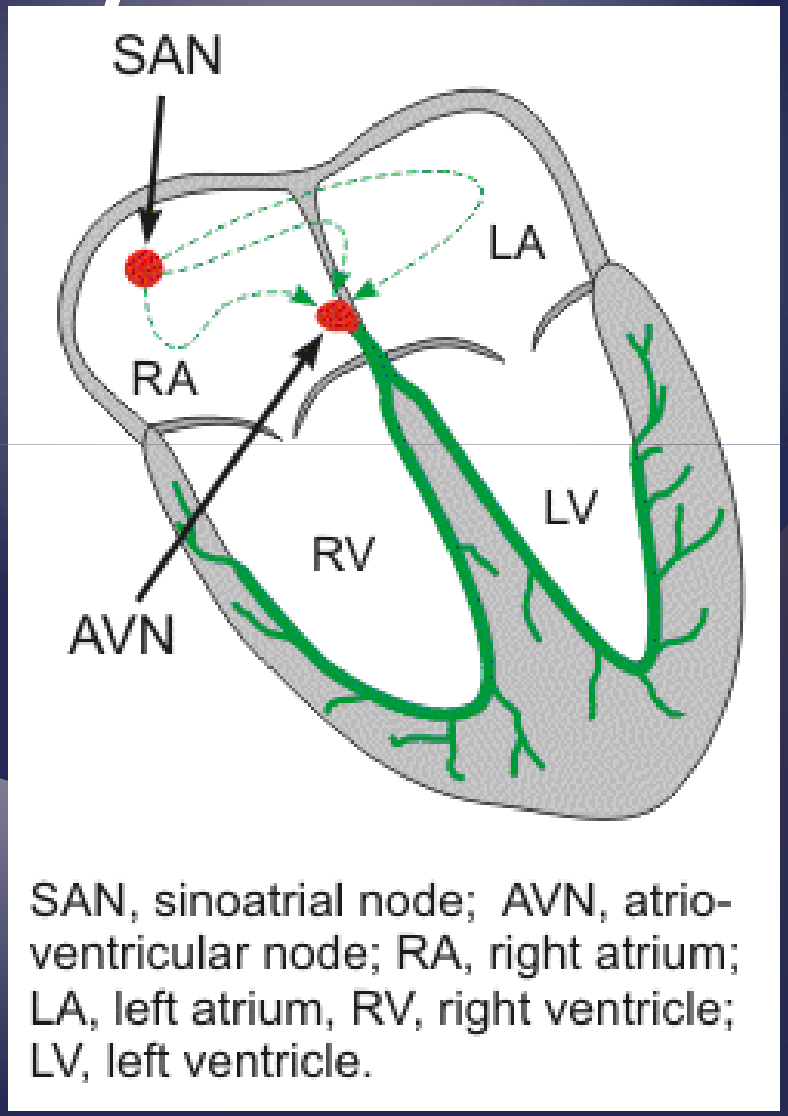
ANTIARRYTHMIC DRUGS

Normal Sinus Rhythm

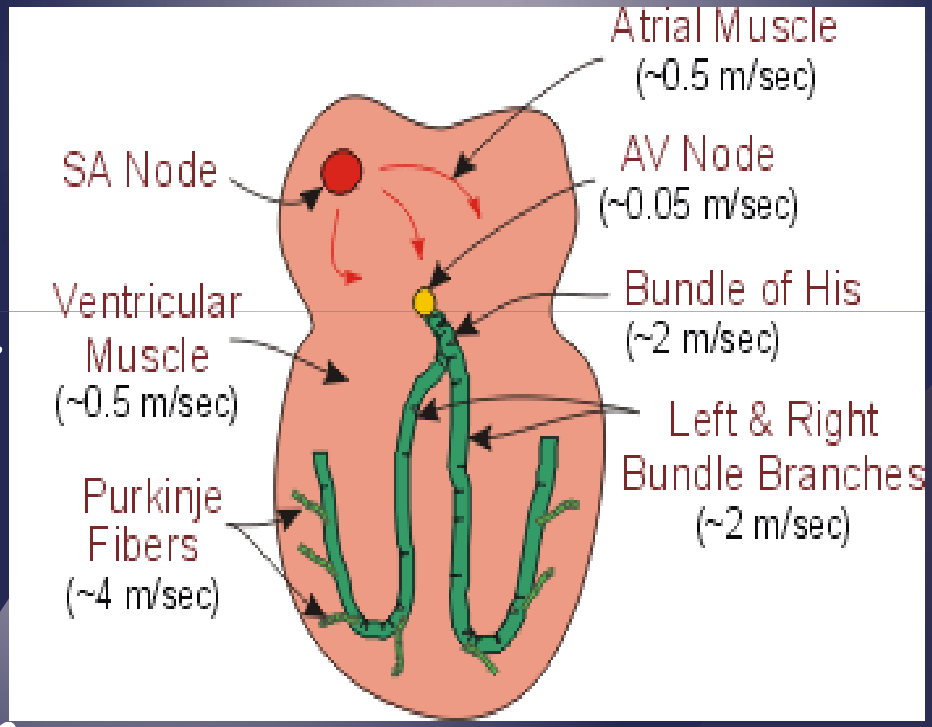
- Heart rhythm is determined by SA node = Cardiac Pacemaker
- Called sinus rhythm
- Specialised pacemaker cells spontaneously generate APs
- APs spread through the conducting pathways
- Normal sinus rate 60-100 beats/min



SAN, sinoatrial node; AVN, atrio-ventricular node; RA, right atrium; LA, left atrium, RV, right ventricle; LV, left ventricle.

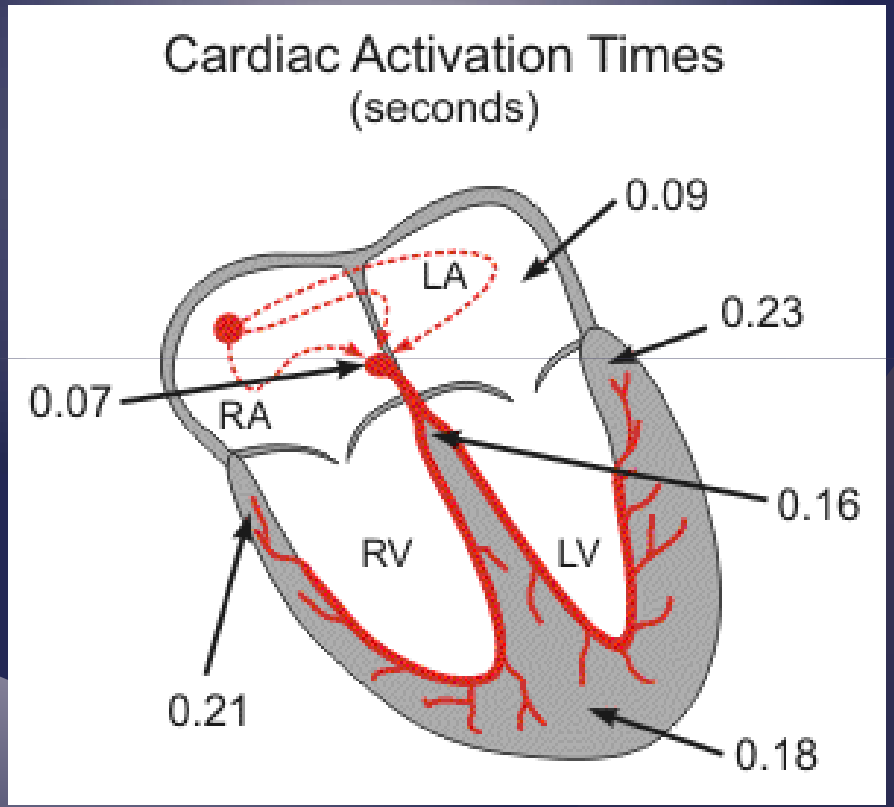
Conducting System

- SAN AP triggers atrial depolarisation
- AVN - Only pathway for AP to enter ventricles
- Conducts slowly: Complete atrial systole before ventricular systole
- Conducts rapidly through His Bundles & Purkinje – Ventricular depolarization & contraction



