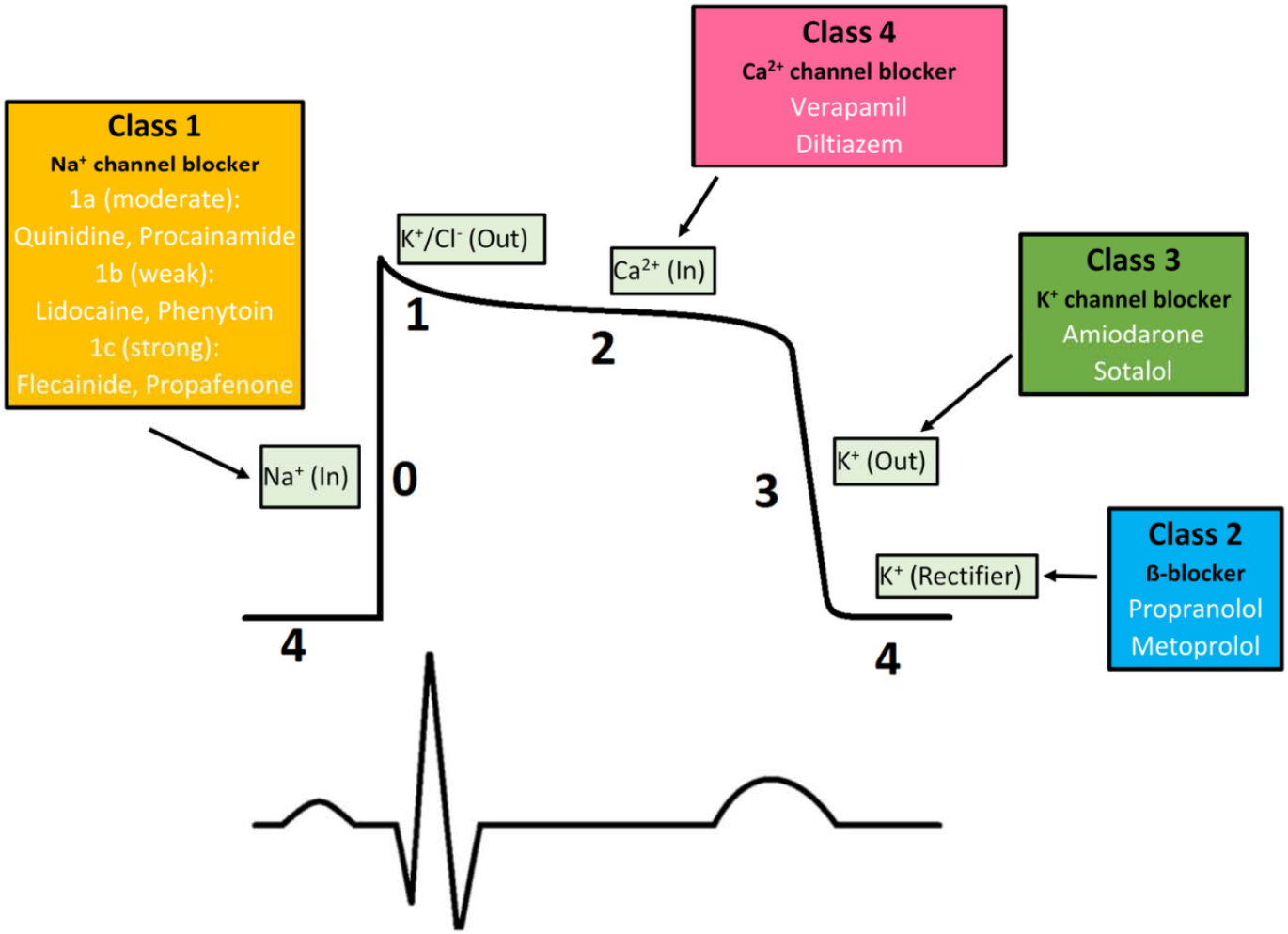


1872-1958

Vaughan Williams – Singh – Henderson classification

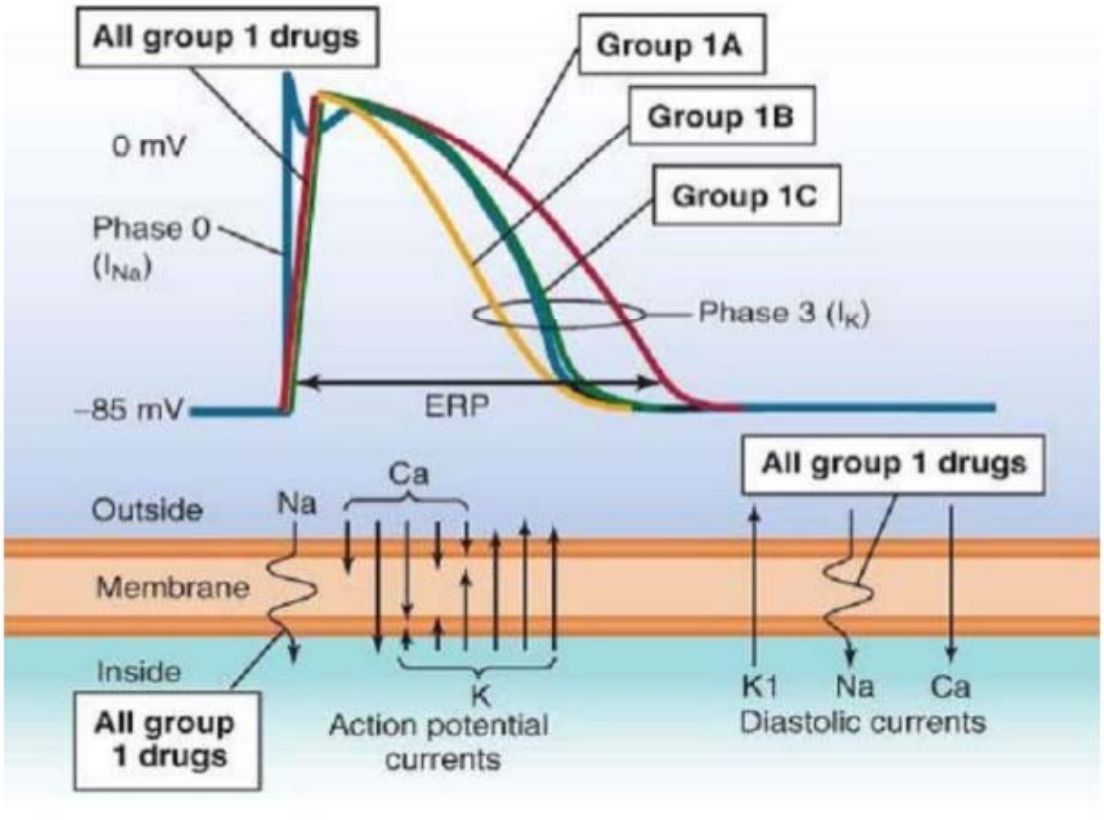
Class	Drugs
Class I. drugs	Na^+ channel blockers
IA	Prototype: Quinidine
IB	Prototype: Lidocaine
IC	Prototype: Flecainide
Class II. drugs	Beta receptor blockers
Class III. drugs	(AP prolongation) K^+ channel blockers
Class IV. drugs	Ca^{2+} channel blockers
Class V. drugs	Bradycardia-inducing drugs

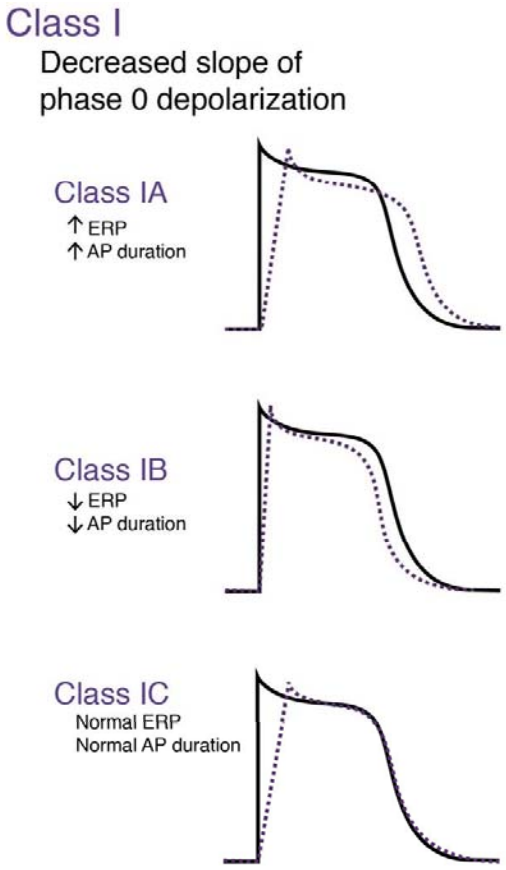
Drugs Affecting the Cardiac Action Potential



