

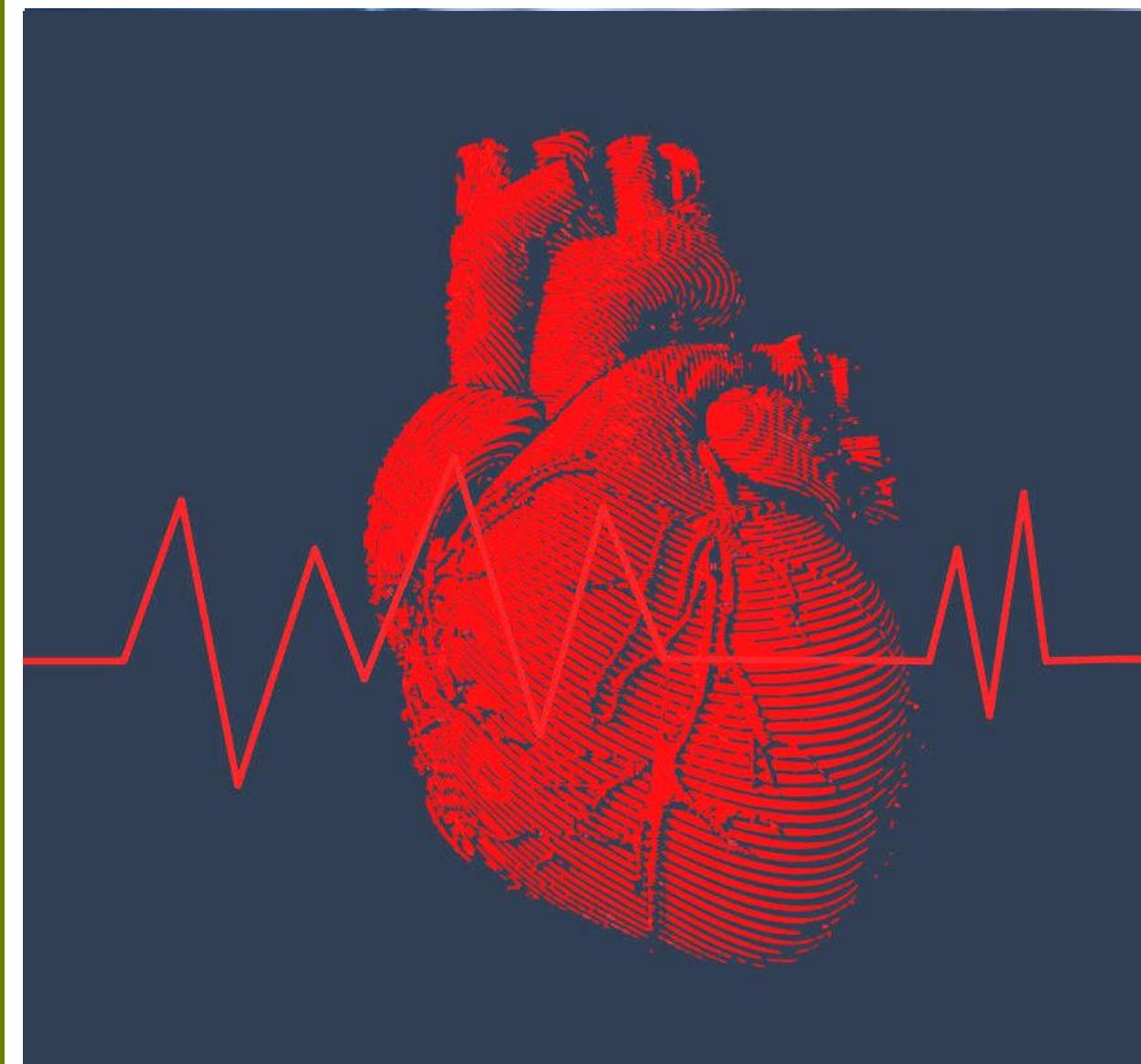


# Antiarrhythmic drugs

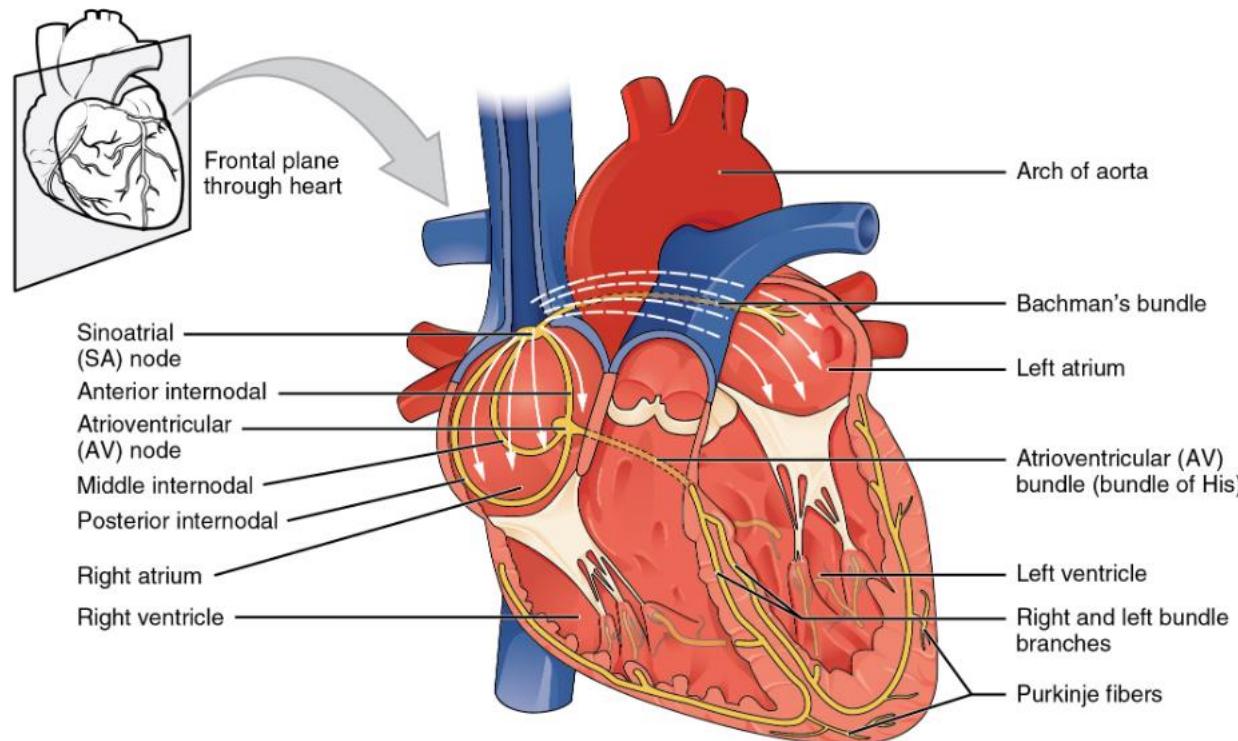
Daniel PRIKSZ

---

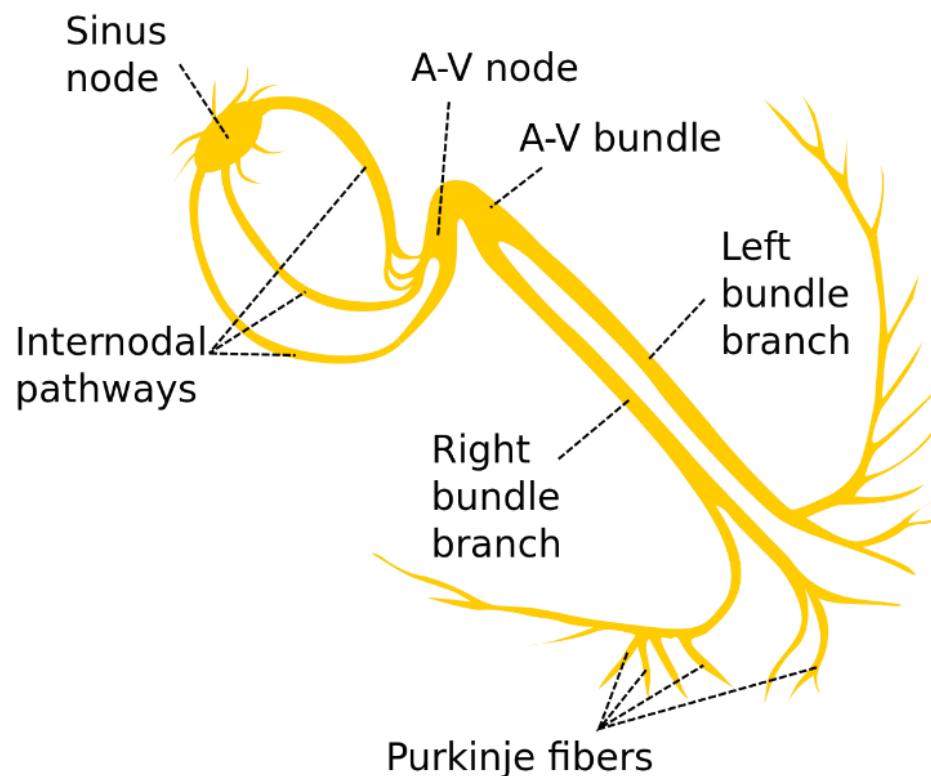
Pharmacology 4th year



# Anatomy of the heart and structure of conduction system

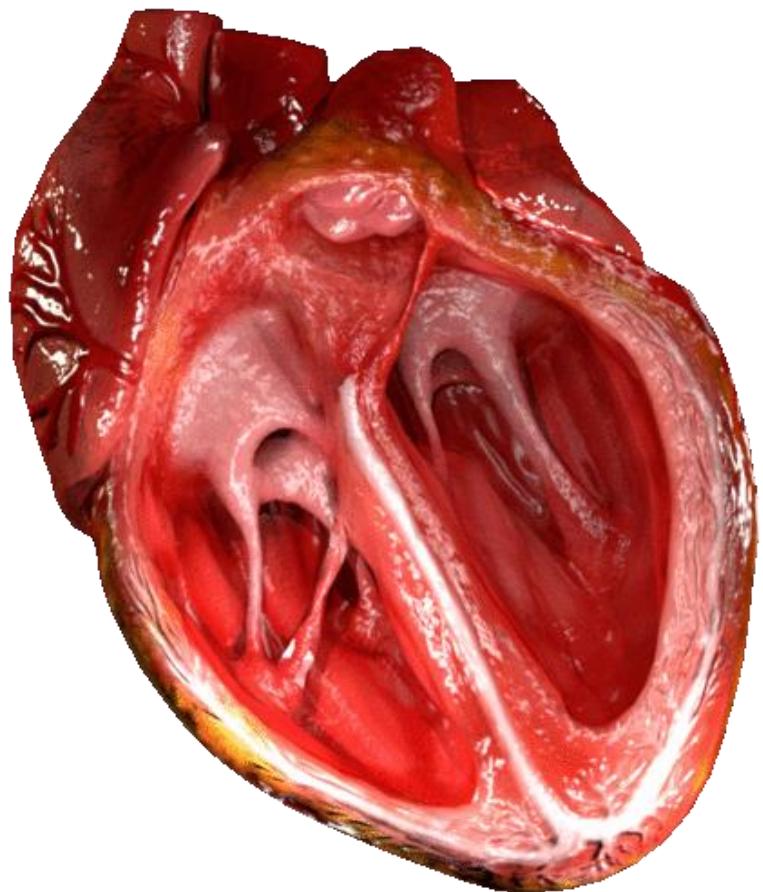


- Nodal cells and contractile cells
- Heart muscle (myocardium) has an exceptional property:
- It has the ability to initiate an electrical potential, that spreads rapidly from cell to cell to trigger the contractile mechanism



- The components of the cardiac conduction system include
  - the sinoatrial node (SAN),
  - the atrioventricular node (AV),
  - the atrioventricular bundle (bundle of His),
  - the AV bundle branches (Tawara),
  - and the Purkinje fibers

# Automaticity (autorhythmicity)

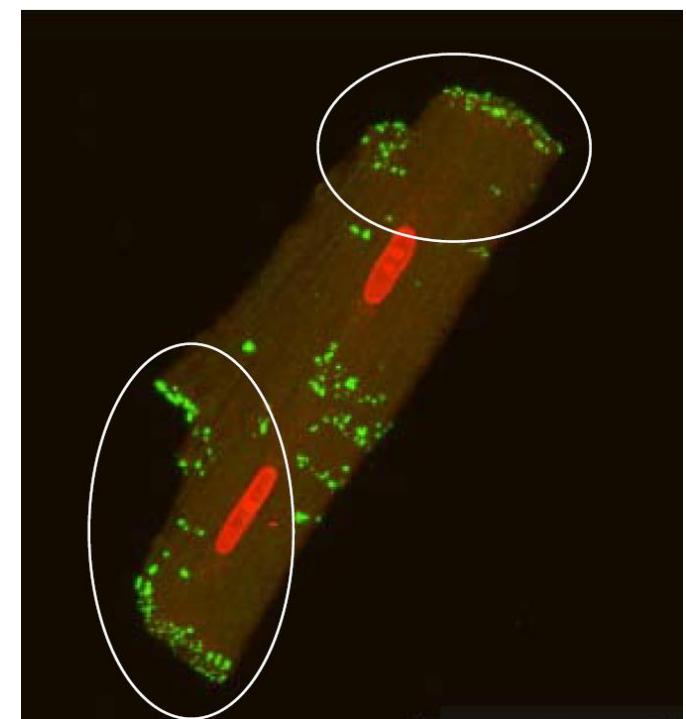
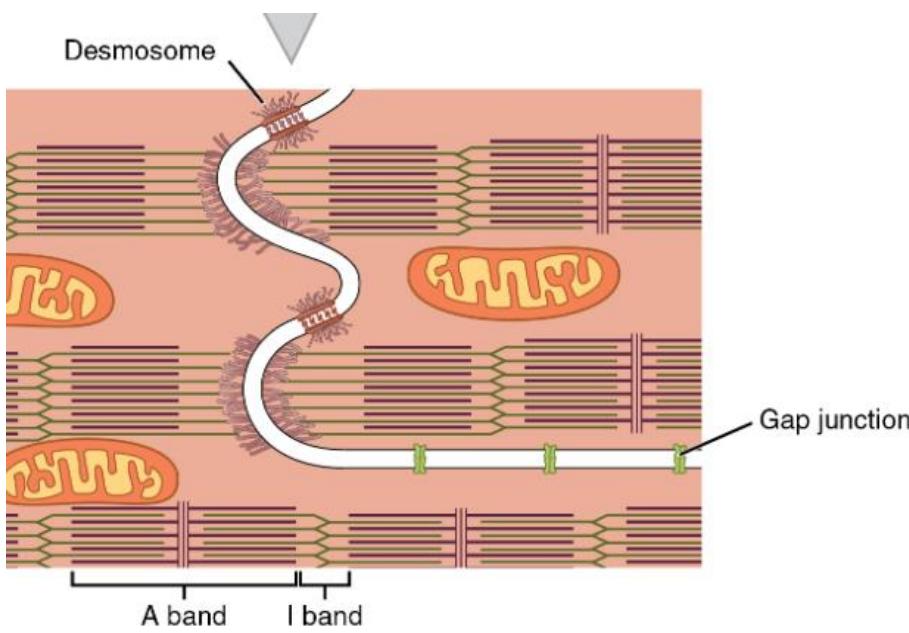


- A fully developed heart maintains the capability of generating its own electrical impulse, triggered by the fastest cells, called automaticity
- This is explained by the phenomenon called spontaneous depolarization (see later)

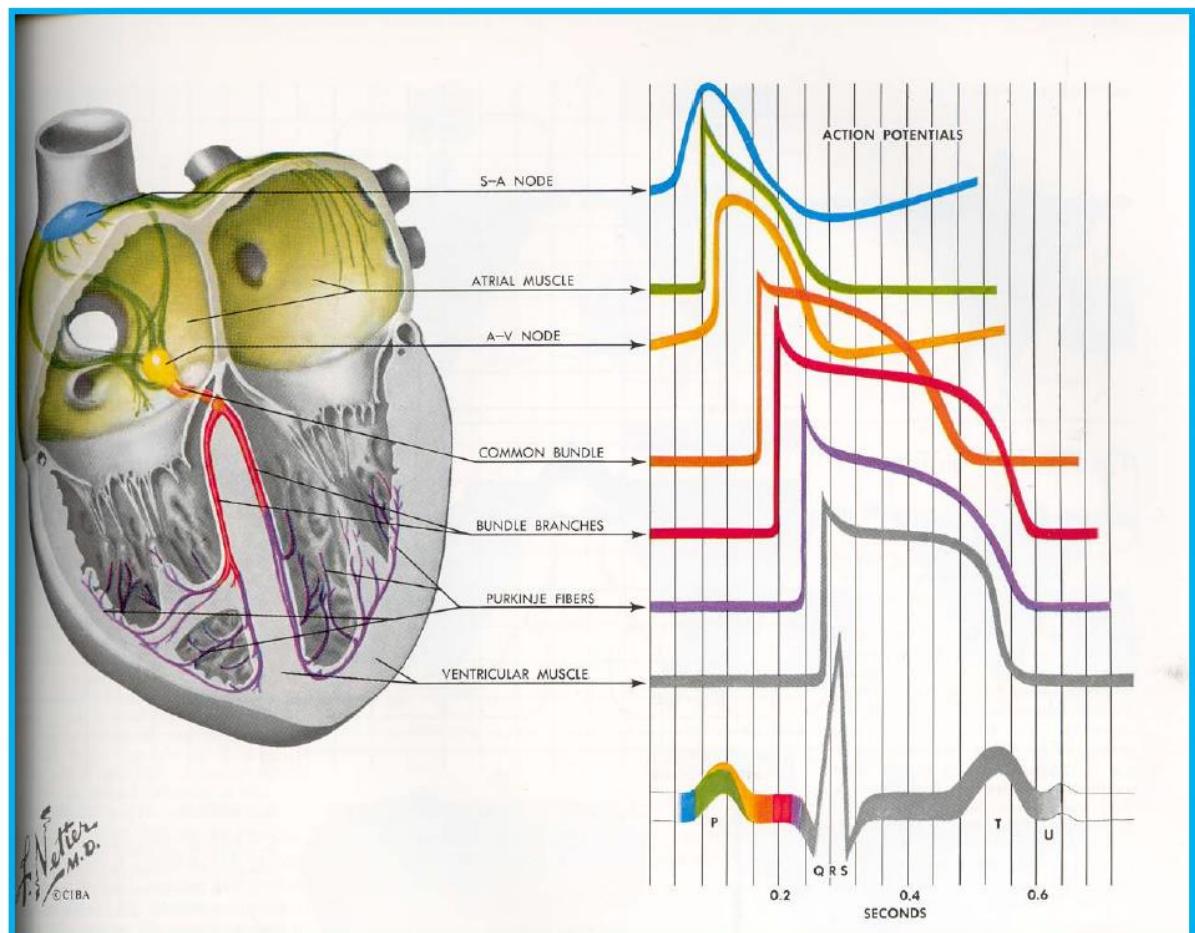
Syncytium:

- each cell is connected to many neighbors with gap junctions, so that electrical impulses spread rapidly,

and the heart acts like a single large cell, one unit, which is called a **syncytium**

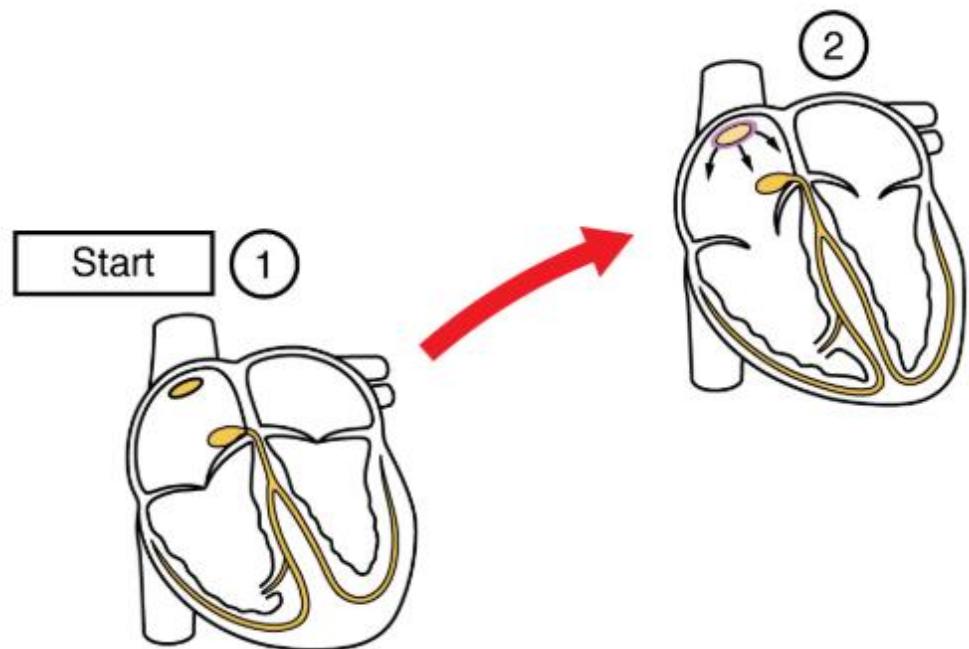


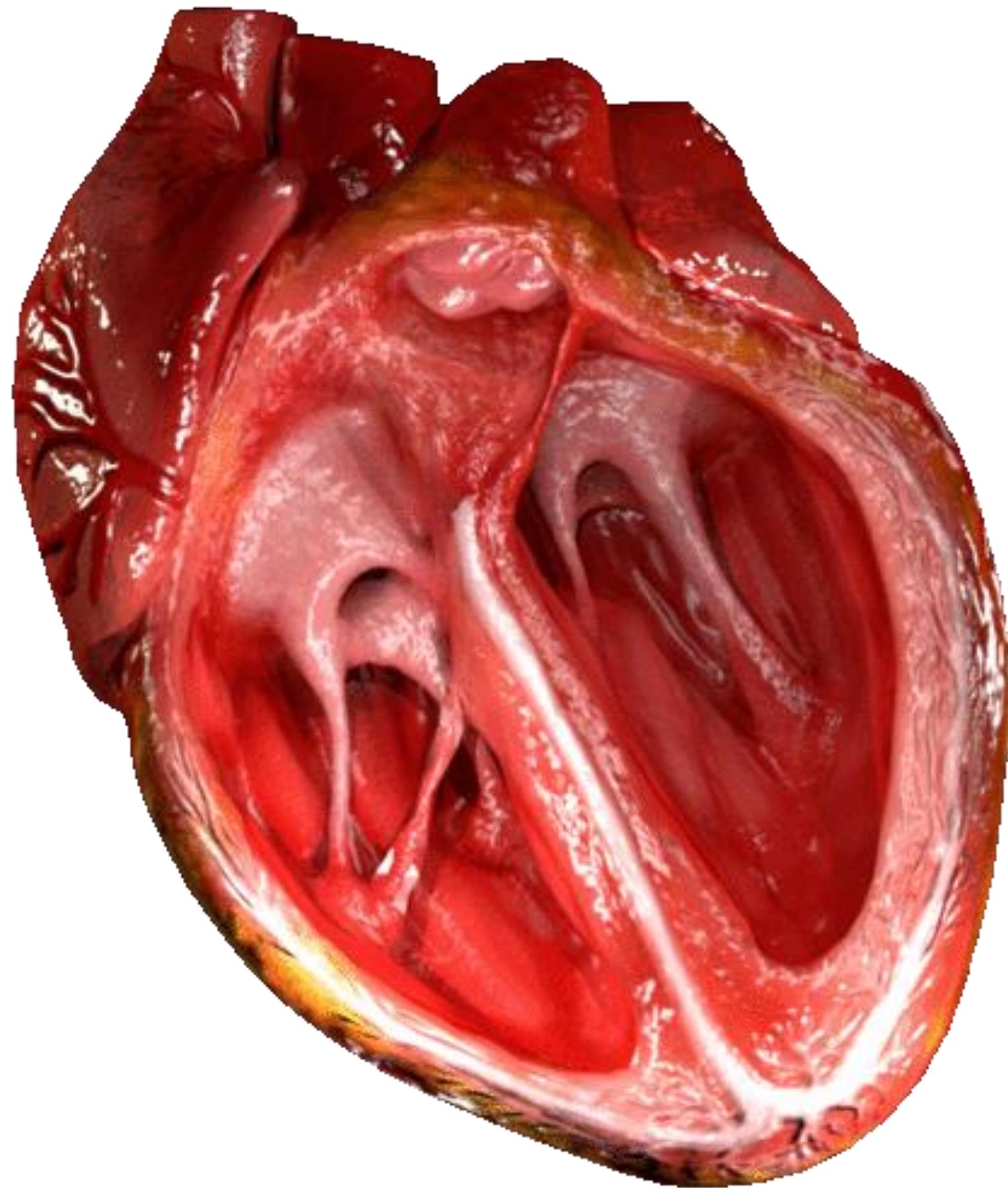
# The SA node is the pacemaker



- The SA node has the highest inherent rate of depolarization and is known as the **pacemaker** of the heart.
- Has the least negative resting membrane potential (-50 mV), which is not stable
- It initiates (sets) the **sinus rhythm**, or normal electrical pattern, followed by contraction of the heart
- without nervous or endocrine control, SAN would initiate a heart rate approximately 80–100 bpm  
(isolated heart)