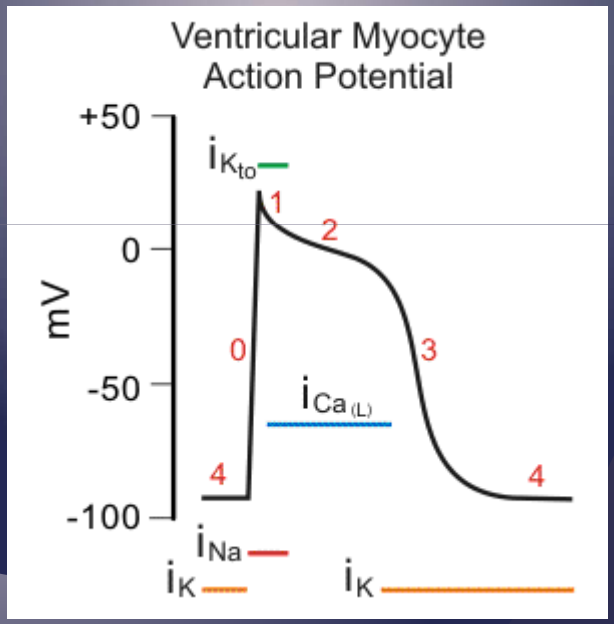
Conducting System

- Permits rapid organized depolarization of ventricular myocytes
- Necessary for the efficient generation of pressure during systole
- Atrial activation complete 0.09s after SAN firing
- Delay at AVN
- Septum activated 0.16s
- Whole ventricle activated by 0.23s



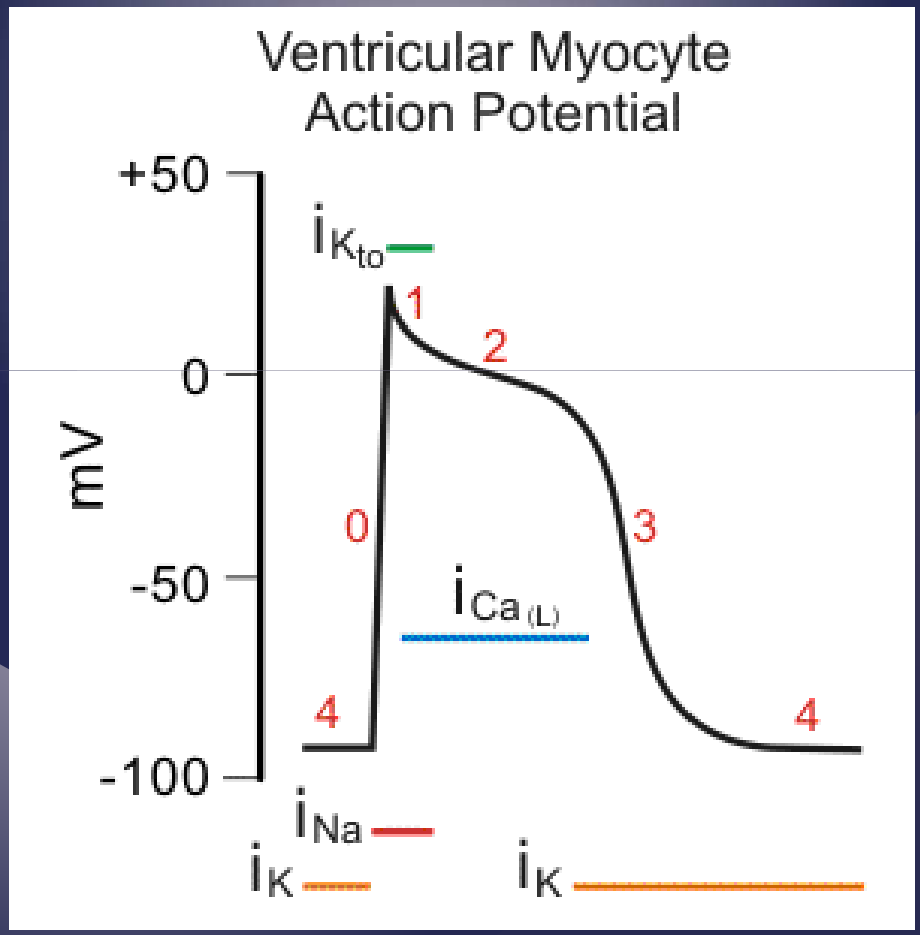
Cardiac Action Potential

- Phase 4: RMP
- AP depolarizes cells to threshold -70mV
- Phase 0: Rapid depolarization
- Caused by a transient opening of fast Na channels
- Increases inward directed depolarizing Na+ currents
- Generate "fast-response" APs



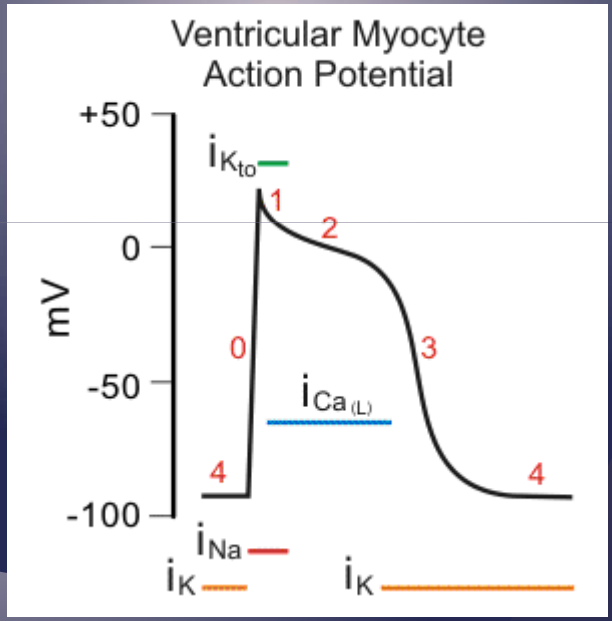
Cardiac Action Potential

- Phase 1: Initial repolarization
- Open K channel: transient outward hyperpolarizing K+ current
- Large increase in slow inward gCa++ occurs at the same time
- L-type CaCh open -40mV
- Repolarization delayed
- Phase 2: Plateau phase
- Plateau phase prolongs AP duration vs APs in nerves and skeletal muscle



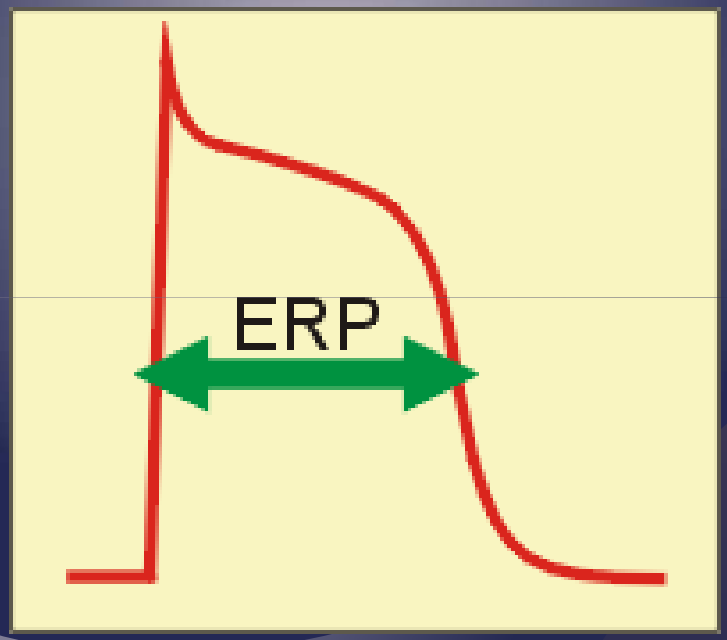
Cardiac Action Potential

- Phase 3: Repolarization
- K channels open
- Inactivation of Ca++ channels
- Action potential in non-pacemaker cells is primarily determined by relative changes in fast Na+, slow Ca++ and K+ conductances and currents