All of the antiarrhythmic drugs have proarrhythmic activity!!!

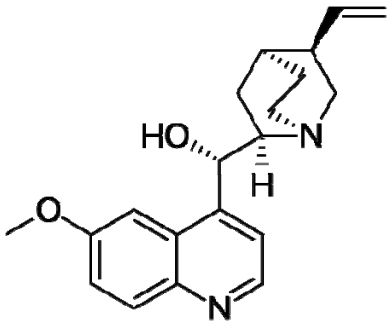
Class I antiarrhythmics





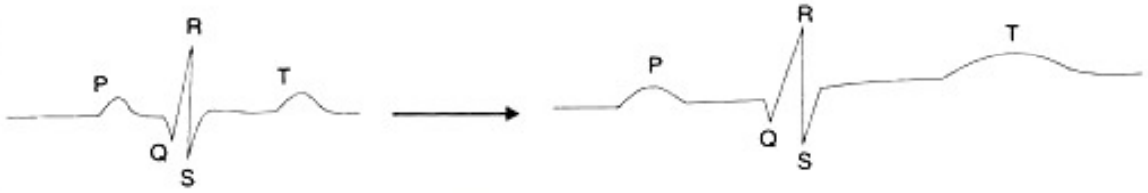
Class IA drugs

- Moderate decrease in velocity of phase 0
- Prolongation of action potential duration
- **QUINIDINE (prototypic drug):**
- **PROCAINAMIDE, DISOPYRAMIDE**
- **Electrophysiological actions:**
  - Reduction of pacemaker activity
  - Prolongation of action potential duration and effective refractory period
  - Decrease of conduction velocity



