Antiarrhythmic Drugs (AADs)

Class I
[Membrane stabilizing agents]

(a)
moderate decrease in dv/dt of phase 0
- Quinidine
- Procainamide
- Disopyramide

(b)
little decrease in dv/dt of phase 0
- Lidocaine
- Mexiletine

(c)
marked decrease in dv/dt of phase 0
- Propafenone
- Flecainide

Class II
(Antiadrenergic agents)
- Propranolol
- Esmolol
- Metoprolol
- Atenolol

Class III
[Agents widening AP]
- Amiodarone
- Dronedarone
- Sotalol
- Dofetilide
- Ibutilide

Class IV
[Ca^{2+} Channel Blockers]
- Verapamil
- Diltiazem

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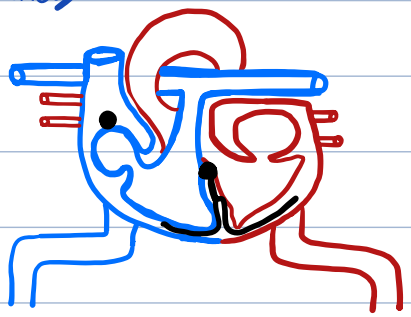
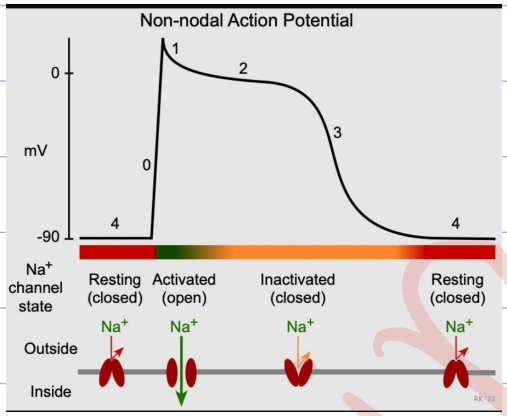
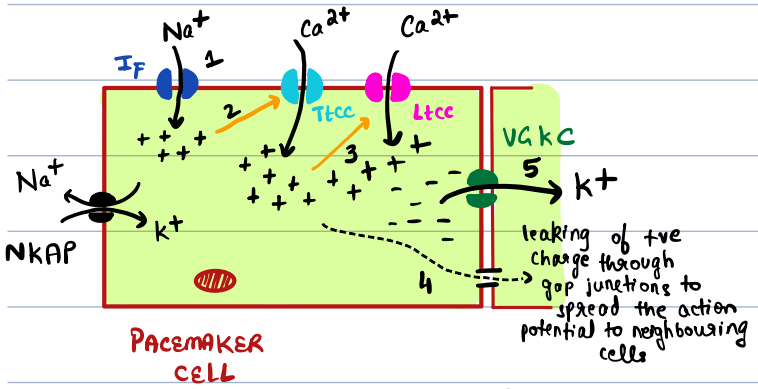
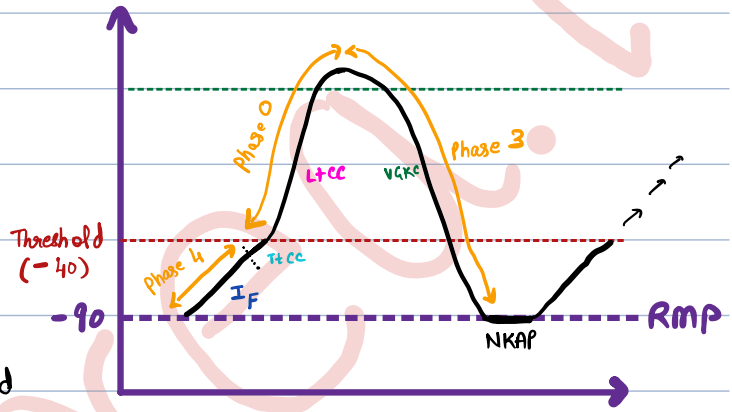
SA node (pacemaker)
↓
AV node
↓
Bundle of His
↓
RBB LBB
↓
Purkinje Fibres









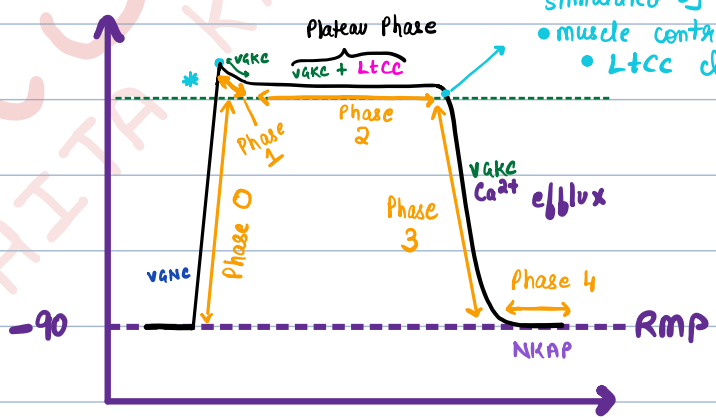
I_F = funny Na^+ inward channel (always open) } close once threshold potential is achieved

TtCC = T-type Calcium Channel
LtCC = L-type Calcium Channel } close once 0mV is crossed

