PHARMACOLOGY

بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

Final | Lecture 1

Agents Used in Cardiac Arrhythmias (Pt.1)

وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

اللهم إنّا نعوذ بك من شرور أنفسنا ومن سيئات أعمالنا

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فريق دوبامين العلمي - THE SCIENTIFIC TEAM OF DOPAMINE -

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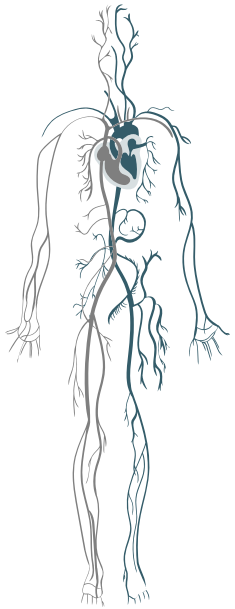
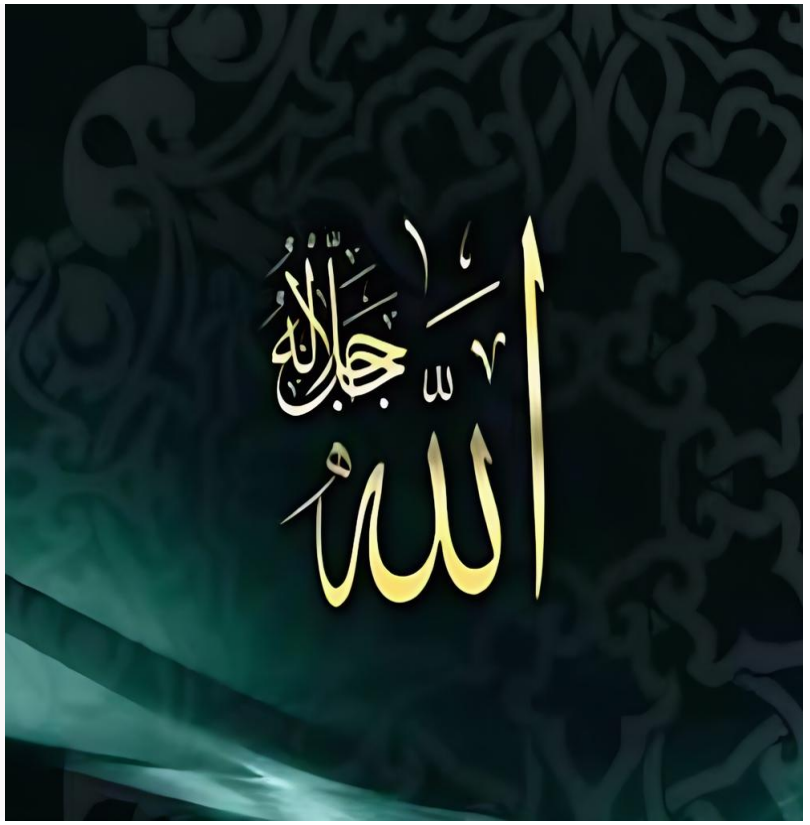


وَلِلَّهِ الْأَسْمَاءُ الْحُسْنَى فَادْعُوهُ بِهَا



المعنى: اسم «الله» دالٌّ على كونه مألوهًا معبودًا، تألهه الخلائق محبة، وتعظيمًا، وخضوعًا، وفزعًا إليه في الحوائج والنوائب، وهو الاسم الجامع لمعاني أسماء الله الحسنى.

الورود: ورد في القرآن (٢٧٢٤) مرة.

الشاهد: ﴿إِنَّنِيٓ أَنَا ٱللَّهُ لَآ إِلَٰهَ إِلَّآ أَنَا۠ فَٱعۡبُدۡنِي وَأَقِمِ ٱلصَّلَوٰةَ لِذِكۡرِيٓ﴾ [طه:١٤].

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اضغط هنا لشرحٍ أكثر تفصيلًا

Agents Used in Cardiac Arrhythmias

In order to treat cardiac arrhythmias, you need to know it's mechanism, origin and type.

Yacoub Irshaid, MD, PhD, ABCP

Department of Pharmacology

Cardiac Arrhythmias

- Cardiac arrhythmias are a **common problem** in clinical practice.
- They may be due to **drugs** or **electrolyte imbalance*** and may follow **myocardial infarction**.
- Anti-arrhythmic drugs are **ineffective** unless **electrolyte imbalances**, hypokalemia, **are corrected***.