Quinidine

- Cinchona plant alkaloid
- Diastereomere of antimalarial quinine
- Ind: Atrial fluttern/fibrillation, ventricular tachyca preventing recurrent VF (in Brugada sy., short QT syndrome), maintain sinus rhythm after cardioversion of atrial fibrillation
- Open state blocker of Na^+ channel and several K^+ channels are blocked
- $\tau_{recovery}$ ~ 3 sec → QRS duration increases modestly (10-20%)
- Prolongs QT (25%)
- In 1 μM blocks I_{Kr}



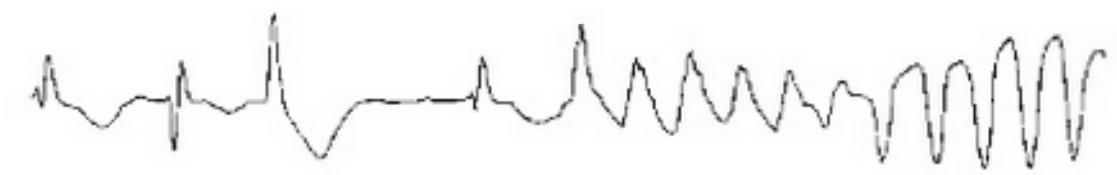
Quinidex, Cardioquin

QUINIDINE side effects

1. Heart: cardiodepression (Ca^{2+} channel blockade), paradoxic tachycardia (atropine-like effects), proarrhythmic actions (QRS interval >50%), tdp can develop in normal plasma cc.!
2. Vessels: hypotension (alpha adrenoceptor inhibition). Incline to embolism (without previous anticoagulant therapy) in patients suffering with atrial fibrillation
3. Skeletal muscle: adynamia , myasthenia gravis-like symptoms (curariform effects)
4. Gastrointestinal: diarrhoe (30-50%) →diarrhea-induced hypokalemia!!!, vomiting, nausea
5. Cinchonism: headache, dizziness, tinnitus
6. Allergic reactions: skin eruptions, angioneurotic edema
7. Hepatitis, bone marrow suppression, lupus syndrome
8. Potent inhibitor of CYP2D6
9. Reduces the clearance of digoxin

Therapeutical use: atrial and ventricular arrhytmias

tdp



Torsades de pointes: Electrophysiological Features

- ventricular origin
- wide QRS complexes with multiple morphologies
- changing R - R intervals
- axis seems to twist about isoelectric line
- This potentially serious arrhythmia occurs in 2% - 8% if patients, even if they have a therapeutic or subtherapeutic quinidine blood level

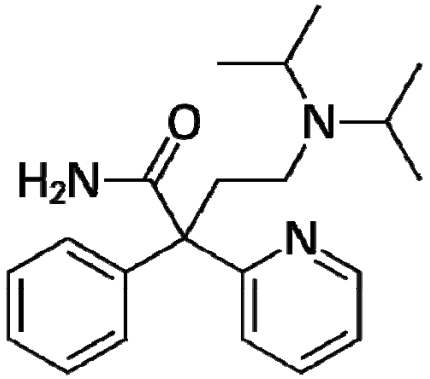
Procainamide

- Local anesthetic procain analogue
- Long-term use avoided because of lupus-related side effects
- Acute management of SVA and VA
- No antimuscarinic activity
- Ganglionic-blocking activity

Pronestyl , Procan SR, Procanbid , Pronestyl-SR

Disopyramide

- Similar to quinidine but
  - antimuscarinic effect is greater
  - No α-adrenergic blocking effect



Norpace, Rythmodan

Class IB drugs

- No reduction in steepness of phase 0
- Decrease of action potential duration
- **LIDOCAINE (prototypic)**
- No action in supraventricular, but in ventricular arrhythmias. Its action can be manifested only in ischemic tissues.
- Ineffective in hypokalemia. K+ replacement!!!

LIDOCAINE

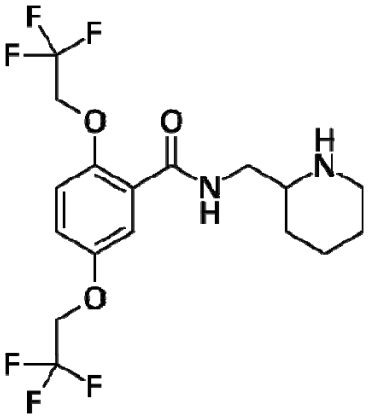
- Blocks open and inactivated Na+ channels.
- **Enteral absorption and bioavailability is very poor!**
- **Overdose:**
  - Nystagmus is an early sign of lidocaine toxicity.
  - One of the least toxic antiarrhythmic agents, but cardiodepressive in congestive heart failure.
  - CNS effects: tonic-clonic seizures. First aid: diazepam i.v.
  - Dose: 1 mg/kg, then 20-50 μg/kg/min (level: 2-5 μg/ml)
- MEXILETINE (orally, less adverse react.,)
  PHENYTOIN (dig.intox.,open heart surg.,epil.pat.)