VGKC = Voltage-gated K^+ Channel

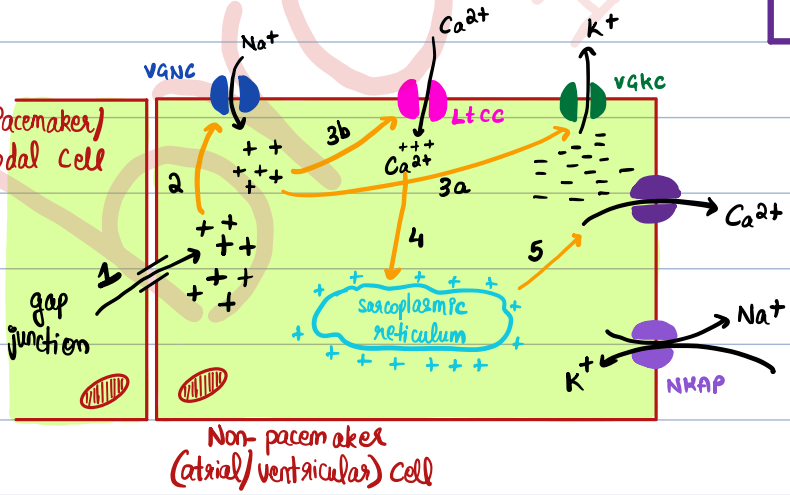
NKAP = Na^+/K^+ ATPase Pump

SLOW AP
(Pacemaker cells/tissue)
[Tissue of nodal System]



- sarcoplasmic reticulum is stimulated by LtCC
- muscle contraction
- LtCC closes

VGNC = voltage-gated Na^+ channel
* closure of inactivation gate of VGNC
VGKC is activated slightly earlier than LtCC resulting in a small dip in the graph.



FAST AP
Atrial & Ventricular Cells
(Non-pacemaker Cells)

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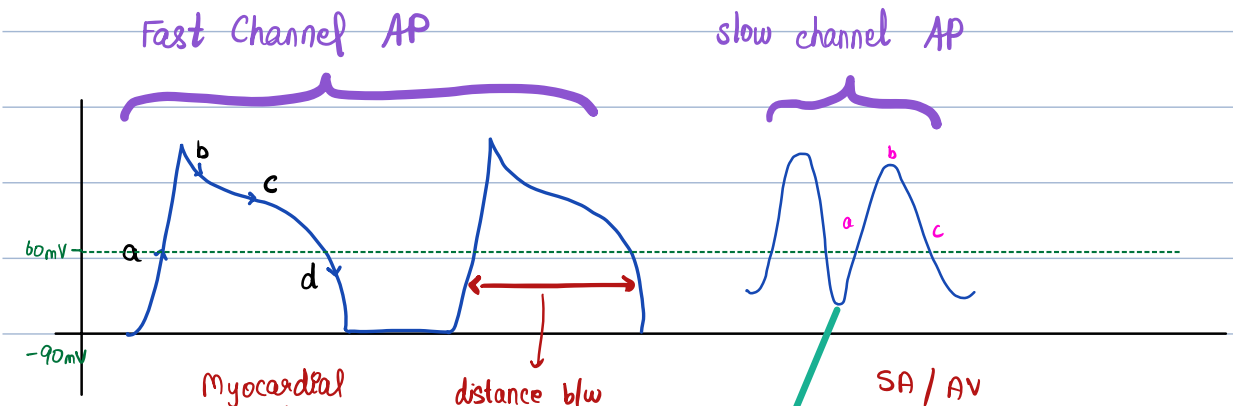
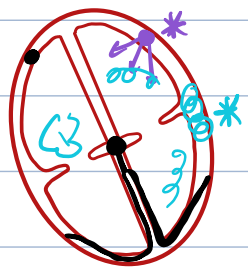


1- ⓐ Na^+ open
2- ⓑ loss of K^+ ions
3- ⓒ opening of Ca^{2+}
4- ⓓ K^+ open

Arrythmias:

Mechanisms

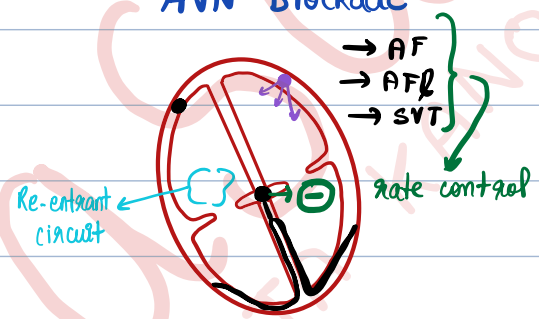


[I] ↑ automaticity
- ↑ SA node
- ↑ AV node

[II] Triggered activity * (of non-pacemaker cells)
- EADs (Early after depolarization)
- DADs (delayed " ")

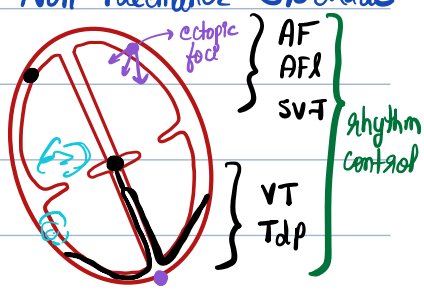
[III] Re-entrant Circuits *
- Anatomical (WPW syndrome)
- Functional

AVN Blockade



[I] β-blockers / Class II AAD
[II] Ca^{2+} Channel blockers (Class IV AAD)
[III] Adenosine (Class V)
[IV] Digoxin (Class V)

