Now, will discuss "AV nodal dependent" Atrial arrhythmia drugs (class II drugs)
EXCEPT WPW

Class II

- β-Blocker
- Digoxin
- Adenosine

PKA → protein kinase A
HCN: Hyperpolarization activated cyclic nucleotide-gated channels

* extends its coverage beyond an updated range of sympathetic β-adrenergic effects to further include → parasympathetic targets.

* Beta adrenergic receptors:

⊕ → β-adrenergic receptor —⊕→ Gs protein —⊕→ Adenylate cyclase ⇒ ↑ cAMP - cytosolic

ATP → cAMP —Binds ⊕→ PKA

- PKA —⊕→ HCN —influence→ pacemaking funny current (I_f)
- PKA —⊕→ Exchange proteins (Epac) → triggers Ca^{+2} release from SR via RyR_2 (ryanodine receptor type 2)
- PKA —phosphorylate→ target proteins (ion channels)

all β-Blockers except Sotalol (effect on K^+ channels ∴ we use it with class III as a selective drug)

Class IIa

Nonselective & selective $β_1$ adrenergic receptor inhibitors (β-Blockers)

Selective	vs	Nonselective
"Slit ge"		"Car properties"
atenolol		Carvedilol
Metoprolol		propranolol

* clinical indication *
↓
in a wide range of tachyarrhythmias
- Sinus tachycardia
- Supraventricular & ventricular tachyarrythmias

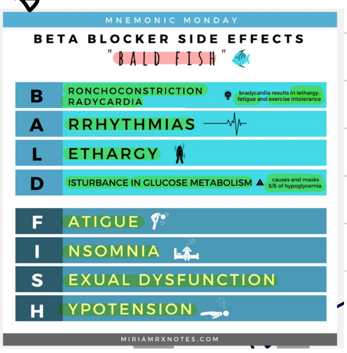
Effect

- ↓ SAN automaticity
- ↓ AVN automaticity
- ↓ ectopic ventricular/atrial automaticity

* β-Blockers SEs *

Voice1

- upregulation of β-receptors with long term therapy, β-Blockers withdrawal
- Sinus bradycardia, AV block
- Cold extermities
- Mask symptoms of hypoglycemia

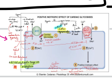


Class IIb

Ex: Digoxin

* 2 principal MoA, selectively employed depending on indications

+ve inotropic (remember from Lec 1 Part)



- ⊖ Activity of Myocardial $Na-K$ ATPase pump
- ↑ force of contraction of Heart
- * Digoxin → ↑ intracellular Na^+ → Drive influx of Ca^{+2} in the Heart & cause ↑ contractility → ↑ CO (cardiac output) → ↓ ventricular filling pressure

AV node inhibition

Digoxin —⊕→ Supraventricular M_2 cholinergic receptors (parasymp. N.S ⊕) → Slows electrical conduction in AV node → ↓ Heart rate (-ve chronotropic)

* clinical indications *
- Sinus tachycardia or
- Supraventricular tachyarrhythmias

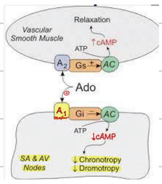
* SE *

- Visual changes (blurring, photophobia, disturbance in vision color)
- GI toxicity: anorexia, nausea, vomiting
- Gynaecomastia, skin rashes
- Cardia adverse effects:
  - Bradycardia
  - AV block
  - Paroxysmal atrial tachycardia
  - Sino atrial arrest
  - Ventricular tachycardia

Class IIc

Adenosine A_1 receptor activators

Ex: Adenosine, ATP



* MoA *

Adenosine exerts
- -ve chronotropic effect: Suppressing automaticity of Cardiac pacemakers
- -ve dromotropic (conduction velocity) effect By ⊖ of AV-nodal conduction

* clinical indications *
- Acute termination of AVN tachycardia
- cAMP mediated triggered VTs (ventricular tachycardia)

* SEs *

- Sinus bradycardia, sinus arrest or AV block ← take care of it (important SE)
- Atrial fibrillation
- GI:
  - Diarrhea.
  - feeling of warmth.
  - indigestion.
  - loss of appetite.
  - nausea or vomiting.
- redness of the face, neck, arms, and occasionally, upper chest.
- stomach pain, fullness, or discomfort.

*we don't see some of them

* Adenosine is the first line treatment for AV nodal dependent Arrhythmia

"AV node" Atrial arrhythmia drugs EXCEPT WPW	Patient have SVT, atrial flatter or atrial fibrillation	Patient have acute SVT, atrial flatter or atrial fibrillation (attack or hypotension)
Beta-blockers and Calcium-channel blockers	Prophylaxis against the recurrent of arrythmia after treatment	
digoxin		Hyperpolarization
adenosine		Complete hyperpolarization

Sources of Disturbances

- **Automatic foci**
  - often at one of the pulmonary veins
- **Small # of localized sources in the form of either a re-entrant**