Class IC drugs

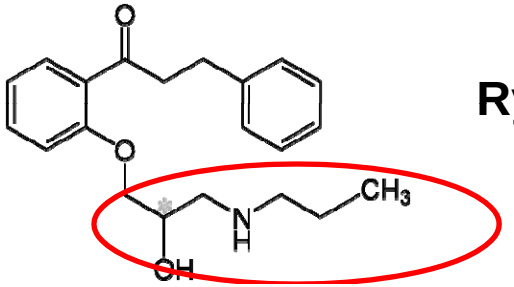
- Strong reduction in steepness of phase 0.
- No change in action potential duration.
- Extraordinary proarrhythmic action. Increase the frequency of sudden cardiac death. Shorten the duration of life expectancy.
- They cause electric inhomogenity: shorten the action potential duration in His-Purkinje system, but not in the working myocardium. Incline to proarrhythmias.

Class Ic drugs

Tambocor, Almarytm, Apocard, Ecrinal



- **FLECAINIDE:** primarily in life-threatening ventricular tachycardia and paroxysmal atrial fibrillation.
- **PROPAFENONE:** its structure is similar to propranolol: slight beta blocking action (asthma!). Generally, it increases the frequency of sudden death. „Torsade de point" arrhythmias.
- Relatively safe in supraventricular rhythm disturbances. „Pocket drug" in paroxysmal atrial fibrillation!



Rythmol SR or **Rytmonorm**

Class II. drugs:
BETA ADRENERGIC RECEPTOR BLOCKERS

Double action: inhibit the arrhythmogenic actions of increased catecholamine release + membrane stabilizing action

Do not shorten the duration of life and do not reduce the life expectancy contrary to the bulk of antiarrhythmic agents.

Therapeutical use: supraventricular and ventricular arrhythmias.

Beta blockers

- 1st generation (non-selective)

Drug	Membr. stab. effect	ISA	Lipid sol.
Pindolol	+	+ + +	+
Timolol	-	+ -	+
Sotalol	-	-	+
Propranolol	+ +	-	+ +
Oxprenolol	+	+	+ +

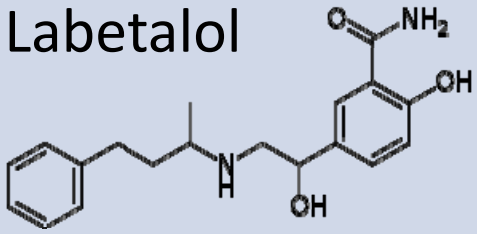
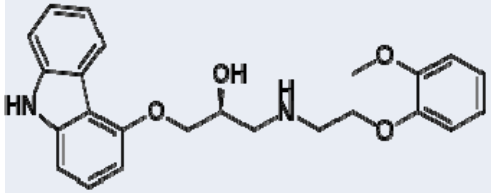
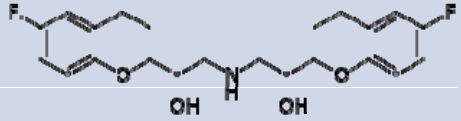
Beta blockers

- 2nd generation (beta1 selective drugs)

Drug	Membr. stab. effect	ISA	Lipid solubility
Metoprolol	+ -	-	+ +
Atenolol	-	-	-
Esmolol	-	-	+ -
Bisoprolol	-	-	+ -

Beta blockers

- 3rd generation (vasodilatory beta blockers)

Drug	Lipid solubility	Mechanism of vasodilation
Labetalol 	+ + +	Alpha-receptor blockade
Carvedilol 	+	Alpha-receptor blockade
Nebivolol 	+ -	NO potentiating effect