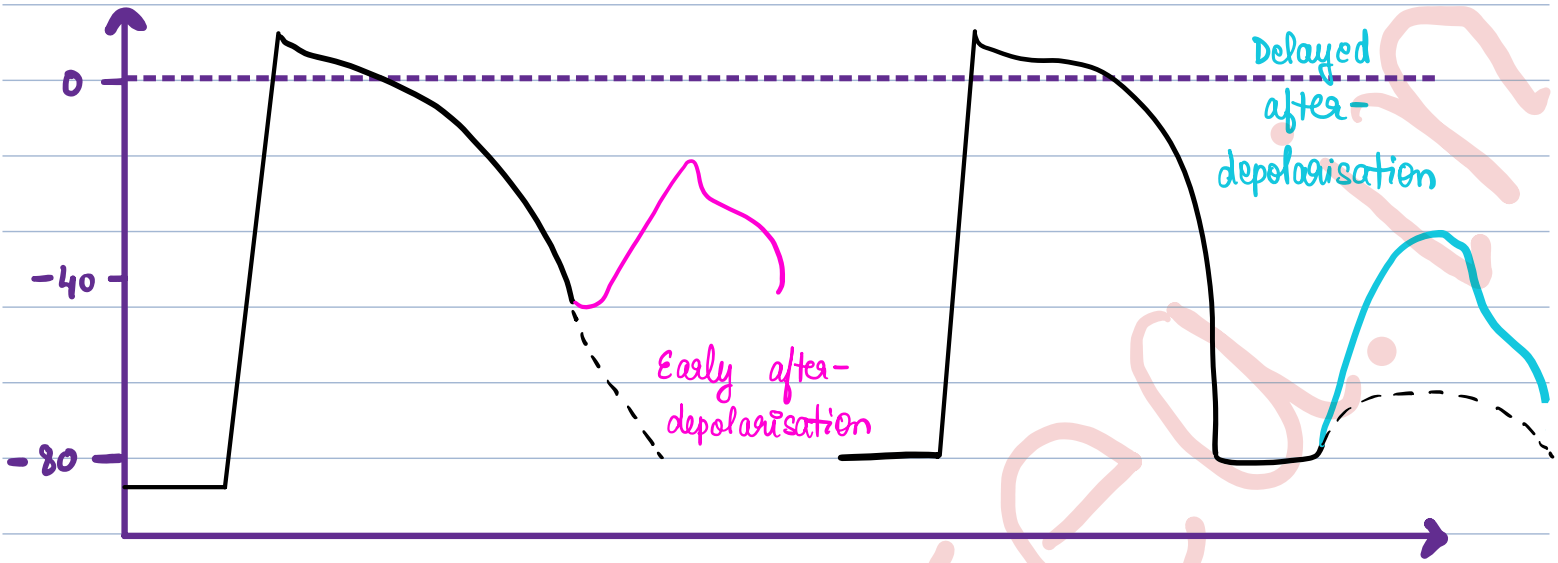
Non-Pacemaker Blockade



[I] Na^+ Channel Blockers (Class I AAD)
[II] K^+ Channel Blockers (Class III AAD)
[III] ± Beta blockers (Class II AAD)

Mechanisms of Arrhythmias:

- Enhanced / ectopic pacemaker activity
- After-depolarizations
  - early
  - delayed
- Re-entry



Enhanced / Ectopic Pacemaker Activity:

→ myocardial cells damaged by ischaemia become partially depolarised ⇒ a current flows between these cells ⇒ Ectopic pacemaker activity of non-pacemaker tissue

→ Increased slope of phase-4 depolarisation in nodal cells ⇒ enhanced pacemaker activity of pacemaker tissue.

(aka triggered arrhythmias)

After-Depolarisations: secondary depolarisations accompanying a normal / premature action potential.

EAD: → repolarisation during phase 3 is interrupted

↓

oscillation of membrane potential

↓

sufficiently large oscillations activate neighbouring tissue

↓

generation of extra impulses propagated

DAD: secondary deflection during phase 4 which may reach threshold potential & initiate a single premature AP.

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(Re-entral arrhythmias)

Re-entry: recirculation of an impulse which causes repetetive activation without the need for a new impulse to be generated.

Circus Movement Re-entry: occurs in an anatomically defined circuit; impulse makes a one-way transit around an obstacle/through an abnormal tract.

- → PVST → atrioventricular reciprocal rhythm in WPW syndrome.
- → Atrial flutter
- Permanent cure - radiofrequency catheter ablation of defined pathway

Functional Reentry: no fixed obstacle

→ functional pathway is created by a premature impulse which travels through electrophysiologically inhomogenous myocardium

→ Ventricular extrasystoles → Polymorphic ventricular tachycardia

→ atrial / ventricular fibrillation

- For re-entry to occur, path length of circuit > wave length (ERP x conduction velocity)

Fractionation of Impulse: asynchronous activation of atrial fibres due to difference in duration of ERP of fibres ⟹ atrial fibrillation

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Important Types of Cardiac Arrhythmias:

Extrasystole [ES]: premature ectopic beats due to abnormal automaticity or after-depolarization

- Atrial ES (AES)
- Nodal ES (NES)
- Ventricular ES (VES)

Paroxysmal Supraventricular Tachycardia (PSVT): sudden onset episodes of atrial tachycardia (150-200 / min) with 1:1 atrioventricular conduction

→ re-entry with or around the AV node or accessory pathways (WPW syndrome)

Atrial Flutter (AFl): atrial rate = 200-350 /min

→ physiological 2:1 to 4:1 or higher AV block (∵ AV node cannot transmit impulses faster than 200/min)

Atrial Fibrillation (AF): atrial rate = 350-550 /min (due to electrophysiological inhomogeneity of atrial fibres) associated with irregular & fast (100-160 /min) ventricular response

↳ atria is dilated ; bag of worms appearance

→ most common chronic arrhythmia

Ventricular Tachycardia (VT): 4 or more consecutive ventricular extrasystoles

Torsades de pointes: life-threatening form of polymorphic VT with rapid QRS complexes

→ long Q-T interval (TdP)

→ Predisposing factors – hypokalemia – hypomagnesemia

Ventricular Fibrillation (VF): irregular, rapid & fractionated activation of ventricular fibres leading to asynchronous contractions ⟹ loss of pumping function

→ fatal unless reverted within 2-5 mins.