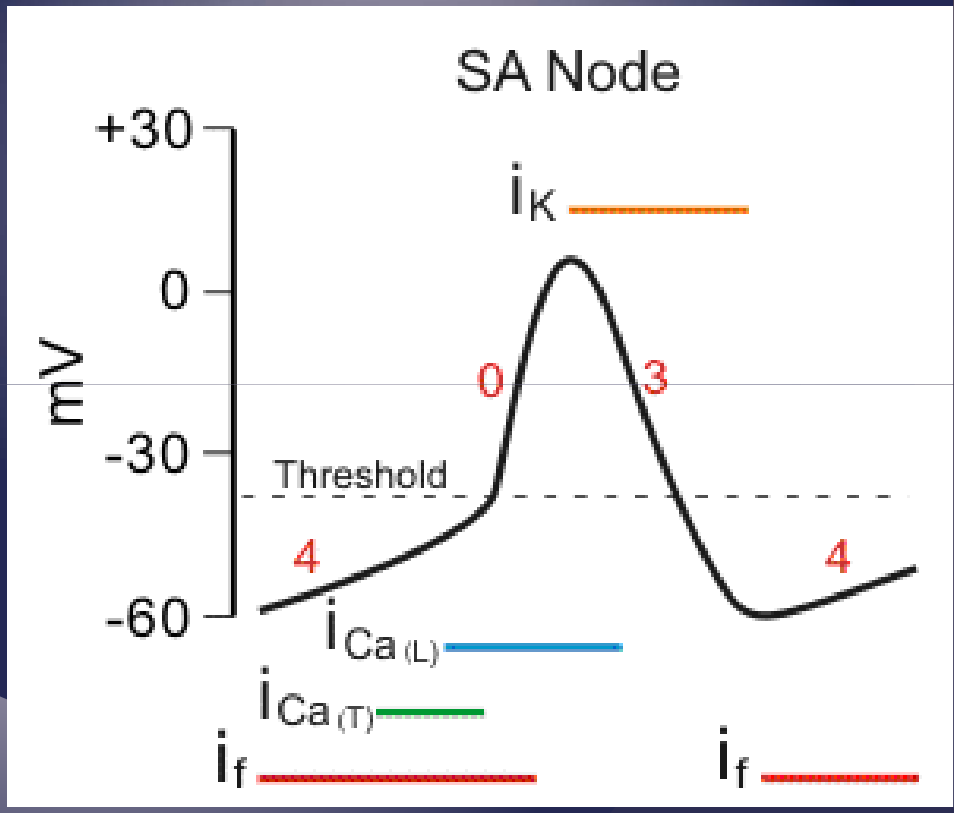
Refractory Periods

- Once an AP is initiated, there is a period (phase 0,1,2, part 3) that a new AP cannot be initiated.
- Effective or Absolute refractory period (ERP or ARP)
- Stimulation of cell by adjacent cell depolarizing does not produce new propagated APs
- Prevents compounded APs from occurring & limits frequency of depolarization and HR



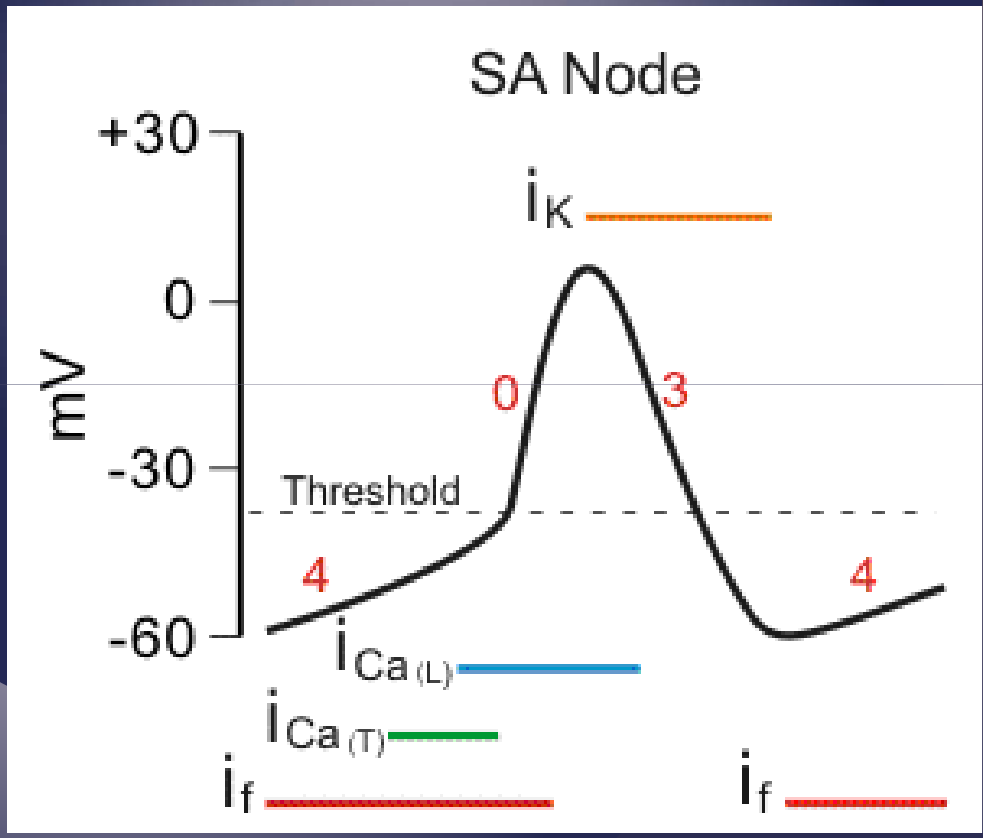
SAN Pacemaker Potential

- Fully repolarized -60mv
- No stable RMP
- Phase 4: Spontaneous depolarization or pacemaker potential
- Slow, inward Na+ channels open - "funny" currents
- Cause the membrane potential to begin to spontaneously depolarize
- During Ph4 there is also a slow decline in the outward movement of K+



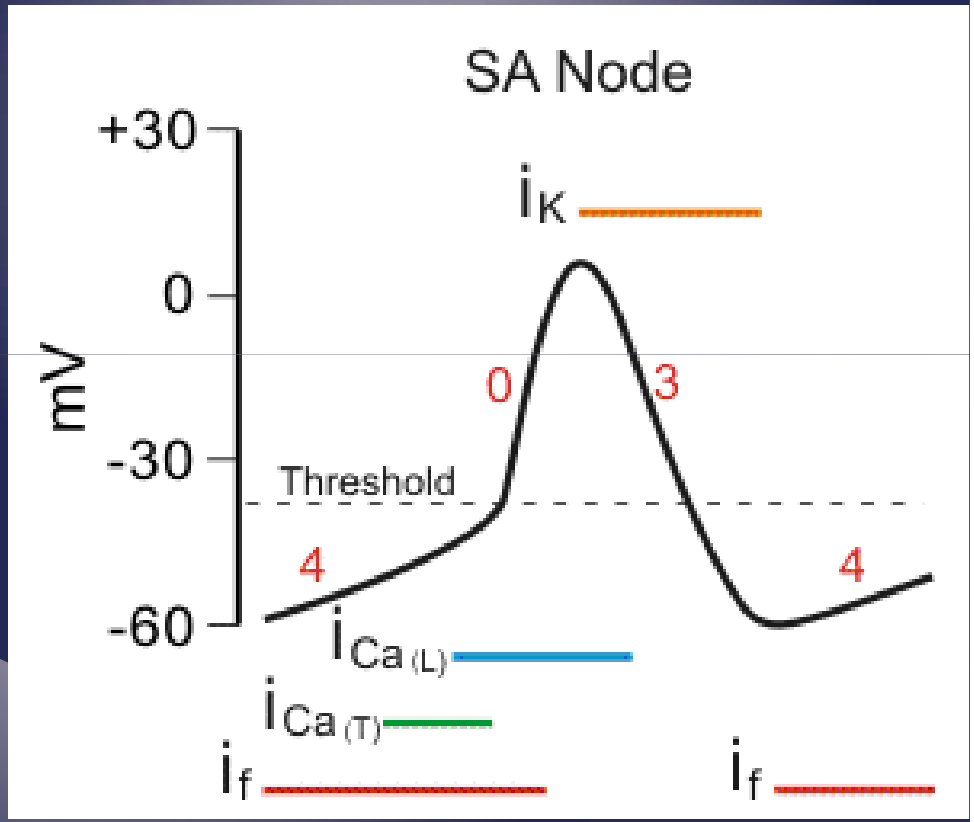
SAN Pacemaker Potential

- -50mV T-type CaCh open
- Ca in: further depolarizes
- -40 mV L-type CaCh open
- More Ca in: further depol
- AP threshold -35mV
- Phase 0: Depolarization
- Primarily caused by Ca++ conductance through the L-type Ca++ channels
- Movement of Ca++ through these is slow so the rate of depolarization (Phase 0 slope) is slower than in other cardiac cells