Drug Induced Cardiac Arrythmias[1]

- **Not only** drugs that cause electrolyte imbalances like diuretics can cause cardiac arrythmias, but rather also groups of drugs that can **prolong QT intervals**.
  - These drugs can precipitate a very dangerous form of arrhythmia, called the **QT interval syndrome**.
  - The risk becomes significantly higher when **two or more QT-prolonging drugs are used together**, because their effects on the QT interval are **additive**.
- **QT interval syndrome** is a condition which eventually leads to a ventricular type of arrhythmias (like ventricular fibrillation where there is no cardiac output → death)

Drug Induced Cardiac Arrythmias(2)

- In addition, conditions or concurrent medications that **inhibit** the metabolism or **elimination** of QT-prolonging drugs can **precipitate** or **exacerbate** the risk, via increasing their plasma concentration and therefore the arrhythmic risk. This includes conditions such as:
  - **Kidney failure**, when the drug normally relies on kidney excretion.
  - **Hepatic impairment**, when metabolism depends on the liver.

Cardiac Arrhythmias

- Rhythms that are **too rapid**, **too slow**, or **asynchronous** can **reduce cardiac output**, and cause **heart failure**.
- **Stretching** of cardiac muscle fibers in heart failure can also be **a cause of arrhythmias itself.**
- **In MI**, ischemic areas in the myocardium that are **still not infarcted** are also **potential sites for arrhythmias**.
- Some arrhythmias can **precipitate more serious or even lethal rhythm disturbances**, such as ventricular fibrillations.
  - **Atrial fibrillation** is not fatal due to the passive filling of the ventricles; however, it should be converted to back to the normal (sinus) rhythm. If not possible, it's needed to focus on **controlling ventricular rate to avoid** the atrial fibrillatory impulses affecting the ventricular rhythm leading to **ventricular fibrillation**.
- In such patients, **antiarrhythmic drugs may be life-saving**.

Cardiac Arrhythmias

- On the other hand, the **antiarrhythmic drugs** are **dangerous** in that they can **precipitate lethal arrhythmias** in some patients, as they affect the electrical activity and the physiology of the heart.
- **Arrhythmias** might be related to the **type or number** (rate) **of impulses.**
  - Tachycardia and bradycardia are arrhythmias.
  - So, arrhythmias refer to any problem in the rate or rhythm of a person's heartbeat.

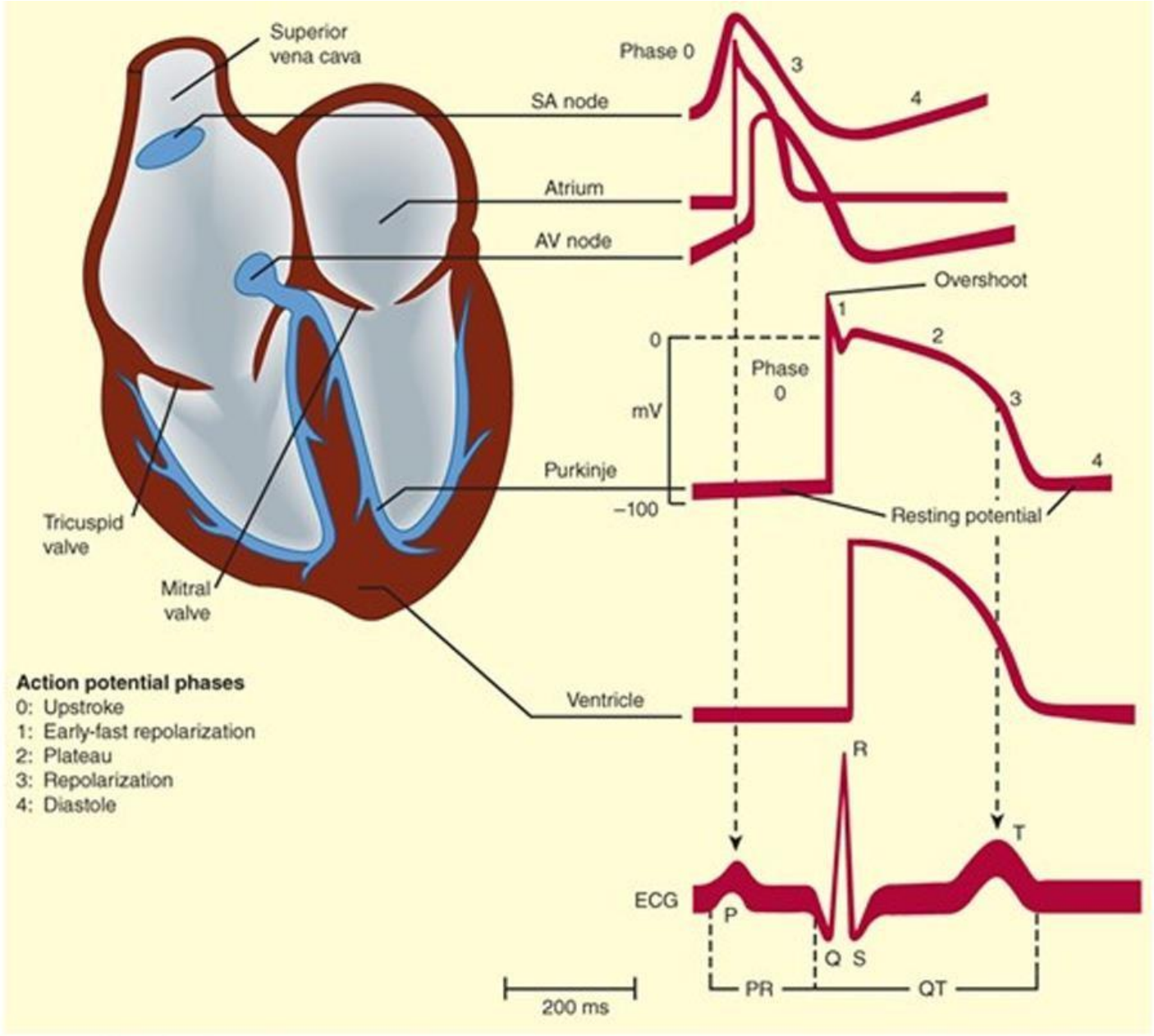
The underlined word is hyperlinked.

