Anti-Arrhythmic Drugs

PHC 721

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Arrhythmia: Abnormal Heart Rhythm
resulting from a perturbation of the normal sequence of impulse initiation or propagation

Cellular Mechanisms (an overview):

1) Bradyarrhythmias (slow heart rhythms; Tx: withdrawal of the offending drug/permanent cardiac pacing)

- Failure of impulse initiation in the SA node ⇒ Sinus Bradycardia
- Failure in the propagation of action potentials from Atria to Ventricles ⇒ dropped beats (heart blocks)

2) Tachyarrhythmias (rapid heart rhythms; Tx: anti-arrhythmic drugs, cardioversion, etc.)

- Sympathetic stimulation (β-adrenergic activation)/Hypokalemia ⇒↑ Automaticity
- *Digitalis* intoxication /Genetic mutation (Ryanodine Rec.) ⇒ intracellular Ca^{2+} overload ⇒ extra beats
- Myocardial ischemia/infarction ⇒ Re-entry

Examples of drug-induced arrhythmias:

- Sinus Tachycardia (e.g., *beta-blocker withdrawal* after chronic therapy)
- Atrial Tachycardia with AV conduction block (e.g., *Digoxin overdose*)

Pharmacological approaches to suppress arrhythmias:

1) Blocking flow through specific ion channels
(↓cell excitability, ↑action potential duration ⇒↑effective refractory period, etc)

2) Altering autonomic function

Examples of Bradyarrhythmias

Supraventricular Arrhythmias: AV conduction pathway deficits (heart blocks)

- 1st degree – lengthened P-R interval
- 2nd degree - skipped "beats"
- 3rd degree (complete heart block) – atria and ventricles are no longer synchronized: atria follow the SA nodal rhythm, whereas ventricles follow the AV nodal rhythm

Normal

First-Degree AV Block

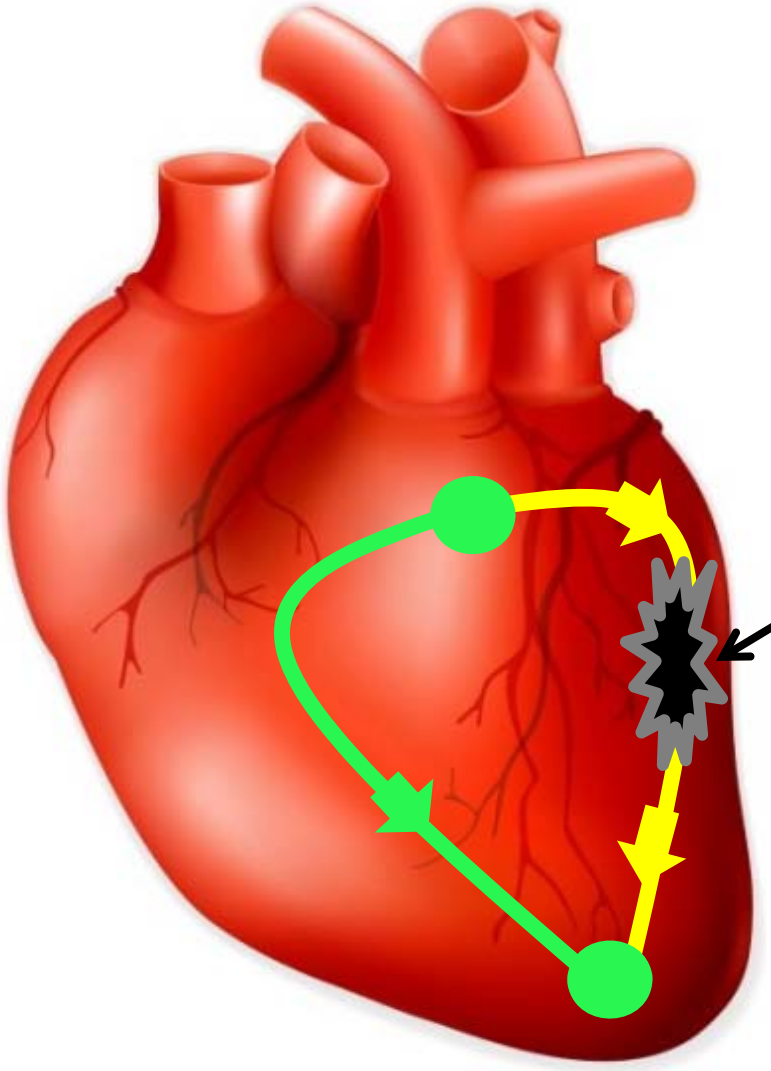
Second-Degree AV Block (2:1)

Third-Degree AV Block

Re-entry: the underlying mechanism of Clinically Important Tachyarrhythmias

Re-entry results from slow conduction in the heart, when impulses propagate between two points through at least two pathways with different effective refractory periods (ERP).
The underlying conditions:

1) Presence of an accessory anatomical pathway made of conductive tissue - Wolff-Parkinson-White syndrome (WPW), or
2) Tissue with electrophysiological characteristics altered by disease (e.g., ischemia, hyperkalemia)



Anti-Arrhythmic drugs suppress the Initiating Mechanism or alter the Re-Entrant Circuit.