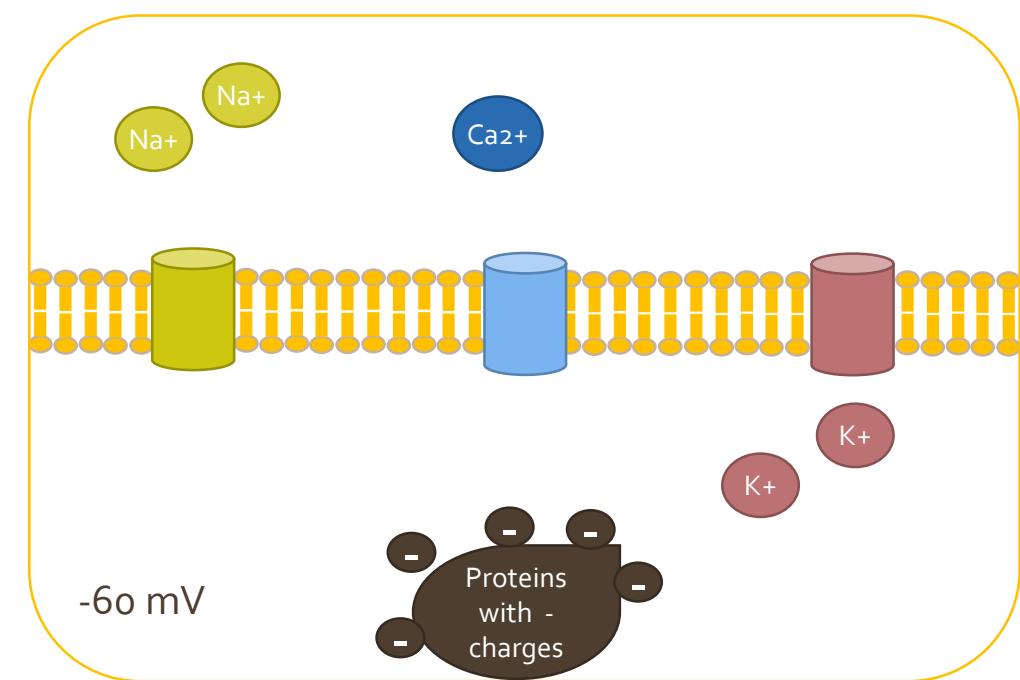
- Normal sinus rhythm: 72 bpm





# What is the underlying mechanism?

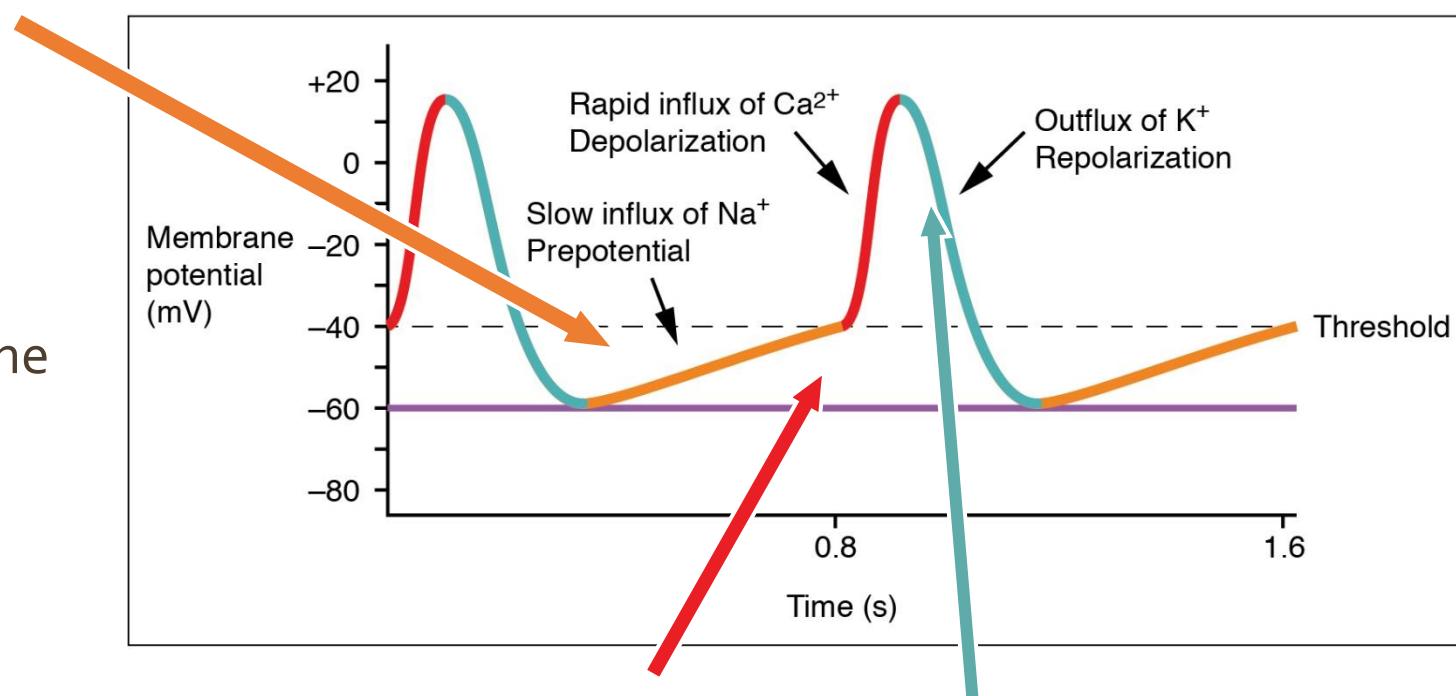
- Cardiac conductive cells do not have a stable resting potential.
- Conductive cells contain a series of sodium ion channels that are very leaky ( $I_f$ , „funny current”)
- these allow a normal and slow influx of sodium ions that causes the membrane potential to rise slowly from an initial value of  $-60$  mV up to about  $-40$  mV.
- This creates the **spontaneous depolarization (prepotential)**



Furthermore, SAN (and AV) lack  $I_{K_1}$ , a  $\text{K}^+$  ion channel that maintains the resting membrane potential in atrial and ventricular tissue.



SAN spontaneously regenerate APs

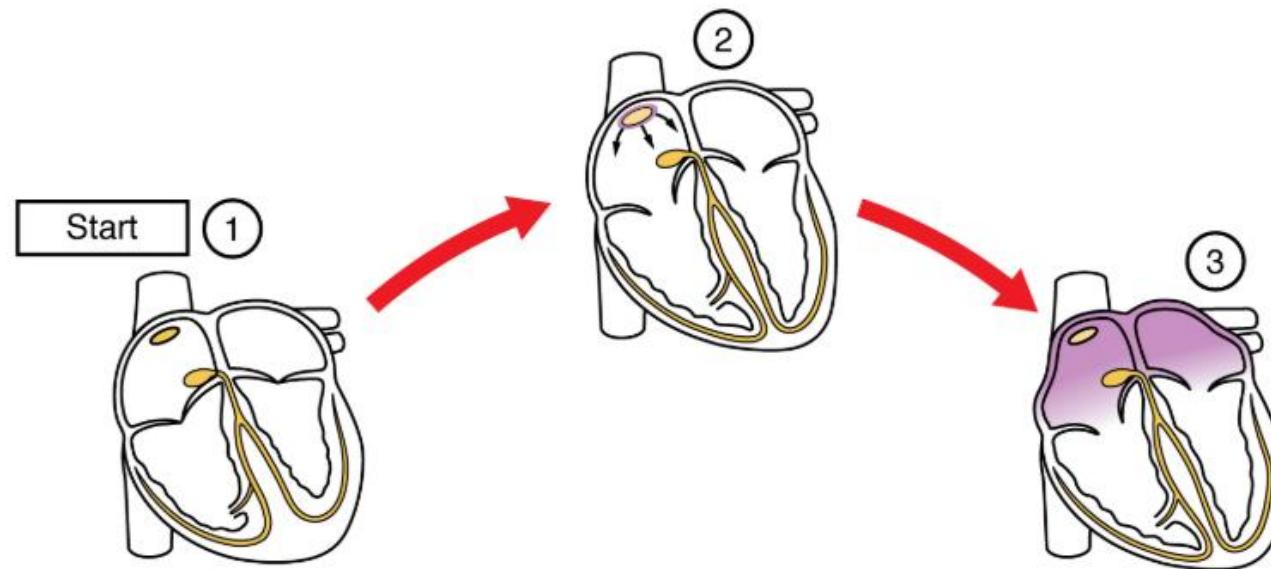


**AP of a „slow response „ tissue (sinus, AV)**

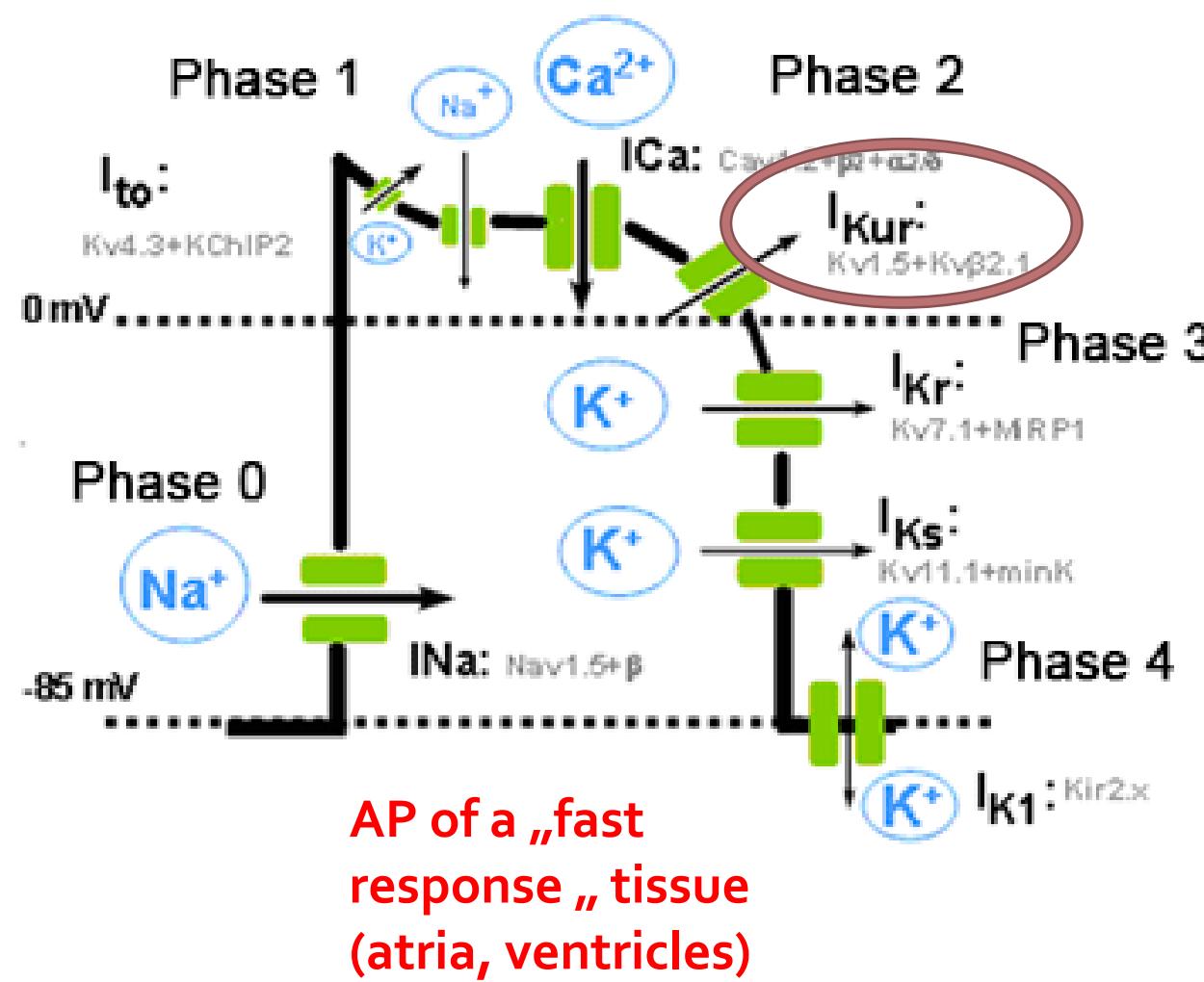
At this point, calcium ion channels open and  $\text{Ca}^{2+}$  enters the cell, further depolarizing it at a more rapid rate until it reaches a value of approximately  $+5$  mV.

At this point, the calcium ion channels close and  $\text{K}^+$  channels open, allowing outflux of  $\text{K}^+$  and resulting in repolarization

# Atrial action potentials



- The impulse from SAN spreads from its initiation throughout the atria, through specialized **internodal pathways**
- There is a distinctly different electrical pattern in the atrial (and ventricular) contractile cells.
- there is a rapid depolarization, followed by a plateau phase and then repolarization

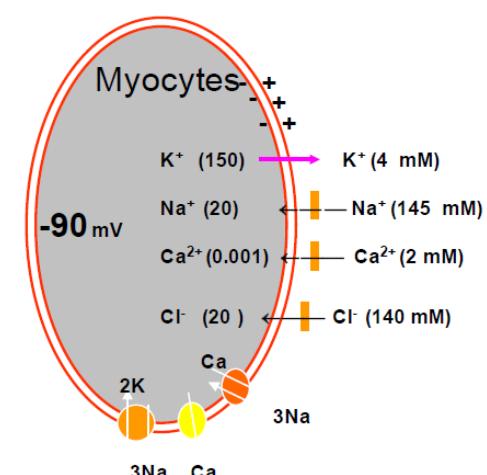


- Contractile cells demonstrate a much more stable resting potential than conductive cells at approximately  $-80\text{ mV}$  for cells in the atria ( $-90$  in ventricle)

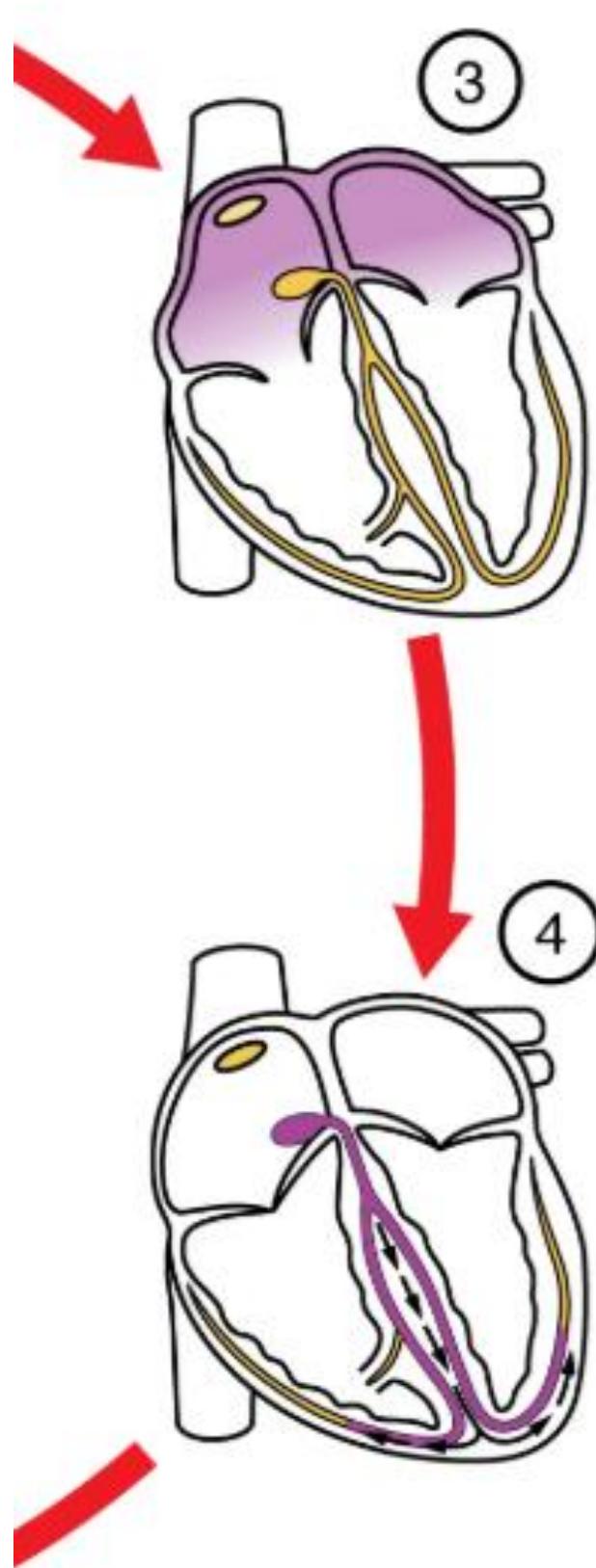
RMP  $\approx K^+$  Equilibrium potential

Nernst equation:

$$E_K = -61 \log[K^+]_i/[K^+]_o = -96\text{ mV}$$

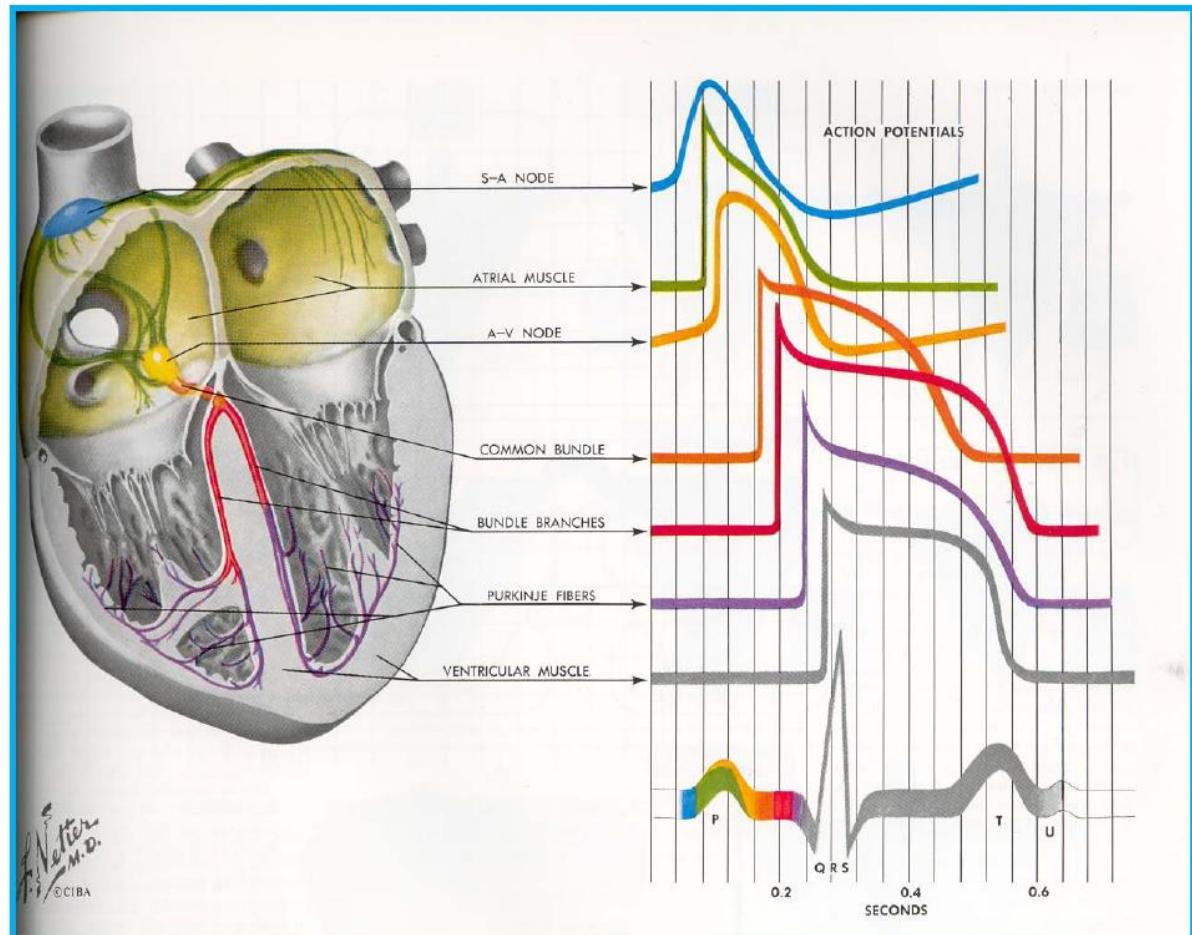


# The AV node

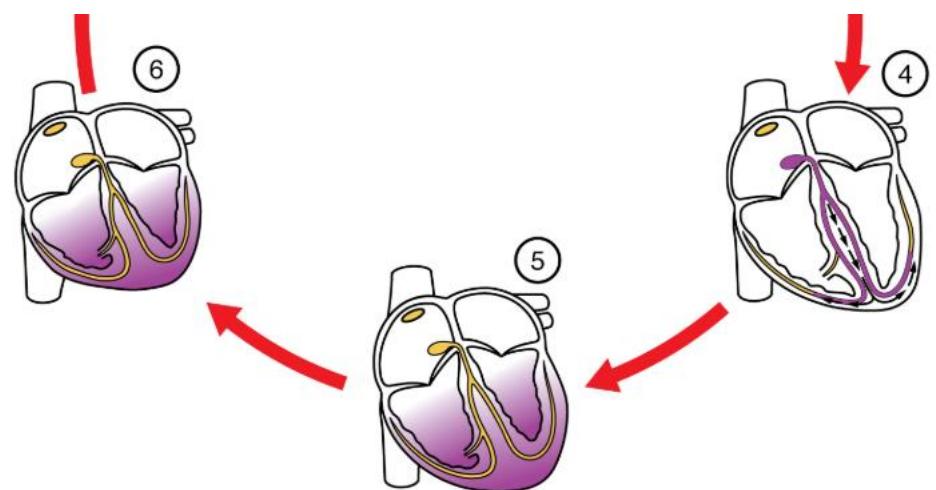


- The septum (anulus fibrosus cordis) prevents the impulse from spreading directly to the ventricles without passing through the AV node, as it is impermeable to electrical propagation
- The AV node **acts as a gatekeeper**, regulating impulse conduction from the atrium to the ventricle.
- **There is a critical pause before the AV node depolarizes and transmits the impulse to the atrioventricular bundle**
- it takes the impulse approximately 100 ms to pass through (0,1 sec)
- This pause is critical to heart function, as it allows the atrial cardiomyocytes to complete their contraction before the impulse is transmitted to the ventricle
  
- With extreme stimulation by the SA node, the AV node can transmit impulses maximally at 220 per minute (max. HR)
- Without the SA node, the AV node alone would generate a heart rate of 40–60 bpm

# The AV bundle (His), AV-branches (TW) and the Purkinje fibers

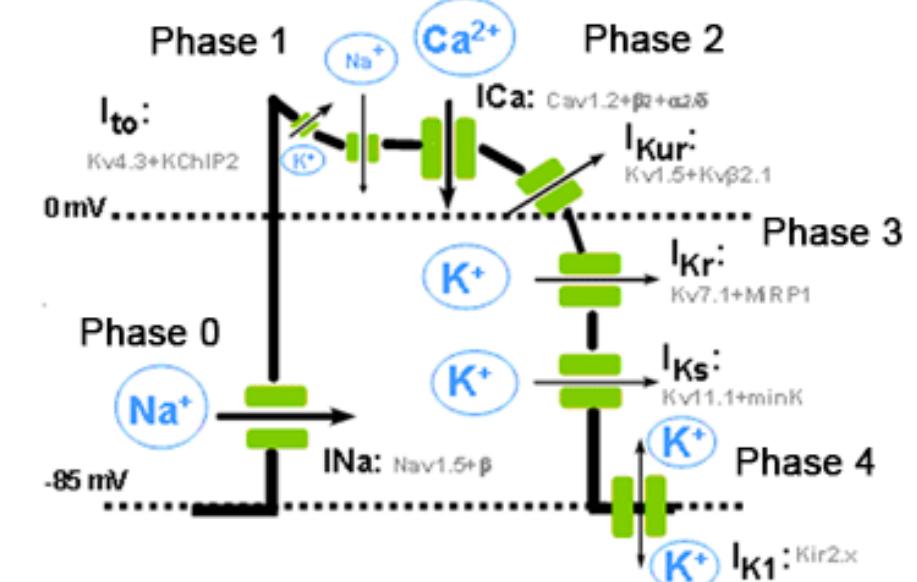
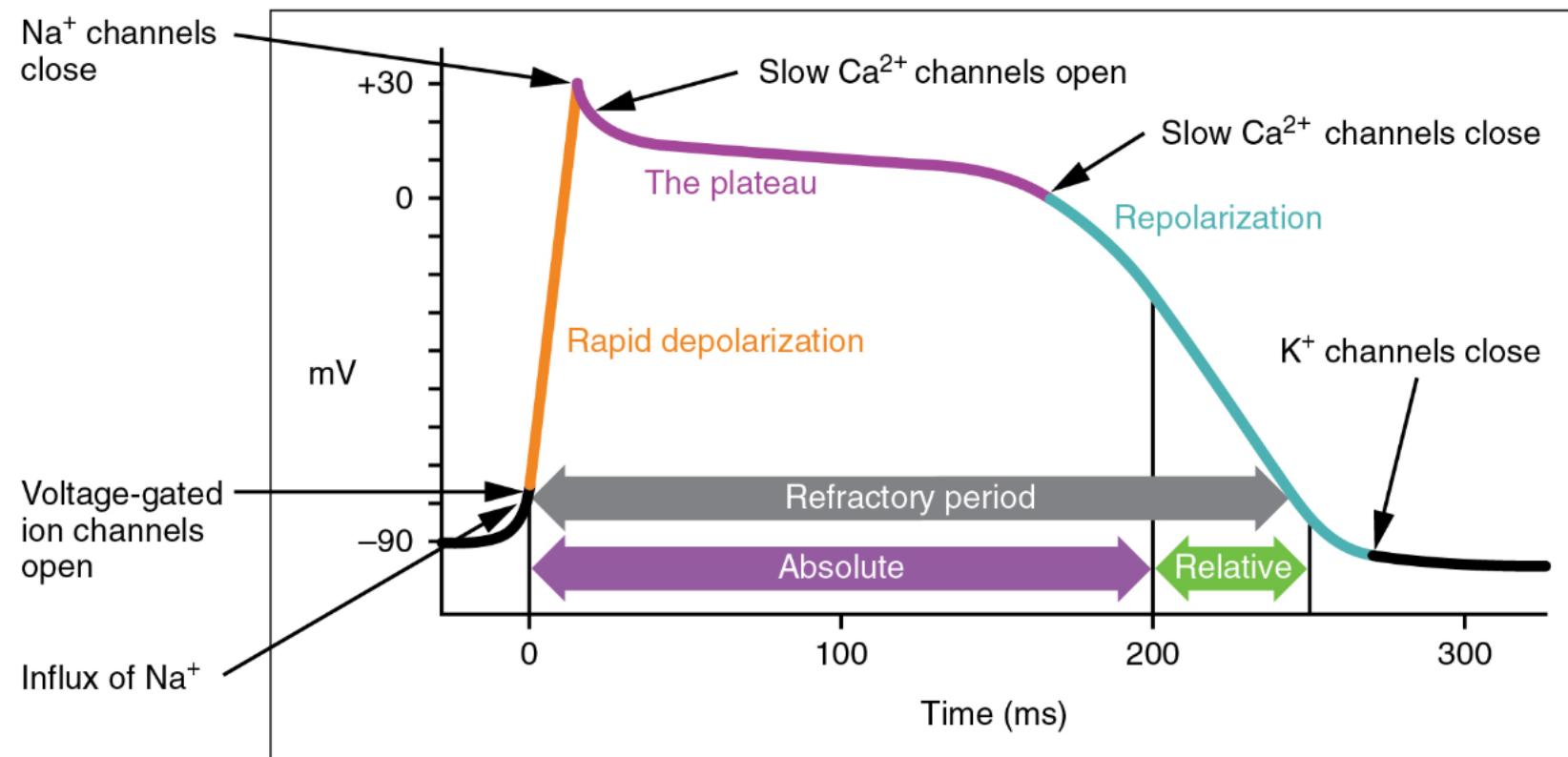