Electrophysiology of Normal Cardiac Rhythm

- The **electrical impulse** that triggers a normal cardiac contraction originates at regular intervals in the **sinoatrial (SA) node** usually at a frequency of **60 - 100 bpm**.
- This impulse **spreads** rapidly **through the atria** and **enters** the **atrioventricular (AV) node**, which is **normally** the **only** conduction **pathway** between the atria and ventricles.
- The impulse **then propagates** down the **His-Purkinje system and invades all** parts of the **ventricles**, beginning with the **endocardial surface** near the apex and ending with the **epicardial surface** at the base of the heart.
- Derangement anywhere in this pathway leads to arrhythmias.

FIGURE 14–1
Schematic representation of the heart and normal cardiac electrical activity (intracellular recordings from areas indicated and electrocardiogram [ECG]).

- Sinoatrial (SA) node, atrioventricular (AV) node, and Purkinje cells display pacemaker activity (**phase 4 depolarization**).
- The **ECG** is the body surface manifestation of the **depolarization** and **repolarization waves** of the heart.
- The **P wave** is generated by **atrial depolarization**, the **QRS** by **ventricular** muscle **depolarization**, and the **T wave** by **ventricular repolarization**.
- Thus, the **PR interval is a measure of conduction time from atrium to ventricle.**
- And the **QRS duration** indicates the **time required for all of the ventricular cells to be activated** (the intraventricular conduction time).
- The **QT interval** reflects the **duration** of the **ventricular action potential**.



More notes on the figure in the next slide.

The Electrophysiological Basis of QRS Morphology(1)

❖ Each cardiac tissue has a distinct action potential shape.

- In **SA, AV and Purkinje** there is spontaneous depolarization (phase 4 slope), which is responsible for generating the next action potential, and therefore the next heartbeat.
- In addition, in SA and AV **phase 1** (transient repolarization) and **phase 2** (plateau) are intermingled and **not shown** (phase 0 -> 3 directly).
- The ventricular action potential is **longer in duration** than the atrial action potential because the ventricle possesses a long plateau phase (phase 2). This long duration results in a **prolonged refractory period**, which is reflected on the ECG as **a long QT interval**. In contrast, the atrial action potential has a much shorter plateau, leading to a **shorter refractory period**.

✓ The duration of the P wave (atrial depolarization) and the QRS complex (ventricular depolarization) are determined by conduction velocity, not by the length of the plateau phase.

The Electrophysiological Basis of QRS Morphology[2]

❖ When evaluating arrhythmias on ECG:
- **Narrow QRS** → typically indicates an atrial arrhythmia.
- **Wide QRS** → more often suggests a ventricular arrhythmia.

- However, this rule is not absolute. Some forms of **ventricular arrhythmias can present with a narrow QRS**, making them easy to mistake for atrial arrhythmias. That's why it's important to take time acknowledging the origin of the arrhythmia to avoid giving drugs based on a wrong diagnosis

Electrophysiology of Normal Cardiac Rhythm

- In the **SA node** phase 4, slow depolarization, is due to the **funny current** (I_f) which produces spontaneous, gradual depolarization due to **slow influx of sodium ions** and a **decrease in potassium permeability**, $\uparrow P_{Na+}$ and $\downarrow P_{k+}$, making the **inside** of the cell **less negative** (-40 mV) which triggers phase 0.
- **The situation is similar in the AV node.**

❖ Purkinje fibers also have spontaneous depolarization but more stable than AV and SA, with a less steep slope.