*Idea is to ∈ AV node

↓

if not: Deal with Atrial & ventricular Myocytes

By:
- β-Blocker
- Ca^{+2} chan. Block

  ] → prophylactic only

- Digoxyn → Affect the Myocyte in opposit to its effect on AV node
- Adenosine → $T_{1/2}$: seconds

Adenosine ↓ **rescue Drug**
- work fast
- end fast

↳ كأنك تفصل ال Heart By Hyperpolarization

⇓ (given as a rapid IV bolus)

K^+ & Ca^{+2}

- Adenosine & Digoxyn → Hyperpolarize AV nodes
- Adenosine ↓
  - receptor on AV node
  - G protein coupled receptor

    ⇓

    Hyperpolarization
- Digoxyn ↓ HyperDepolarize cardiac Myocyte ⟹ close to arythmia

K^+	Ca^{+2}
AV	Myo
Hyperpolar	Hyper-Depolariz
	↓ May cause Arrhythmia

✓ Adenosine تعطي احسن ::

Now, will discuss Monomorphic Ventricular arrythmia & (Atrial) WPW drugs (class I drugs)

class I Drugs → list cardiac Na^+ channel blockers

(Nav 1.5) → Na^+ channels in Cardiac Myocytes

* Different class I actions → influence their clinical indications for arrhythmias → affecting Different regions of Heart

* Class Id : drugs acting on recently reported late Na currents.

Class Ia — Moderate Block

- quinidine
- procainamide
- "quickly protect the disco" - disopyramide

bind to the open state of Nav1.5 with moderate dissociation time constants (τ) of ≈1 to 10 seconds (moderate block)

- ↓ AP conduction velocity (Action potential)
- ↑ ERP & APD (Effective refractory period & Action potential Duration)

* clinical application *

Supraventricular tachyarrhythmias (atrial fibrillation)

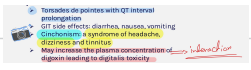
Ventricular tachycardia — Main use

- Pts without QT interval prolongation

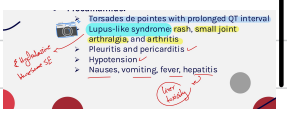
SEs

contraindication with Digoxin

Quinidine



procainamide



contraindicated to → prolonged QT interval

* Effective & very proarrhythmic *

Class Ib — Weak Block

- Lidocaine

Baby → Can Drink Vodka → Lidocaine

* for Mono foci

drugs bind to the Nav1.5 **inactivated** state with relatively rapidly dissociation time constant τ of ≈0.1 to 1.0 second (weak block)

- ↓ APD & ERP in Normal ventricular Muscle & purkinje cells.

* clinical applications *

Ventricular tachyarrhythmias

Ventricular tachycardia & Ventricular Fibrillation

* SEs *

CNS Effects

Slurred speech — Drowsiness — Dizziness — Muscle twitching — Seizures

Class Ic — (Most efficient) Strong Block

- Propafenone
- Flecainide

* for polymorphic foci

Also bind to the inactivated Nav1.5, from which they dissociate more slowly, over τ >10 seconds (marked block)

- ↓ AP conduction velocity
- Maintain Normal ERP & APD

* clinical applications *

Supraventricular tachycardias

- Atrial fibrillation
- A. flutter
- A. tachycardia

Ventricular tachyarrhythmias resistant to other treatment

* SEs *

Flecainide

- Ventricular tachycardia in presence of ischemic heart disease or old MI
- Vision problems
- Headache, dizziness
- Has been shown to have teratogenic effects

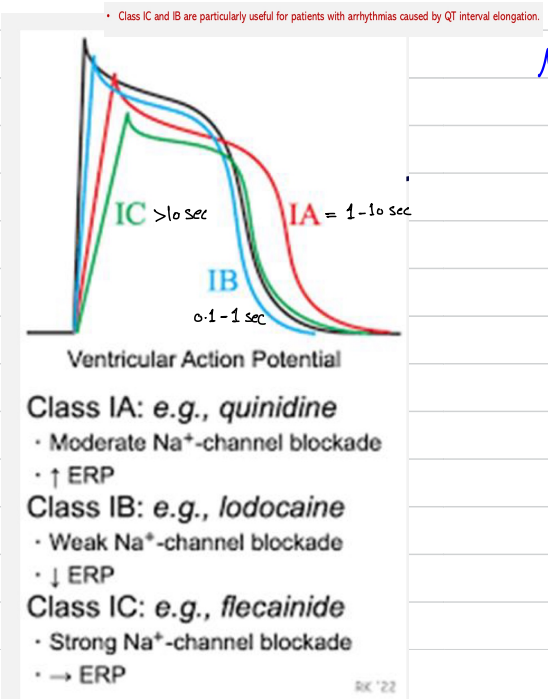
propafenone

Ventricular tachycardia in presence of ischemic heart disease or old MI
Slowed sinus rate
Dizziness, chest pain, shortness of breath
N/V, constipation/ diarrhea

* Do not ↑ QT interval ✓ *

contraindicated to → MI & Coronary Heart Disease

* good choice for pts with WPW *



Now, will discuss Polymorphic ventricular arrythmia drugs (class III drugs)
The last one 🥳

لما الـ Na^+ مايجاوب :. نعطل الجأ لـ K^+

Class III

*class III agents includes wider ranges of voltage-dependent K^+ channel blockers

After phase 0 depolarization, complex components of transient inward current (I to) contribute to early rapid phase 1 AP repolarization.