- **atrioventricular bundle, or bundle of His,** proceeds through the interventricular septum before dividing into two **atrioventricular bundle branches**
- The left bundle branch supplies the left ventricle, and the right bundle branch the right ventricle
- The **Purkinje fibers** spread the impulse to the myocardial contractile cells in the ventricles.
- They extend throughout the myocardium



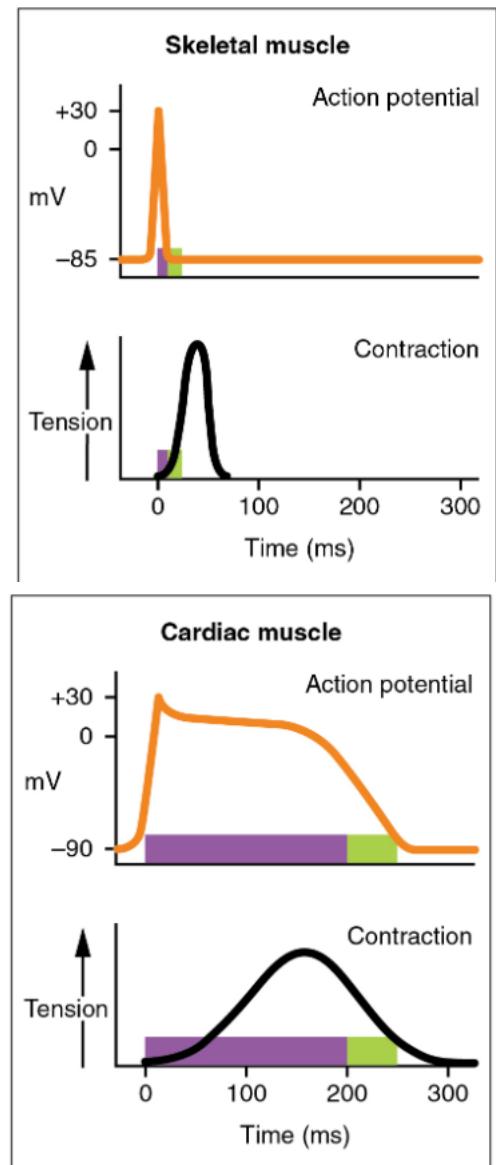
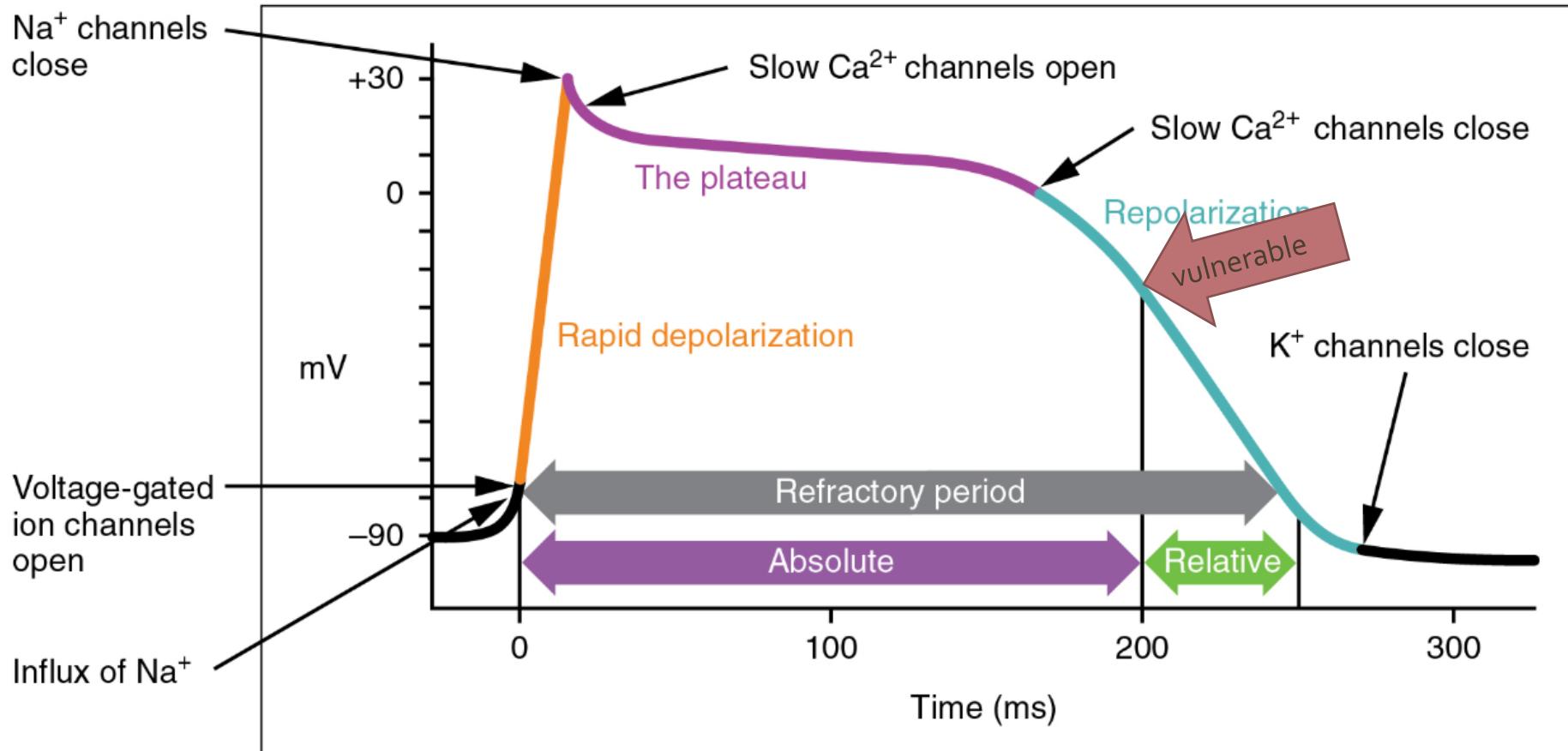
- The left ventricular areas first excited are the anterior and posterior paraseptal wall and the central left surface of the interventricular septum. The last part of the left ventricle to be activated is the posterobasal area.

# Ventricular action potentials



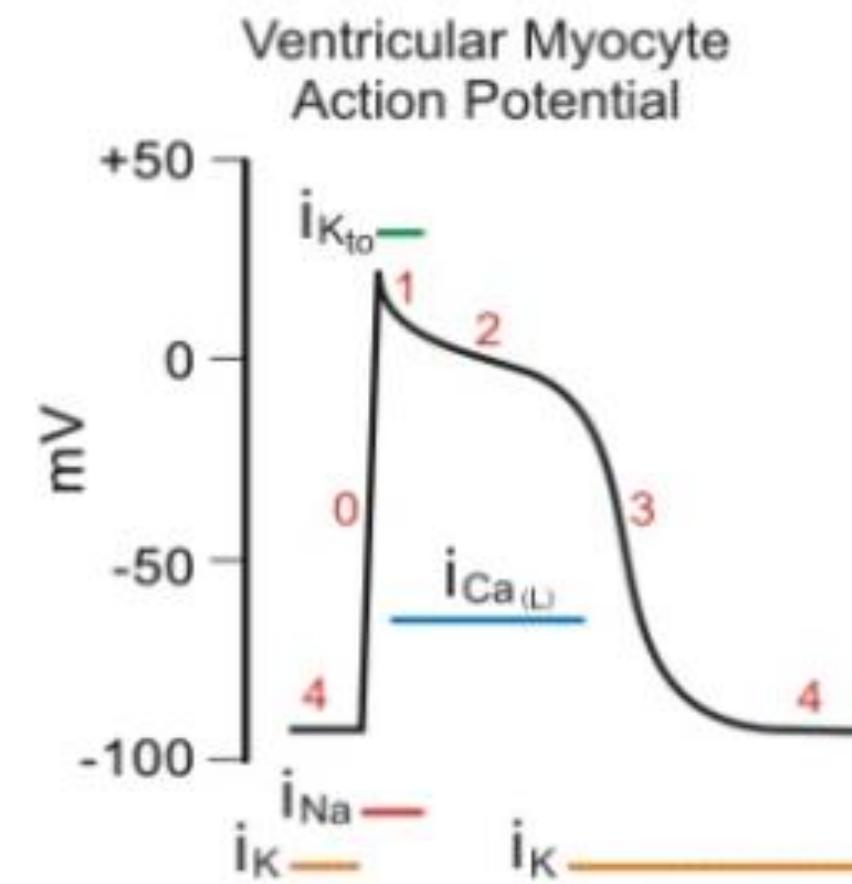
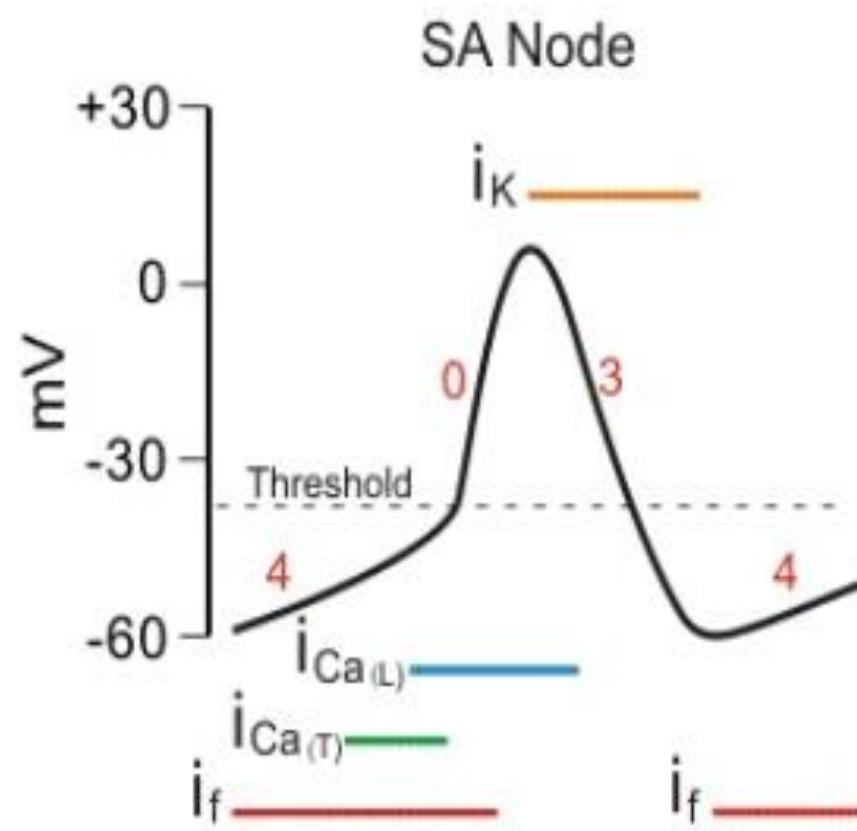
- when stimulated by an action potential, voltage-gated channels rapidly open
- This rapid influx of positively charged sodium ( $\text{Na}^+$ ) ions raises the membrane potential to approximately  $+30 \text{ mV}$ ,
- Depolarization is followed by the plateau phase,
- This is due in large part to the opening of the  $\text{Ca}^{2+}$  channels, allowing  $\text{Ca}^{2+}$  to enter the cell while few  $\text{K}^+$  channels are open, allowing  $\text{K}^+$  to exit the cell (175 ms)
- Once the membrane potential reaches approximately zero, the  $\text{Ca}^{2+}$  channels close and  $\text{K}^+$  channels open, allowing  $\text{K}^+$  to exit the cell. (75 ms)
- Delayed rectifier currents (collectively termed  $I_K$ ) (HERG) increase with time, whereas  $\text{Ca}^{2+}$  currents inactivate (and so decrease with time); as a result, cardiac cells repolarize (phase 3)

# The role of the refractory period



- The absolute refractory period for cardiac contractile muscle lasts approximately 200 ms, and the relative refractory period lasts approximately 50 ms, for a total of 250 ms.
- This extended period is critical, since the heart muscle must contract to pump blood effectively and the contraction must follow the electrical events.
- **Without extended refractory periods, premature contractions would occur in the heart**
- **In the relative refractory period, strong impulses could generate an AP, which is the basis of certain cardiac arrhythmias**
- **Most of the antiarrhythmic agents extend this ERP, effective refractory period**

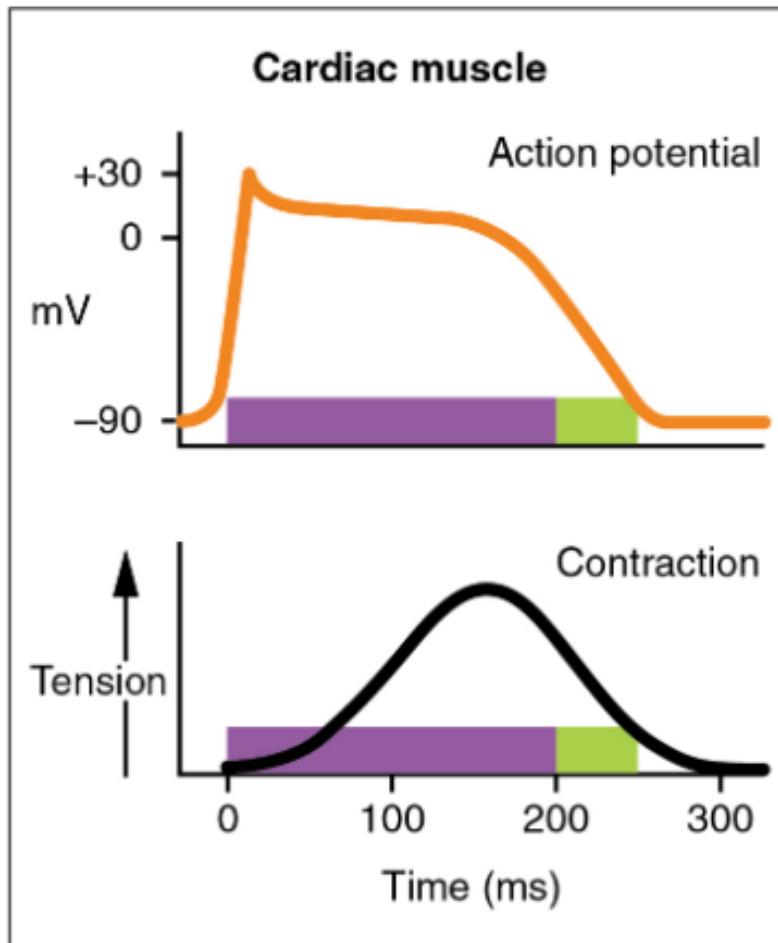
# Slow vs. fast action potentials



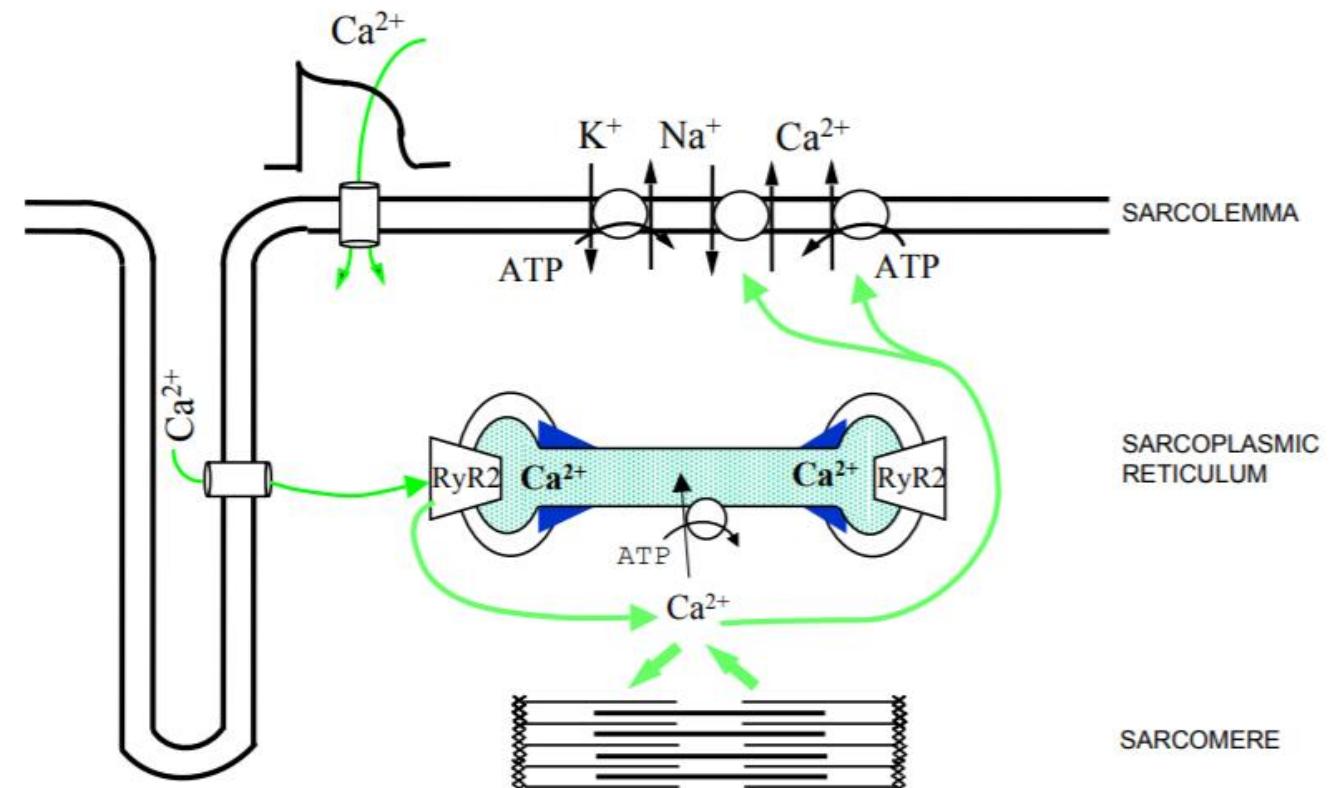
- Upstroke: L-type Ca channels

- Upstroke: VG Na channels

# Ventricular myocytes and the excitation-contraction coupling



## $\text{Ca}^{2+}$ induced $\text{Ca}^{2+}$ release

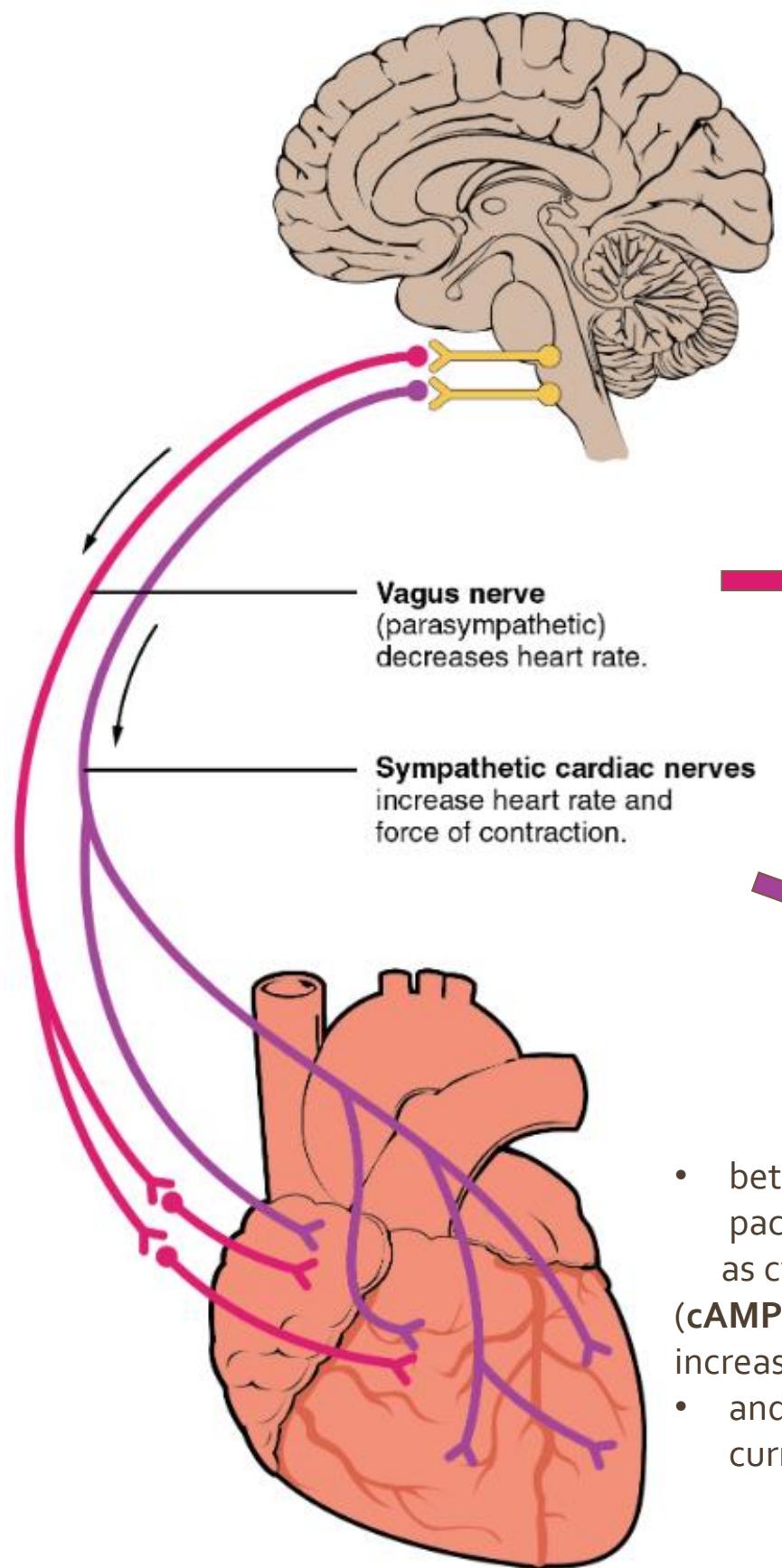


- $\text{Ca}^{2+}$  enters from sacrolemmal  $\text{Ca}^{2+}$  channels, diffuses to the SR  $\text{Ca}^{2+}$  release channel (ryanodine receptor), and causes a large  $\text{Ca}^{2+}$  release.
- SR  $\text{Ca}^{2+}$  release raises intracellular  $\text{Ca}^{2+}$  from  $10^{-7} \text{ M}$  to  $10^{-5} \text{ M}$ , enough to cause  $\text{Ca}^{2+}$  binding to troponin, displacing tropomyosin, causing actin-myosin cross bridge cycling

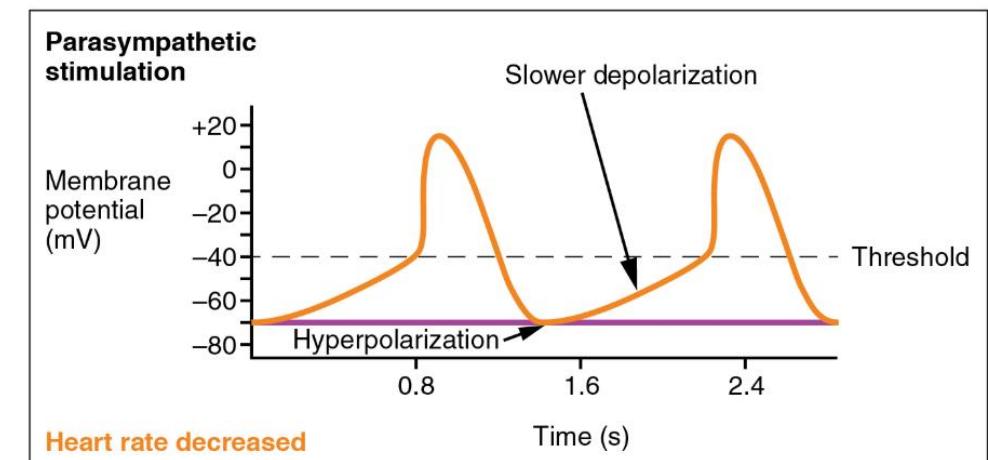
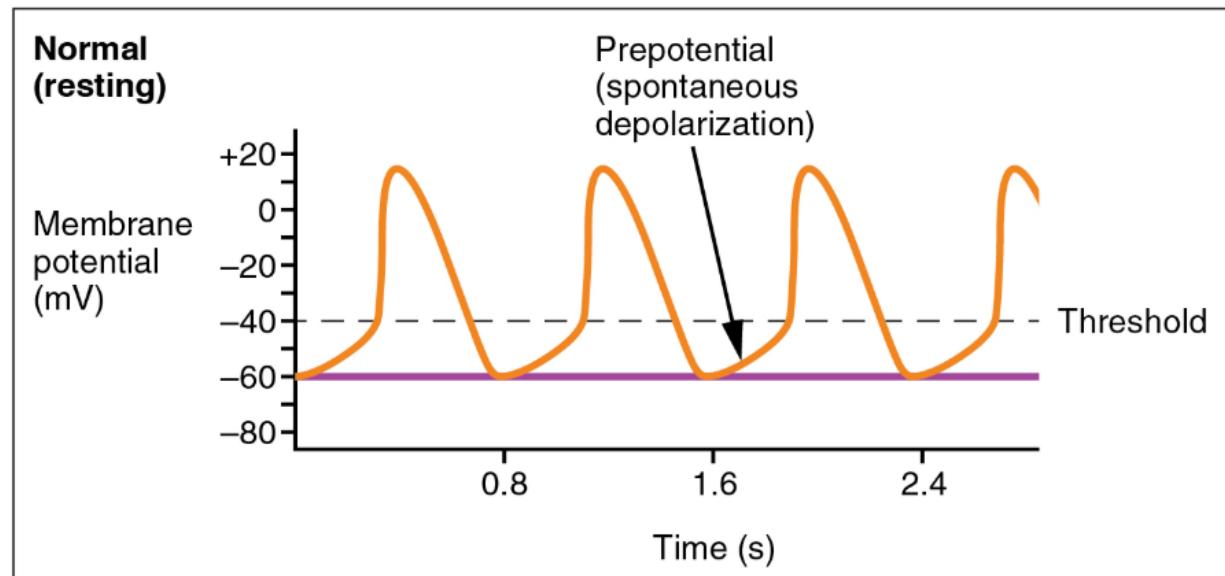
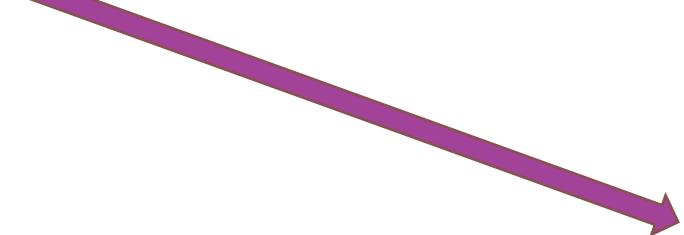
### Removal of calcium ions:

- SERCA 75%
- NCX 25 %

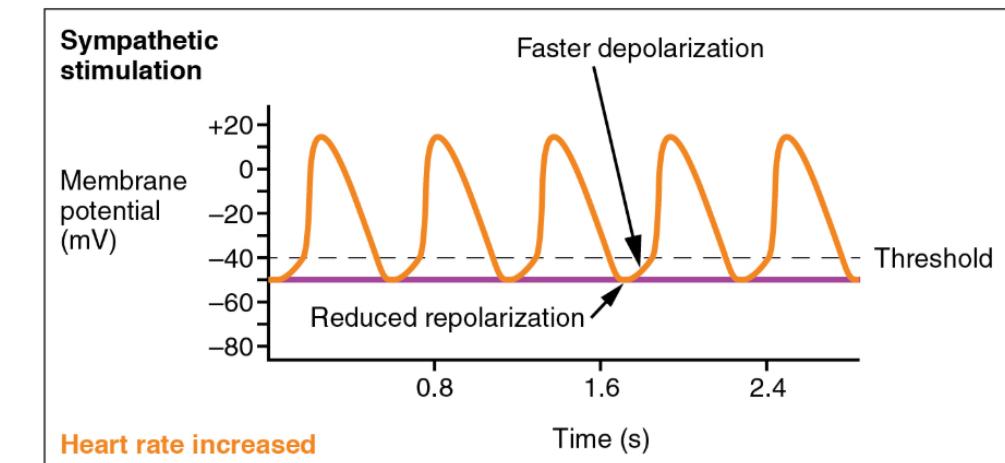
# Autonomic influences



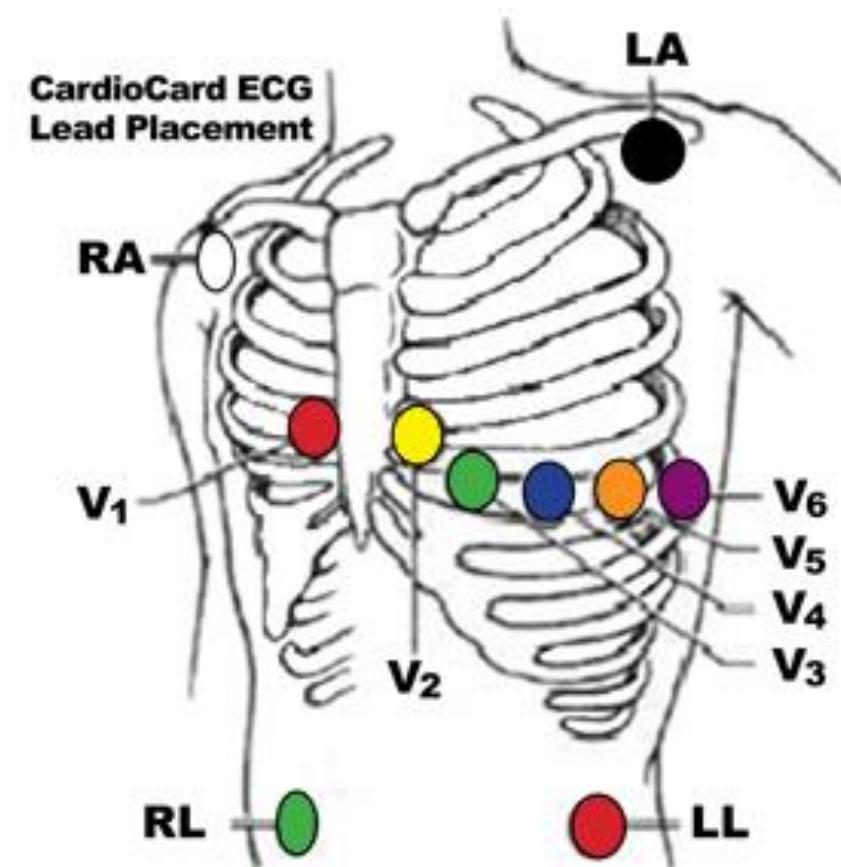
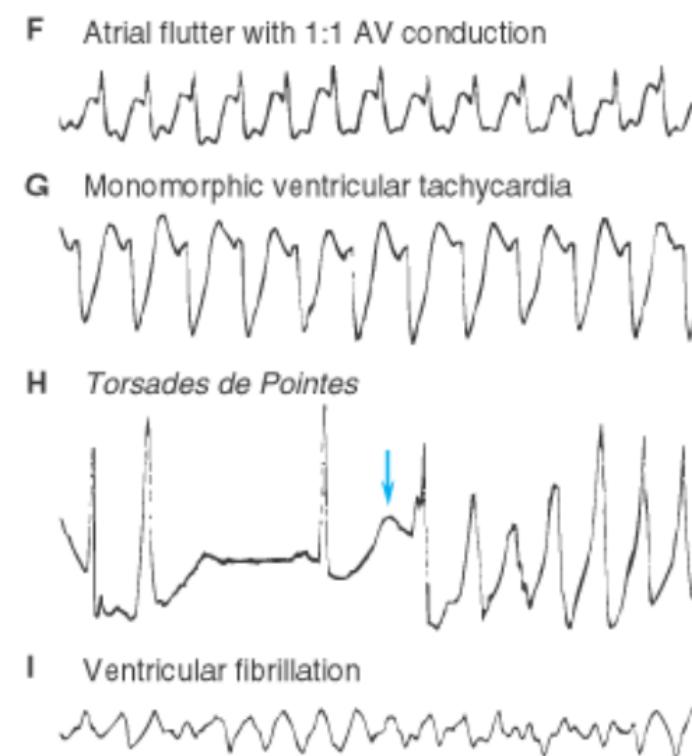
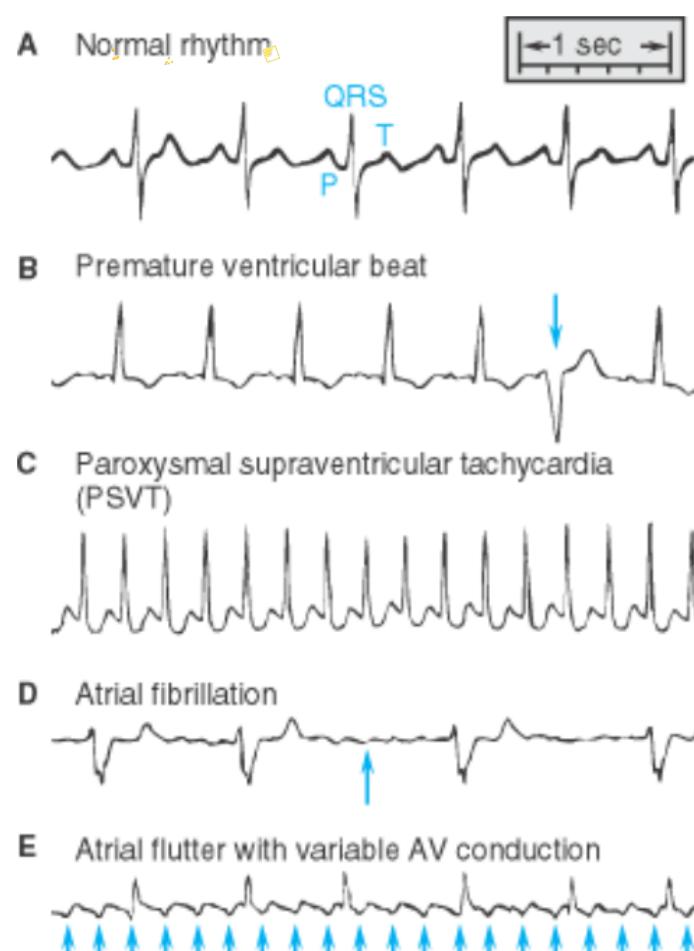
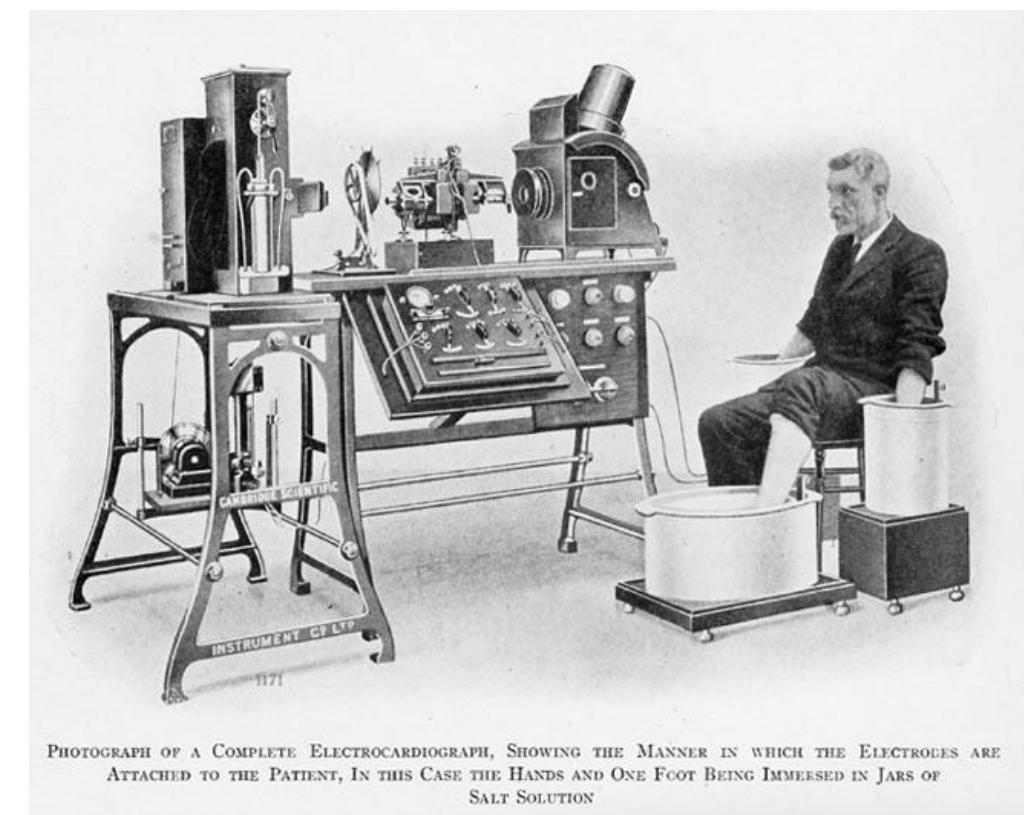
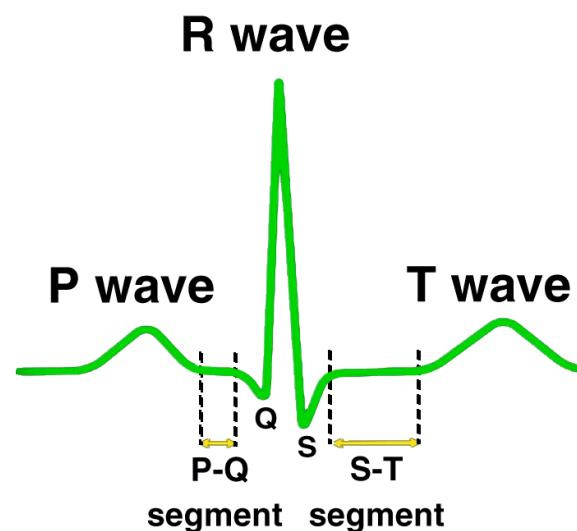
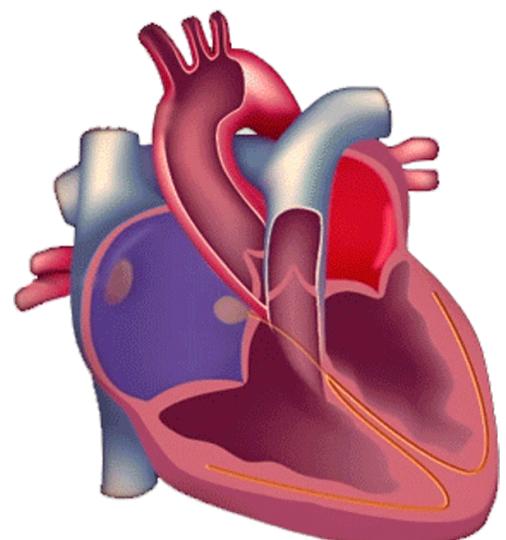
- negative chronotropic effect of vagal stimuli is mediated by  $I_f$  inhibition
- and via the activation of an ACh-dependent  $K^+$  current

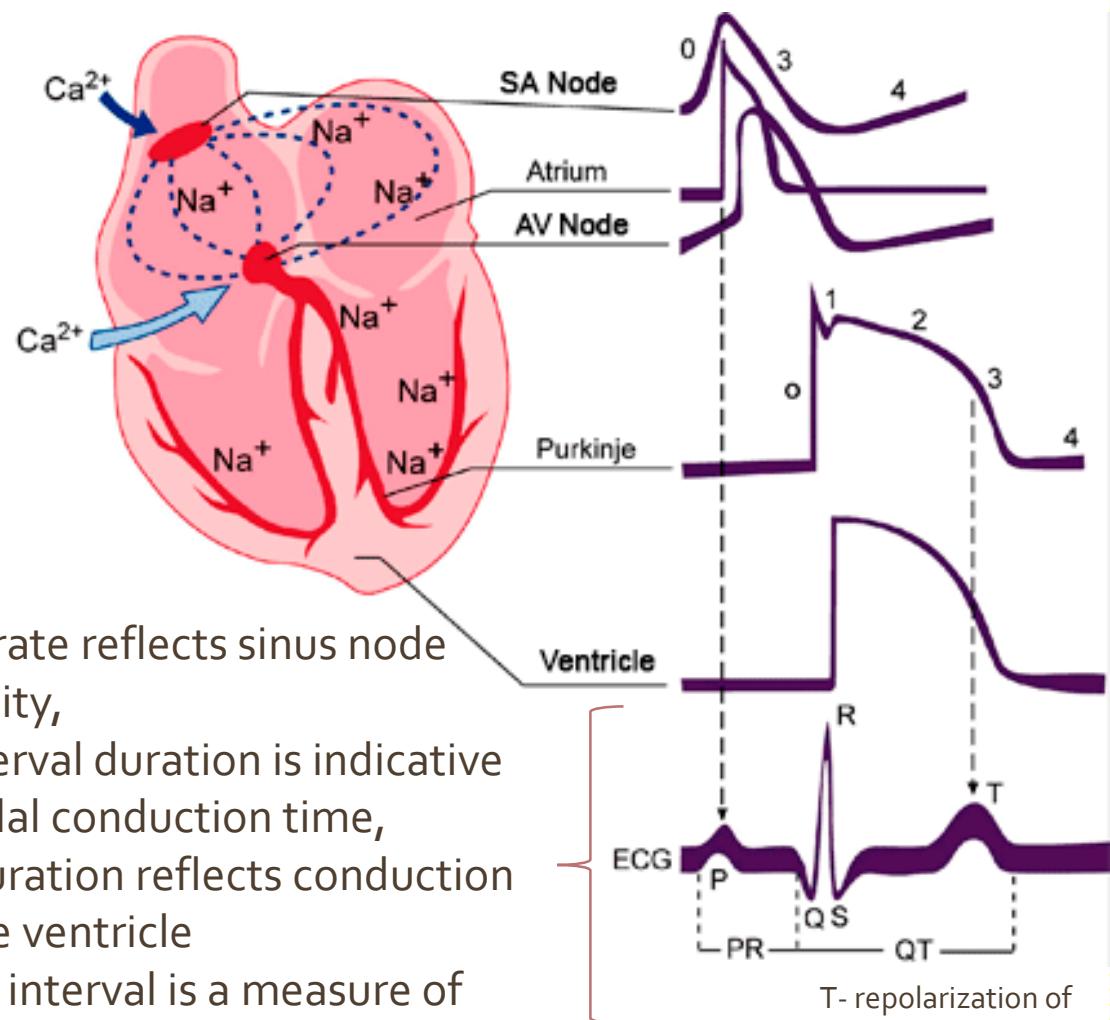


- beta<sub>1</sub> activation increases the slope of pacemaker potential, as cyclic adenosine monophosphate (cAMP) bind directly to f-channels and increase their open probability
- and cAMP also increases  $Ca^{2+}$  inward current (upstroke)



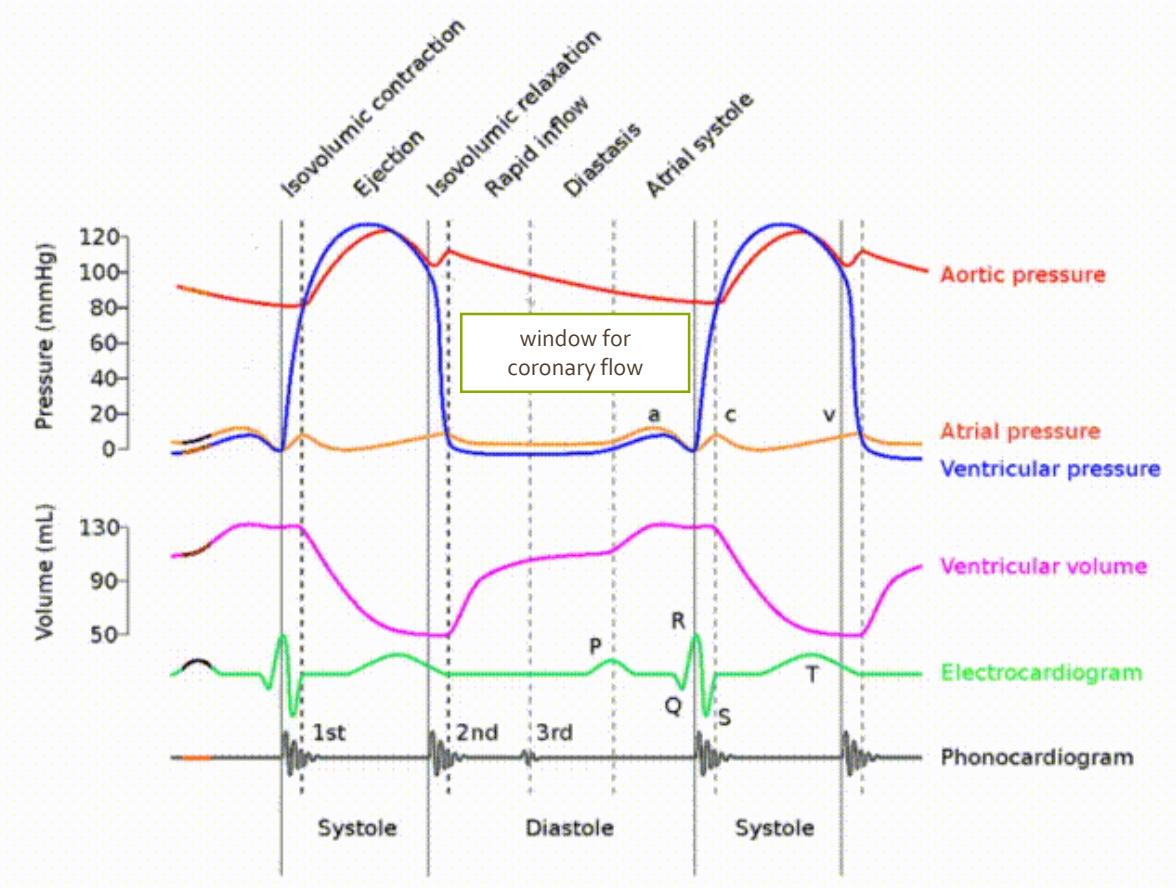
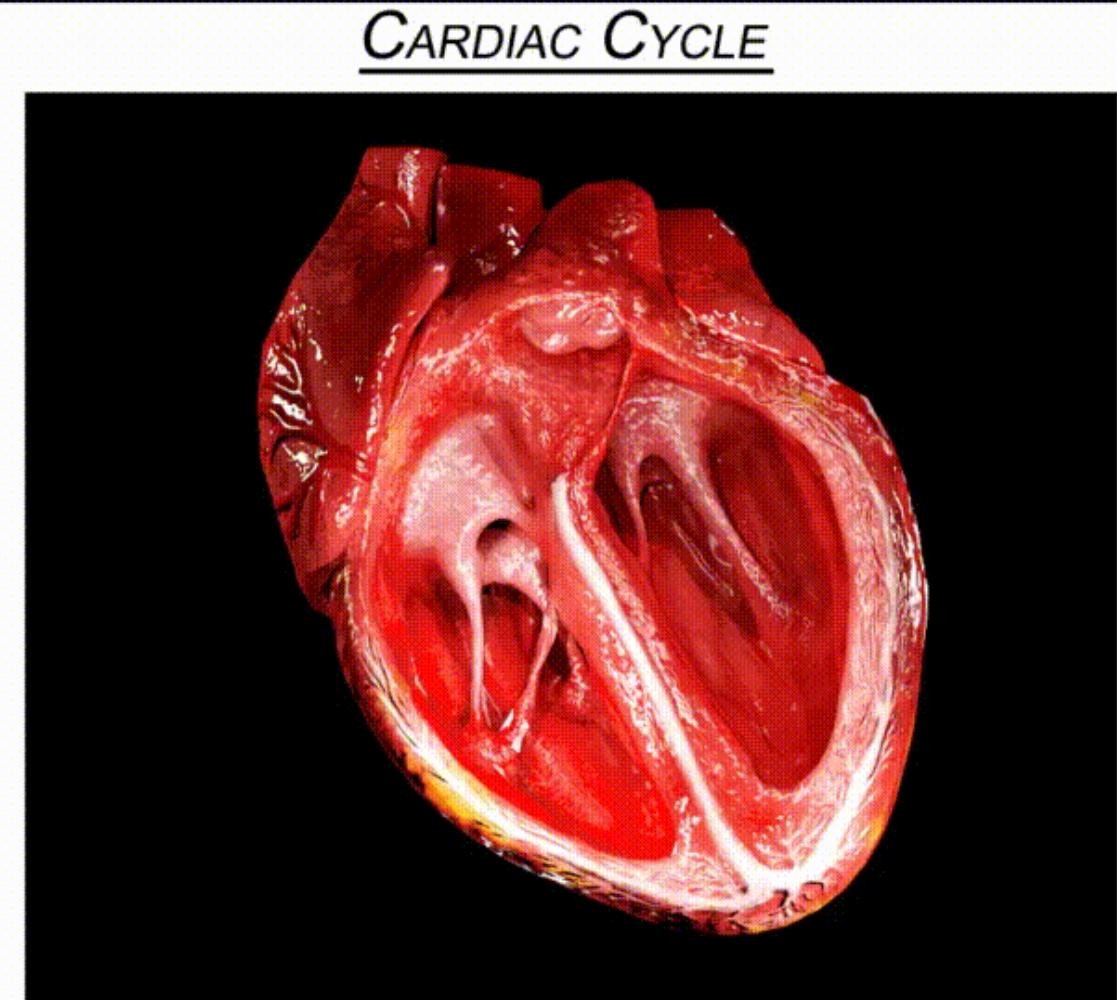
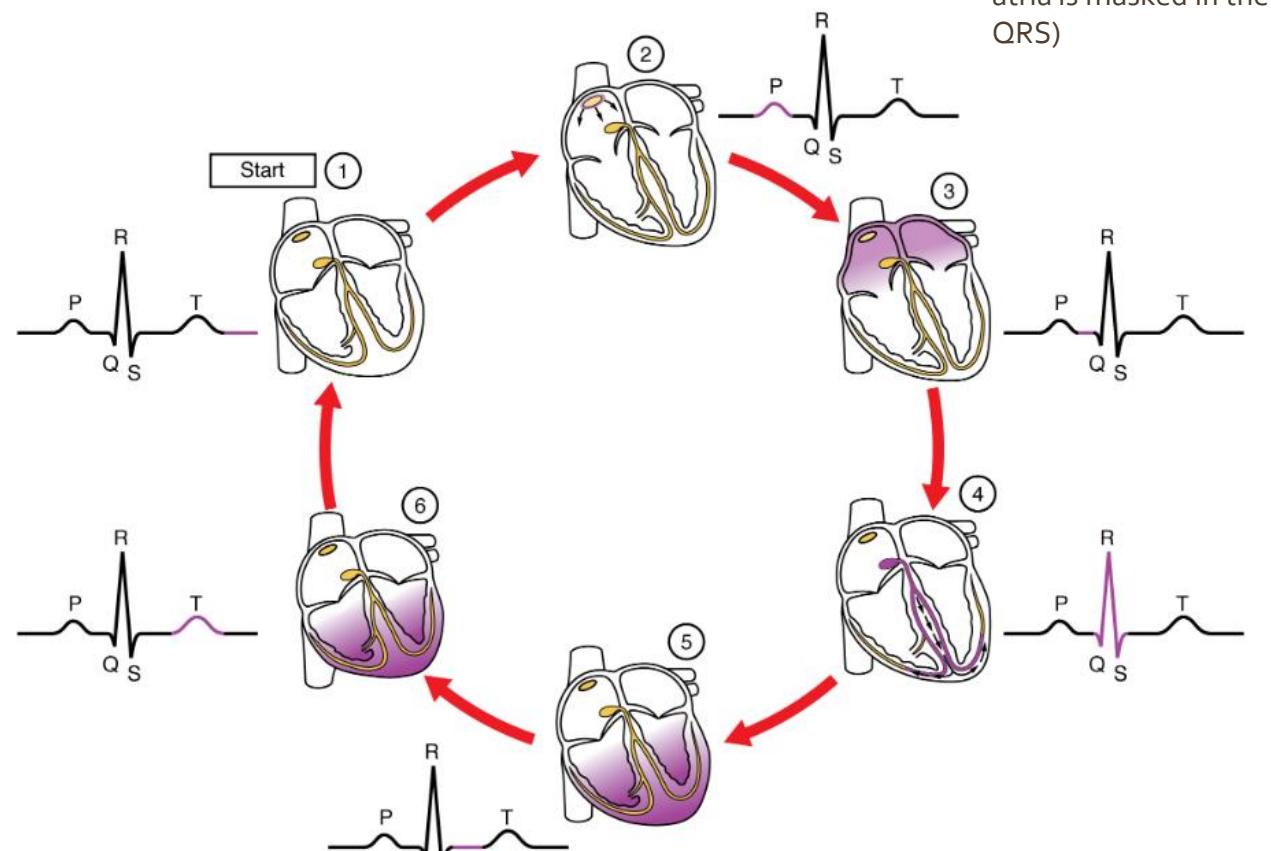
The electric properties of the heart can be monitored by the surface ECG (or EKG)