- In the **His-Purkinje system**, phase 4 depolarization is not stable, yet more stable that AV and SA nodes, but gradual depolarization due to **slow inward leak of sodium** which makes the membrane potential **less negative towards the threshold for excitation**. This triggers the next action potential.

Electrophysiology of Normal Cardiac Rhythm

- The **upstroke** (phase 0) of the action potential is due to the **inward sodium current (I_{Na})**, in contractile, and not rhythmic, cells.
- The **maximum upstroke** velocity of the action potential is **very fast and very brief** and is followed by **inactivation** of these channels.
- This inactivation contributes to the **early repolarization** phase of the action potential (phase 1).
- In some cardiac myocytes, **phase 1** is also due to a **brief increase in potassium permeability** due to the activity of channels generating fast and slow transient **outward currents.**

Electrophysiology of Normal Cardiac Rhythm

- **Sustained depolarization** during the plateau (phase 2) is due primarily to the activity of **calcium channels.**
- Cardiac calcium channels **activate and inactivate** in a manner similar to sodium channels, but in the case of the **most common** type of calcium channels (**the L type**), the transition occur **more slowly** and **at more positive potentials**.
- After activation, these channels **eventually inactivate** decreasing the permeability to calcium, and **the permeability to potassium begins to increase**, leading to final repolarization (phase 3) of the action potential.

Mechanisms of Cardiac Arrhythmias

❖ **Factors that can precipitate or exacerbate arrhythmias:**

- **Ischemia.**
- **Hypoxia**.
- **Acidosis or alkalosis**; acid-base imbalance can **exacerbate** but not precipitate arrhythmias.
- **Electrolyte abnormalities;** electrolyte imbalances can precipitate and exacerbate arrhythmias. Also, they can **fail the effect of anti-arrhythmic drugs,** therefore**,** patients must be **tested** for imbalances before giving anti-arrhythmic drugs, especially **potassium and magnesium**.
- **Excessive catecholamine exposure**, leading to a shorter diastole time and affecting ventricular perfusion.
- **Autonomic influences** such as anti-cholinergics causing tachycardia.

Mechanisms of Cardiac Arrhythmias

❖ **Factors that can precipitate or exacerbate arrhythmias:**

- **Drug toxicity** (digitalis or antiarrhythmic drugs), see next slide.
- **Overstretching of cardiac fibers** such as in congestive heart failure **and the presence of scarred or diseased tissue** which can cause interruption of conduction.

- However, all arrhythmias result from (1)**disturbances in impulse formation** and/or (2)**disturbances in impulse conduction**.

Arrhythmias and Drug Toxicity

- Digitalis has a **narrow therapeutic index**, and it is not considered first-line treatment for any major cardiovascular condition today.
- As previously mentioned, medications that **prolong the QT interval** can be **pro-arrhythmic**.
  - Examples include some macrolide antibiotics (such as **erythromycin**) and certain **antihistamines**.
- These drugs **increase the risk of polymorphic ventricular tachycardia**, including the subtype **torsades de pointes**, where each QRS complex appears different because they originate from varying ventricular sites.
- Torsades may deteriorate into ventricular fibrillation, which is life-threatening, especially in polypharmacy (taking more than 5 drugs).
- If two drugs cause **QT prolongation**, you must change at least one of them.

Mechanisms of Cardiac Arrhythmias

1. Disturbances of Impulse Formation:

- Pacemaker activity is **regulated** by both sympathetic and parasympathetic nervous system.
- Therefore, **factors that antagonize or enhance these effects can alter normal impulse formation**, producing either bradycardia or tachycardia.

Mechanisms of Cardiac Arrhythmias

- Under certain circumstances, when SA node is not functioning or when **AV block** is present, **abnormal activity** can be generated by **latent pacemakers** in cells that show slow phase 4 depolarization **(Purkinje cells**).
- Under these conditions, ectopic pacemakers may take over, which were **suppressed** by overdrive suppression, and the heart rate will correspond to the intrinsic firing rate of whichever fibers become the dominant pacemaker, for example, 40 bpm if Purkinje fibers took over.
- **Abnormalities in impulse formation can also be the result of <u>after</u>depolarizations** (Figure 14-5).

Mechanisms of Cardiac Arrhythmias

- These can be either **early afterdepolarizations** (EADs), which occur during **phase 3**, repolarization, of the action potential, or **delayed afterdepolarizations** (DADs), which occur during **phase 4**.
- **EADs** are usually **triggered** by factors that **prolong action potential duration**, including some anti-arrhythmic drugs.
- When this **prolongation** occurs in **ventricular cells**, there is often a **corresponding increase in the QT interval** of the ECG.
- It's important to note that **some types** of QT prolongation are **congenital** and develop early in life without any drug intake. **Females** naturally **have long QT** and are more susceptible.

