

Antiarrhythmias

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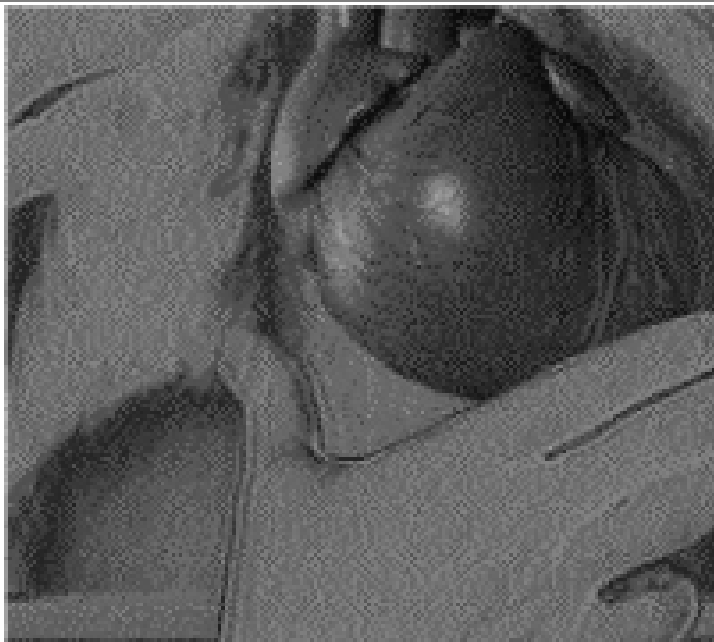
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Agents used in the treatment of HT, CHF, Arrhythmia and Angina

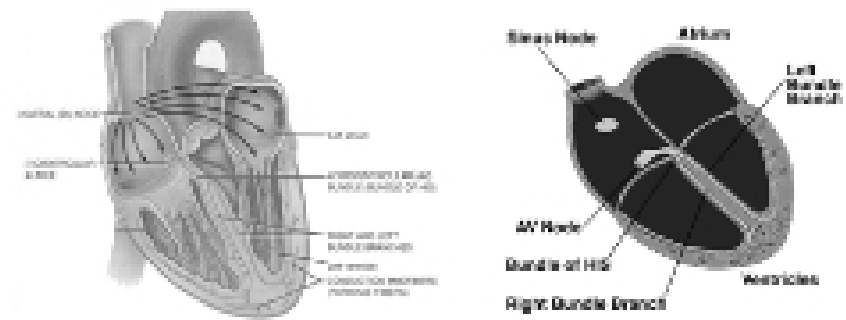
Drug Class	Hypertension	CHF	Arrhythmia	Angina	Contraindications/Cautions/Notes
Beta-Blockers	✓✓✓ ✓	✓✓	✓✓✓ ✓	✓✓✓ ✓	Caution: CHF (unstable CHF, bronchospasm, significant bradycardia); diabetes, asthma (use β_1 -selective)
Ca ²⁺ -Blockers	✓✓✓ ✓		✓✓✓ ✓	✓✓✓ ✓	CHF, gingival hyperplasia, constipation, cardiac depression
ACEI or ARBs	✓✓✓ ✓	✓✓✓ ✓			Low CHF, renal stenosis, glossitis, fetogenic, dry cough (ACEI), taste, hyperkalemia
Diuretics	✓✓✓ ✓	✓✓✓			Low CHF, hypokalemia (CC); glucose intolerance (diuretics)
Cardiac glycosides		✓✓✓ ✓	✓		Many ionic interactions, [K ⁺] important, low K ⁺ → toxicity
Vasodilators	✓✓✓	✓✓			Flushing, dizziness, headache, reflex tachycardia, combo ionic
Na ⁺ -Channel blockers			✓✓✓ ✓		Effects enhanced in depolarized tissue
Nitrate		✓✓		✓✓✓ ✓	Tolerance, flushing, dizziness, headache, reflex tachycard, 50 Hz