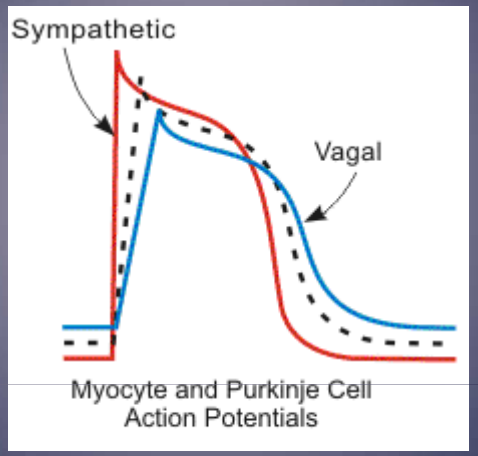
SAN Pacemaker Potential

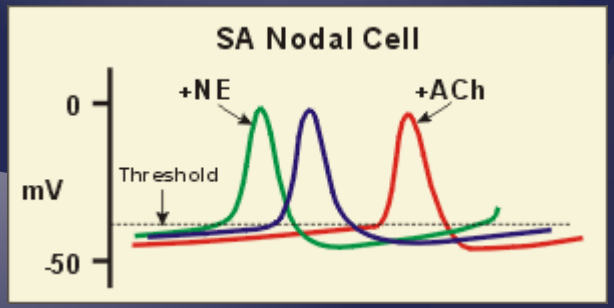
- Phase 3: Repolarization
- K+ channels open
- Increase the outward hyperpolarizing K+ currents
- At the same time the L-type Ca++ channels close
- gCa++ decreases
- Inward depolarizing Ca++ currents diminish
- Repolarization



Regulation of Cardiac APs

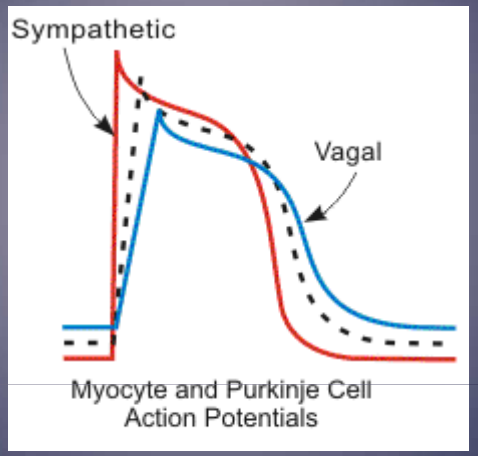
- SNS - Increased with concurrent inhibition vagal tone:
- NA binds to B1 Rec
- Increases cAMP
- Increases Ca and Na in
- Decreases K out
- Increases slope phase 0
- Non-Nodal tissue:
- More rapid depolarisation
- More forceful contraction
- Pacemaker current (If) enhanced
- Increase slope phase 4
- Pacemaker potential more rapidly reaches threshold
- Rate increased

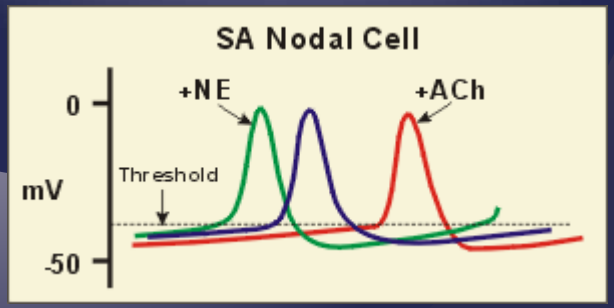




Regulation of Cardiac APs

- PSNS (Vagal N)
- Ach binds M2 rec
- Increases gK+
- Decreases inward Ca & Na
- Non-Nodal tissue:
- More rapid depolarisation
- More forceful contraction
- Pacemaker current (If) suppressed
- Decreases pacemaker rate
- Decrease slope of Phase 4
- Hyperpolarizes in Phase 4
- Longer time to reach threshold voltage





What is an Arrhythmia ?

- Irregular rhythm
- Abnormal Rate
- Conduction abnormality

What are the causes of arrhythmia formation?

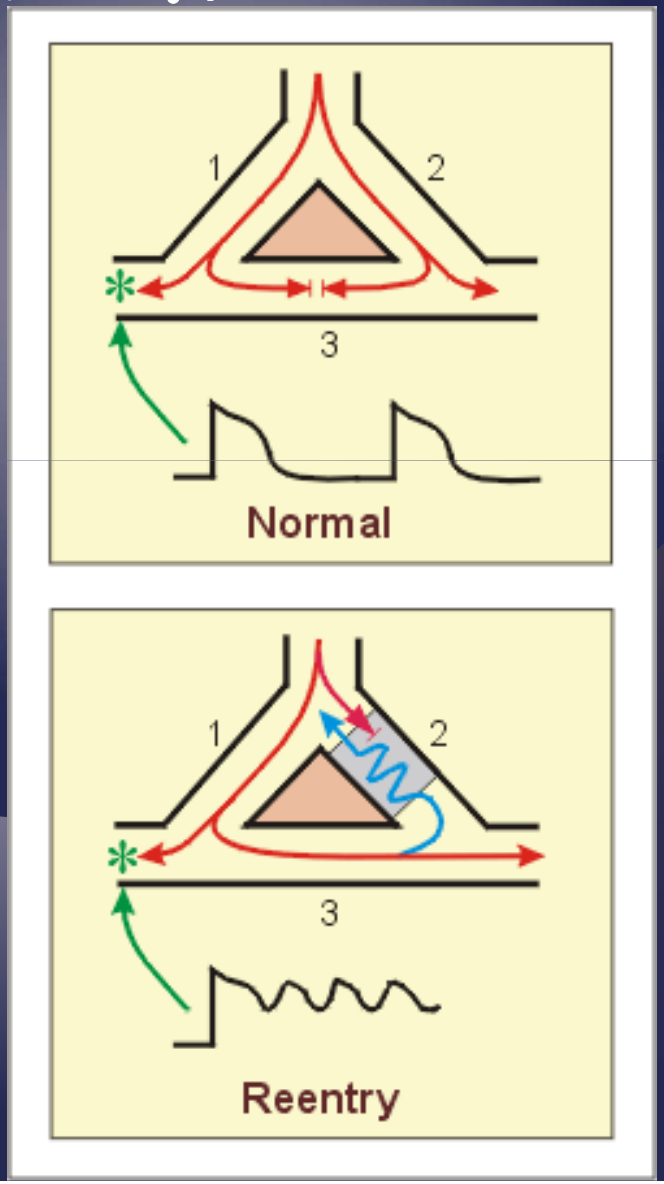
- EAD
- DAD
- Reentry

What causes an arrhythmia?