Mechanisms of Cardiac Arrhythmias

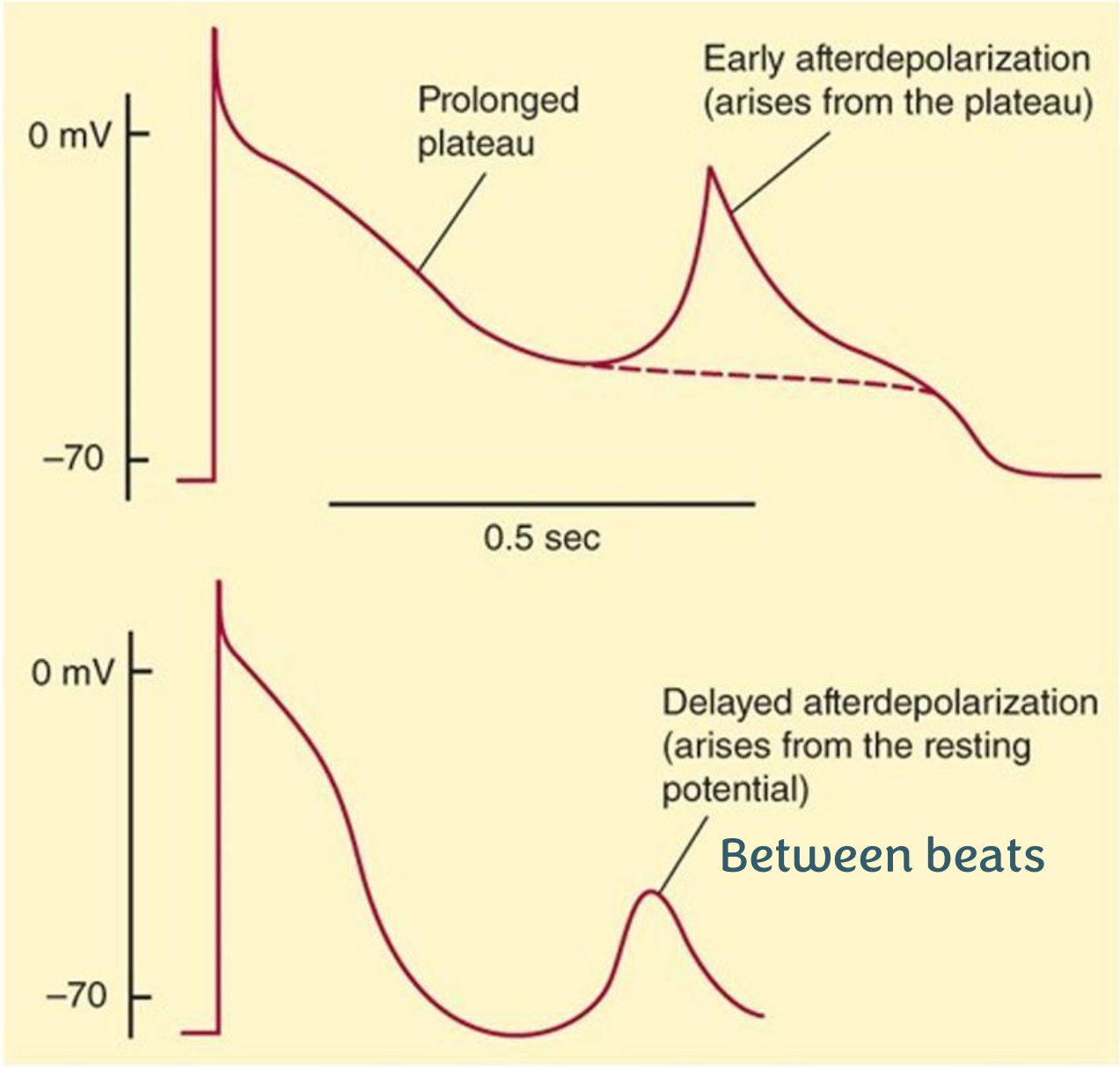
- A number of diverse **drugs** can produce **drug-induced long QT** (LQT) **syndrome**, which is typically due to **block of rapidly activating delayed rectifier potassium channels** responsible for repolarization during phase 3.
  - ➢ Therefore, drugs currently being developed take into consideration these aspects like QT prolongation and metabolism by **CYP3A4**.
- Many **forms of LQT** syndrome are **exacerbated** by factors that **prolong action potential duration**, including **hypokalemia** and **slow heart rates.**
  - ✓ Prolonging action potentials (QT intervals) → EAD → one impulse can reproduce multiple impulses → triggering arrhythmia.