Heart Physiology

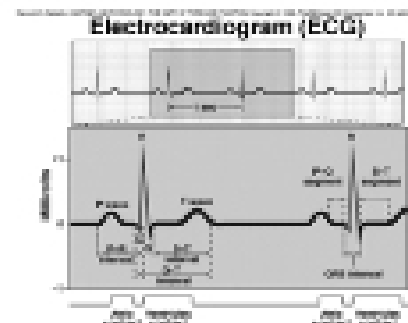
Closed system
 Supply nutrients/O₂

Pressure driven
 Remove metabolites

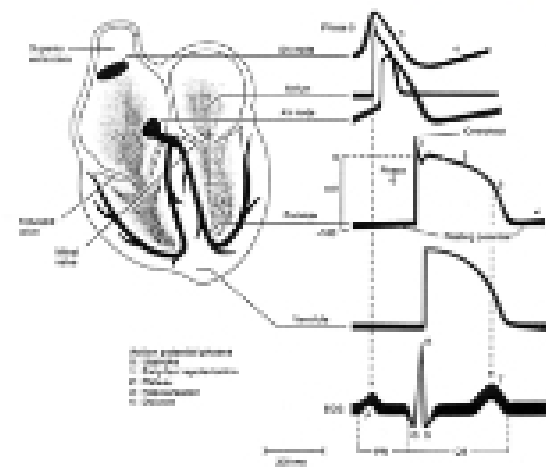


Heart Physiology

- P - atria depolarization
- QRS - ventricle depolarization
- PR - conduction A-V
- T - ventricle repolarization
- QT - duration ventricle of repolarization

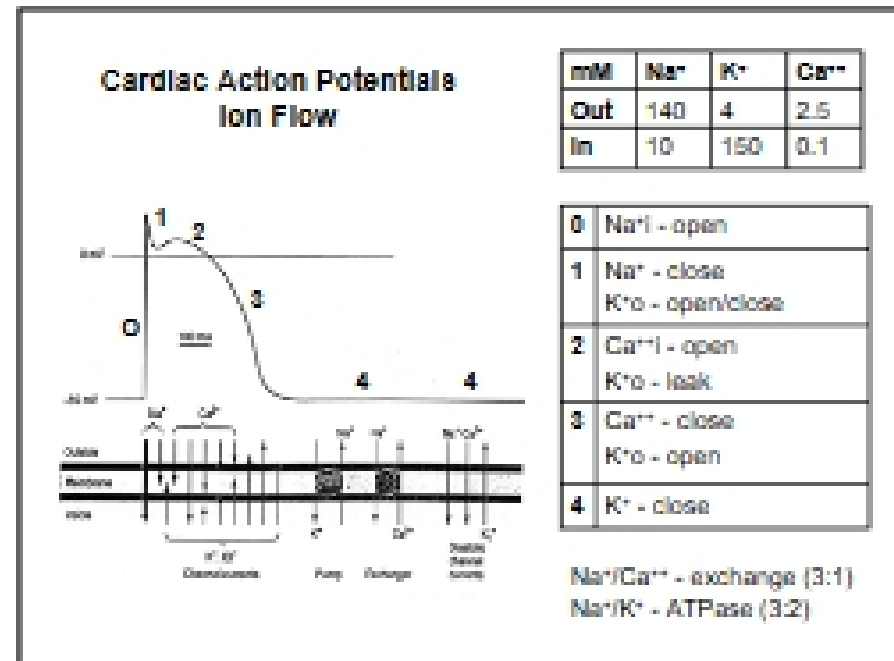
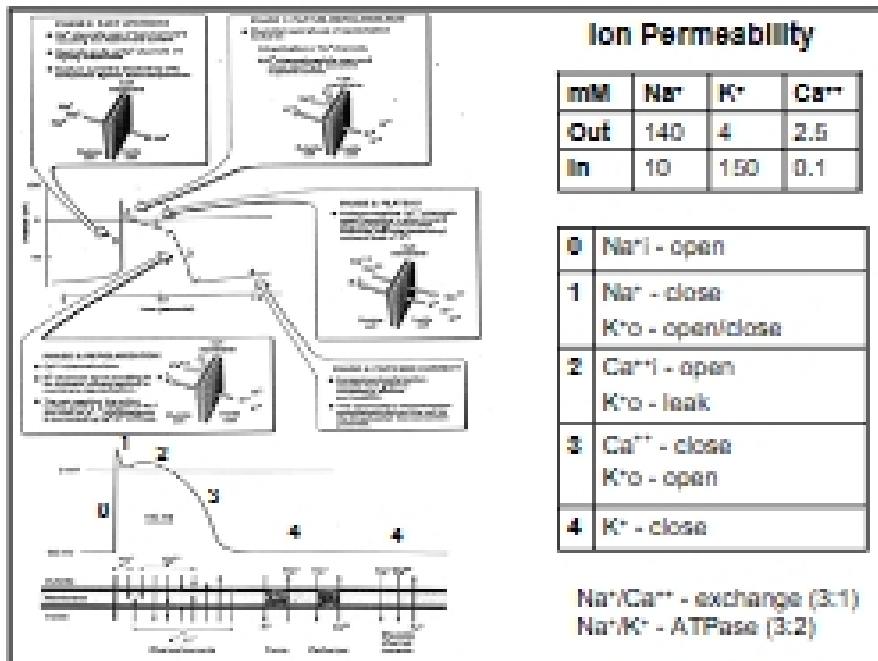