*They Block Multiple K^+ channel targets ⟹ prolonged ↓repolarization reserve ↑ERP

Atrial purkinjie ventricular

Myocyte AP recovery

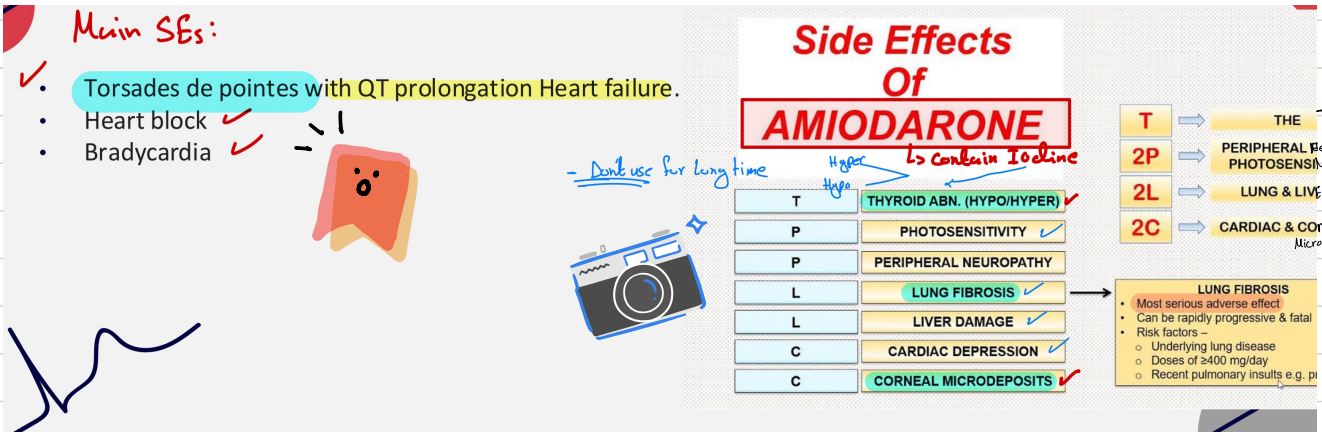
Ex

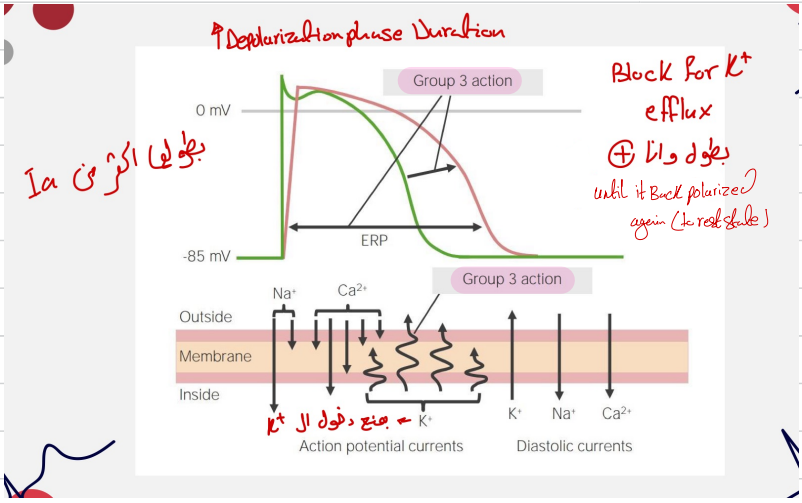
Selective
- dofetilide
- ibutilide
- Sotalol

non-Selective
- Amiodarone
- Amiodarone

➢ If the ventricular arrhythmia is caused by sympathetic overactivation, then **sotalol** is a better choice than **amiodarone.**

Main SEs:
- Torsades de pointes with QT prolongation Heart failure.
- Heart block
- Bradycardia





Atrial arrhythmias

WPW →		**class Ic (flecainide)**		
"AV nodal dependent" Atrial arrhythmia	After treatment as → prophylaxis	**Beta-blockers and Calcium-channel blockers**	We might also use **Dofetilide and Ibutilide**	To stop atrial arrhythmia → **Class Ic**
	Patient have acute SVT, atrial flatter or atrial → fibrillation (attack or hypotension)	**Adenosine & Digoxin**		

Ventricular arrhythmias

Monomorphic Ventricular arrythmia I	patients with arrhythmias caused by QT interval elongation	Class Ib (lidocaine) & class Ic (flecainide)	Class Ia ✗	
	Old MI, congestive heart failure, or angina pectoris	Class Ib (lidocaine) ✓	Class Ic & Class Ia ✗	
Polymorphic ventricular arrythmia drugs III	Most polymorphic cases except 👇 [redacted]	Amiodarone		
	ventricular arrhythmia is caused by sympathetic overactivation	sotalol		