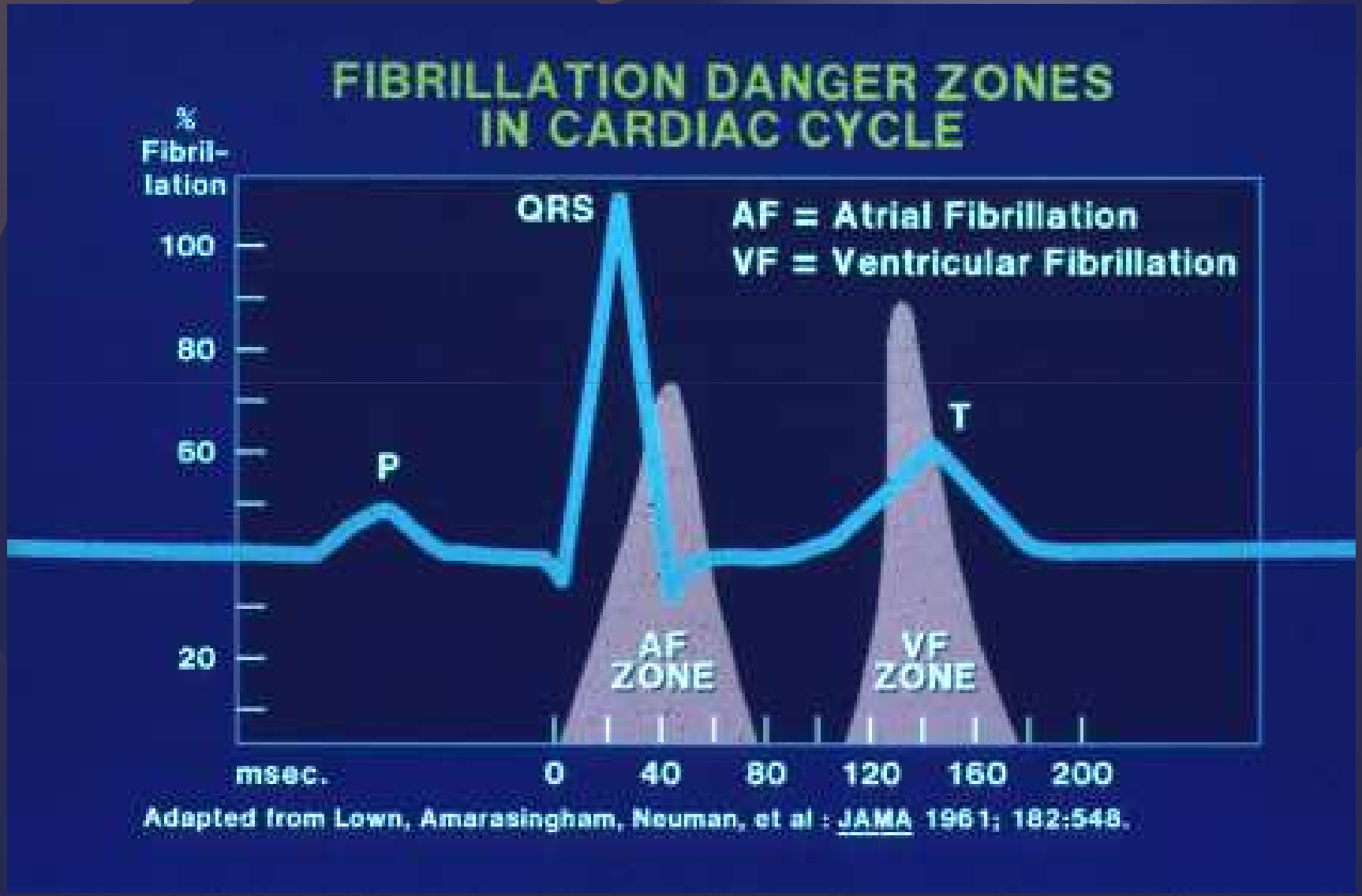
- Changes in automaticity of the PM
- Ectopic foci causing abnormal APs
- Reentry tachycardias
- Block of conduction pathways
- Abnormal conduction pathways (WPW)
- Electrolyte disturbances and DRUGS
- **Hypoxic/Ischaemic tissue can undergo spontaneous depolarisation and become an ectopic pacemaker**

Re-Entry Mechanism

- Branch 2 has a unidirectional block
- Impulses can travel retrograde (3 to 2) but not orthograde.
- An AP will travel down the branch 1, into the common distal path (br 3), then travel retrograde through the unidirectional block in branch 2.
- When the AP exits the block, if it finds the tissue excitable, it will continue by traveling down (reenter) the branch 1.
- If it finds the tissue unexcitable (ERP) the AP will die.
- Tming is critical –AP exiting the block must find excitable tissue to propagate.
- If it can re-excite the tissue, a circular pathway of high frequency impulses (tachyarrhythmia) will become the source of APs that spread throughout a region of the heart (ventricle) or the entire heart.



R on T


FIBRILLATION DANGER ZONES
IN CARDIAC CYCLE
% Fibril-lation
100
80
60
20
QRS
P
T
AF = Atrial Fibrillation
VF = Ventricular Fibrillation
AF ZONE
VF ZONE
msec.
0
40
80
120
160
200
Adapted from Lown, Amarasingham, Neuman, et al : JAMA 1961; 182:548.

Rationale for Antiarrhythmic Drugs

- Restore normal rhythm, rate and conduction or prevent more dangerous arrhythmias

1. Alter conduction velocity (SAN or AVN)

   Alter slope 0 depolarisation or refractoriness

2. Alter excitability of cardiac cells by changing duration of ERP (usually via changing APD)

   ERPinc – Interrupts tachy caused by reentry

   APDinc – Can precipitate torsades

3. Suppress abnormal automaticity

Vaughan-Williams Classification

Class	Mechanism	Example
I	Na channel blockers Membrane Stabilisers	Lignocaine
II	Beta Blockers	Metoprolol
III	K channel blockers	Amiodarone
IV	Ca channel blockers	Verapamil
Other	Digoxin. Adenosine. MgSO4. Atropine	

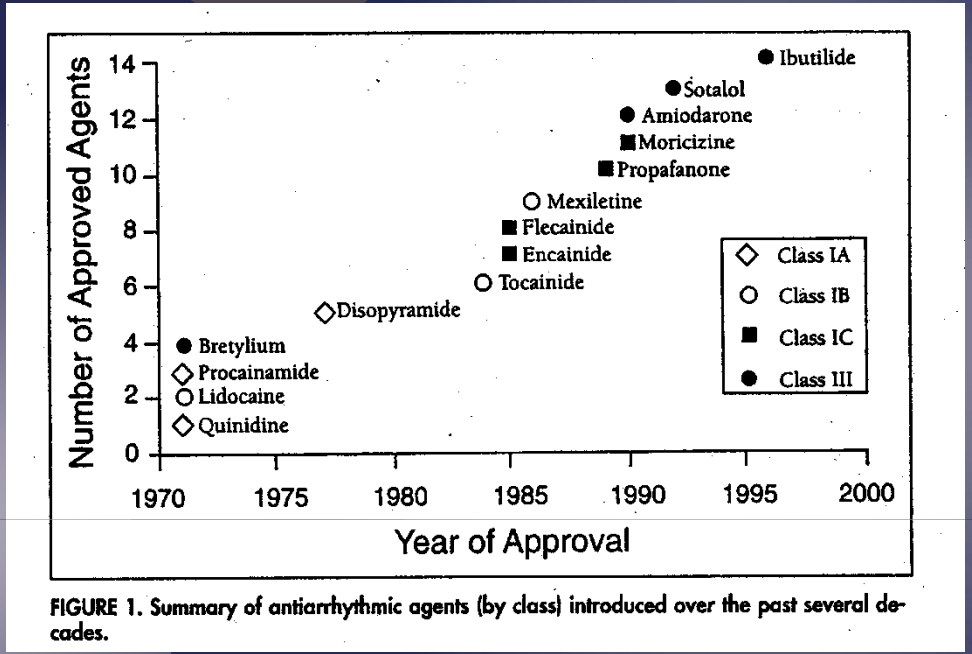


FIGURE 1. Summary of antiarrhythmic agents (by class) introduced over the past several decades.

Antiarrhythmic drugs

Class I A Agents

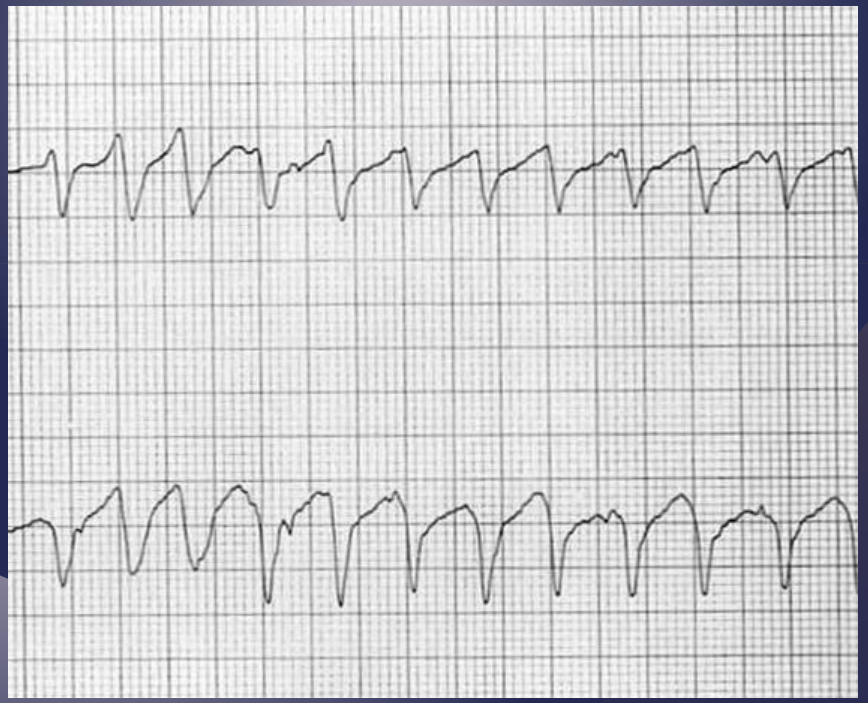
- Block open ACTIVATED Na channels
- Slow phase 0 depolarisation - upstroke of AP
- Lengthen APD and ERP.
- Prolong QRS duration on ECG
- Anticholinergic S/E. Also blocks K Ch.
- Greater affinity for rapidly firing channels
- Disopyramide: Prevent rec VT. - Inotrope
- Quinidine: SVT and VT. Torsades
- Procainamide