FIGURE 14–5

Two forms of abnormal activity, **early** (top) and **delayed afterdepolarizations** (bottom).

In both cases, abnormal depolarizations **arise during or after** a normally evoked **action potential**.

They are therefore often referred to as **"triggered" automaticity**; that is, they **require** a normal action potential for their initiation.



Mechanisms of Cardiac Arrhythmias

- **DADs**, on the other hand, often occur when there is an **excess accumulation of intracellular calcium**, especially at fast heart rates.
- DADs are also called **calcium induced arrhythmias**.
- They are thought to be **responsible for arrhythmias** associated with **digitalis toxicity**, **excess catecholamine stimulation**, and **myocardial ischemia.**

DADs: Delayed after depolarizations

Mechanisms of Cardiac Arrhythmias

2. Disturbances of Impulse Conduction:

A. The **most common** form of conduction disturbance **affects the AV node**, **causing** various degrees of **heart block**.

- The result can be a **simple slowing of impulse propagation,** delayed conduction, through the AV node, which is reflected by an **increase in the PR interval** of the ECG.

or

- At the extreme, the result can be **complete heart block,** atrioventricular dissociation, where **no impulses** are conducted from the **atria to the ventricles**.

Mechanisms of Cardiac Arrhythmias

- In this situation, AV block, ventricular activity must be generated by a **latent pacemaker**, such as a Purkinje cell, or by an **artificial pacemaker**.
- Because the AV node is typically **under the tonic influence of the parasympathetic nervous system,** which slows conduction, **AV block** can sometimes be **relieved by antimuscarinic agents** like atropine.

Mechanisms of Cardiac Arrhythmias

❖ **Disturbances of Impulse Conduction:**

B. A **serious form** of conduction abnormality involves **reentry** (also known as "**circus movement**").

- In this situation, **one impulse fails to dissipate**, and **reenters** and **excites areas of the heart more than once**.
- The path of the reentering impulse may be **confined to very small areas**, such as tissue within or near the AV node or where a Purkinje fiber, which is most affected because it has bifurcations, makes contact with the ventricular wall (Figure 14-6), or it may involve **large portions** of the atria or ventricles.

Explanation in the following slide.