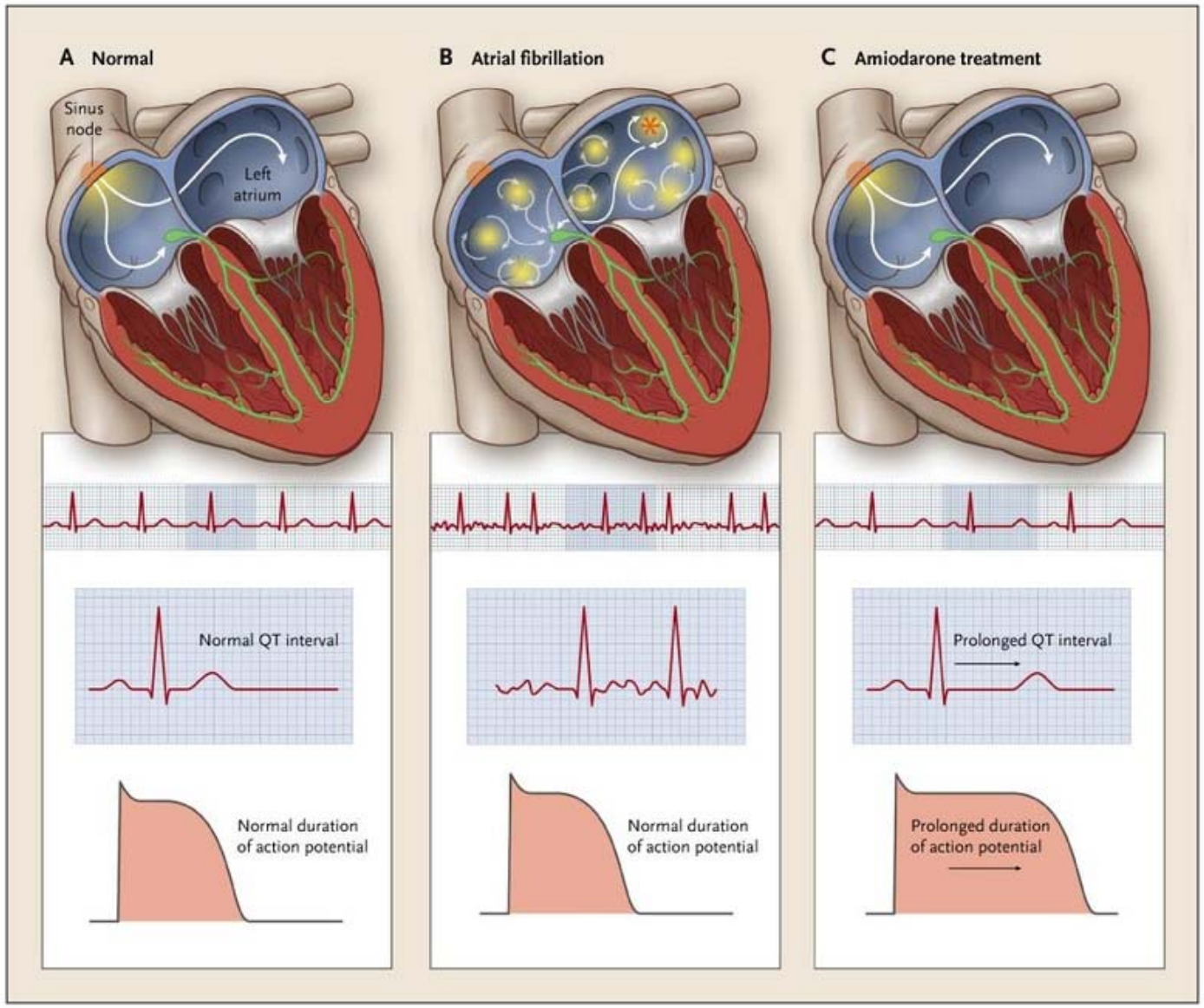
Class III. drugs:
POTASSIUM CHANNEL BLOCKERS

- **„MIXED" DRUGS:**
  - **Amiodaron, Dronedaron**
  - **Sotalol**
  - **Bretylium**
- **„PURE" POTASSIUM CHANNEL BLOCKERS**
  - **Ibutilid, Dofetilid: better profile of side effects, hopeful in treatment of atrial fibrillation**

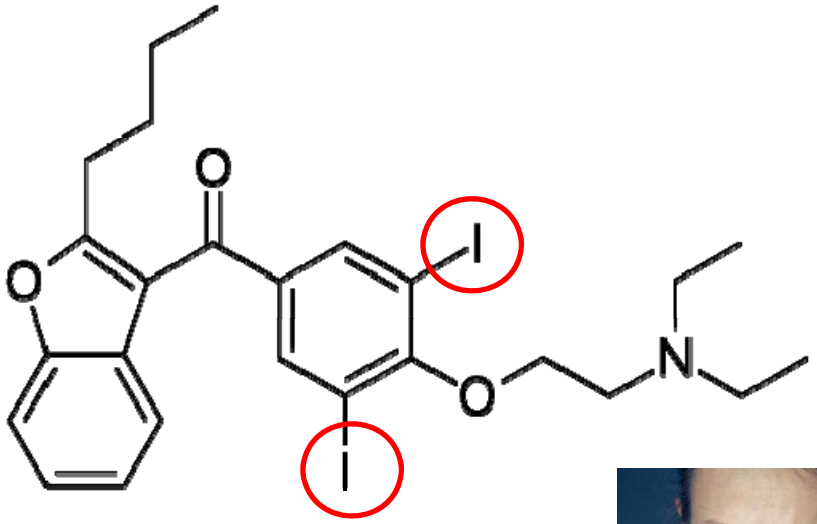
Amiodarone

- The widest spectrum among antiarrhythmic agents.
- It can be classified mainly to Class III and I, but has also Class II and IV actions!
- Highly lipophylic. Onset of action is very slow in peroral application (1-3 months). Half-life is also very long (1-3 months).
- It can be effective in all types of arrhythmias. The arrhythmia-related death is decreased.