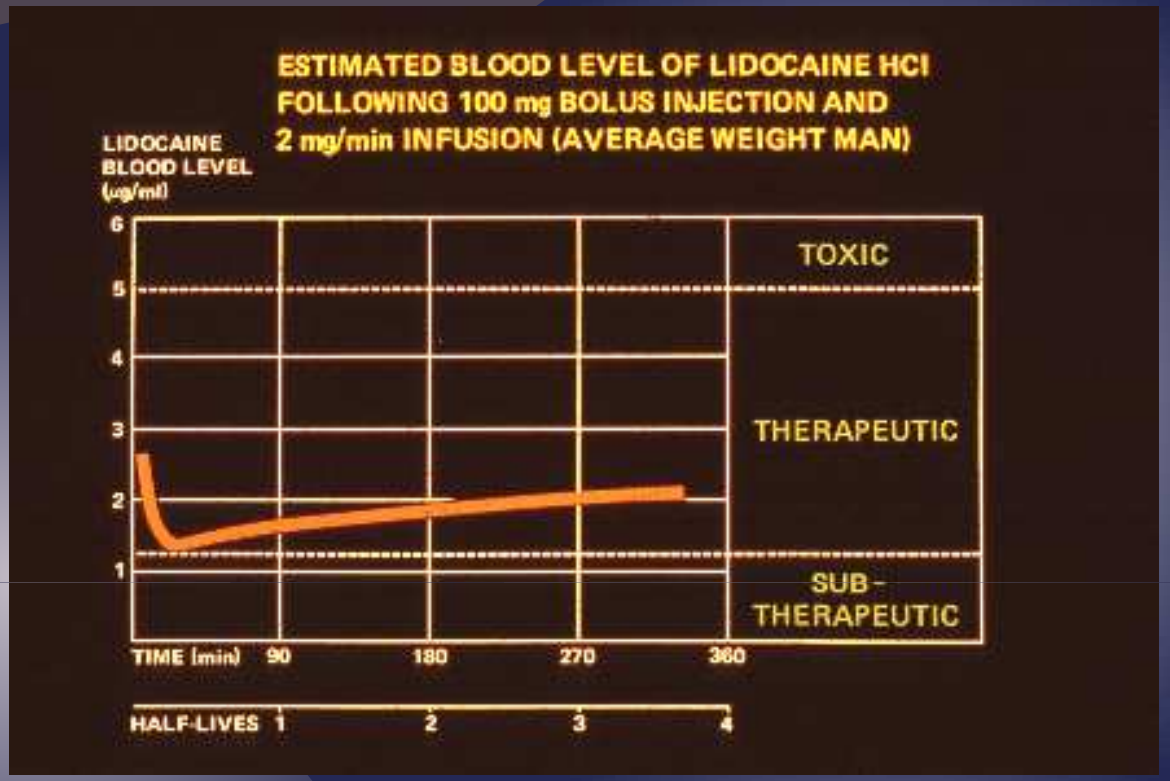
Class I B Agents

- Block INACTIVATED Na channels
- Slow phase 0 depolarisation- Slows upstroke of AP
- Shorten APD and ERP
- Ratio ERP/APD is increased
- Greater affinity for ischaemic tissue that has more inactivated channels, little effect on normal cells – dissociates quickly (0.5sec)
- Lignocaine: VT in heart with normal EF
- Phenytoin

LIGNOCAINE

- - Cardiac arrest: 1-1.5 mg/kg to max 3mg/kg
- - Stable wide complex tachycardia: Start lower 0.5
- Especially in presence of ischaemia
- Not if poor cardiac function (Poor EF)
- Watch for signs of toxicity
- New algorithm only in cardiac arrest
- Infusion within 10 min of effect - 1-4 mg/min





Lidocaine infusion

Class I C Agents

- Block Na channels.
- Most potent Na channel block
- Dissociate very slowly (10-20 sec)
- Strongly depress conduction in myocardium
- Slow phase 0 depolarisation - upstroke of AP
- No effect on APD
- No effect on QRS
- Flecainide: Prophylaxis in paroxysmal AF
- Propafenone

Class II Agents

- Beta Blockers - Block B1 receptors in the heart
- Decrease Sympathetic activity
- Non-Nodal Tissue:
- Increase APD and ERP
- SA and AVN:
- Decrease SR
- Decrease conduction velocity (Block re-entry)
- Inhibit aberrant PM activity

ATENOLOL

- selective B-Blocker
- Indications: Convert or Slow rate in SVTs
- 2nd line after Adenosine/Digoxin/Diltiazem
- IV atenolol 5 mg over 5 minutes
- Repeat to maximum 15 mg.
- 50 mg PO BID if IV works
- Contraindiactions:
- Asthma
- CCF. Poor EF. High degree heart block.
- Ca channel blockers. Cocaine use.