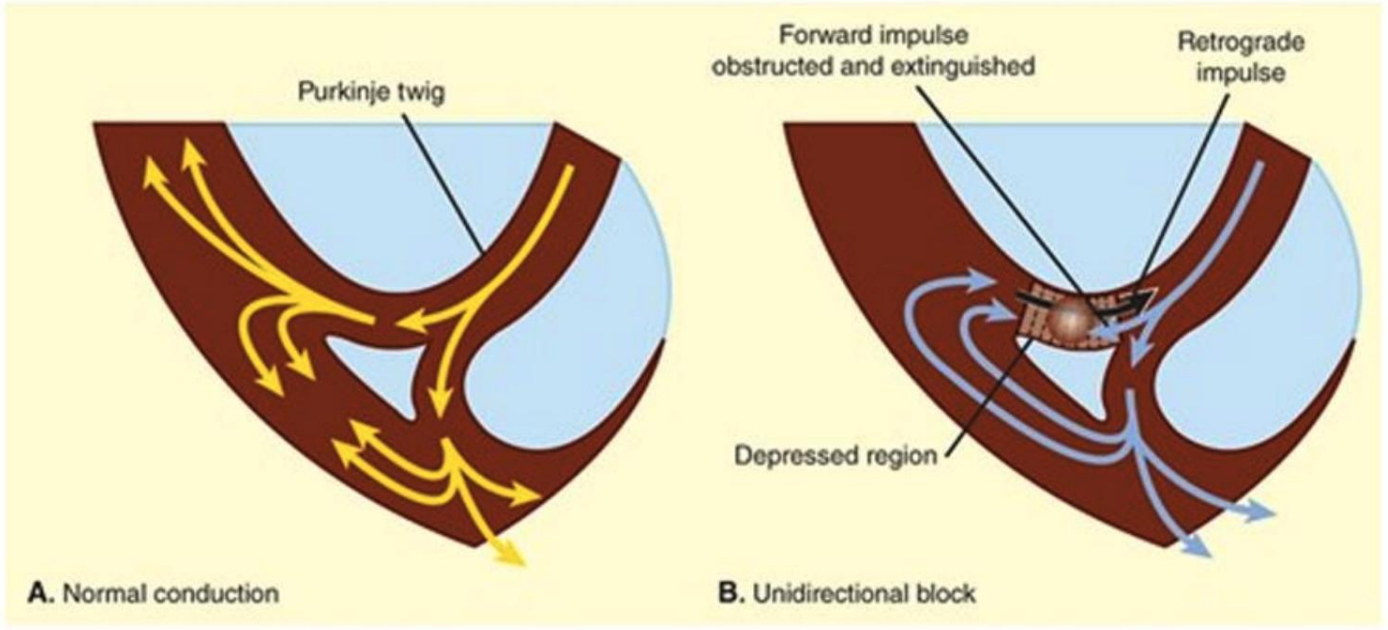


FIGURE 14–6

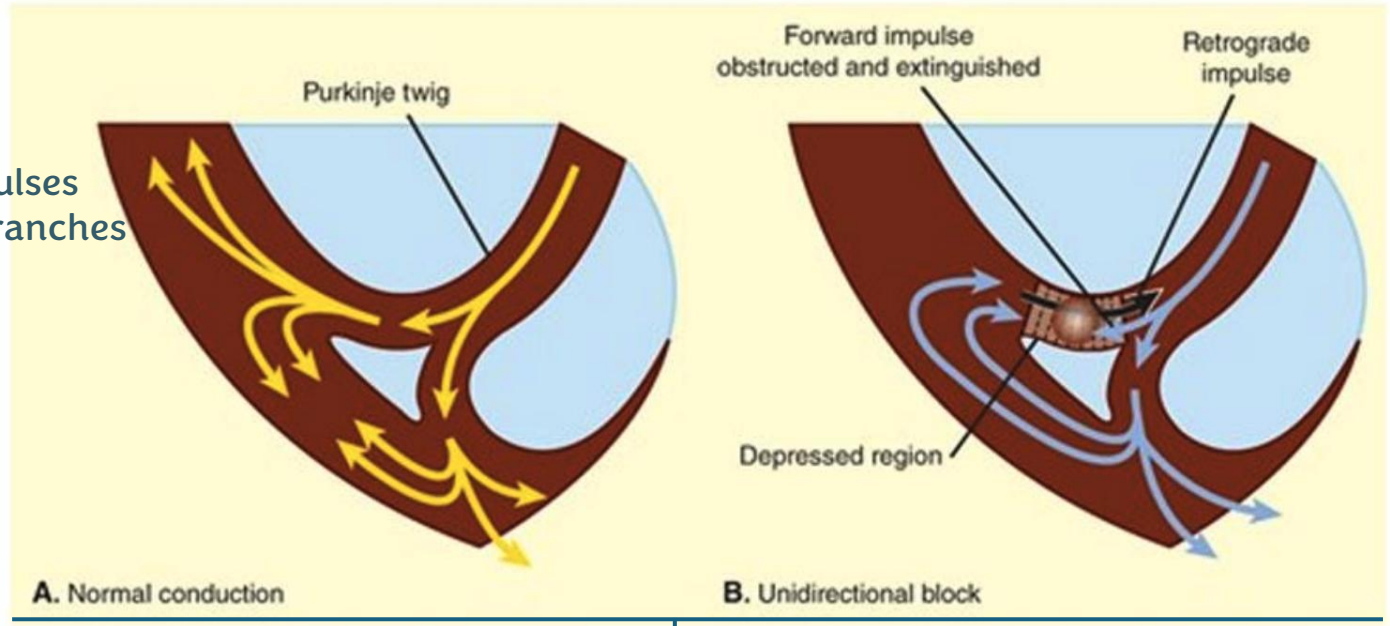
Schematic diagram of a **reentry circuit** that might occur in small bifurcating branches of the Purkinje system where they enter the ventricular wall.

A: Normally, electrical **excitation** branches around the circuit, it is **transmitted** to the ventricular branches and becomes **extinguished** at the other end of the circuit due to collision of impulses.

B: An area of unidirectional block (refractory period) develops in one of the branches, **preventing anterograde impulse transmission** at the site of block, but the retrograde impulse may be **propagated** through the site of block **if the impulse finds excitable tissue**; that is, **the refractory period is shorter than the conduction time.** This impulse can **re-excite** tissue it had previously passed through, and a reentry arrhythmia is established.

Impulse Re-entry; Circus Movement

Branching of impulses into ventricular branches



A: Normally, branches meet and cancel each other out, doesn't affect the synchronous behavior of the heart.

B: In abnormal conditions where an area is blocked or repolarized, once the impulse returns, the refractory period might have ended allowing re-entry of the same impulse to its site of origin, which reactivates the same area of the heart again, leading to the re-entry arrhythmia.