Amiodarone

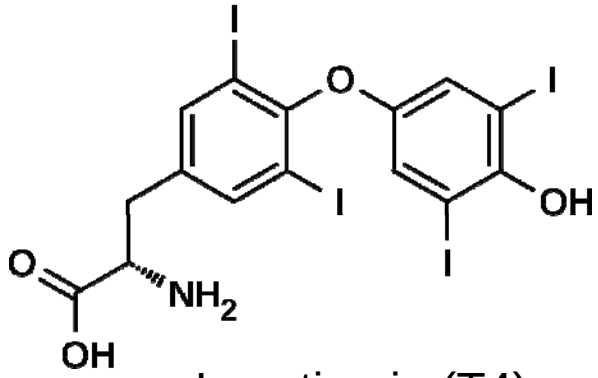

A Normal
Sinus node
Left atrium
Normal QT interval
Normal duration of action potential
B Atrial fibrillation
Normal duration of action potential
C Amiodarone treatment
Prolonged QT interval
Prolonged duration of action potential

Amiodarone

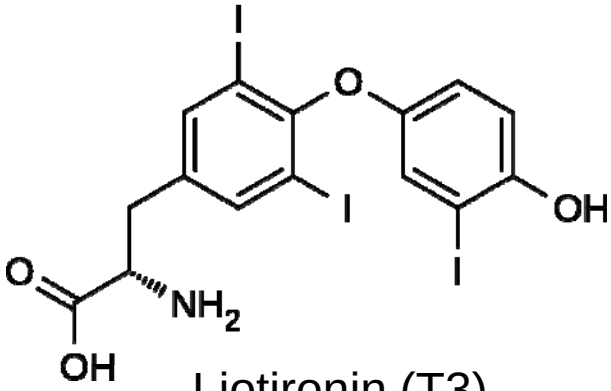


1. Hypothyroidism cca. 5%

2. Hyperthyroidism cca. 1%



Levotiroxin (T4)

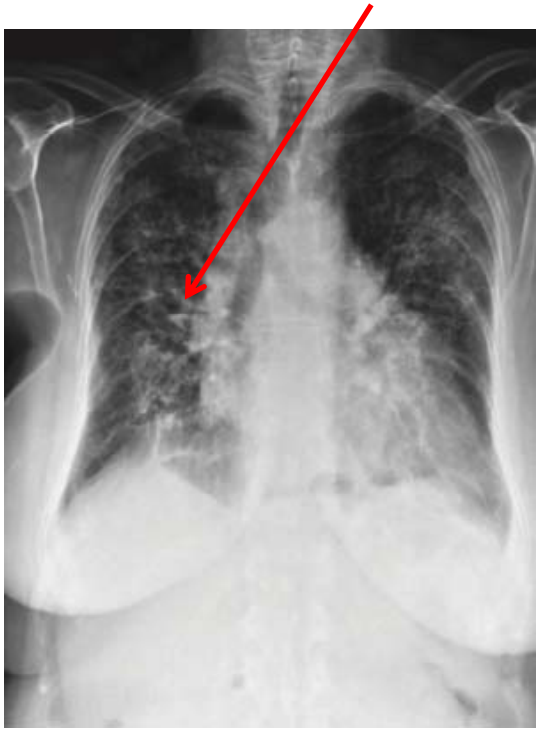


Liotironin (T3)

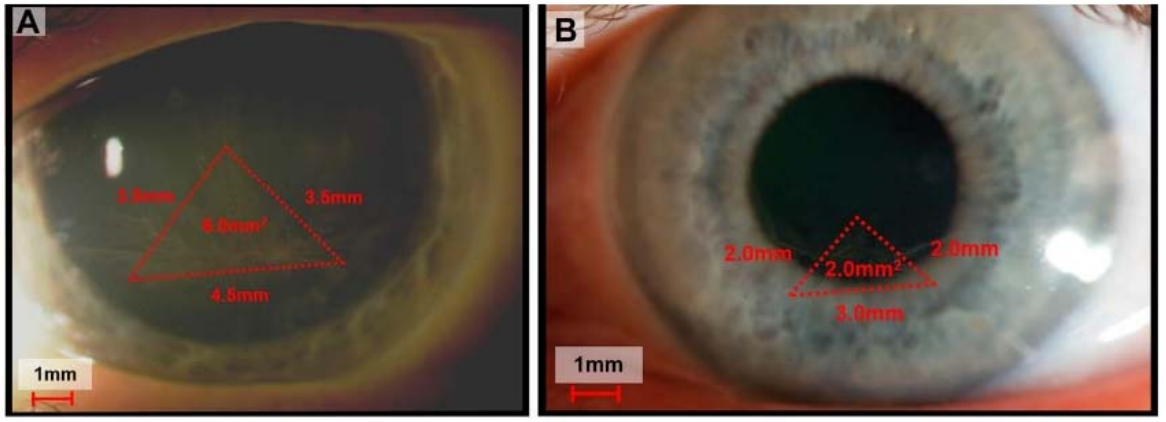
Amiodarone

Pulmonary fibrosis (15%)

Irreversible!