Post MI: Beta blockers

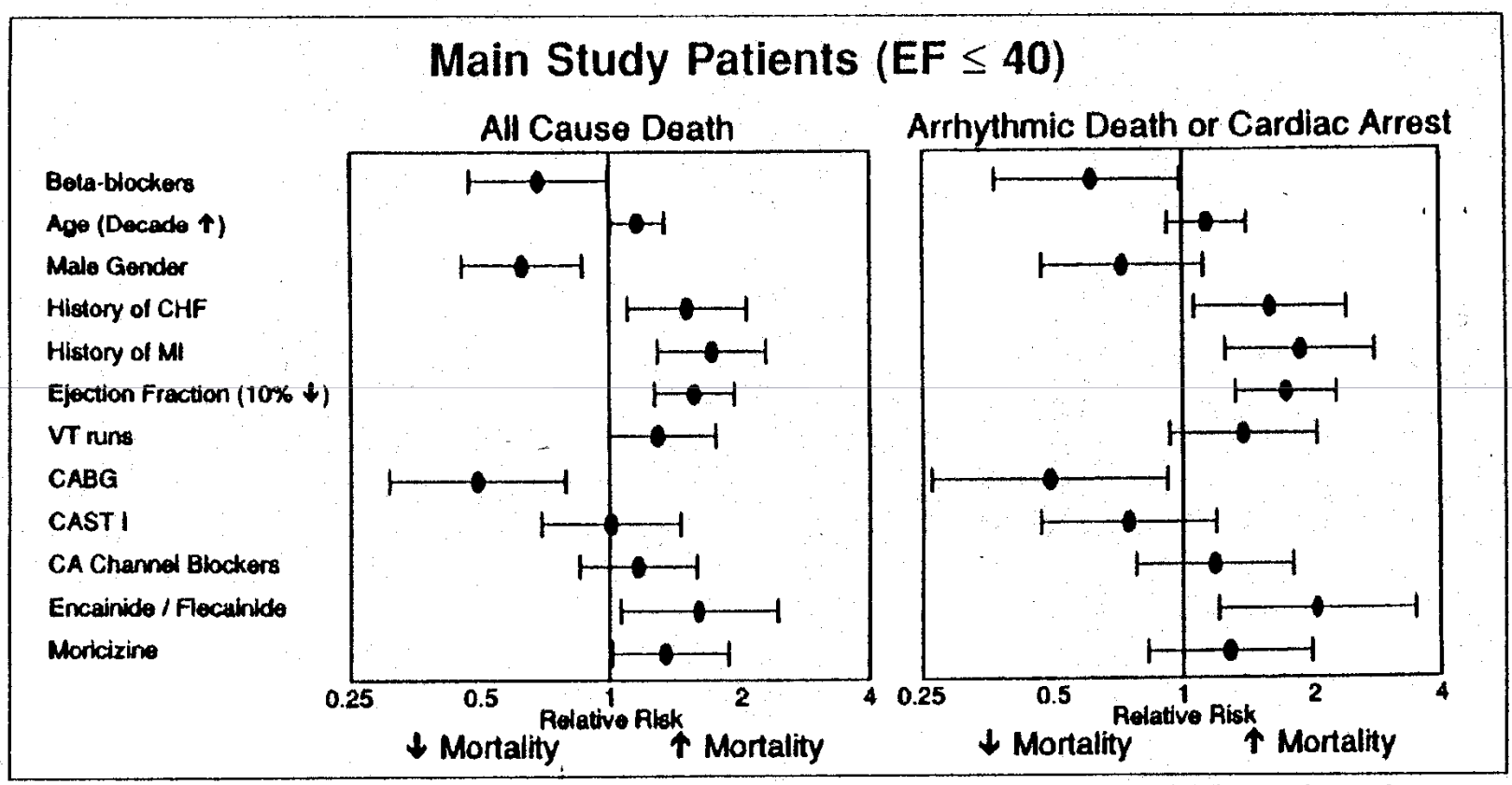


FIGURE 4. Effect of β-blocker therapy and other clinical/historical variables on mortality of 1,735 main study patients with an ejection fraction ≤40% after adjustment for associated variables. Hazard ratios and 95% confidence interval for end points of all-cause death (192 total events) and arrhythmic death or nonfatal cardiac arrest (115 total events) are given. CA = calcium; CABG = coronary artery bypass grafting after the index myocardial infarction; CAST = Cardiac Arrhythmia Suppression Trial; CHF = congestive heart failure; MI = myocardial infarction; VT = ventricular tachycardia.

Class III Agents

- Anti-Fibrillatory agents.
- Block K channels
- Prolong repolarisation
- Prolong APD and ERP
- Useful in Re-Entry tachycardias
- AMIODARONE (also Class IA, II BB)
- SOTALOL (also Class II BB)

AMIODARONE

- Most tachyarrhythmias
- OK if impaired LV function
- Rate control and converts rhythm
- Cardiac arrest: 300 mg IV push (max 2.2g/24hrs)
- Stable VT: 150 mg IV repeat 10 min or infusion 360 mg IV over 6 hrs (1mg/min)
- Maintenance infusion: 540 mg over 18 hrs (0.5mg/min)
- Side Effects:
- Hypotension. Negative Inotropy. Prolonged QT.
- Photosensitivity. Thyroid disorders.
- Pulmonary alveolitis. Neuropathy.

Amiodarone

- Meta-analysis: confers some benefits of survival
- CAMIAT and EMIAT trials found a reduction in arrhythmic deaths but with no effect on total mortality

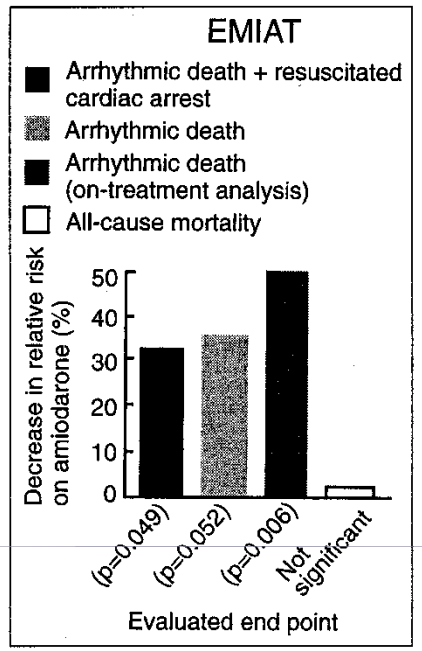


FIGURE 4. Principal outcomes on amiodarone in the European Myocardial Infarction Amiodarone Trial (EMIAT). (Reprinted with permission from *Clin Cardiol.*[78])

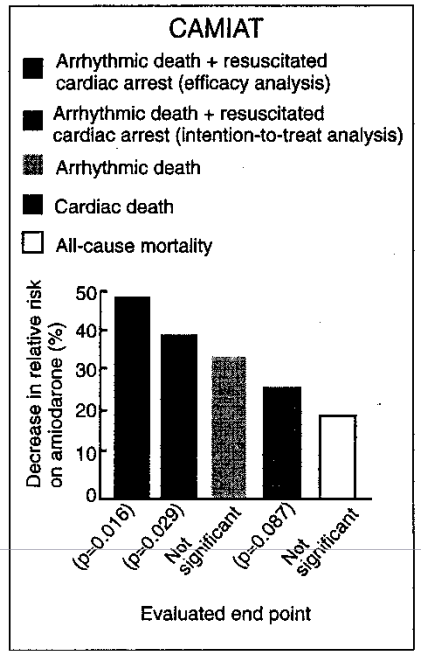


FIGURE 5. Principal outcomes on amiodarone in the Canadian Myocardial Infarction Amiodarone Trial (CAMIAT). (Reprinted with permission from *Clin Cardiol.*[78])

CAMIAT/EMIAT trials

Class IV Agents

- Calcium Channel Blockers
- Bind to L-type Ca channels
- Vascular SmM, Cardiac nodal & non-nodal cells
- Decrease firing rate of aberrant PM sites
- Decrease conduction velocity
- Prolong repolarisation
- Especially active at the AVN
- VERAPAMIL
- DILTIAZEM

VERAPAMIL

- Narrow complex tachycardias
- Terminates PSVT/SVT
- Rate control in AFib/Aflutter
- NOT WPW or VT or high degree block
- NOT with BBlockers
- Negative Inotropy
- Vasodilation – Hypotension
- Dose: 5mg IV bolus. Rpt 15 min max 30 mg
- Diltiazem less adverse effects

What does Adenosine Do?

- Purine nucleoside
- Acts on A1 adenosine receptors
- Opens Ach sensitive K channels
- Inhibits Ca in current – Suppresses Ca dependent AP (Nodal)
- Increases K out current – Hyperpolarisation
- Inhibits AVN > SAN
- Increases AVN refractory period

ADENOSINE

- Interrupts re-entry and aberrant pathways through AVN – Diagnosis and Treament
- Drug for narrow complex PSVT
- SVT reliant on AV node pathway
- NOT atrial flutter or fibrillation or VT
- <u>Contraindications:</u>
- VT – Hypotension and deterioration
- High degree AV block
- Poison or drug induced tachycardia
- Bronchospasm but short DOA

ADENOSINE

- Carotid massage and vagal maneuvers first
- Rapid IV push 6mg – 12 mg – 12 mg
- Flush with 20ml
- Record rhythm strip
- FLUSHING
- CHEST PAIN
- ASYSTOLE/BRADY
- VENTRICULAR ECTOPY

What does Digoxin Do?

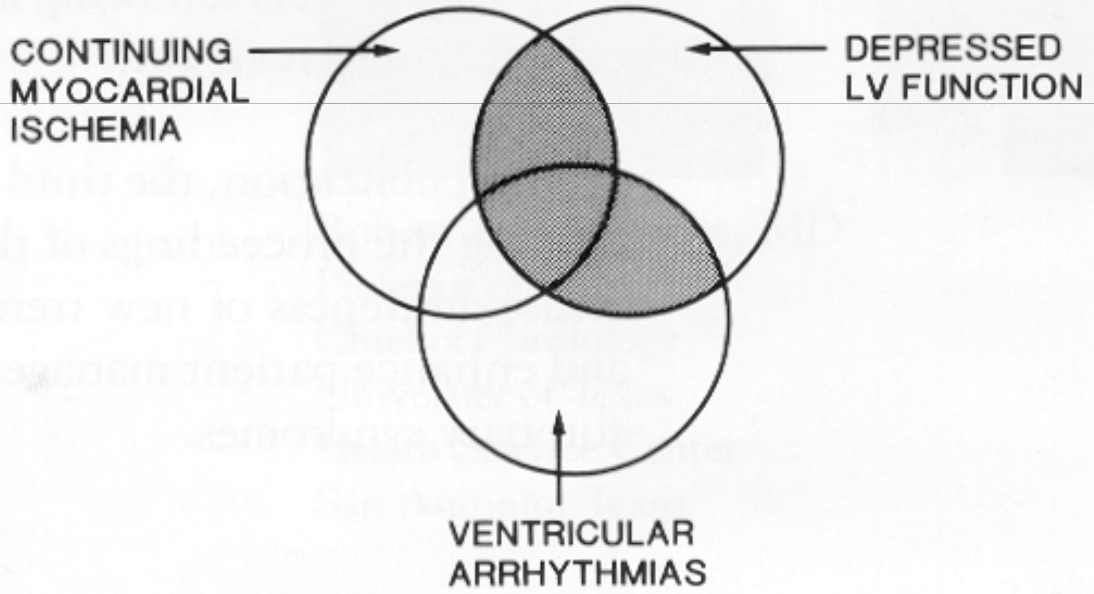
- Cardiac glycoside
- Blocks Na/K ATPase pump in heart
- Less ECF Na for Na/Ca pump
- Increased IC Ca
- Inotropic: Increases force of contraction
- AVN increased refractoriness
- Decreases conduction through AVN and SAN
- Negative chronotrope: Slows HR