→ most common cause of sudden cardiac death

AV block: due to depression of impulse conduction through AV node & bundle of His

First degree: slowed conduction resulting in prolonged P-R interval (> 0.21 s)

Second degree: dropping of beats (some supraventricular complexes are not conducted)

Third degree: no supraventricular complexes are conducted. aka complete heart block.

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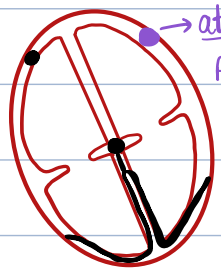
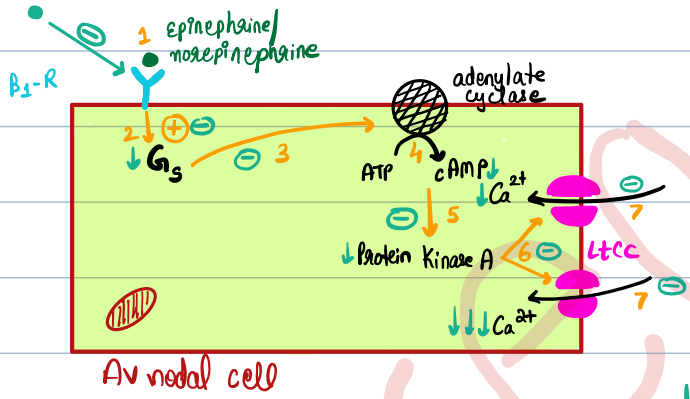
β-blockers (Type II): Metoprolol, Atenolol, Propranolol, Esmolol



→ atrial focus generating APs faster than SA node

G_s = G - stimulatory protein

6 = phosphorylation of LtCC



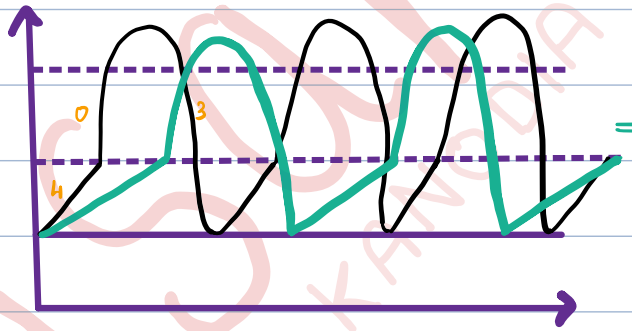
- Atrial fibrillation (AF)
- Atrial flutter (AFl)
- Supraventricular tachycardia (SVT)

→ Rate control

Inhibition of opening of LtCC

↓ Slope of phase 4 & phase 0

⇒ decreased frequency of APs



Propranolol: for rapid action ⇒ injected i.v. 1 mg/min (max. 5 mg) under close monitoring

- usual oral antiarrhythmic dose ⇒ 40-80 mg 2-4 times a day.
  - → useful in Tx of inappropriate sinus tachycardia

Esmolol: mainly used for arrhythmias associated with anaesthesia

MINIBLOCK 100 mg/10 mL, 250 mg/10 mL inj. ; 0.5 mg/kg in 1 min followed by 0.05 - 0.2 mg/kg/min i.v. infusion.

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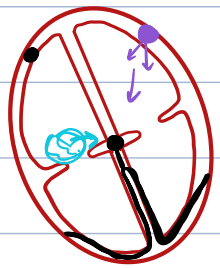
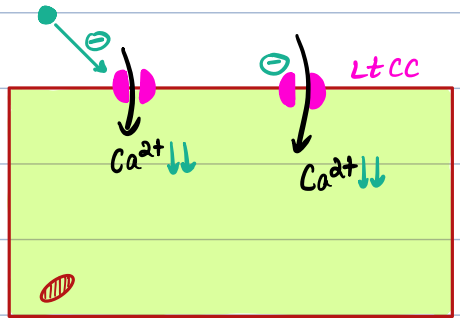
Ca^{2+} Channel Blockers (CCBs): (Type IV) Verapamil, Diltiazem

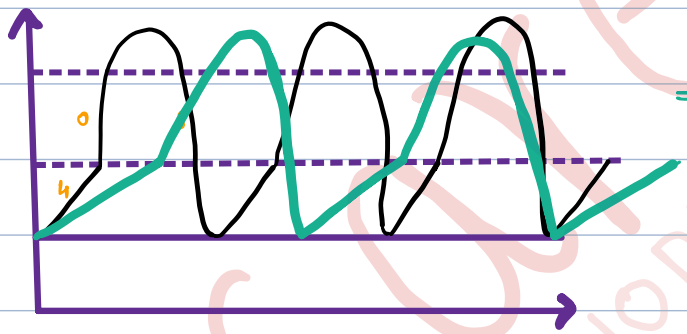




- AF
- AFl
- SVT

→ Rate control

Inhibition of opening of LtCC
↓
↓ Slope of phase 4 & phase 0
↓
⇒ decreased frequency of APs



Verapamil: C/I in partial heart block & sick sinus (due to -ve inotropic activity)

CALAPTIN 40, 80 mg tab; 120, 240 mg SR tab, 5mg/2ml inj.

Uses – PSVT

– To control ventricular rate in AF or AFl

Diltiazem: DILZEM 30, 60, 90 mg tabs, 25 mg/5ml inj.