Heart Physiology



Closed system
 Pressure driven
 Supply nutrients/O₂
 Remove metabolites

- P - atria depol.
- QRS - ventricle depol.
- PR - conduction A-V
- T - ventricle repol.
- QT - duration ventricle repolarization



Characteristics of Arrhythmias

Definitions:

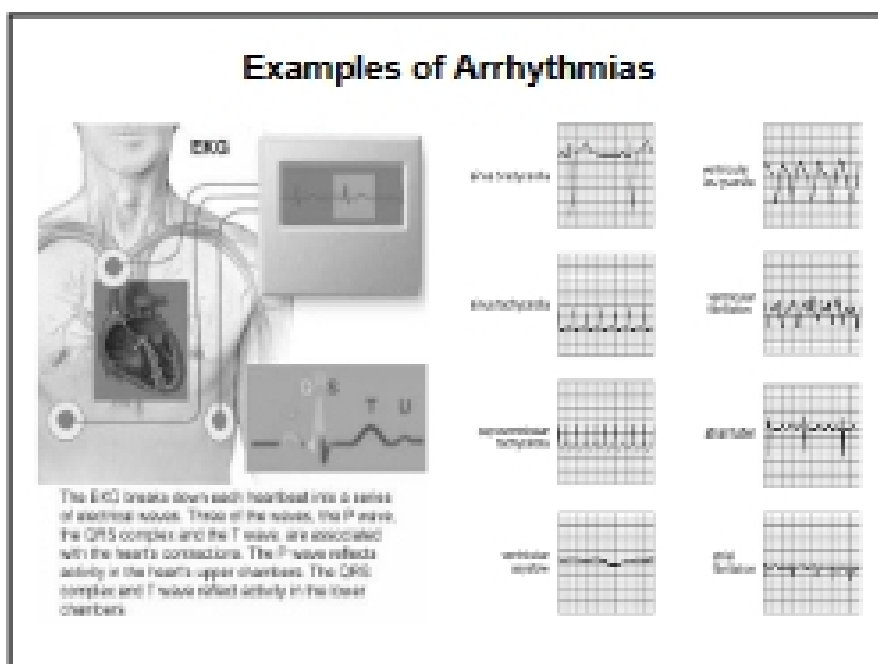
- normal sinus rhythm (60-90bpm), SA node pacemaker
- arrhythmia; any abnormality of firing rate, regularity or site of origin of cardiac impulse or disturbance of conduction that alters the normal sequence of activity of atria and ventricles.