Reduces ventricular response to SVTs

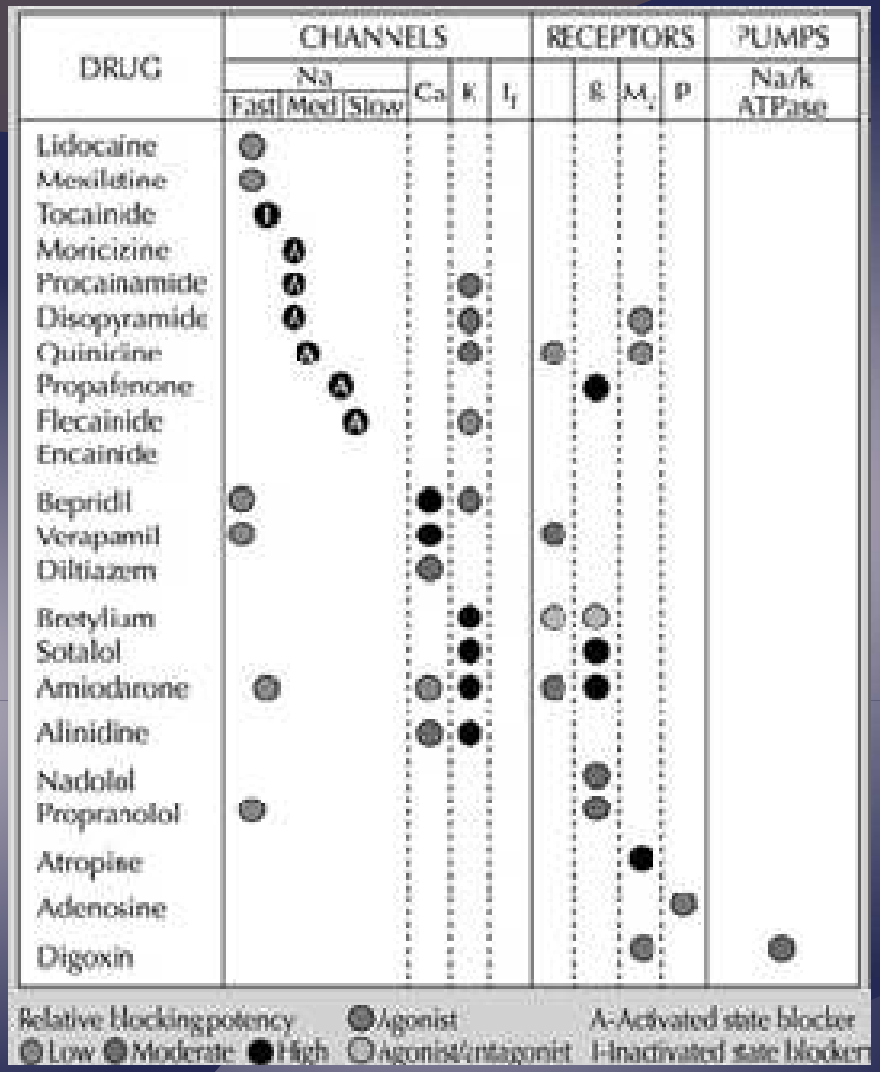
DIGOXIN

- Contraindications: WPW. SSS.
- Elderly or renal failure – reduce dose or TOXICITY
- 0.25 to 0.5 mg IV; then 0.25 mg IV every 4 to 6 hours to maximum of 1 mg
- 0.125 to 0.25 mg per day IV or orally

Factors Indicating a Higher Risk of Reinfarction



Ventricular arrhythmias – clinical situations



Sicilian Gambit (1991)

Post MI – antiarrhythmic therapay

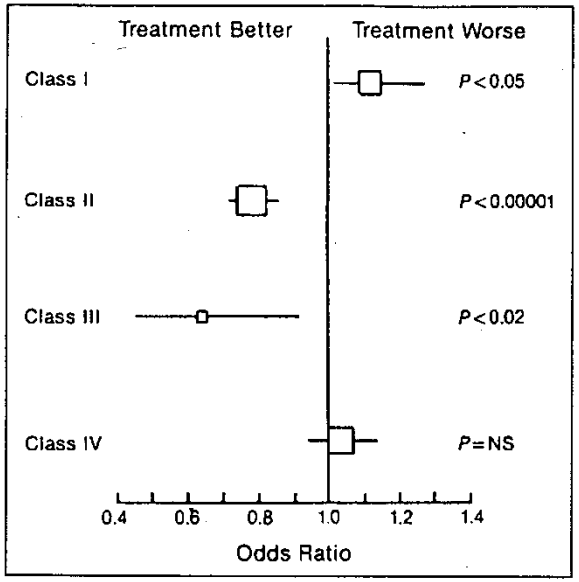
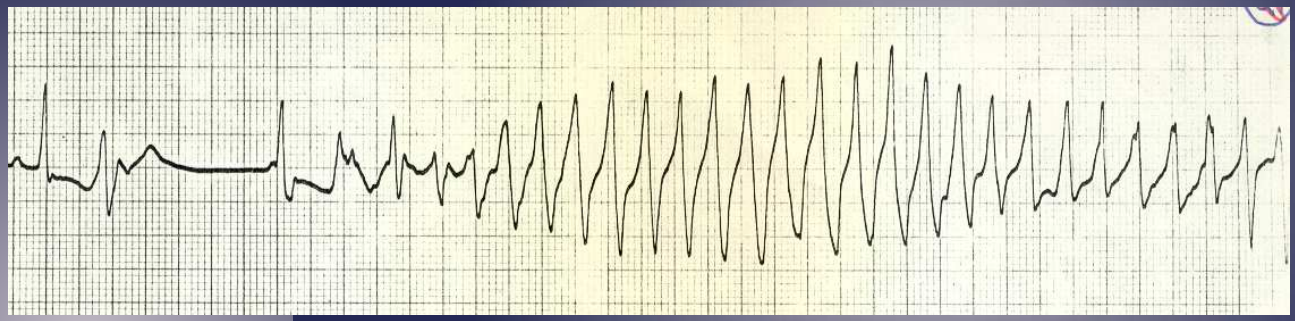


FIGURE 1. The mean results of meta-analysis of randomized trials with antiarrhythmic agents in survivors of acute myocardial infarction. The impact of the various electrophysiologic agents on mortality compared with that on placebo or no treatment. The odds ratios (with 95% confidence intervals) for treatment are presented. The figure is based on the data reported by Yusuf and Teo.[15] Note that class I agents *increase* mortality; β blockers and class III agents (essentially amiodarone) *decrease* it; the effects of calcium antagonists appear to be neutral, but individual agents may either slightly decrease or increase mortality.



Torsades de pointes

Prospective studies

- – CAST I. fleicainid, encainid (1989)
- – CAST II. moricizin (1992)
- – SWORD l-sotalol (1996)

Take-Home Message

- Anti-arrhythmics are also pro-arrhythmics
- Dangerous side effects
- If patient is unstable rather cardiovert
- Ablation
- Beta-blockers
- Amiodarone
- OMV (Oxygen, Monitor, Vein)