Mechanisms of Cardiac Arrhythmias

- **Some forms of reentry are strictly anatomically determined**.
- For example, in **Wolff-Parkinson-White syndrome**, the reentry circuit consists of atrial tissue, the AV node, ventricular tissue, and an accessory AV connection (**bundle of Kent**, a bypass tract), which provides a pathway of re-entry for the same impulse back into the atrial tissue and excitation of same areas again. This condition is treated surgically.
- Generally, depending on **how many round trips through the pathway a reentrant impulse makes before dying out**, the arrhythmia may manifest as **one or a few extra beats** or as a **sustained tachycardia,** tachyarrhythmia.

Mechanisms of Cardiac Arrhythmias

- Circulating impulses can also give off **“daughter impulses”** that can spread to the rest of the heart.
- In cases such as atrial or ventricular fibrillation, **multiple reentry circuits** may meander (**wander**) through the heart in apparently **random paths**, resulting in the **loss of synchronized contraction**.

Mechanisms of Cardiac Arrhythmias

- **How can reentry occur?** There are three key elements:
  1. First, there is an **obstacle** (anatomic or physiologic normal bifurcation) **to homogeneous impulse conduction**, thus establishing a **circuit** around which the **reentrant wave front can propagate.**
  2. The second element is **unidirectional block** at some point in the circuit. That is, something has occurred such that an impulse reaching the site **initially encounters refractory tissue.**
  3. Finally, **conduction time** around the circuit must be **long** enough so that by the time the impulse **returns** to the site after traveling around the obstacle, the **tissue is no longer refractory**.
- In other words, **conduction time** around the circuit must **exceed** the effective **refractory period** duration in the area of unidirectional block.

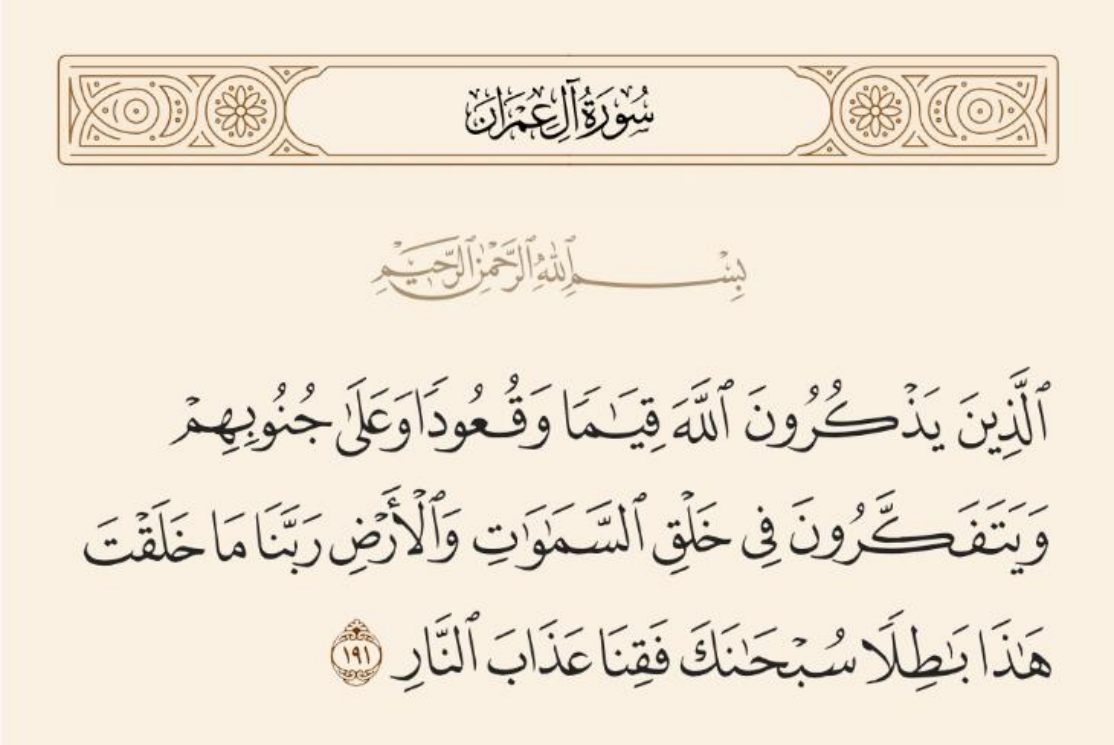
PHARMACOLOGY QUIZ LECTURE 1

External Resources

رسالة من الفريق العلمي

Additional sources:

1. Lippincott Illustrated Reviews Pharmacology, 6th edition.
2. Arrhythmia Overview - Mechanism of bradyarrhythmia and tachyarrhythmia,
3. Armando Hasudungan on Yt: [Link]



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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	11 20	- “Plateau”	Some concepts regarding QRS complex and AP were revised. And the slide was split into 2 “repolarization”
V1 → V2			