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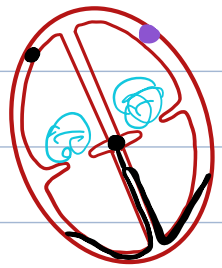
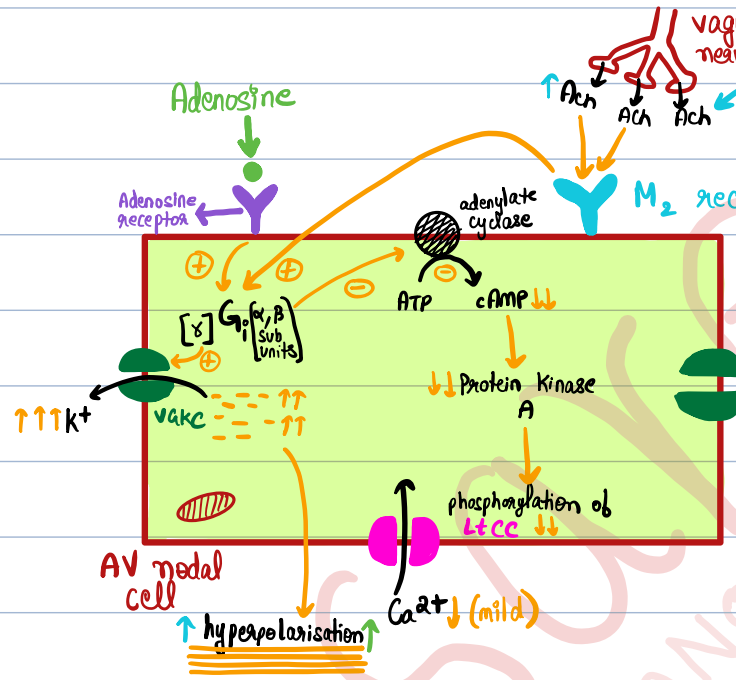
↳ particularly indicated in SVT (due to short action ∴ AF, AFl ✗✗)

Adenosine & Digoxin (Type V):

↳ primarily used in AF + $HF_{r}EF$ (AFl, SVT ✗✗)

G_i = G-inhibitory protein





Both Adenosine & Digoxin

↓

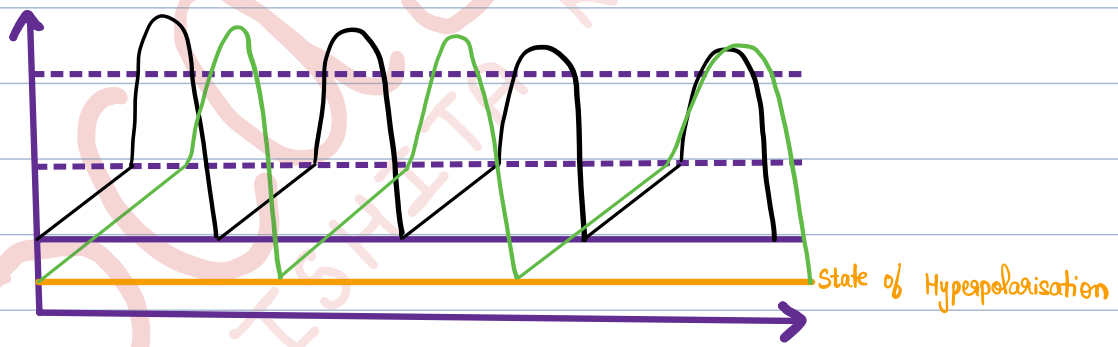
Hyperpolarize the cell

↓

Increase the time required to achieve threshold potential

↓

decreased frequency of AP



Adenosine: ADENOJECT, ADENOCOR 3 mg adenosine (base) per ml in 2ml & 10ml amp.

Other uses :- diagnosis of tachycardias dependent on AV node.

- to induce brief coronary vasodilatation during certain diagnostic procedures
- to produce controlled hypotension during Sx.

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↳ low therapeutic index drug

→ Digoxin ⇒ obtained from plant Digitalis lanata.

↳ c/I ⇒ partial/complete heart block

→ commonest arrythmia associated with digoxin = Bigeminy.

Dose:- daily maintenance dose = 0.125 – 0.5 mg

Precautions & Contraindications of Digoxin:

- Hypokalemia: enhances digitalis toxicity
- Elderly, renal or severe hepatic disease: patients are more susceptible to digoxin toxicity
- Thyrotoxicosis: patients are more prone to develop digitalis arrhythmias
- Hypothyroidism: slowed digoxin elimination
- Ventricular tachycardia: digitalis precipitates ventricular fibrillation
- Partial AV block: may be converted to complete AV block with digitoxin
- WPW syndrome

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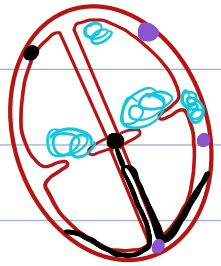
Na^+ Channel Blockers (Type I): act in open & inactivated state of Na^+ Channels

Type Ia: Disopyramide, Quinidine, Procainamide (only theoretically used)

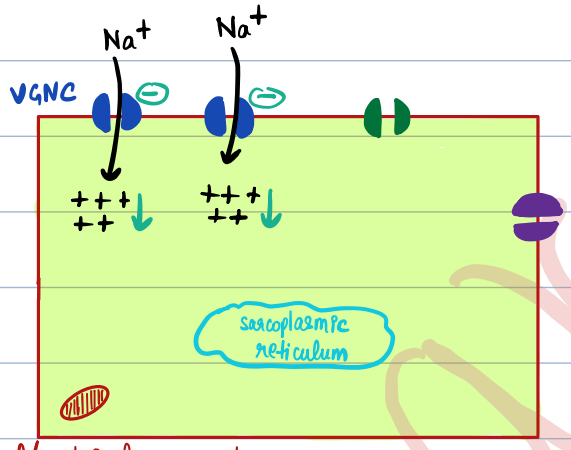
Type Ib: Lidocaine, Mexiletine, Tocainide