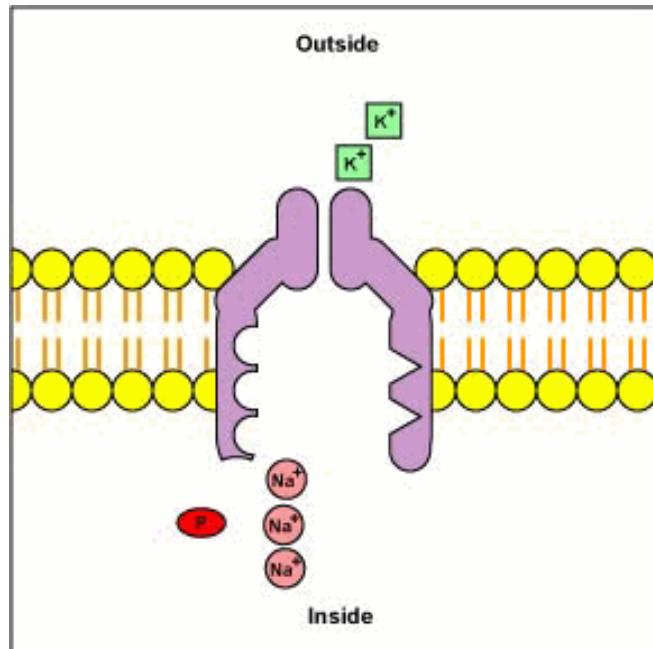


## The ECG

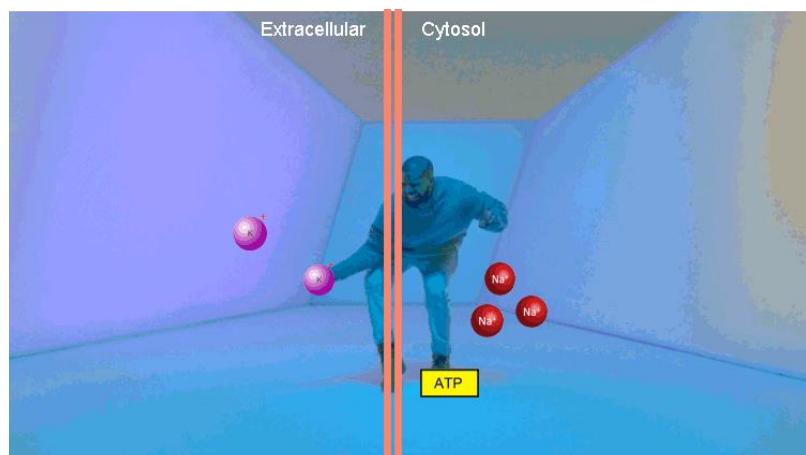
- (1) Heart rate reflects sinus node automaticity,
- (2) PR-interval duration is indicative for AV nodal conduction time,
- (3) QRS duration reflects conduction time in the ventricle
- (4) the QT interval is a measure of ventricular action potential duration.



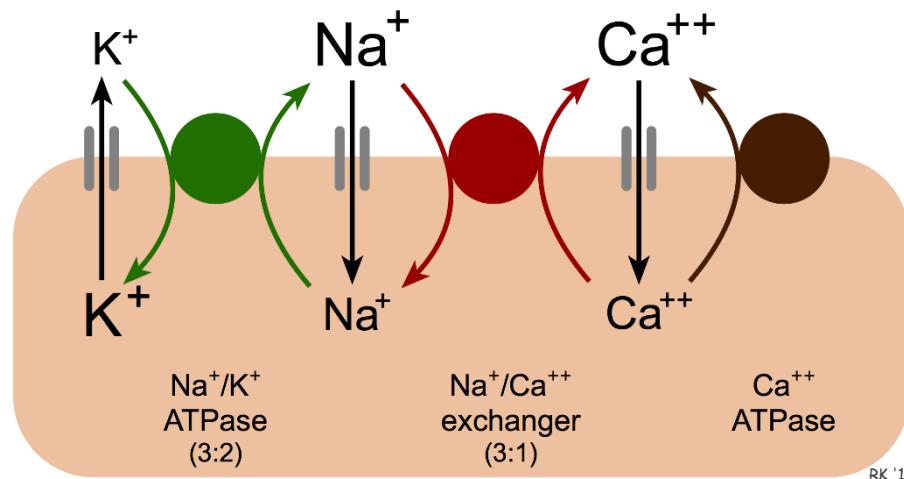
# Maintenance of intracellular homeostasis



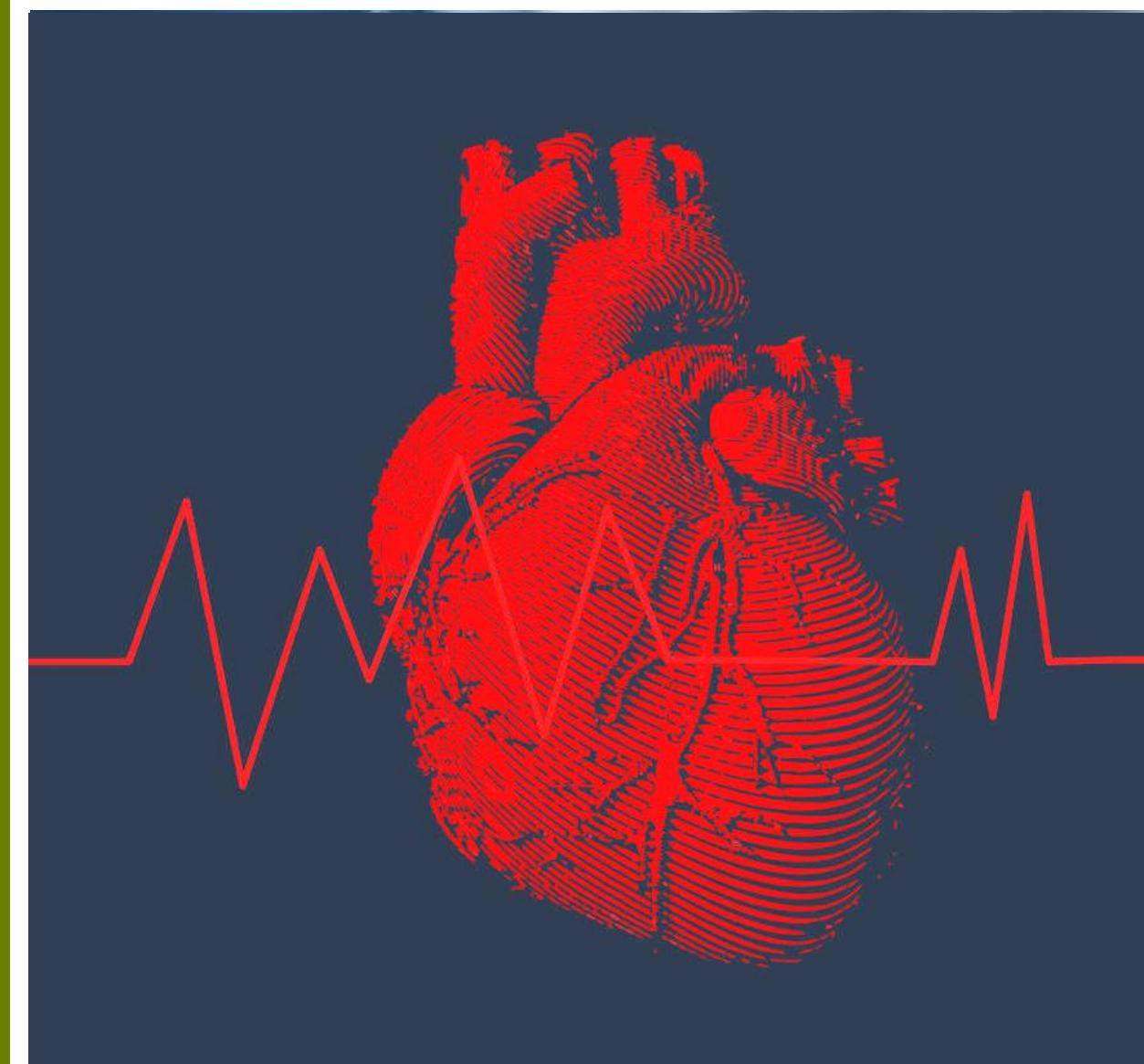
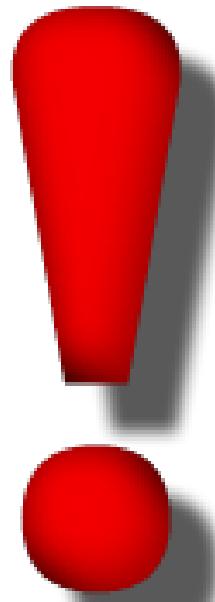
- With each action potential, the cell interior gains Na<sup>+</sup> ions and loses K<sup>+</sup> ions
- The Na<sup>+</sup>,K<sup>+</sup>-ATPase extrudes three Na<sup>+</sup> ions for every two K<sup>+</sup> ions shuttled from the exterior of the cell to the interior;
- as a result, the act of pumping itself generates a net outward (repolarizing) current
- Restores the original resting potential



- Removal of intracellular Ca<sup>2+</sup> occurs by both an ATP-dependent Ca<sup>2+</sup> pump (SERCA) which moves Ca<sup>2+</sup> ions back to the sarcoplasmic reticulum
- and an electrogenic sodium Na<sup>+</sup>-Ca<sup>2+</sup> exchange mechanism (NCX) on the cell surface, which exchanges three Na<sup>+</sup> ions from the exterior for each Ca<sup>2+</sup> ion extruded.



# MECHANISMS OF CARDIAC ARRHYTHMIAS



# Causes of arrhythmias

**Channelopathies** (cardiac channelopathies are caused by mutations affecting genes associated with various cardiac membrane channels)

**Anatomical abnormalities, structural heart diseases**

Other heart diseases causing electromechanical remodelling (heart failure, post-AMI, hypertension, cardiomyopathies)

**Ischemia  
Electrolite disturbances**

**Hormonal diseases  
Side effect of drugs**

# Mechanisms of arrhythmias

- Arrhythmias (or dysrhythmias) occur when the normal impulse generation is perturbed
- Clinically, arrhythmias are classified according to
  - The site of origin (ventricular, atrial, junctional)
  - The direction of change in the heart rate (brady-, tachy) – here we summarize tachy-arrhythmias

**3 major mechanisms have been identified that underlie cardiac arrhythmias**

Mechanisms

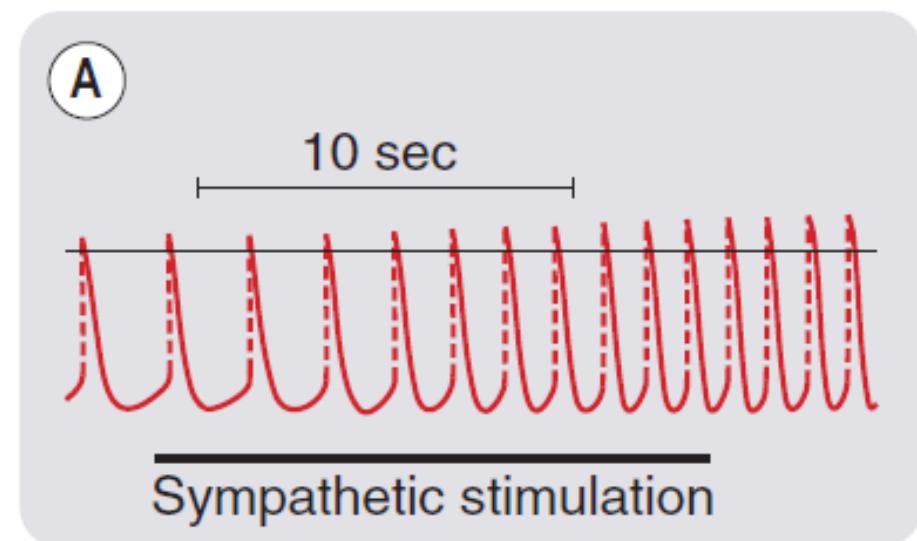
Enhanced automaticity

Triggered activity  
(EAD and DAD)

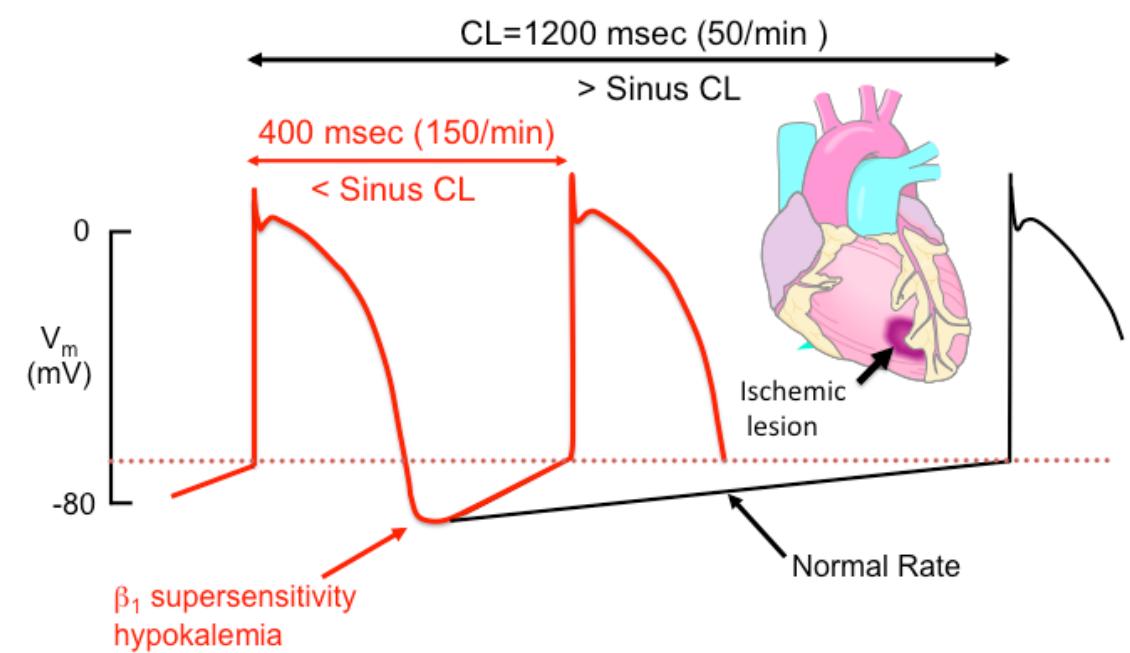
Re-entry mechanism

# 1. Enhanced automaticity

- 1. Enhanced automaticity may occur in the nodal cells
  - **Adrenergic stimulation**, hypokalemia, and mechanical stretch of cardiac muscle cells accelerate pacemaker rate,
- 2. automatic behavior may occur in sites that ordinarily lack spontaneous pacemaker activity;
  - e.g., in ventricular cells (e.g., by ischemia) may produce such "abnormal" automaticity
- When impulses propagate from a region of enhanced normal or abnormal automaticity, arrhythmias result



## Ectopic Normal Automaticity



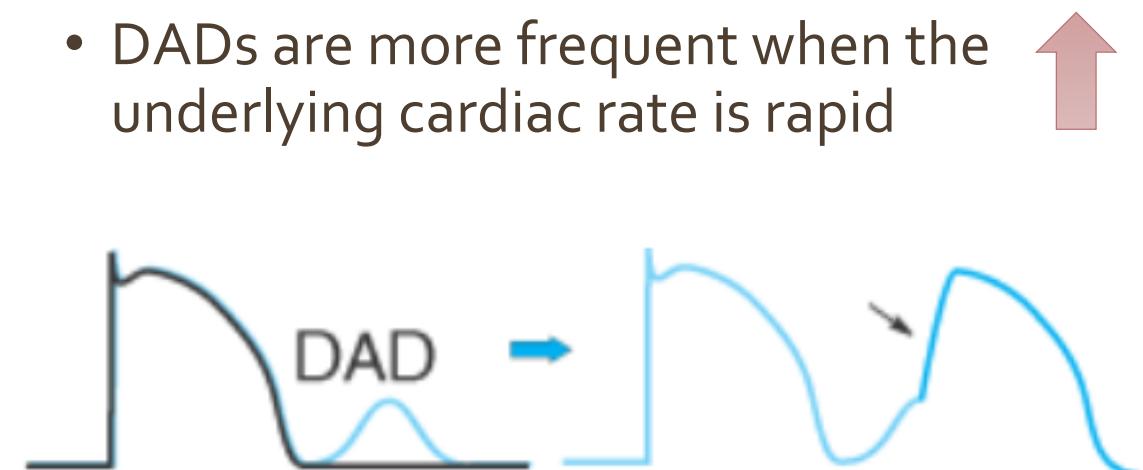
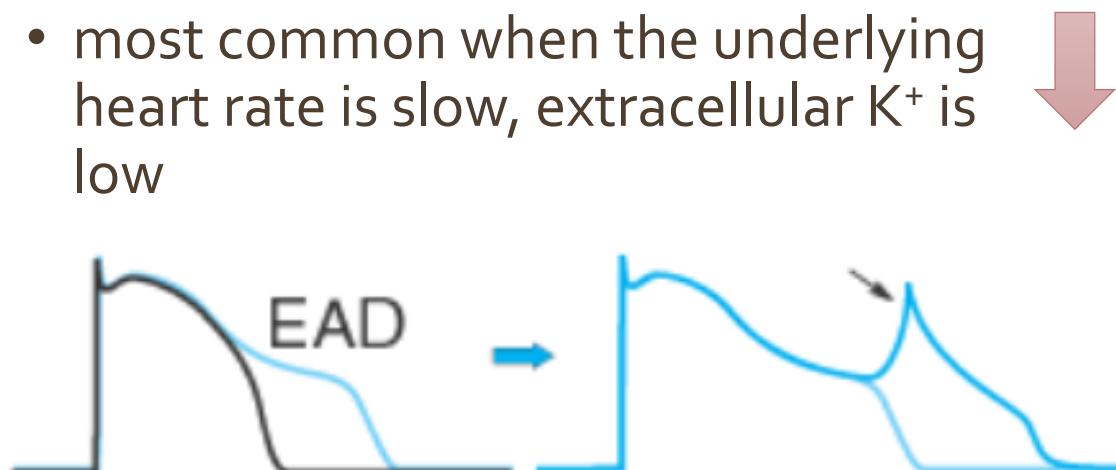
## 2. Triggered activity (early and delayed afterdepolarizations)

Normal cardiac action potential may be interrupted or followed by an abnormal depolarization

If this abnormal depolarization reaches threshold, it may, in turn, give rise to secondary upstrokes - extrasystolic (ectopic) beats are generated

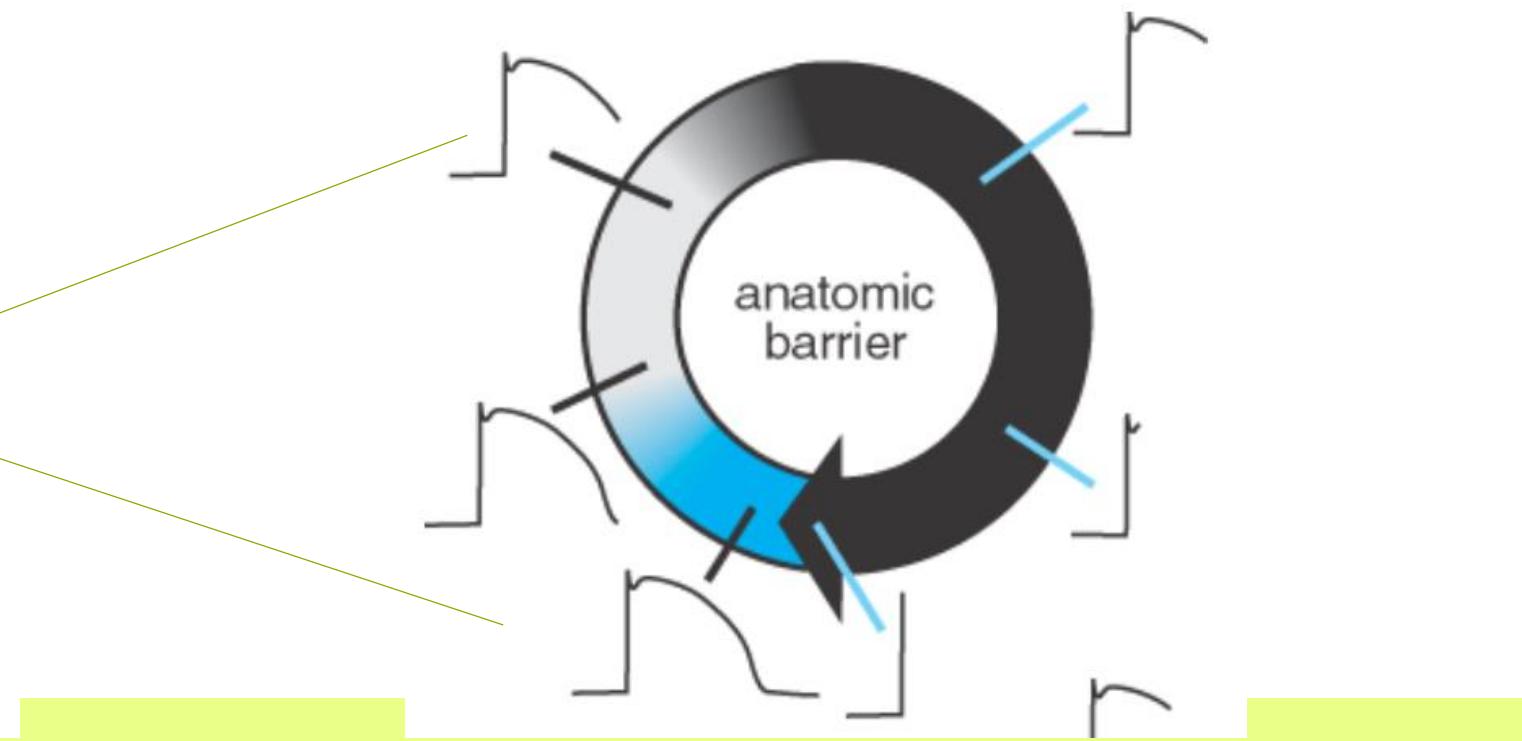
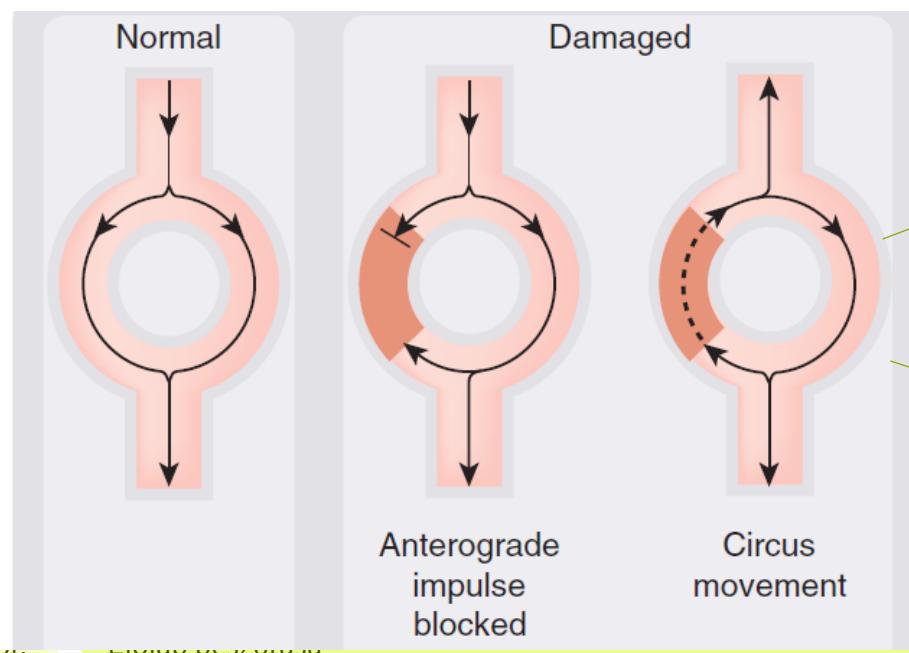
### Two major forms : EAD, DAD

- EAD: the key abnormality is marked prolongation of the cardiac action potential
  - When this occurs, phase 3 repolarization may be interrupted by an *early afterdepolarization* (EAD)
  - most common when the underlying heart rate is slow, extracellular K<sup>+</sup> is low
- DAD: under conditions of intracellular Ca<sup>2+</sup> overload (e.g., myocardial ischemia, adrenergic stress, digitalis intoxication, or heart failure),
  - a normal action potential may be followed by a *delayed afterdepolarization* (DAD)
  - DADs are more frequent when the underlying cardiac rate is rapid