Corneal microdeposits (90-100%)



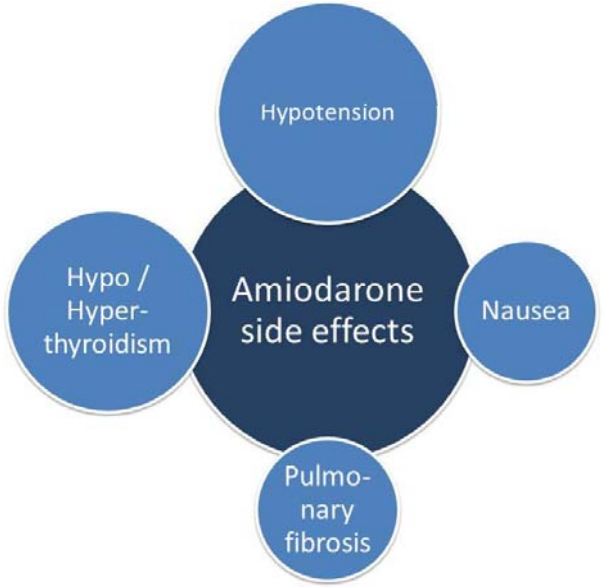
Left eye. Area of corneal deposits in cornea verticillata (vortex keratopathy). A, Before and (B) 3 months after application of topical heparin eye drops 3 times daily. The area of central corneal deposits was measured during slit-lamp examination. Applying the Heron formula, the area of a triangle was mathematically calculated, and the results were rounded to one decimal place. Magnification is (A) 1 cm = 1 mm (10:1) and (B) 0.9 cm = 1 mm (0.9:1).

Amiodarone

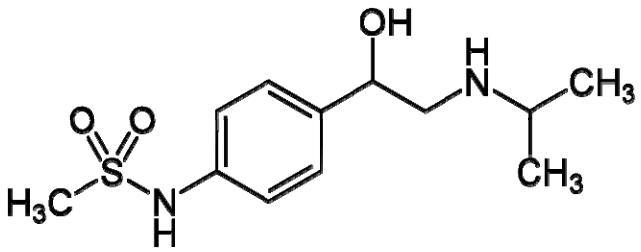
Skin hyperpigmentation and photosensibility

Amiodarone side effects

- Hypo-, hyperthyreosis
- Corneal microprecipitations
- Pulmonary fibrosis
- Skin decoloration – photosensibility
- Hypotension
- Nausea
- Hepatic dysfunction
- Peripheral neuropathy



Sotalol



- D-sotalol: pure K channel blocker
- L-sotalol: non selective beta blocker
- D-sotalol increased lethality of postinfarction patients by 5% (SWORD trial). Recently, only racemic form can be used!
- Useful in supraventricular and ventricular arrhythmias! „Torsade de point” can be occured!

Betapace, Sotalex, Sotacor, Sotylize

Torsades de Pointes

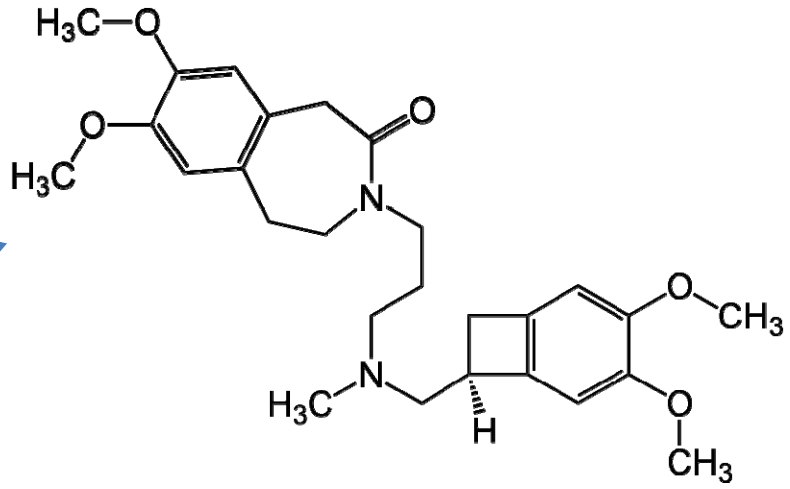
- **Class IA**
  - **Quinidine** **2-8%**
  - **Procainamide** **2-3%**
  - **Disopyramide** **2-3%**
- **Class III**
  - **d,l-Sotalol** **1-5%**
  - **d-Sotalol** **1-2%**
  - **N-acetylprocainamide** **3-4%**
  - **Amiodarone** **< 1%**

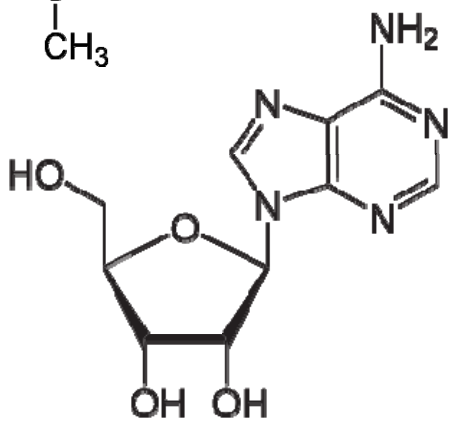
CLASS IV. DRUGS: Ca^{2+} channel antagonists (CCBs)