Type Ic: Flecainide, propafenone
→ effective only in ventricular tachyarrhythmias

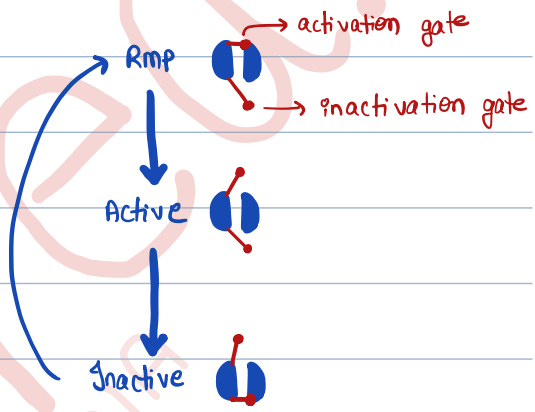


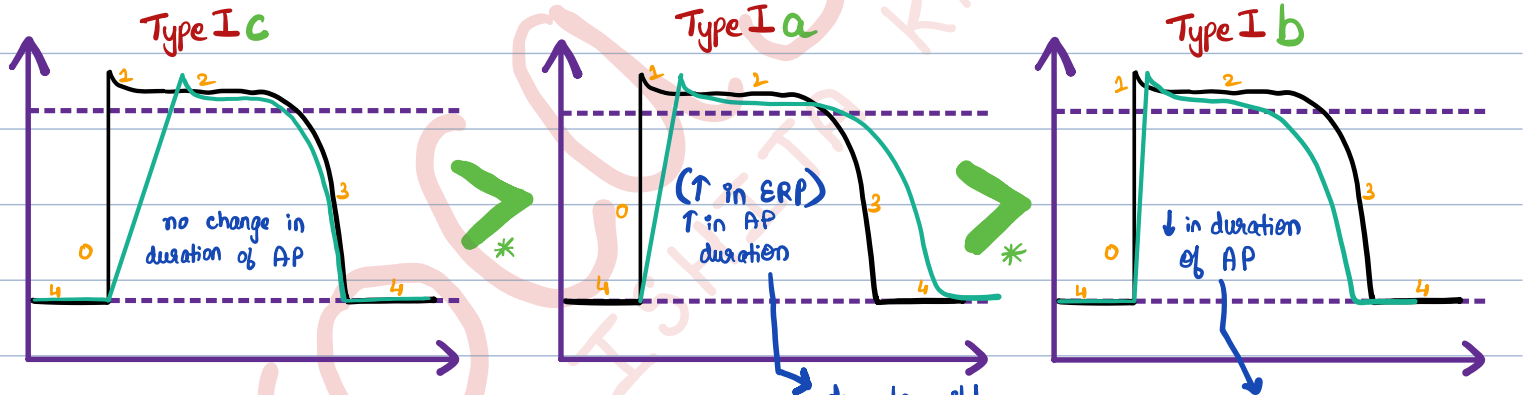
- AF
- AFl
- VT
- Tdp

→ cardiovert



Atrial/ventricular myocyte or re-entrant circuit cells





phase 0 slope ⇒ c < a < b

* degree of Na^+ Channel blockade (slope of phase 0 ↓)

due to mild simultaneous K^+ channel blockade

(ERP = effective refractory period)

due to ↓ in ERP

Cardioversion: use of quick low-energy shocks to restore a regular heart rhythm

→ not the same as defibrillation (defibrillation uses higher-energy shocks)

→ given via electrode patches connected to the cardioversion machine (cardioversion pads)

Quinidine:

ECG changes ⇒ ↑PR & QT intervals ⇒ Change in shape of T-wave may be seen
⇒ broaden QRS complex

Use: In a dose of 100-200 mg TDS ⇒ to maintain sinus rhythm after termination of AF or AFL

QUINIDINE SULPHATE 200 mg tab ; NATCARDINE 100 mg tab.

↳ used for haemodynamically stable ventricular tachycardia

Procainamide: → second line drug to terminate monomorphic VT

Dose:
- For abolition of arrhythmia: 0.5-1 g oral/i.m. followed by 0.25-0.5 g every 2 hours (or)
- 500 mg i.v. loading dose (25 mg/min) followed by 2mg/kg/hour ; maintenance dose = 0.5 g every 4-6 hours

PRONESTYL 250 mg tab , 1 g/10 ml injection

Disopyramide: primary indication ⇒ 2nd line drug for prevention of recurrences of ventricular arrhythmias

Dose: 100-150 mg 6-8 hourly oral

NORPACE 100, 150 mg cap. ; REGUBEAT 100 mg tab.

Lidocaine / Lignocaine: → ineffective in atrial arrhythmias ; used to suppress VT & prevent VF.

Dose: given only by i.v. route : 50-100 mg bolus followed by 20-40 mg every 10-20 min or 1-3 mg/min infusion.

XYLOCARD, GESICARD 20 mg/ml inj. (5, 50 ml vials)

→ propranolol prolongs t ½ of lidocaine ; cimetidine increases plasma levels of lidocaine.