Occurrence:

- 80% of patients with acute myocardial infarctions
- 50% of anaesthetized patients
- about 25% of patients on digitalis

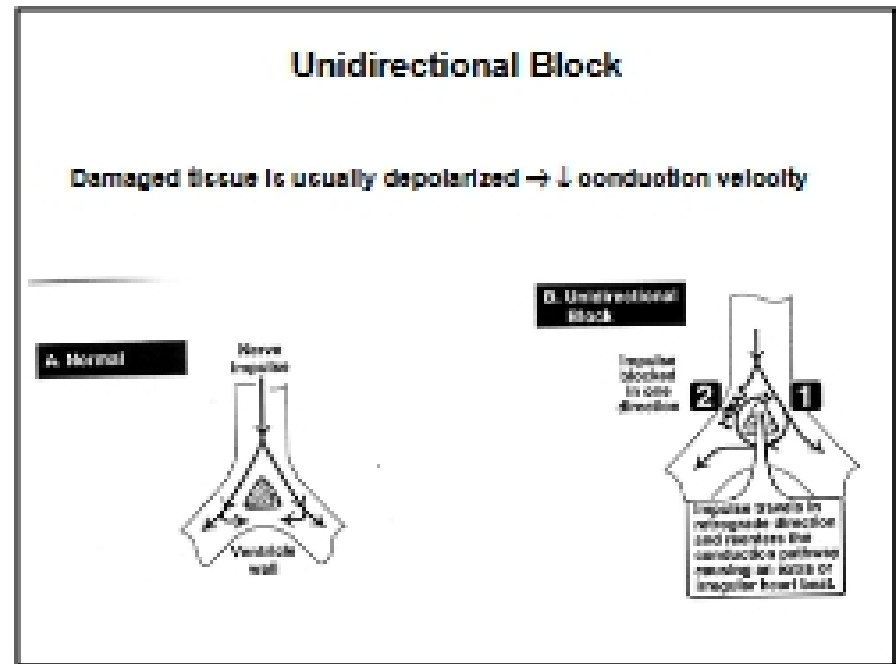
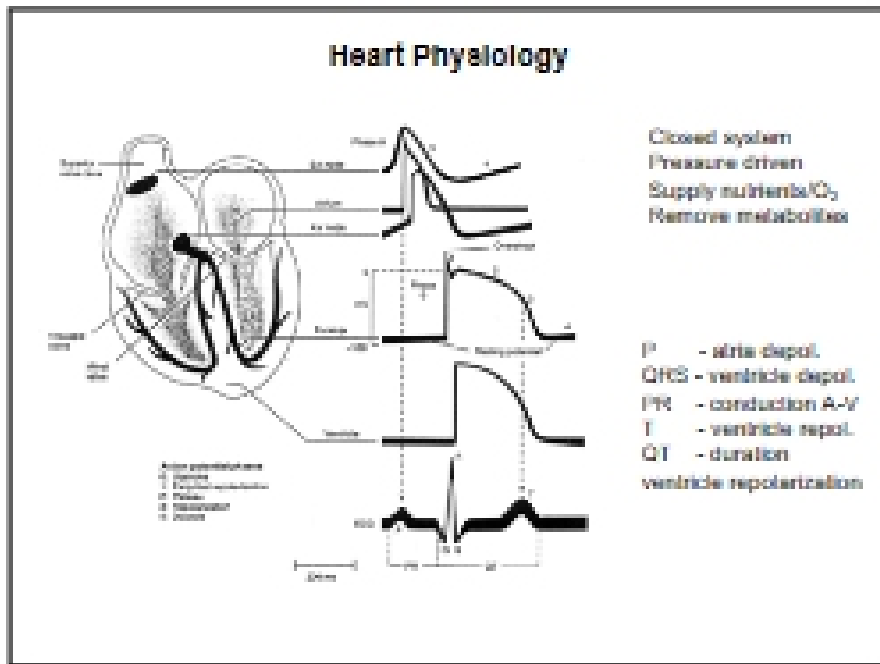
Classification of arrhythmia