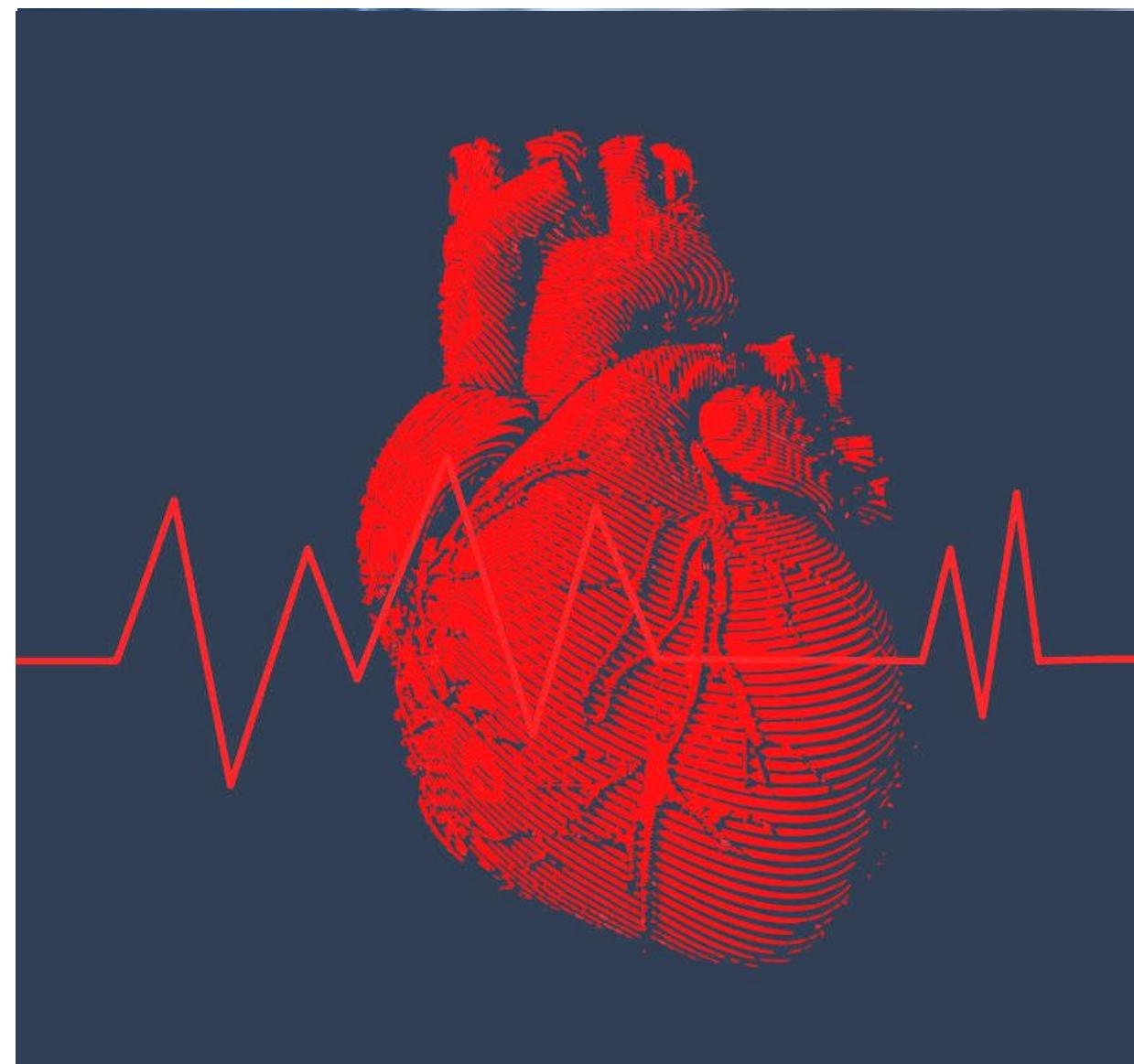
### 3. Re-entry mechanism

- Re-entry or circus movement is a multicellular mechanism of arrhythmia.  
Re-entry can occur in atria, ventricle or nodal cells
- The impulse re-activates regions of the myocardium after refractory period, causing continuous circulation of APs
- It can result from anatomical anomalies or myocardial damage (ischemia)
- A simple „ring of tissue” may maintain reentry circuits, when an undirectional or transient block is present
- Normally, the impulse propagate in both directions, and die out when the two meet
- If the damaged area is blocked (conducts slowly), it can be activated from backwards, forming a circus movement of APs – it is the basis of many types af arrhytmias
- **Anatomically Defined Re-entry:** Re-entry can occur when impulses propagate by more than one pathway between two points in the heart,
- WPW sy. patients have **accessory connections** between the atrium and ventricle
- When the impulse re-enters the atrium, it then can re-enter the ventricle *via* the AV node, re-enter the atrium *via* the accessory pathway, and so on



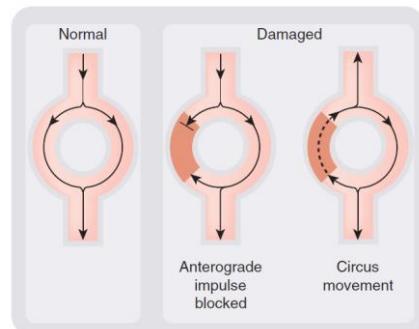
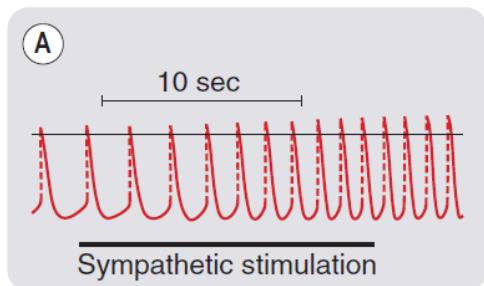


# Clinical manifestations



# Supraventricular tachycardias (SVT)

- Atrial frequency is higher than 100 bpm
- Originates from SAN, atrial myocardium, or AV-junctional region
- Usually non-life threatening
- Symptoms: palpitations, faint, shortness of breath
- Mechanisms:
  - enhanced automaticity or
  - re-entrant circuits



## Classification:

- Sinus tachycardia
- Sinoatrial nodal reentrant tachycardia
- Inappropriate sinus tachycardia
- Focal atrial tachycardia
- Atrial flutter
- Atrial fibrillation
- AV nodal reentrant tachycardia (AVNRT)
- AV reciprocating tachycardia (AVRT)  
(including Wolff-Parkinson-White syndrome)

Sinoatrial

Atrial

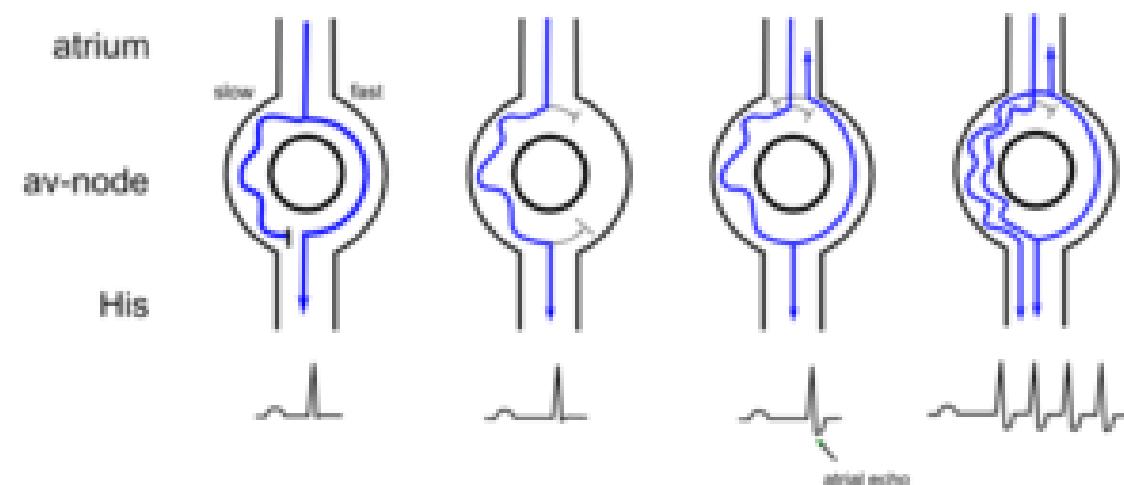
Atrio-  
ventricular

Often „narrow QRS” (120 ms) (except Tawara-szárblókkal)

# Most common SVTs

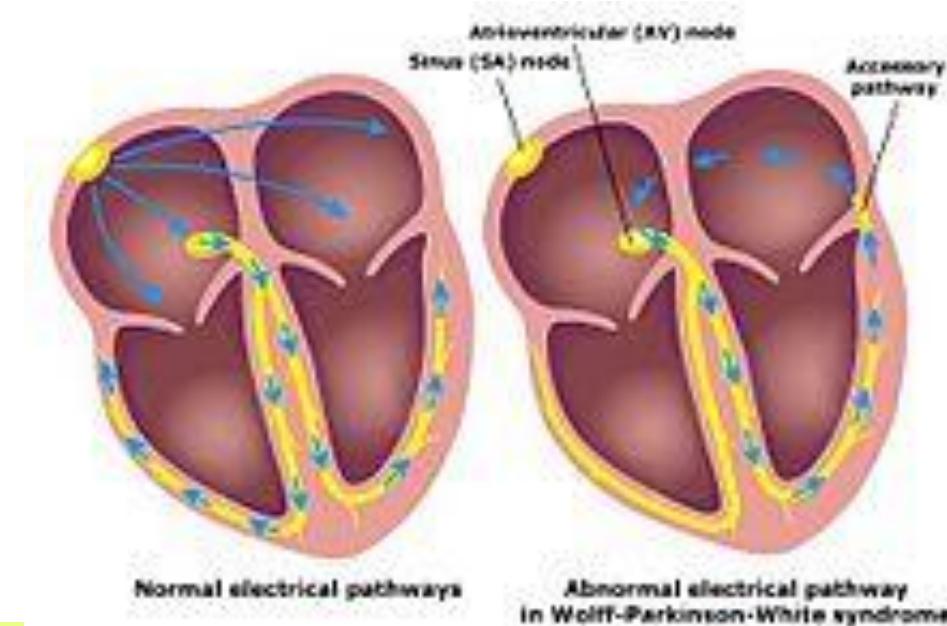
## AVNRT

- most common regular supraventricular tachycardia (55% of all cases)
- First episode: early 30s, more common in women, often mistaken with panic attacks
- Symptoms: rapid palpitations, fluttering sensation in the neck (j. ext. „frog sign“) -near-simultaneous contraction of the atria and ventricles - the right atrium contracts against a closed tricuspid valve
- HR is btw 140 and 280 bpm
- Mechanism: a re-entrant circuit within the AV node (slow-fast)
- may be terminated by physical manoeuvres that increase the activity of the vagus nerve



## AVRT (WPW)

- The underlying mechanism involves an **accessory electrical conduction pathway** between the atria and the ventricles (The bundle of Kent)
- one type is WPW (preexcitation with anterograde accessory pathway)
- Typical macro-reentry
- Anatomically normal heart, however certain anomalies predispose (Ebstein, persistens d. Botalli)
- 30 % paroxysmal atrial fibrillation
- Anterograd: fast, broad, irregular, QRS
- Vagolytic maneuvers may be effective



# Most common SVTs

## Atrial flutter (pitvarlebegés)

- 10 % of all SVTs
- Incidence increases by age, more common in men
- Closely related and coincides with fibrillation
- poor contraction of the atrial chambers of the heart  
- this leads to pooling of the blood in the heart and can lead **embolisation**
- Mechanism: a re-entrant circuits in the atria, electrophysiological remodelling
- characteristic "**flutter waves**" (ECG f-waves) at a regular rate of 200 to 300 bpm
- In case of normal AV: only half of these impulses will be conducted, giving a ventricular rate of 150/minute, or a 2:1 heart block
- Could be 3:1, 4:1 , 5:1 AV nodal block
- **Persistent form (months) causes tachycardia-induced cardiomyopathy (LVEF decreases)**

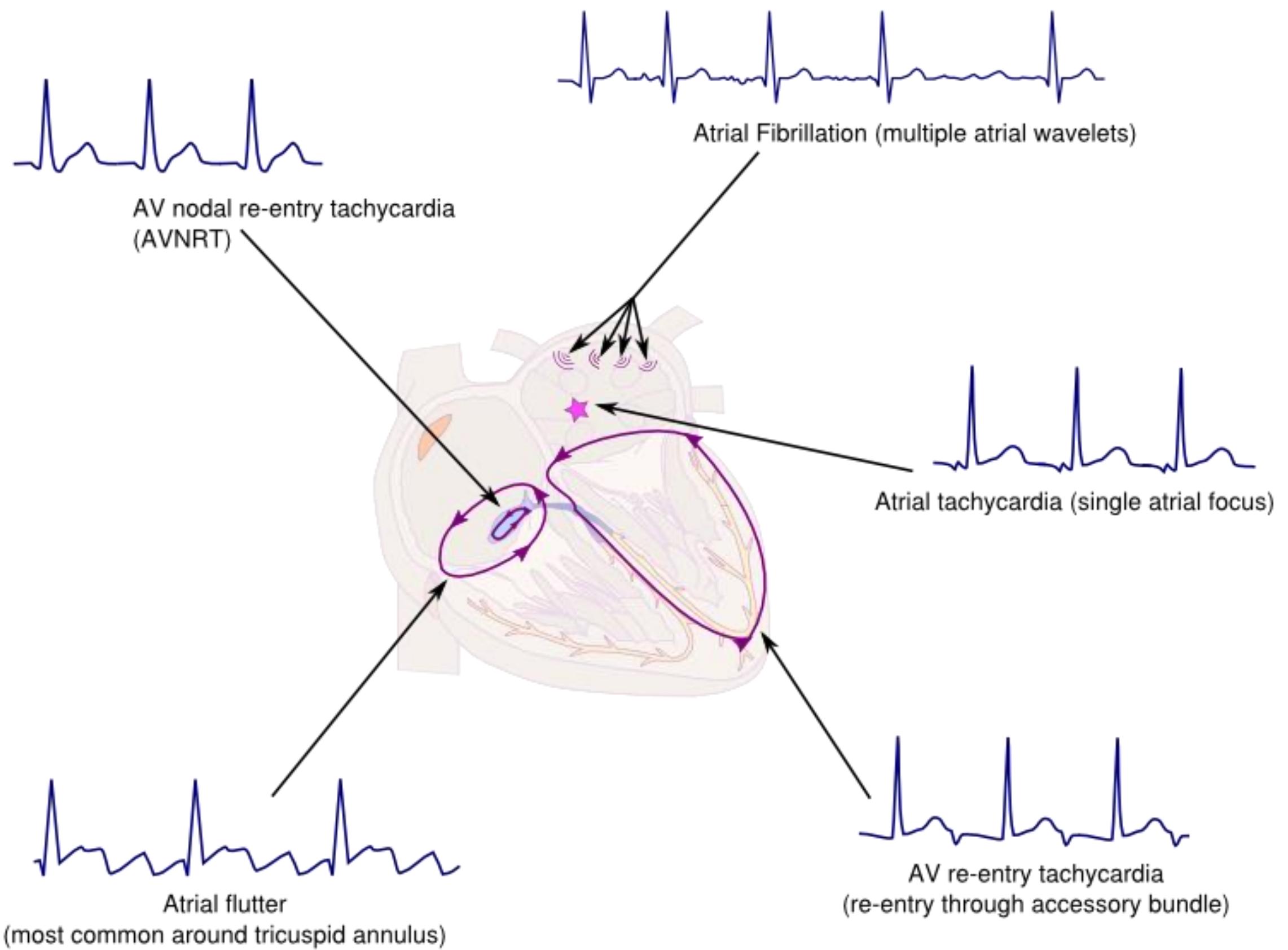


## Atrial fibrillation (pitvarremegés)

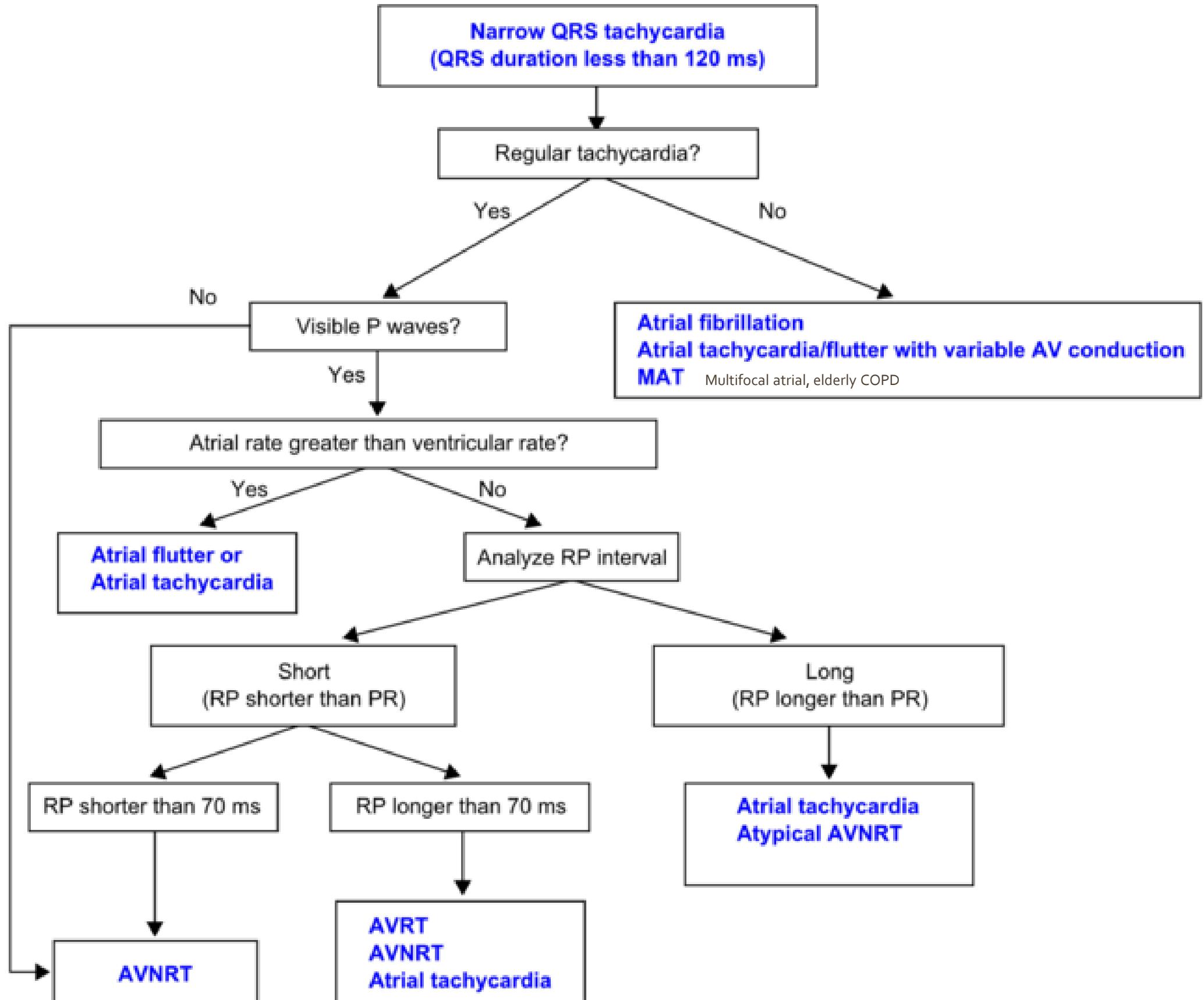
- the most common serious abnormal heart rhythm (2 % of the pop.)
- rapid and irregular beating of the atria causing irregular ventricular rhythm
- rapid electrical discharges produced in the atria and adjacent parts of the pulmonary veins (reentry or electric rotors)
- Paroxysmal, persistent, permanent
- Blood congestion in the atria causes hypercoagability, thrombus formation – when sinus rhythm is restored, the risk of embolization increases!! (stroke, mesenteral or limb ischemia)
- CHADS<sub>2</sub> score (stroke risk evaluation)
- Anticoagulation: i.v. heparin, s.c. LMWH, long-term: aspirin, warfarin
- Control the rhythm / frequency ??



# Summary (SVTs)

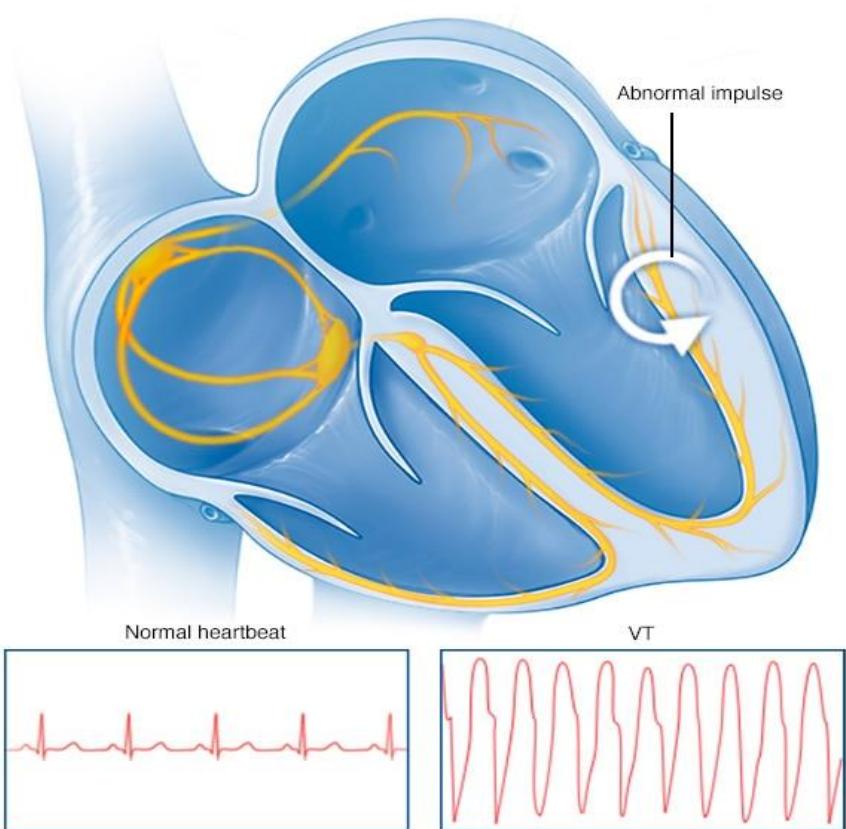


# Differential diagnosis (SVTs)



# Ventricular tachyarrhythmias

- Much more serious, could be life-threatening
- Ventricular arrhythmias are almost always wide-QRS-complex arrhythmias (QRS > 120 ms)
- (Diff Dg: may be an SVT with block, but if post-aMI: 95 % VT)
- Often occur due to post-AMI, ischemic myocardial scarring, (or coronary heart disease, aortic stenosis, cardiomyopathy, electrolyte problems (e.g., low blood levels of magnesium or potassium), inherited channelopathies)

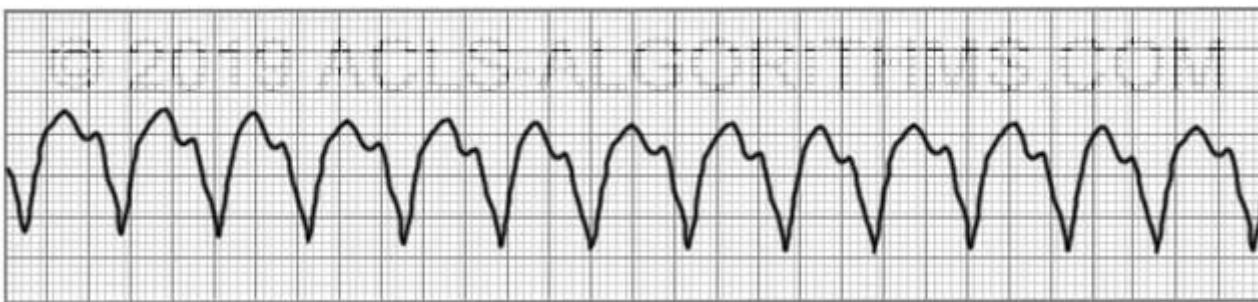


- **Ventricular tachycardia (V-tach or VT)** is a type of regular, fast heart rate that
  - Mechanism: re-entry electrical circuit in the heart
  - Frequency between 100-300 bpm
  - Permanent (>30 sec) or not
- **Monomorphic** (stable QRS morphology) (Scar-related monomorphic ventricular tachycardia is a frequent cause of death in patients having survived an AMI)
- **or polymorphic** (has beat-to-beat variations in morphology); with prolonged QTc interval
  - One form is the so called torsade de pointes – potentially fatal

# Ventricular arrhythmias

## Monomorphic VT

- Regular wide QRS
- Causes: Ischemic heart disease, DCM
- Palpitation, shortness of breath, syncope, heart block



## Ventricular fibrillation

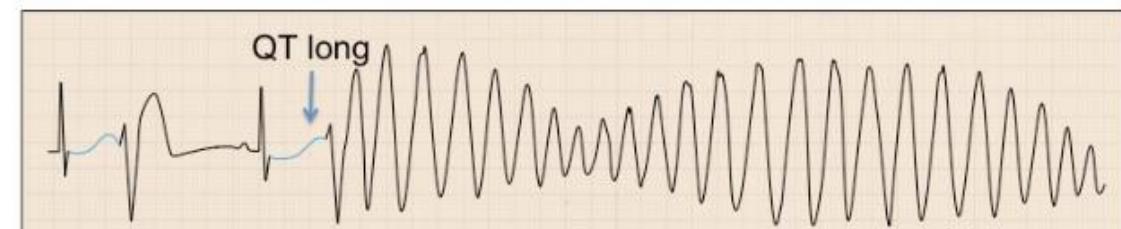
- Disorganised activity, no pump function
- Fatal, results in cardiac arrest
- can occur due to AMI, cardiomyopathy, Brugada syndrome, long QT syndrome, electric shock, or intracranial hemorrhage
- Treatment: defibrillation, if failed: 300 mg i.v. amiodarone