Uses of Lidocaine: • suppress VT • prevent VF

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Mexiletine: Bradycardia, hypotension, attenuation of AV block may attend i.v. injection of mexiletine

Dose: 100-250 mg i.v over 10 min., 1 mg/min infusion

oral - 150-200 mg TDS with meals

Use:- In Post-infarction sinister ventricular arrhythmias as an alternative to lidocaine

Propafenone: Dose: 150 mg BD - 300 mg TDS

RHYTHMONORM, PRADIL 150 mg tab.

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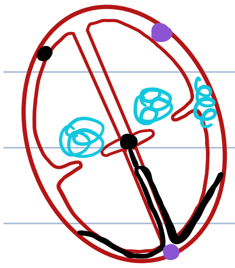
K⁺ Channel Blockers (Type III):

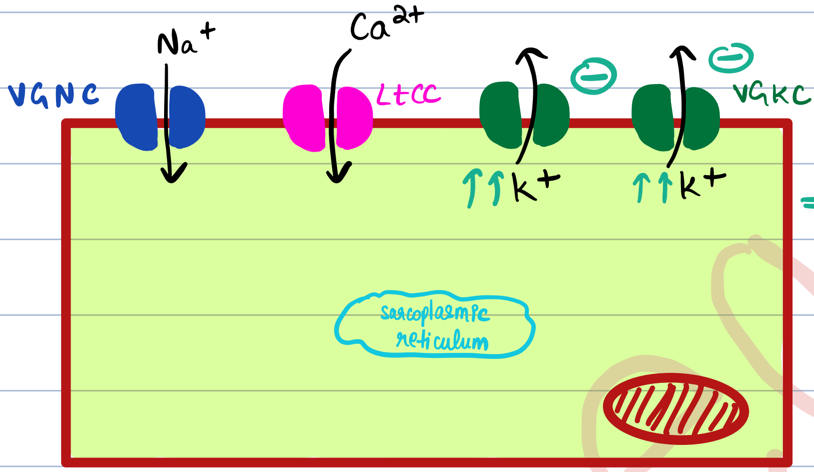
[AIDS] Amiodarone, Ibutilide, Dofetilide & Dronedarone, Sotalol



- AF
- AFl
- VT

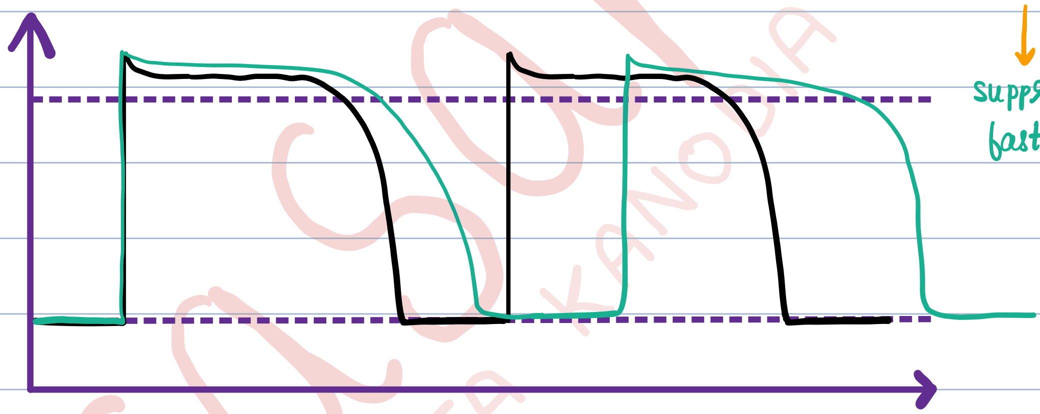
} → rate control

(cardio-version)



⇒ decreased K+ efflux
↓
slower phase 1, phase 2 & phase 3
↓
↑ERP
↑AP duration
↓
suppression of fast impulses

VT= ventricular tachyarrhythmia



↑ in duration of AP
↑ in ERP

Amiodarone, Sotalol } → suppress both atrial & ventricular tissue

All others → suppress atrial tissue only

Amiodarone: Dose: mainly used orally 400-600 mg/day for few weeks, followed by 100-200 mg OD for maintenance therapy, 100-300 mg (5mg/kg) slow i.v inj. over 30-60 min.

CORDARONE, ADARONE, EURHYTHMIC 100, 200 mg tabs., 150 mg/3mL inj.

→ increases digoxin & warfarin levels (by reducing their renal clearance)

Dronedarone: c/I in moderate to severe CHF, 2nd/3rd degree AV block, permanent AF.

Dose: 400 mg BD oral; MULTAQ, DILSAVE 400 mg tab.

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Sotalol: c/I in prolonged QT interval

SOTALAR 40 mg tab, SOTAGARD 40, 80 mg tabs.

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Indications of AADs:

AF/AFl

Rate Control
[⊖ AVN]
- → β-blockers
- → CCBs
- → Digoxin (+ HF, EF)

Cardioversion
⊖ triggered non-pacemaker cells & re-entrant circuits
- → Na^+ Channel blockers
  - → Ia → Procainamide
    - ↳ WPW + AF/AFl [Avoid anything that ⊖ AVN]
  - → Ic → Flecainide, Propefenone
    - ↳ ϕ CAD / Post MI / HF / LVH
- → k^+ Channel Blockers
  - ↳ ✓ Acute AF/AFl (for conversion to NSR)

[NSR = normal sinus rhythm]

SVT
⊖ AV node
↓
Rate Control
- → ACUTE - Adenosine
- → PROPHYLACTIC THERAPY TO PREVENT RECURRENCE
  - → β-blocker
  - → CCBs

PAC (Premature Atrial Complexes)
- due to ↑ sympathetic activity ↓↓

∴ DOC: β-blockers

Tdp (Polymorphic VT with a prolonged QT-interval)
- due to AADs (Type Ia, III AADs)
  - ↳ ↑ duration of AP / ERP
- due to antibiotics (macrolides, tetracyclines, fluoroquinolones)
- antipsychotics, antidepressants