- NON-DIHYDROPIRIDIN CALCIUM CHANNEL BLOCKERS, VERAPAMIL and DILTIAZEM
  - In rhythm disturbances, where re-entry involves the AV junction. No ventricular actions.
  - Therapeutic use: paroxysmal supraventricular tachycardia, atrial fibrillation (frequency control)

CLASS V. DRUGS: MISCELLANEOUS AND SELECTIVE BRADYCARDIA-INDUCING AGENTS

- Digoxin
- Atropin
- Ivabradine
- Adenosine
- Magnesium sulphate
- Trimagnesium tricitrate





Digoxin

- **Mode of action**
  - **Na-K ATPase inhibition**
  - **Positive inotrope**
  - **Vagotonic**
- **ECG changes**
  - **Increases PR interval**
  - **Depresses ST segment**
  - **Decreases QT interval**
- **<u>Use</u>: SVT (not WPW)**
- **<u>Kinetics</u>**
  - **$t_{1/2}$ = preemie (61hrs), neonate (35hrs), infant (18hrs), child (37hrs), adult (35-48hrs)**
- **<u>Interactions</u>**
  - **Coumadin- ↑ PT**
  - **↑ Digoxin level**
    - **Quinidine, amiodarone, verapamil**
    - **↓ renal function/renal tubular excretion (Spironolactone)**
    - **Worse with ↓ K^+, ↓ Ca^{++}**

Digoxin toxicity

- **Nausea/vomiting, lethargy, visual changes**
- **Metabolic**
  - **Hyper K^+, Ca^{++}**
  - **Hypo K^+, Mg^{++}**
  - **Hypoxemia**
  - **Hypothyroidism**
- **Proarrhythmia**
  - **AV block- decreased conduction**
  - **SVT- increased automaticity**
  - **VT- delayed afterdepolarizations**

Digoxin toxicity treatment

- **GI decontamination**
  - **Ipecac/lavage/charcoal w/ cathartic**
- **Arrhythmias**
  - **SA node /AV node depression- Atropine; if dig > 6, may need pacing**
  - **SVT- Phenytoin or β -blocker**
  - **VT- Lidocaine (1 mg/kg) or Phenytoin**
  - **Potassium infusion**
  - **Ca chelating**

- **DC Cardioversion may cause refractory VT/VF!!**

Adenosine

- **Mode of action**
  - **Vagotonic**
  - **Anti-adrenergic**
  - **Depresses slow inward Ca^{++} current**
  - **Increases K^{+} conductance (hyperpolarizes)**
- **ECG/EP changes**
  - **Slows AV node conduction**
- **Uses**
  - **SVT- termination of reentry**
  - **Aflutter- AV block for diagnosis**
- **Kinetics**
  - **$t_{1/2}$ = < 10 secs**
  - **Metabolized by RBCs and vascular endothelial cells**
- **Dose**
  - **IV: 100-300 μg/kg IV bolus**

Adenosine

- **Drug interactions**
  - **Methylxanthines (caffeine/theophylline)**
- **Side effects**
  - **AFib/ sinus arrest/ sinus bradycardia**
  - **Bronchospasm**
  - **Flushing/headache**
  - **Nausea**
- **Great medicine: quick onset, quick degradation.**

Circulation. 1991 Oct;84(4):1831-51.

The Sicilian gambit. A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. Task Force of the Working Group on Arrhythmias of the European Society of Cardiology.

[No authors listed]

Abstract

The Queen's Gambit is an opening move in chess that provides a variety of aggressive options to the player electing it. This report represents a similar gambit (the Sicilian Gambit) on the part of a group of basic and clinical investigators who met in Taormina, Sicily to consider the classification of antiarrhythmic drugs. Paramount to their considerations were 1) dissatisfaction with the options offered by existing classification systems for inspiring and directing research, development, and therapy, 2) the disarray in the field of antiarrhythmic drug development and testing in this post-Cardiac Arrhythmia Suppression Trial (CAST) era, and 3) the desire to provide an operational framework for consideration of antiarrhythmic drugs that will both encourage advancement and have the plasticity to grow as a result of the advances that occur. The multifaceted approach suggested is, like the title of the article, a gambit. It is an opening rather than a compendium and is intended to challenge thought and investigation rather than to resolve issues. The article incorporates first, a discussion of the shortcomings of the present system for drug classification; second, a review of the molecular targets on which drugs act (including channels and receptors); third, a consideration of the mechanisms responsible for arrhythmias, including the identification of "vulnerable parameter" that might be most accessible to drug effect; and finally, clinical considerations with respect to antiarrhythmic drugs. Information relating to the various levels of information is correlated across categories (i.e., clinical arrhythmias, cellular mechanisms, and molecular targets), and a "spread sheet" approach to antiarrhythmic action is presented that considers each drug as a unit, with similarities to and dissimilarities from other drugs being highlighted. A complete reference list for this work would require as many pages as the text itself. For this reason, referencing is selective and incomplete. It is designed, in fact, to provide sufficient background information to give the interested reader a starting frame of reference rather than to recognize the complete body of literature that is the basis for this article.