In some cases, drugs suppress the trigger, but also promote re-entry.

Decreased
Conduction Velocity

Shorter ERP
(i.e., faster recovery)

The excitation wave
'**re-enters**'
the pathway

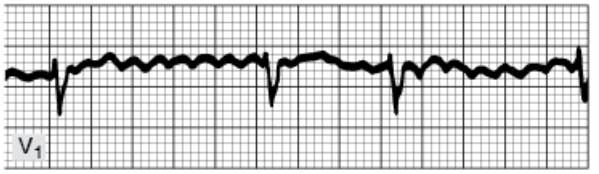
Examples of Tachyarrhythmias

<u>Atrial arrhythmias:</u> Excitation spreading from an independently discharging (ectopic) focus in the atria

- Atrial extrasystole

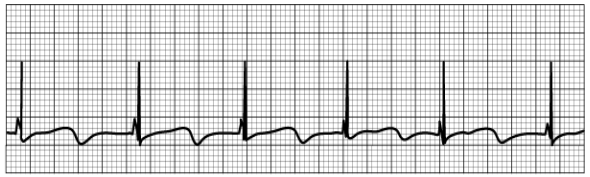
Atrial extrasystole

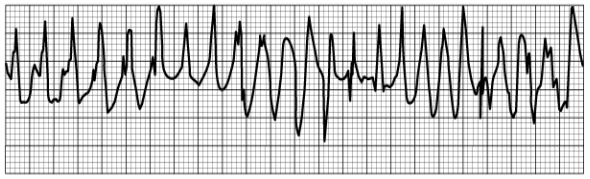
- Atrial fibrillation



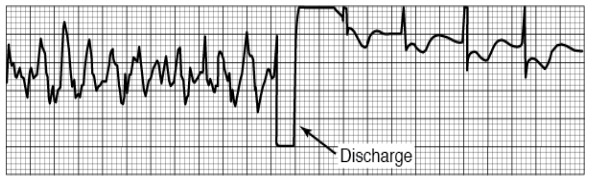
Atrial fibrillation

<u>Ventricular Arrhythmias:</u> Premature beats that originate in an independently discharging (ectopic) ventricular focus





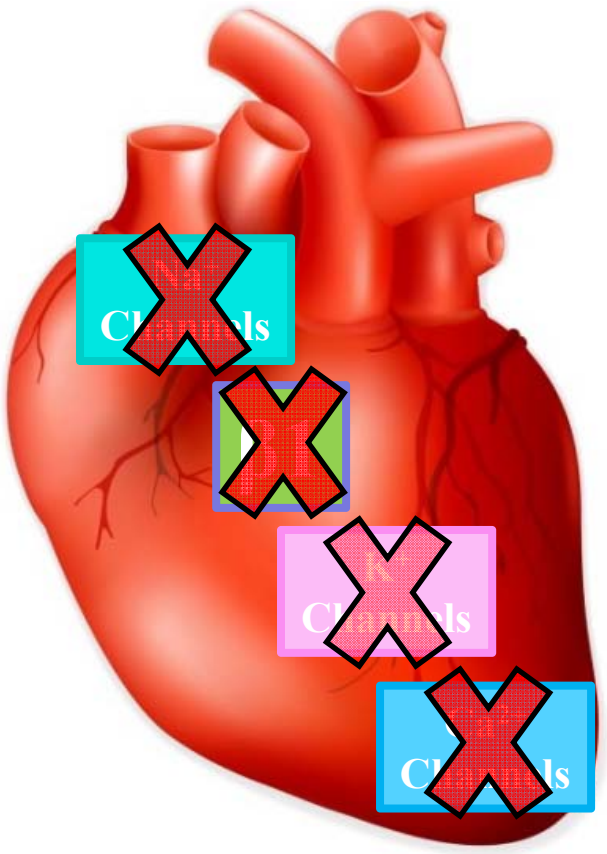
- Ventricular fibrillation



Pharmacotherapy of Arrhythmias

Four Classes of Antiarrhythmic Drugs:

Class I: Sodium Channel Block
Class II: Beta-adrenergic Block
Class III: Action Potential Prolongation
Class IV: Calcium Channel Block



Class I: Na^+ Channel Blockers:
Lidocaine, *Quinidine*,

Class II: β-adrenergic Blockers:
Propranolol, ***Bisoprolol***
Labetalol
Sotalol (also K^+ channel blocker)

Class III: Drugs that Prolong Action Potential
(mostly K^+ Channel Blockers):
Amiodarone

Class IV: Ca^{2+} Channel Blockers:
Verapamil

Class I: Na^+ Channel Blockers

Mechanisms of Action:

- Blockade of cardiac Na^+ channels:
$\Rightarrow \downarrow$ excitability threshold $\Rightarrow \downarrow$ automaticity;

- Blockade of cardiac K^+ channels:
$\Rightarrow \uparrow$ Action Potential Duration (e.g., Quinidine, but not Lidocaine)

Dental Implications:

- Quinidine is a potent inhibitor of CYP2D6 (e.g., ↓ Codeine-to-Morphine metabolism) ⇒ ↓ ***Opioid Analgesia***

- Reversal of local Lidocaine anesthesia (by vasodilating agents, such as Phentolamine) can result in a dangerous **cardiac depression** (↓ contractility), particularly in patients with a liver or kidney disease that may significantly increase the elimination half-life of Lidocaine.