Aim: ↓ QT interval

∴ → Type Ib AAD (↓ AP duration)
- → Magnesium
- → Drugs that ↑ HR

Discontinue drugs that prolong QT-interval

PVCs - ↑↑ sympathetic activity
→ β-blockers

VT - ↑↑ sympathetic activity
→ β-blockers

Cardioversion
⊖ triggered non-pacemaker cells & re-entrant circuits
- → Na^+ Channel blockers
  - → Ia - last line drugs in this case
  - → Ib - Lidocaine
    - ↳ best post MI patient having VT
- → k^+ Channel Blockers
  - - Amiodarone
  - - Sotalol

} effect in ventricular tissue

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Adverse Effects of AADs:

β-blockers:

- ϕ Bradycardia } due to ⊖ AVN
- ϕ AV block } due to ⊖ AVN
- ϕ Hypotension (in patients with d. HF) } due to ↓ contractility

} β_1 receptor effects

- ϕ Bronchospasm (COPD / Asthma) – β_2 action
  - C/I ↑

- ϕ Hypoglycemia unawareness ($\beta 1 + \beta 2$ action) ∴ DM → C/I

- ϕ Concomitant use of Cocaine (bind to α_1 receptors) → vasoconstriction → ↑SVR → ↑↑BP
  - if cocaine binds to β_2 receptors ⊖→ vasodilation ⊖→ ↓SVR ⊖→ ↓BP

} neutralize each other ✓✓

→ β-blocker prevents binding of cocaine to β_2 receptor ∴ ↗ cocaine-induced hypertension

Ca^{2+} Channel Blockers:

- ϕ Bradycardia
- ϕ AV blockade
- ϕ Hypotension (in patients with d. HF)
  - C/I ↑
- ϕ Constipation (due to ↓ GI motility)
- ϕ edema (due to vasodilatory effect)

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Adenosine:

ϕ Coronary steal Syndrome
(dilatation of non-plaque/healthy coronary vessels)

ϕ Bronchospasm

ϕ Sense of impending doom

ϕ Flushing (due to vasodilation of cutaneous blood vessels)

ϕ Hypotension (due to vasodilation of systemic arteries)

Digoxin:

ϕ cholinergic side effects (nausea, vomiting, diarrhoea, blurry vision, hyperaphea, confusion, diuresis in CHF, disorientation) (due to ↑ Ach release from vagus nerve)

- Inhibition of Na^+/K^+ ATPase pump → ↑ K^+ in ECF ⇒ ϕ hyperkalemia
  - ↑ Na^+ in cell
  - ↓ Na^+ in ECF
  - Inhibition of Na^+ gradient (higher Na^+ outside the cell)
  - inhibits Na^+/Ca^{2+} exchanger
  - ↑ Ca^{2+} in cell → ↑ risk of delayed after-depolarisations ⇒ ϕ VT
  - ↑ contractility
  - ∴ beneficial in HF, EF

ϕ bradycardia

ϕ anorexia, nausea, vomiting, diarrhoea

- ↓ K^+ exacerbates digoxin toxicity ⇒ ∵ K^+ normally, competes with digoxin at Na^+/K^+ ATPase pumps → ↑ inhibition of Na^+/K^+ ATPase pumps
- antidote for digoxin toxicity ⇒ DIGIBIND
- Hypomagnesemia
  Hypokalemia
  Hypercalcemia
  } increase digoxin toxicity

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Treatment of Digoxin Toxicity:

- Reduce dose: 1st degree heart blocks, ectopic beats
- Atropine: advanced heart block
- KCl: increased automaticity
- Antiarrhythmic: ventricular arrhythmias
- Fab antibodies: toxic serum concentration, acute toxicity

Drug Interactions of Digoxin:

- Diuretics: cause hypokalemia which ↑ risk of digitalis arrhythmias
- Calcium: synergises with digitalis → precipitates toxicity
- Quinidine: reduces binding of digoxin to tissue proteins & reduces its renal & biliary clearance

↓

plasma concentration of digoxin doubles

↓

toxicity

- Adrenergic drugs: can induce arrhythmias in digitalized patients
- Propranolol, verapamil, Diltiazem, disopyramide: additively depress AV conduction & oppose positive inotropic action

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Na^+ Channel Blockers :

Type Ia : ϕ prolonged QT-interval ⟹ ↑ risk of early after-depolarisation ⟹ ↑ risk of Tdp

- Disopyramide - ϕ anticholinergic side effects (dry eyes & mouth, urinary retention, constipation, tachycardia) delirium, hypertension
- Quinidine - ϕ Cinchonism (headache, vertigo, visual changes)
- Procainamide - ϕ Drug-induced SLE

Type Ib : ϕ CNS depression (altered mental status, depression)
ϕ CNS stimulation (↑ risk of seizures)

Type Ic : underlying CAD/MI/HF/LVH ⇒ ϕ ↑ risk of arrhythmias, V fib & sudden cardiac death

K^+ Channel Blockers :

ϕ prolong Q-T interval ⟹ ↑ risk of early after-depolarisation ⟹ ↑ risk of Tdp

- Amiodarone: (long-term use)
  - ϕ interstitial lung disease
  - ϕ low T_3, T_4
  - ϕ high T_3, T_4 (∵ amiodarone is primarily composed of iodine)
  - ϕ fibrosis of liver ⟹ hepatotoxicity
  - ϕ bluish discolouration in skin & around the cornea (patchiness)

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