## Polymorphic VT

Irregular, wide QRS

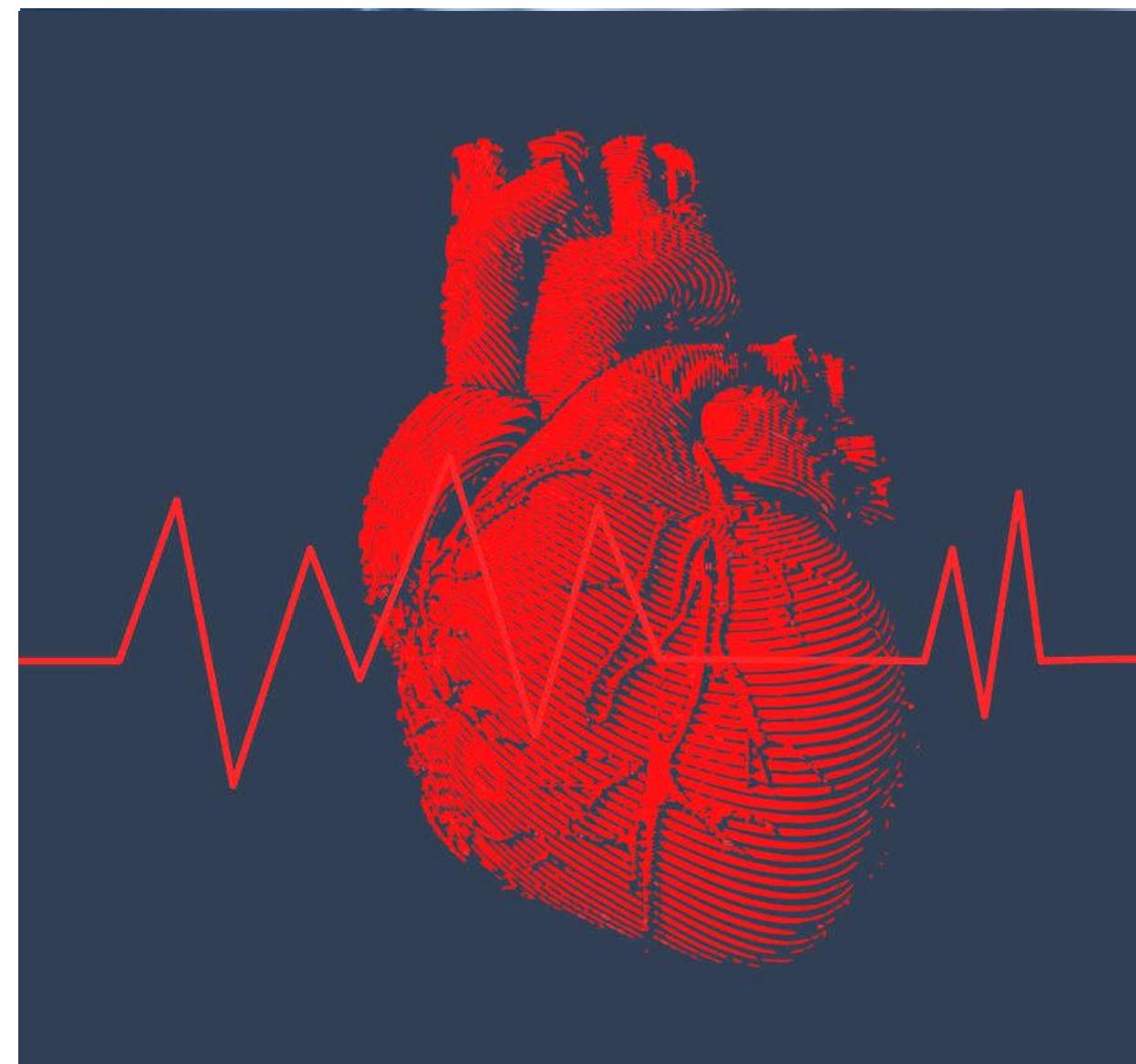
- Causes: Long-QT syndrome, myocardial ischemia, bradycardia or arrest, Electrolite disturbances: low K+, low Mg<sup>2+</sup>
- If persistent: cardiac arrest
- Treatment: DC shock, electrolite correction



Torsade de pointes



# Antiarrhythmic treatments



# Available treatment strategies

1. Vagal maneuvers (increasing vagus activity: short AV block (SVTs))
2. **Antiarrhythmic drugs**
3. DC cardioversion (the application of a shock *synchronised* to the underlying heartbeat)
4. Defibrillation (is not synchronised; VF)

## Curative:

- Catheterablation, cryoablation (abnormal areas are destroyed)
- ICD (able to perform cardioversion, defibrillation: capable of correcting most life-threatening cardiac arrhythmias)

- Carefully diagnose!
- Evaluate co-morbidities, watch for patient-specific contraindications
- Minimize the risk (pro-arrhythmogenic drugs!)
- Anticoagulation!
- Monitor electrolyte disturbances (plasma Na<sup>+</sup>, Ca<sup>2+</sup>, Mg<sup>2+</sup> and mostly K<sup>+</sup> levels!)
- Some Arrhythmias Should Not Be Treated (CAST study)

• **Treat the patient, not the ECG!**



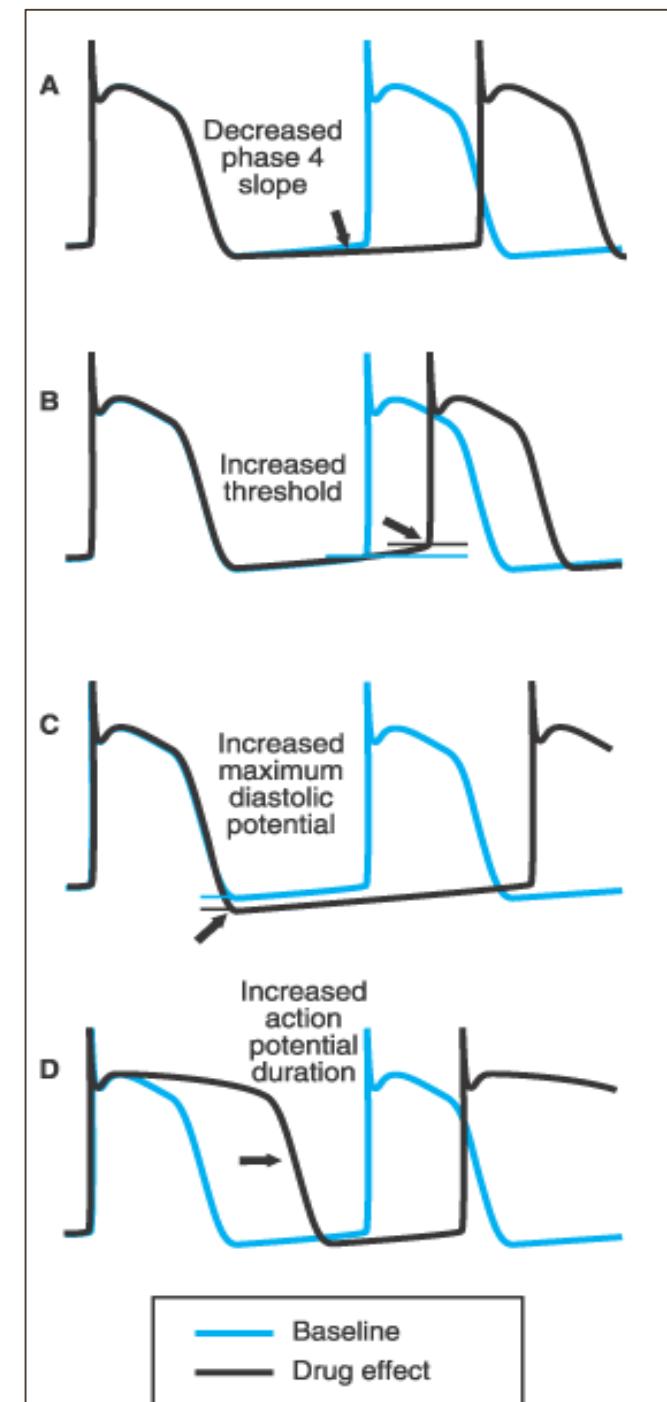
# Antiarrhythmic drugs

## Mechanism of drug action:

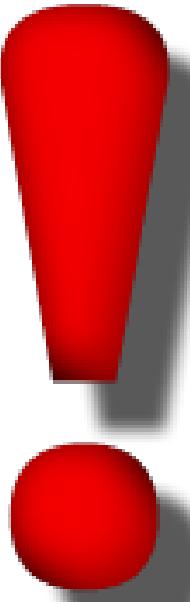
- interference with the inward or outward currents
- Prolong (or shorten) AP
- Prolong refractoriness
- slow AV nodal conduction



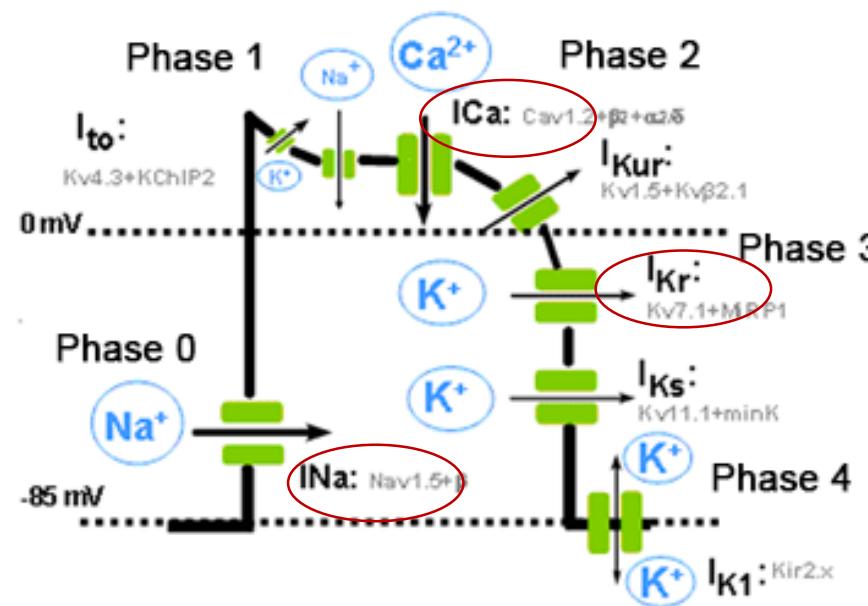
- **ALL of the currently available antiarrhythmic drugs are pro-arrhythmic at the same time, by altering currents, they may generate arrhythmias!**



# Classifying Antiarrhythmic Drugs (<sub>Singh-</sub> Vaughan Williams)

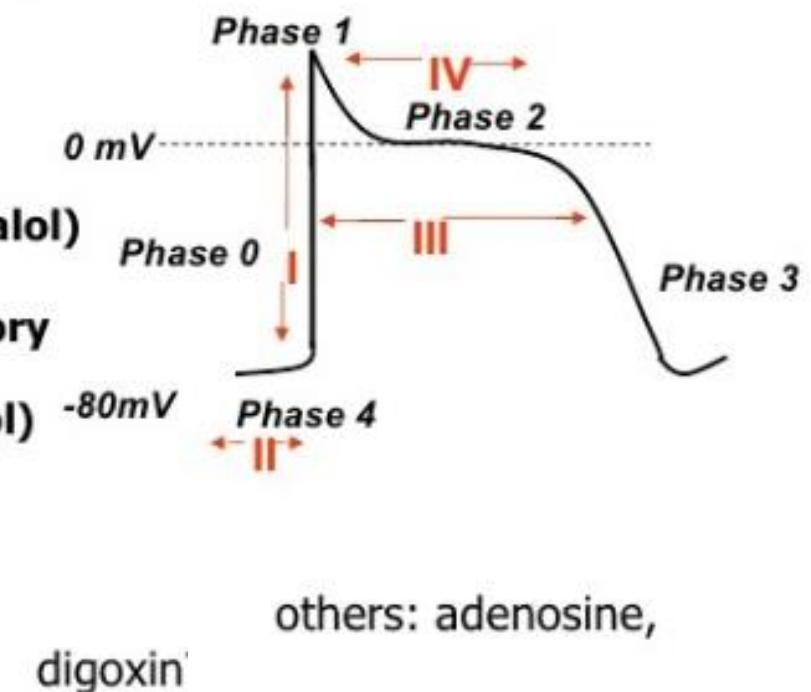


- The most common classification was proposed by Vaughan Williams in 1970 (others: Sicilian, Oxford)
- Originally, it is a classification for antiarrhythmic mechanisms
- Drug may be fit in these categories based on their electrophysiological properties
- Although, many drugs only neatly fit, and have multiple actions



- **Class I:** blocks VG sodium channels ( $\text{Na}^+$ )
  - Harrison subgroups: Ia, Ib, Ic
- **Class II:** beta-receptor blockers
- **Class III:** prolongs action potential ( $\text{K}^+$ ) (ERP)
- **Class IV:** Ca channel blockers ( $\text{Ca}^{2+}$ )
- **Class V** (or miscellaneous): do not fit to any of the previous categories

- **Class I: block sodium channels**
  - Ia (quinidine, procainamide, disopyramide) ↑AP
  - Ib (lignocaine) ↓AP
  - Ic (flecainide) ↔AP
- **Class II:  $\beta$ -adrenoceptor antagonists (propranolol, sotalol)**
- **Class III: prolong action potential and prolong refractory period (suppress re-entrant rhythms) (amiodarone, sotalol)**
- **Class IV: Calcium channel antagonists. Impair impulse propagation in nodal and damaged areas (verapamil, diltiazem)**



# „NO BADBOYS KEEP CLEAN”

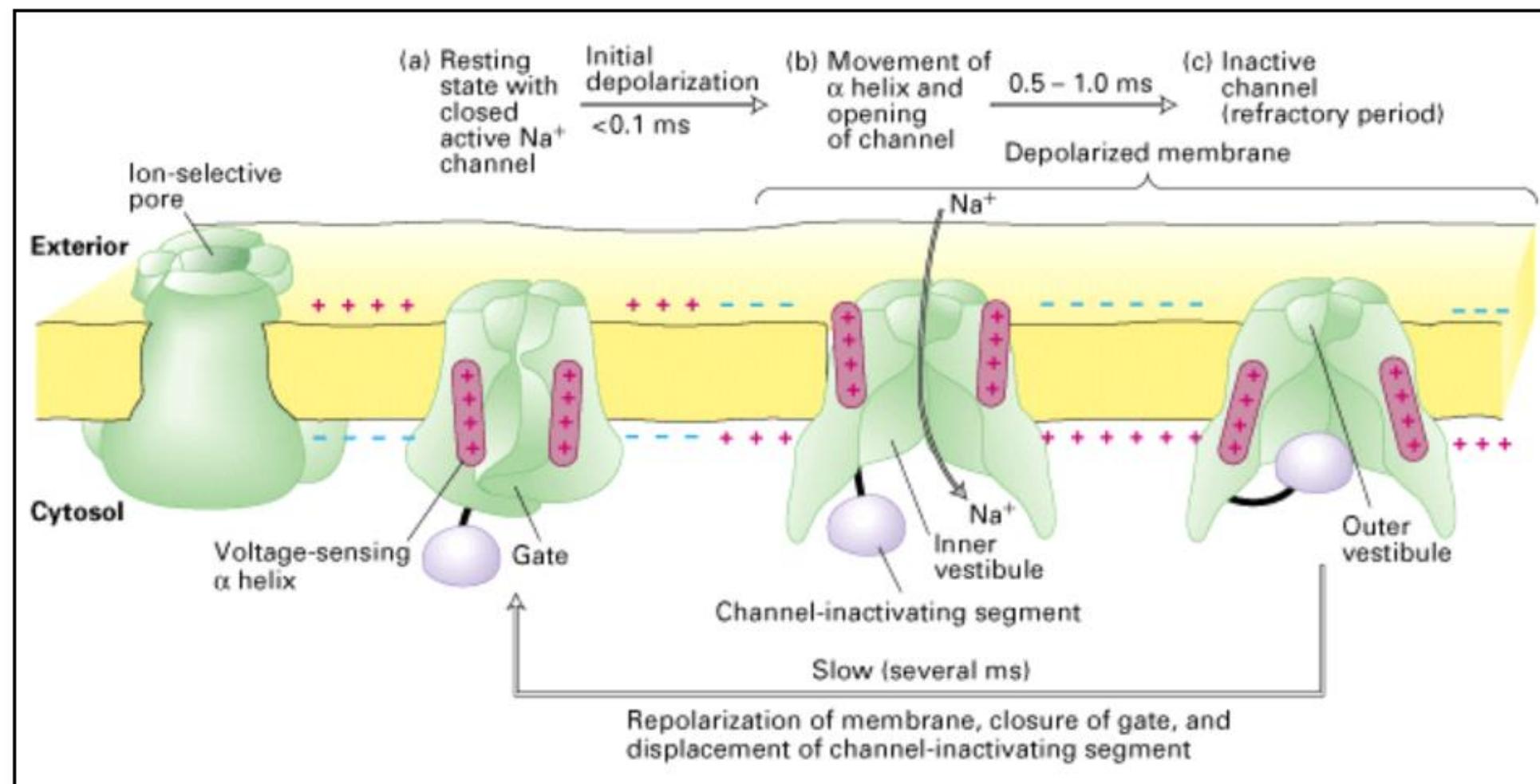
Na+      BB      K+      Ca<sub>2+</sub>

- **Class I:** blocks VG sodium channels (Na+)
  - Harrison subgroups: Ia, Ib, Ic
- **Class II:** beta-receptor blockers
- **Class III:** prolongs action potential (K+) (ERP)
- **Class IV:** Ca channel blockers (Ca<sub>2+</sub>)
- **Class V (or miscellaneous):** do not fit to any of the previous categories

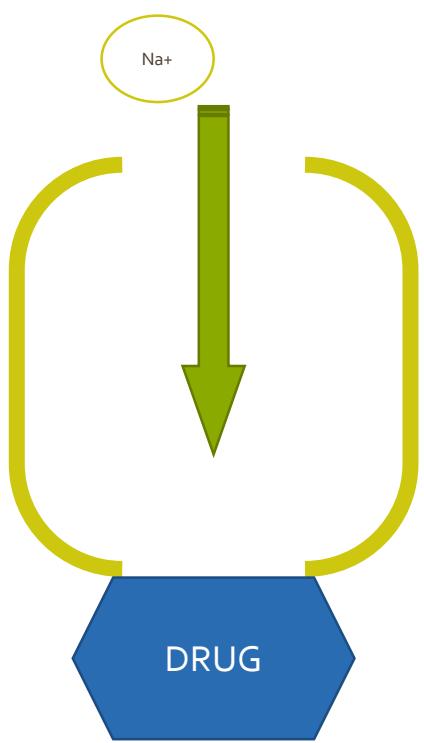
# Class I

- Block VG sodium channels (like local anaesthetics), but with different characteristics -
- Harrison subgroups: they are further classified by drug-receptor interaction kinetics by a concept called ***use-dependent channel block***:

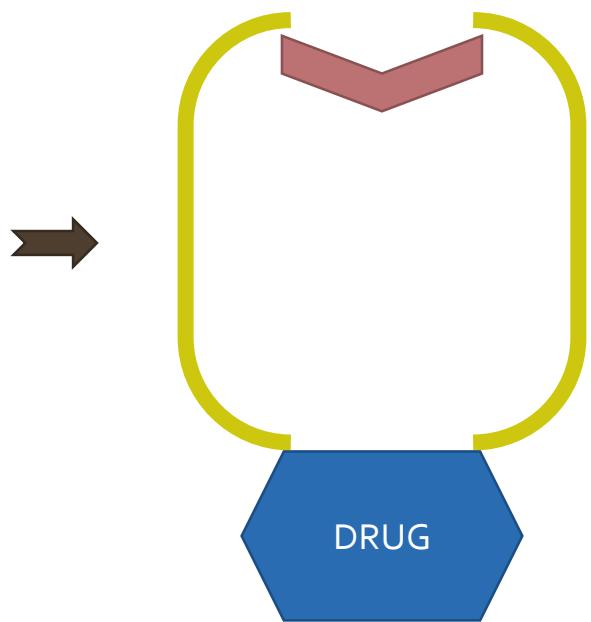
- **Sodium channels exist in 3 functional states (conformations): open (activated), refractory (inactivated), and resting**
- **After activation, they need time to return into resting state, only after they can open again**
- **Class I drugs exert state-dependent binding – prefer activated and refractory channels**
- drugs bind to Na<sup>+</sup> channels and block them, and with each diastolic interval (resting phase), drugs dissociate, and the block is released



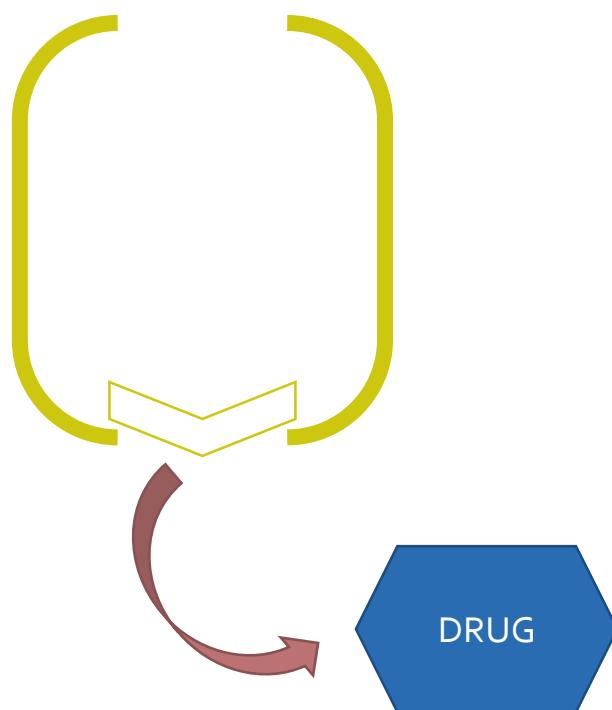
*Active*



*Inactive*



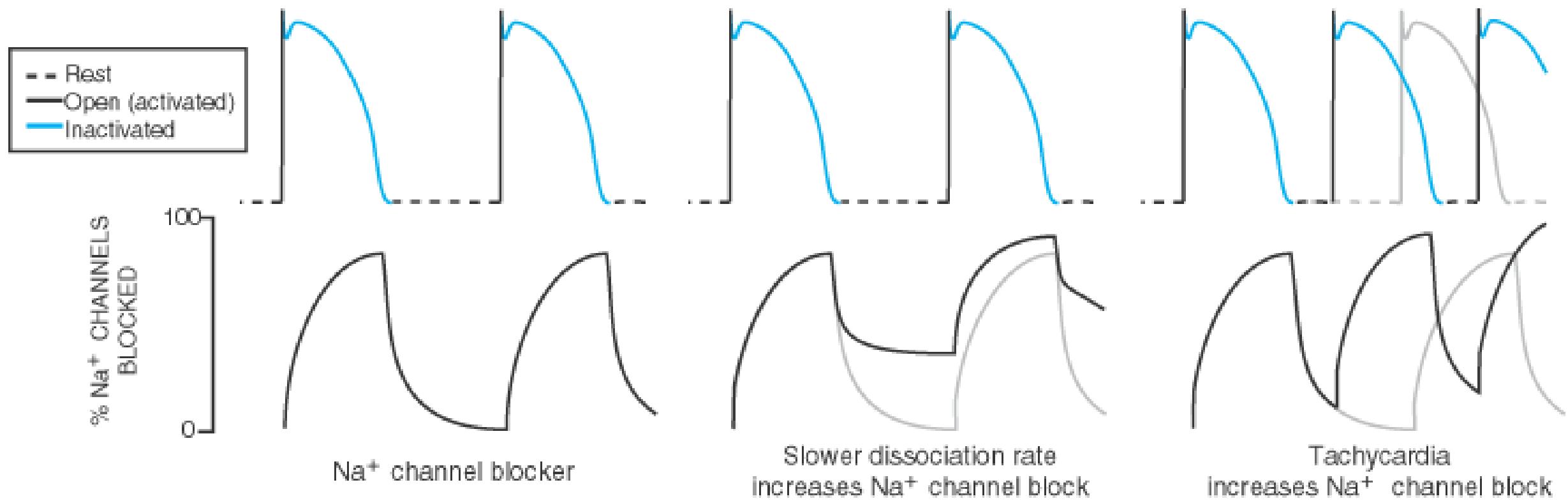
*Resting*



# Class I a, Ib, Ic

- Class I drugs bind to active and refractory channels, and dissociate when the channel is at resting phase
- Their action therefore show „use-dependency”: **the more frequently the channels are activated (tachycardia), the greater the degree of block produced**

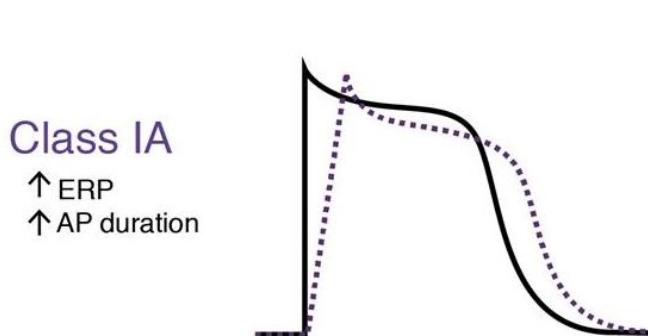
- Drugs in Class Ib, that have rapid dissociation kinetics, dissociate within the timeframe of a NORMAL heartbeat, and do not have a great effect on frequency
- Class Ia and Ic drugs exert slow dissociation kinetics - block conduction even at normal heart rates (do not have time to dissociate at the resting phase)
- In case of rapid heartbeat (shortened resting phase), even Ib drugs cannot dissociate – block the APs, slow HR, block premature beats



# Class Ia – procainamide, disopyramide, quinidine

## Police Department Questioned

- ( $\text{Na}^+$ ) channel block (with intermediate association/dissociation kinetics)
- Also have weak  $\text{K}^+$  channel blocking effect, affects QRS complex
- prolong the action potential and have intermediate effect on the o phase of depolarization
- $\text{Na}^+$  channel blockade results in an increased threshold for excitability and decreased automaticity



### Indications:

- not frequently used
- AF, VF
- Procainamide: WPW

### Quinidine

- diastereomer of the antimalarial quinine
- prolongs the QT interval up to 25%,
- actually tends to shorten the PR interval as a result of its vagolytic properties, also dilates vessels

**Adverse Effects:** Diarrhea thrombocytopenia

- Quinidine also can produce cinchonism, a syndrome that includes headache and tinnitus QT-interval prolongation and *torsades de pointes*

**Procainamide** exerts electrophysiological effects similar to those of quinidine

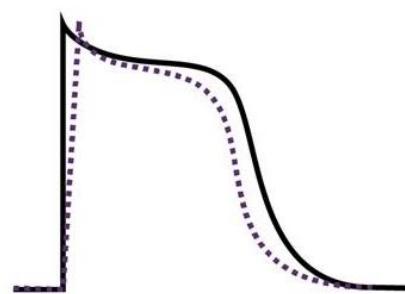
- but lacks quinidine's vagolytic and adrenergic blocking activity.
- is better tolerated than quinidine, but may induce TdP, and drug-induced lupus syndrome

# Class Ib – lidocaine, mexiletine, phenytoin, tocainide

## The Little Man

- $\text{Na}^+$  channel block (fast association/dissociation);
- usually exerts no significant effect on PR or QRS duration; QT is unaltered or slightly shortened
- class 1b shorten the action potential of myocardial cell and has weak effect on initiation of phase 0 of depolarization

Class IB  
 $\downarrow$  ERP  
 $\downarrow$  AP duration



### Indications:

- not frequently used
- Only ventricular arrhythmias
- After AMI, but not routinely

### Lidocaine (Lidicain-EGIS™)

- Rapid kinetics: Recovery from block is very rapid, so lidocaine exerts greater effects in depolarized (e.g., ischemic) and/or rapidly driven tissues
- i.v. 1-3 mg/kg
- Used in treatment of VT and prevention during and immediately after myocardial infarction
- However: due to increased risk of asystole, is not administered routinely

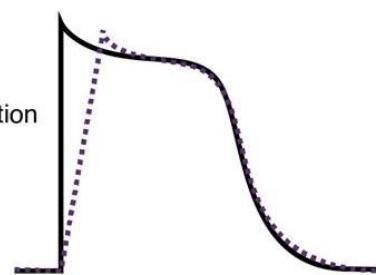
**Mexiletine** is an analog of lidocaine that have been modified to reduce first-pass hepatic metabolism and permit chronic oral therapy

# Class Ic – flecainide, propafenone, encainide

## For Pushing Extasy

- $\text{Na}^+$  channel block (slow association/dissociation)
- has the strongest effect on the initiation phase o. of depolarization
- Contraindicated in struct. HD, AMI
- Pharmacologic cardioversion (i.v. (2mg/ttkg)

Class IC  
Normal ERP  
Normal AP duration



### Indications:

- SVTs (AF) (WPW)
- cardioversion
- NOT after AMI

### Propafenone (RYTMONORM™)

- Propafenone prolongs PR and QRS durations
- Chronic therapy is used to maintain sinus rhythm in patients with SVTs, including atrial fibrillation
- 2 mg/kg or 450-600 mg per os

### Adverse effects

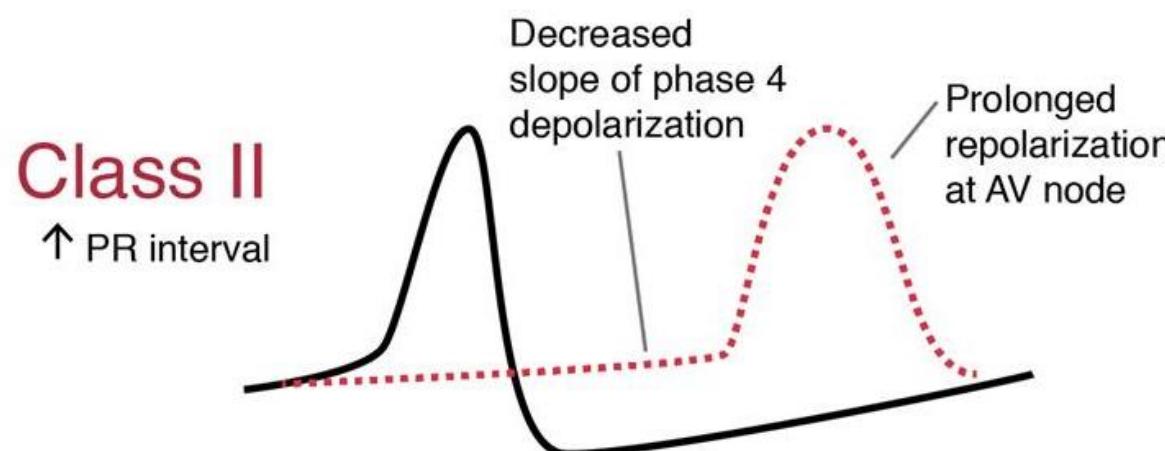
- exacerbation of heart failure, sholuld be avoided in structural heart disease!
- In case of A flutter:  $\text{Na}^+$  channel block decreases conduction velocity and hence slows atrial flutter rate. Normal AV nodal function permits a greater number of impulses to penetrate the ventricle (2:1 to 1:1), and heart rate actually may increase!!