Sympatholytic Agents: β-Adrenergic Receptor Antagonists

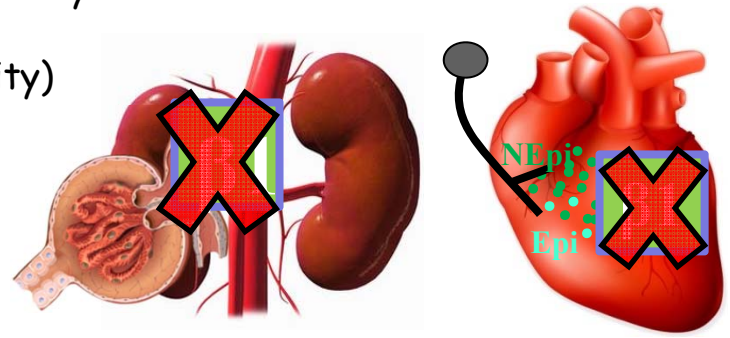
Duplicate

Mechanism of Action:

Blockade of β-adrenergic receptor signaling. The blood pressure-lowering effect of beta-blockers is not completely understood:

↓ Renin secretion,

↓ Cardiac Output (↓ HR/Contractility)



Indications:

- Hypertension, Exertional Angina, Congestive heart failure (↓ mortality)
- Arrhythmias (e.g., prevention of arrhythmias triggered by emotional stress)

Side effects / Contraindications:

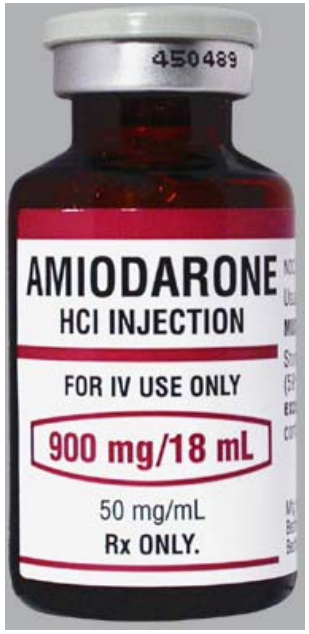
- Life-threatening bronchoconstriction / Asthma
- Altered sensitivity to Insulin (↑risk of hypoglycemia) / Diabetes
- *Abrupt discontinuation may cause Sudden Death and exacerbate Angina*

Dental Implications:

- **NSAIDs** can blunt antihypertensive effects of β-blockers

- **Epinephrine (in local anesthetics) can severely rise blood pressure (⇒ reflex bradycardia) in patients on non-selective β-antagonists:**
  Epi causes severe systemic vasoconstriction (*via* α-adrenoceptors), when applied intravascularly in the absence of functional β2 receptors (blocked by non-selective β-blockers) whose normal action is vasodilatory.

Class III: Drugs that Prolong Action Potential (primarily K^+ Channel Blockers)



Mechanism of Action:

Blockade of cardiac K^+ channels:
↑ Action Potential Duration ⇒ ↑ refractoriness ⇒ ↓ abnormal automaticity

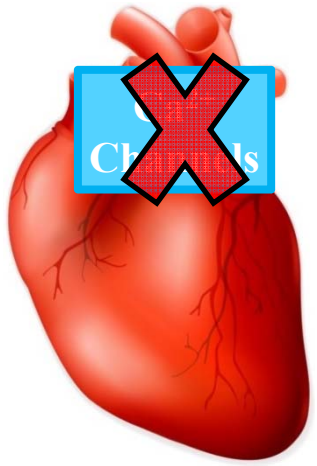
Side effects:
Inhibition of cytochrome P450 (CYP) drug-metabolizing enzymes by Amiodarone and its metabolites.

Dental Implications:
Long-term treatment with Amiodarone may lead to blue-grey discoloration of sun-exposed areas of the skin (most commonly on the face and neck) and oral hyperpigmentation.

Class IV: Ca^{2+} Channel Antagonists

Mechanism of Action:

Blockade of L-type Ca^{2+} channels:
↓ firing rate in the SA node and slow AV conduction



Indications:

- Arrhythmias

Side effects:

-↑ plasma concentration of Digoxin and other drugs by Verapamil (inhibition of P-glycoprotein transporter activity ⇒ ↓ renal tubular elimination)
- Inhibition of CYP3A4 drug-metabolizing enzyme.

Dental Implications:

Gingival Hyperplasia