- Characteristics:**
 - flutter – very rapid but regular contractions
 - tachycardia – increased rate
 - bradycardia – decreased rate
 - fibrillation – disorganized contractile activity
- Sites Involved:**
 - ventricular
 - atrial
 - sinus
 - AV node
 - Supraventricular (atrial myocardium or AV node)



Mechanisms of arrhythmias

- Abnormal impulse generation (abnormal automaticity)**
 - automaticity of normally automatic cells (SA, AV, His)
 - generation of impulses in normally non-automatic cells
 - development of phase 4 depolarization in normally non-automatic cells
 - 'triggered activity' due to afterdepolarizations
 - early afterdepolarization
 - delayed afterdepolarization
- Abnormal impulse conduction (more common mechanism)**
 - AV block – ventricle free to start own pacemaker rhythm
 - Re-entry: re-excitation around a conducting loop, which produces tachycardia
 - unidirectional conduction block
 - establishment of new loop of excitation
 - conduction time that outlasts refractory period



Strategy of Antidysrhythmic Agents

Suppression of dysrhythmias

- A. Alter automaticity
 - i. decrease slope of Phase 4 depolarization
 - ii. increase the threshold potential
 - iii. decrease resting (maximum diastolic) potential
- B. Alter conduction velocity
 - i. mainly via decrease rate of rise of Phase 0 upstroke
 - ii. decrease Phase 4 slope
 - iii. decrease membrane resting potential and responsiveness
- C. Alter the refractory period
 - i. increase Phase 2 plateau
 - ii. increase Phase 3 repolarization
 - iii. increase action potential duration

Classification of Antidysrhythmic Drugs

Vaughan-Williams classification (1970), subsequently modified by Harrison.

Helpful, But?

1. based on electrophysiological actions in normal tissue
2. presumes a mechanism of action of antidysrhythmic drugs
3. consists of four main classes and three subclasses
4. does not include actions of other agents (ie. adenosine)

Vaughan-Williams Classification

Subclass	Mechanism	Prototype
IA.	Mod. block I _{Na} ; slow conduction; ↑ APD	Quinidine Procainamide
IB.	Min. block I _{Na} ; slow conduction (less); shorten I _{h3} repolarization	Lidocaine Phenytoin
IC.	Marked block I _{Na} ; slow conduction; no change APD or repolarization. Increased suppression of Na channels	Flecainide Encainide
Class II	Beta blockers; decrease adrenergic input. No major effect on APD, suppress I _{h4} depolarization	Propranolol others
Class III	Prolong repolarization/refractory period other means than exclusively I _{Na} block (mainly K ⁺ channel blockade).	Amiodarone Bretylium
Class IV	Ca channel blockers. Slow conduction and ↑ effective refractory period in normal tissue (A-V node) and Ca-dependent slow responses of depolarized tissue (atria, ventricle, Purkinje)	Verapamil Diltiazem
Others	Adenosine, Digoxin, Anticoagulants, ANS agents	

Action Potential – Ion Flow

mM	Na ⁺	K ⁺	Ca ²⁺
Out	140	4	2.5
In	10	150	0.1

0	Na ⁺ - open K ⁺ - open/close
1	Na ⁺ - close K ⁺ - open/close
2	Ca ²⁺ - open K ⁺ - leak
3	Ca ²⁺ - close K ⁺ - open
4	K ⁺ - close

Na⁺/Ca²⁺ - exchange (3:1)
Na⁺/K⁺ - ATPase (3:2)