### Flecainide (TAMBOCOR)

- very long  $t_{\text{recovery}}$  from  $\text{Na}^+$  channel block
- In the CAST study, flecainide increased mortality in patients convalescing from myocardial infarction
- approved for the maintenance of sinus rhythm in patients with SVTs, including atrial fibrillation, only in whom structural heart disease is absent
- 2 mg/kg or 200-300 mg per os
- **Adverse effects:** dose-related blurred vision , proarrhythmic in strucural heart disease or depressed LVEF

# Class II – beta blockers (metoprolol, propranolol, esmolol)

- They act by blocking the effects of catecholamines at the  $\beta_1$ -adrenergic receptors,
- thereby decreasing sympathetic activity on the heart, which reduces intracellular cAMP levels and hence reduces  $\text{Ca}^{2+}$  influx.
- are particularly useful in the treatment of SVTs, as they decrease conduction through the AV node (Afib, Aflut) – Rate (Freq.) CONTROL
- As VTs are frequent after AMI due to increased sympathetic tone, beta blockers are effective in post-AMI (reduce mortality)



**Esmolol** has short elimination half-life (9 minutes) (50-200 ug/kg/min)

- Intravenous esmolol is useful in clinical situations in which immediate  $\beta$  adrenergic blockade is desired (e.g., for rate control of rapidly conducted atrial fibrillation)

**Adverse effects** of  $\beta$ -blockade include fatigue, bronchospasm, hypotension, impotence, depression, masking of the symptoms of hypoglycemia in diabetic patients

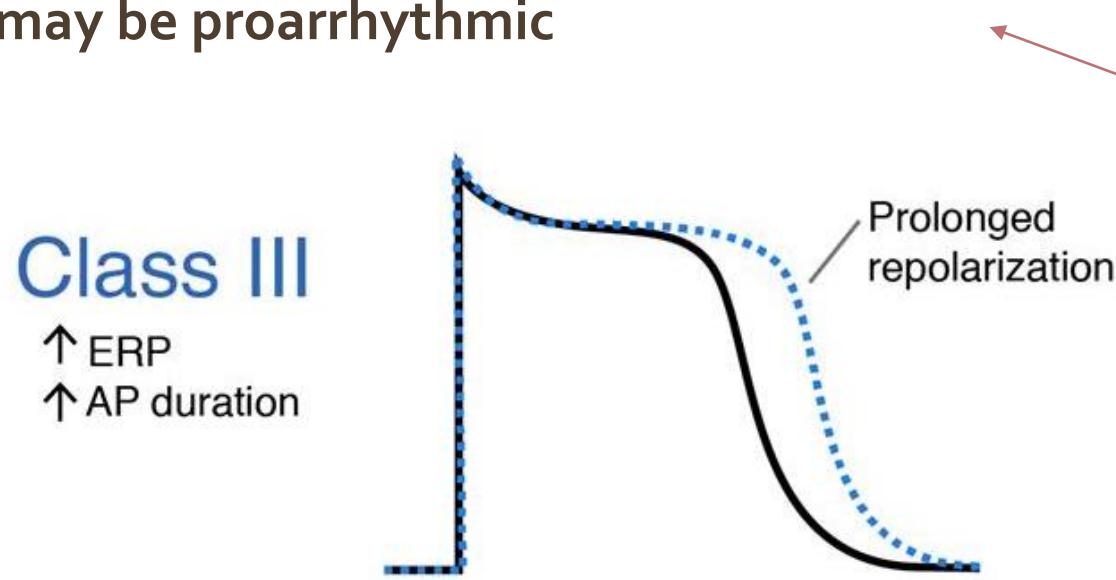
**Metoprolol** (Betaloc<sup>®</sup>) 100-200 mg orally

Indications:

- SVTs (AF)
- Rate control
- Post-AMI

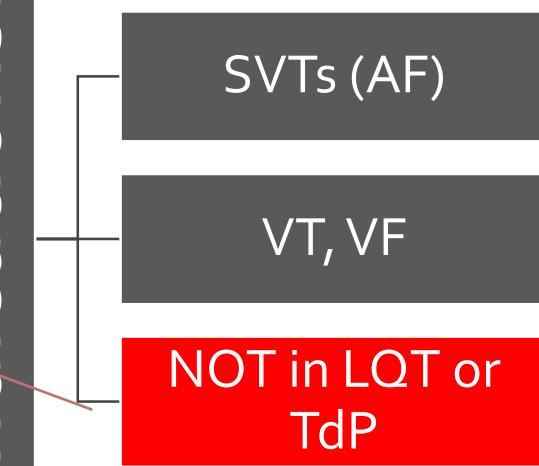
# Class III – amiodarone, sotalol<sub>(racemic)</sub>, dofetilide, ibutilide

- predominantly block the potassium channels, thereby prolonging repolarization
- conduction velocity is not decreased
- The prolongation of the refractory period, combined with the maintenance of normal conduction velocity, **prevent re-entrant arrhythmias**
- The class III agents exhibit reverse-use dependence (their potency increases with slower heart rates, and therefore improves maintenance of sinus rhythm)
- **Class III agents have the potential to prolong the QT interval of the ECG, and may be proarrhythmic**
- Ibutilide is the „pure” AP-prolonging drug, the other have multiple actions
- In the DIAMOND studies dofetilide did not affect mortality in patients with advanced heart failure



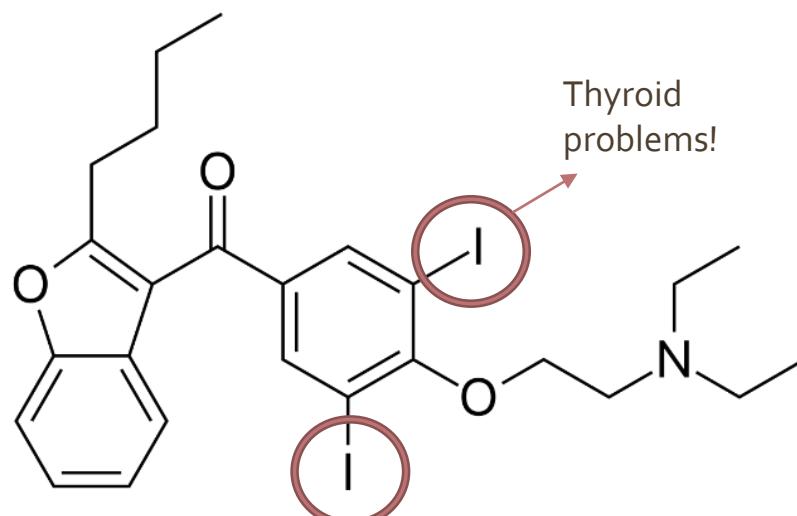
## K<sup>+</sup>channel block – atrial and ventricular re-entry prevention

Indications:



# Amiodarone (Cordarone™)

- One of the most valuable antiarrhythmic in many settings – relatively safe in case of structural heart diseases!
- exerts a multiplicity of pharmacological effects
  - Amiodarone blocks inactivated  $\text{Na}^+$  channels.
  - also decreases  $\text{Ca}^{2+}$  current
  - and transient outward delayed rectifier and inward rectifier  $\text{K}^+$  currents
  - exerts a noncompetitive adrenergic blocking effect
- BUT many side effects: is highly lipophilic, is concentrated in many tissues, and is eliminated extremely slowly; consequently, adverse effects may resolve very slowly



## Indications:

- therapeutic plasma amiodarone concentration range of 0.5 to 2 mg/ml has been proposed
- When i.v: to the central vein, cause in the periphery it may cause phlebitis
- slow accumulation in tissue, a high-dose oral loading regimen (e.g., 800 to 1600 mg/day) usually is administered for several weeks before maintenance therapy is started

**Adverse Effects (6 Ps):** Hypotension, nausea

Long-term:

- corneal microdeposits (which often are asymptomatic), hepatic dysfunction, neuromuscular symptoms
- photosensitivity, and hypo- or hyperthyroidism
- **pulmonary fibrosis**, which can be **rapidly progressive** and fatal
- (Despite the marked QT prolongation and bradycardia typical of chronic amiodarone therapy, *torsades de pointes* is unusual)

SVTs (AF), WPW

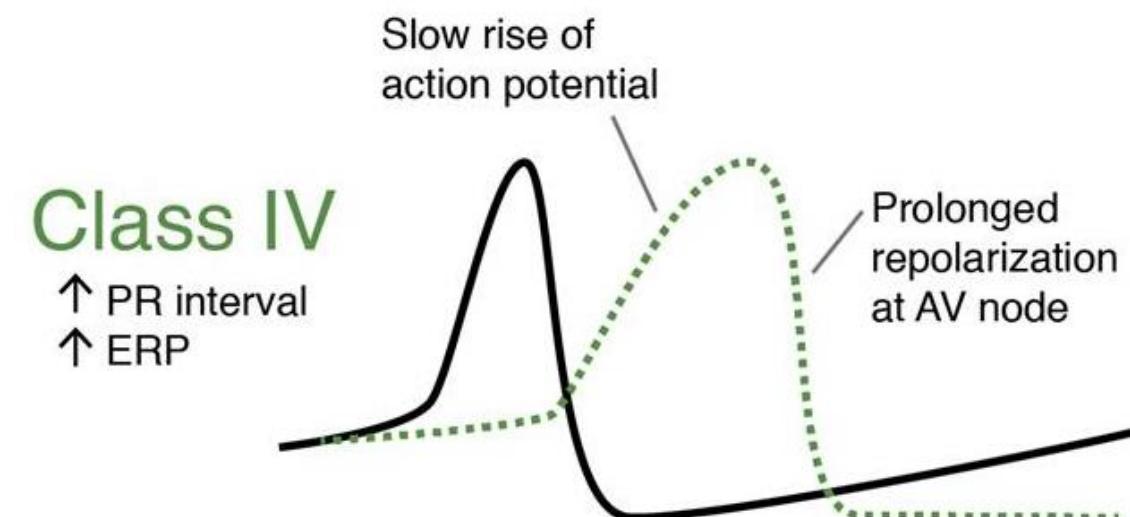
VT, VF

NOT in LOT or  
TdP



# Class IV – calcium channel blockers (verapamil, diltiazem)

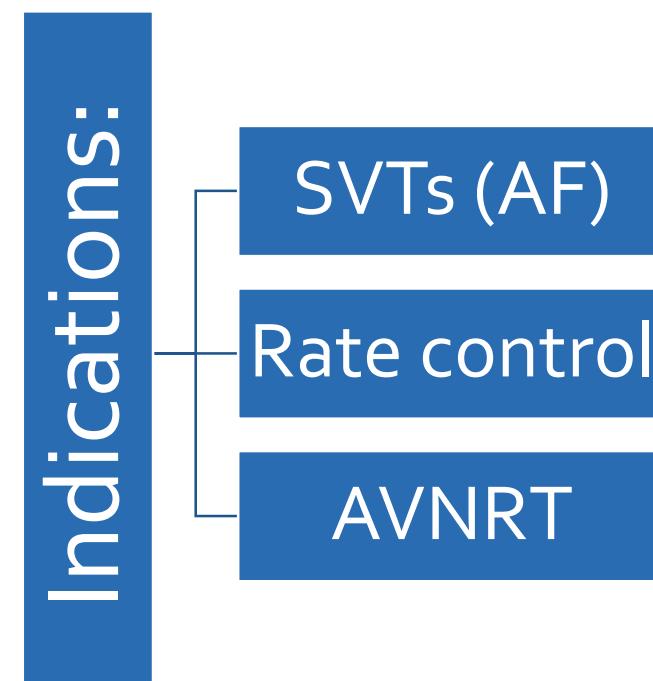
- Class IV agents are slow non-dihydropyridine calcium channel blockers
- They decrease conduction through the AV node, PR interval increases (Rate (Freq.) CTRL)
- They reduce the contractility of the heart (contraind.: HF!)
- However, in contrast to beta blockers, they allow the body to retain adrenergic control of heart rate and contractility
- Terminate SVTs by causing partial AV block
- Suppress premature ectopic beats (EADs) and may DADs



- Indications: AV reentry, DAD-mediated VF,
- Temporary rhythm control of Aflutter, Afib
  - Do not reduce post-AMI mortality

**Adverse effects** of i.v.verapamil or diltiazem is hypotension, particularly with bolus administration

- Severe sinus bradycardia or AV block also occurs, especially in those who receive b-blockers!

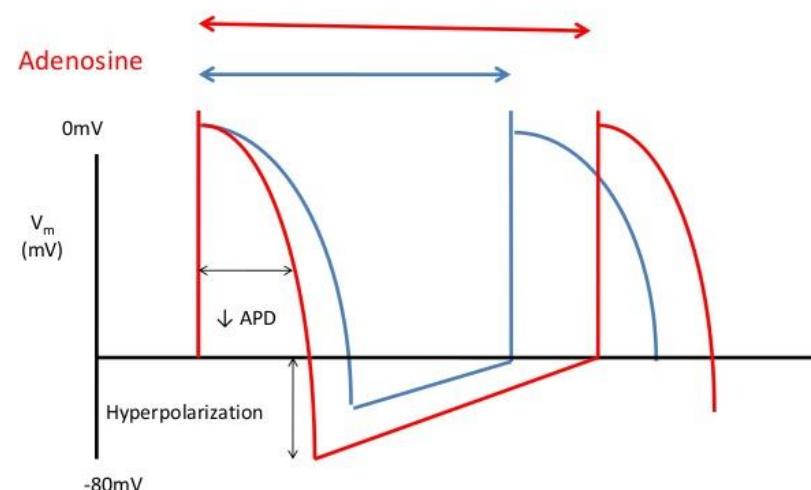


# Adenosine (Adenocor™ inj.)

- Adenosine is a naturally occurring nucleoside (A<sub>1</sub> receptor, G<sub>i</sub>)
- is administered as a rapid intravenous bolus (emergency units)
- for the acute termination of re-entrant supraventricular arrhythmias
- Adenosine activates acetylcholine-sensitive K<sup>+</sup> current in the atrium and sinus and AV nodes, hyperpolarization, and slowing of normal automaticity
- Also inhibit Ca<sup>2+</sup> currents thus increase AV nodal refractoriness



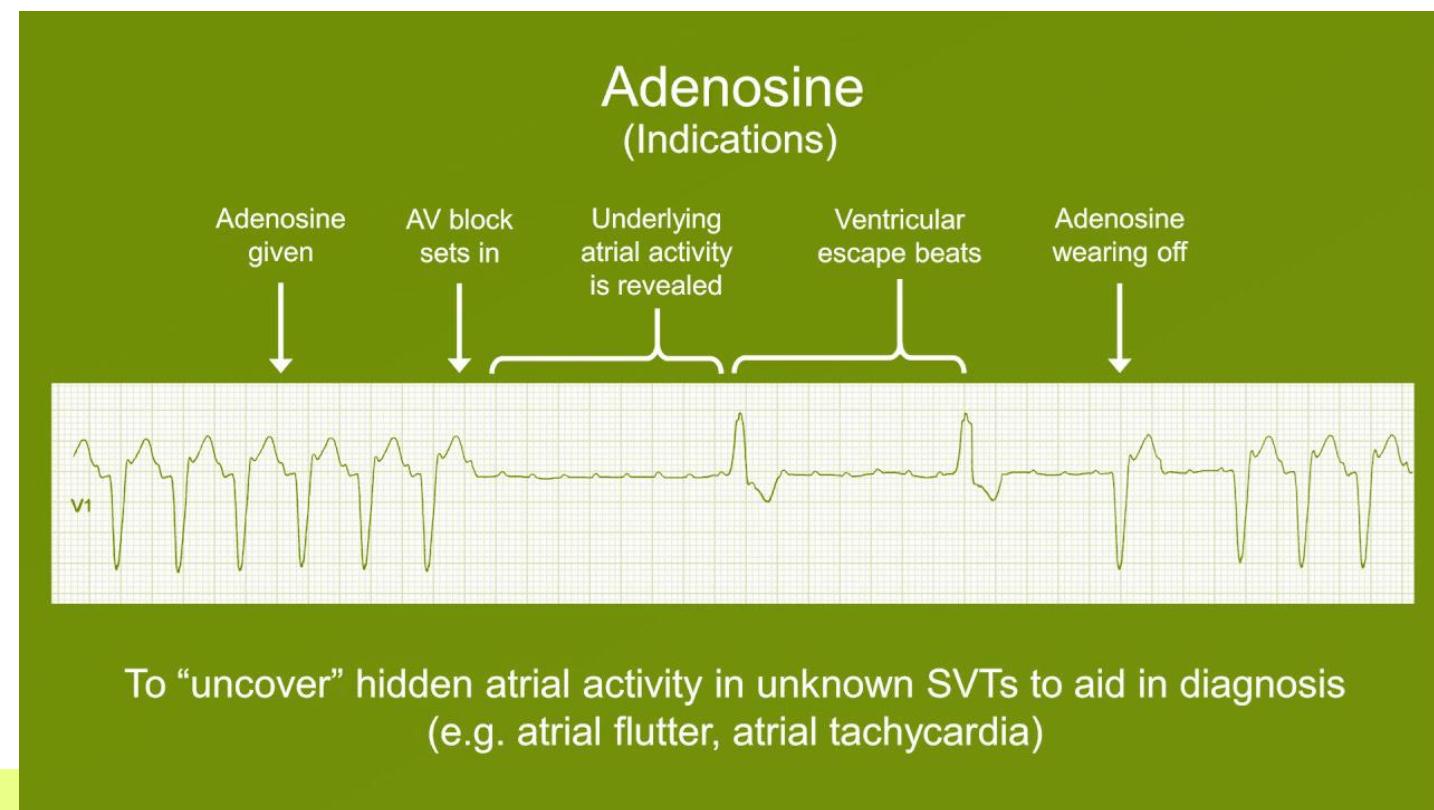
- Specifically blocks AV nodal conduction



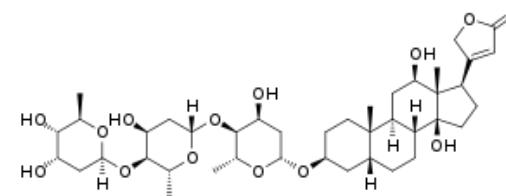
- Dose: 6 mg bolus, under ECG monitor!
- Role in differential diagnosis:
  - AVNRT and AVRT terminates under adenosine action
  - Flutter – adenosine may reveal f waves
  - No effect on VT

**Adverse effects:** A major advantage of adenosine therapy is that adverse effects are short-lived

- Transient asystole is common but spontaneously recover
- patients feel a sense of chest fullness and dyspnea and flush
- (Antidote: aminophylline)

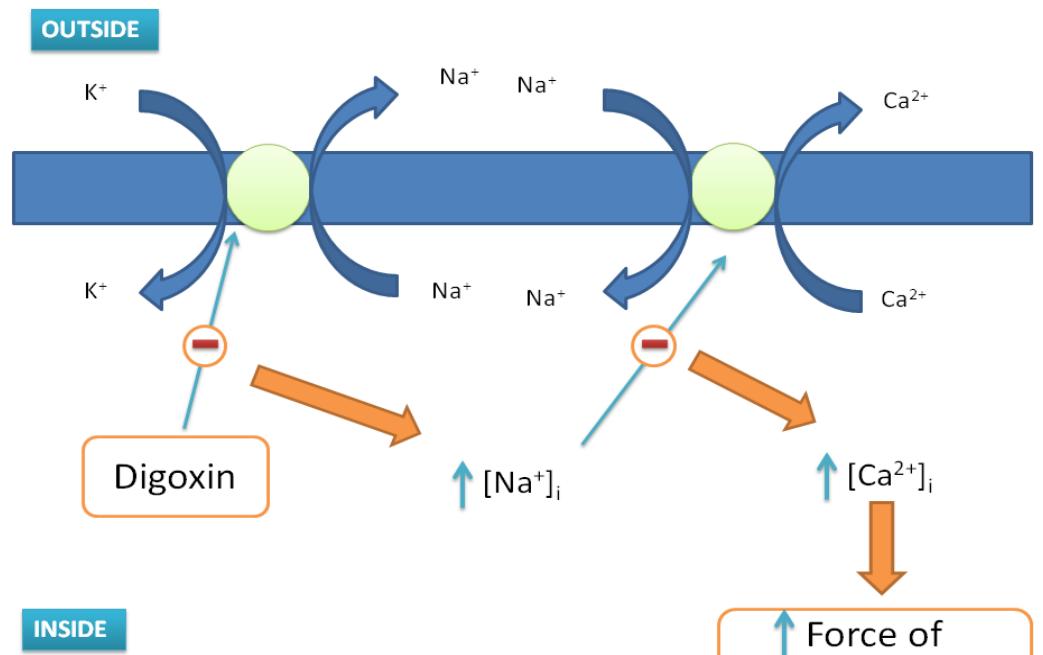


# Others: Digoxin, Magnesium sulphate



## Digoxin (digitalis glycosides) (Digoxin-RICHTER™)

- increase the rate of automaticity, force of contractions
- But vagotonic at the same time, resulting in inhibition of  $\text{Ca}^{2+}$  currents in the AV node!
- major "indirect" effects are shortening of atrial action potentials, and increases in AV nodal refractoriness
- Valuable in terminating re-entrant arrhythmias involving the AV node and in controlling ventricular response in patients with atrial fibrillation
- Cardiac glycosides may be especially useful because many such patients have **heart failure**, which can be exacerbated by other AV nodal blocking drugs



**Side effects:** Arrhythmias, nausea, disturbances of cognitive function, and blurred or yellow vision are the usual manifestations

- Due to  $\text{Ca}^{2+}$  overload, DAD-related tachycardias occur along with impairment of sinus node or AV nodal function
- Contraindications: WPW, SSS
- Antidote: DigiBIND

## MgSO<sub>4</sub> (MAGNESIUM SULFURICUM PHARMAMAGIST inj.)

- The intravenous administration of 1 to 2 g MgSO<sub>4</sub> is effective in preventing recurrent episodes of *torsades de pointes*, (even if the serum Mg<sup>2+</sup> concentration is normal)
- Mechanism: an effect on the inward current, possibly a  $\text{Ca}^{2+}$  current, responsible for the triggered upstroke arising from EADs is possible
- Intravenous Mg<sup>2+</sup> also has been used successfully in arrhythmias related to digitalis intoxication

# Take home messages:

- Automaticity, differences between slow and fast action potentials
- Mechanisms of arrhythmias: EAD, DAD, reentry
- Vaughan Williams classification of drugs
- Antiarrhythmics are pro-arrhythmic at the same time (evaluate risks/benefits)

**Treat the patient, not the ECG!**





Thank you  
for your  
attention!

