ANTIARRHYTHMIC DRUGS

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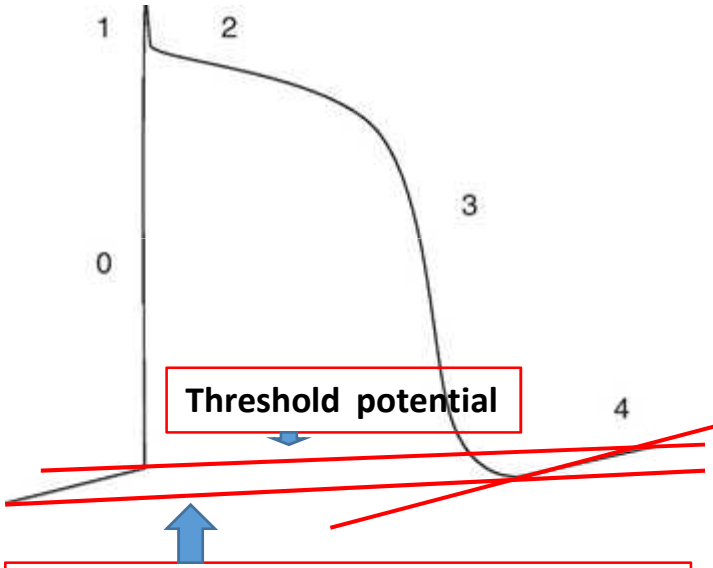
Arrhythmias

- „Arrhythmia is the disturbance of the regular rhythm of cardiac contractions” (Gottsegen, 1967).
- Pathogenesis of arrhythmias is complex. The main pathogenetic factors:
- 1. Faulty impulse initiation
- Early afterdepolarization
- Late afterdepolarization
- 2. Faulty impulse conduction

Arrhythmias

- **1. FAULTY IMPULSE INITIATION**



Determining factors of pacemaker activity

The slower the frequency of the heart is

1. the more negative the MDP (Ach, adenosine)

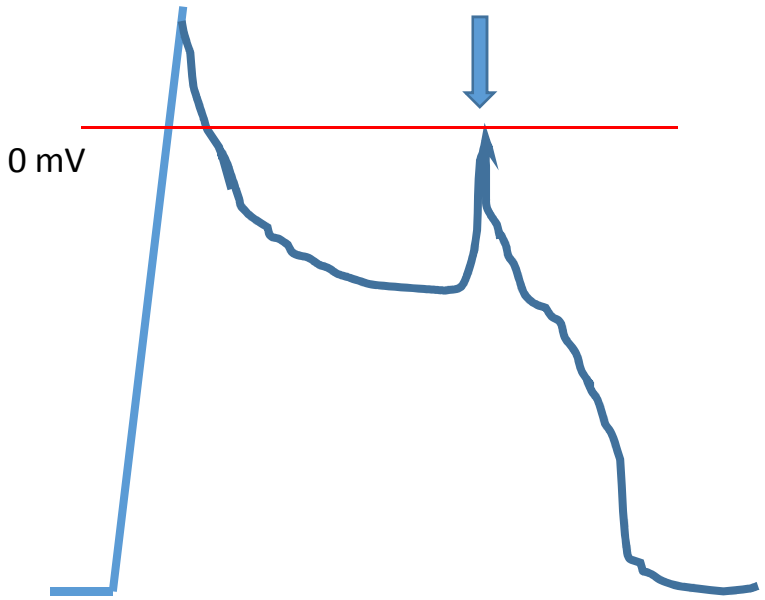
2. the less steep the diastolic depolarization

3. the more positive the threshold potential

Steepness of diastolic depolarization

Arrhythmias

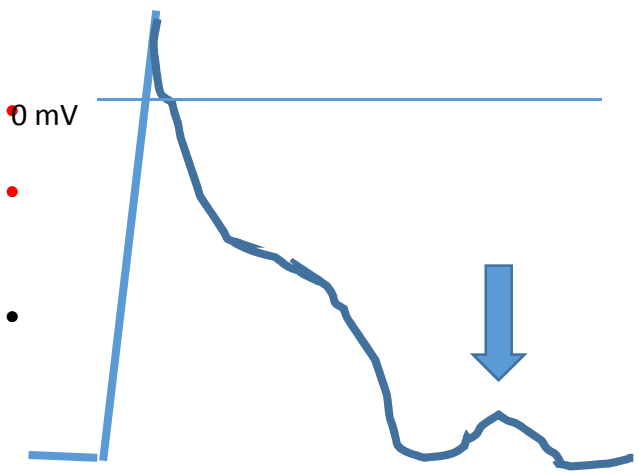
- **EARLY AFTERDEPOLARIZATION**



- Pathological prolongation of depolarization. Causes:
- Hypokalemia
- Disturbance of HERG „human ether a-go-go gene” (inhibition of I_{kr} current)
- Potassium channel inhibitors
- **Therapy:** K+ substitution, Mg2+ replacement, drugs inducing faster depolarization (verapamil, mexiletin, etc.)

Arrhythmias

- **DELAYED AFTERDEPOLARIZATION**



Calcium „overload”

Backround: 1. ischemia,

2. digitalis intoxication

Therapy:

Calcium channel blockers (verapamil)

Beta adrenergic receptor blockers

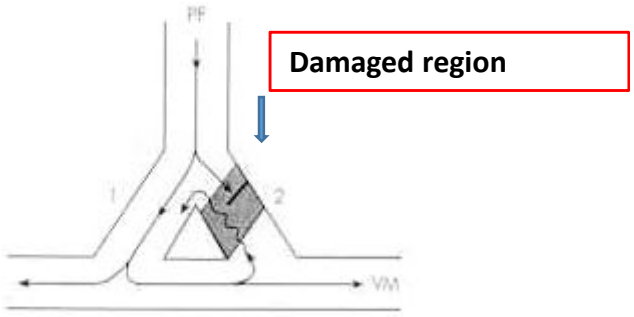
- **(propranolol, bimoclolol, etc.)**

Na channel blockers (lidocain)

Arrhythmias

2. FAULTY IMPULSE CONDUCTION

DEVELOPMENT OF RE-ENTRY



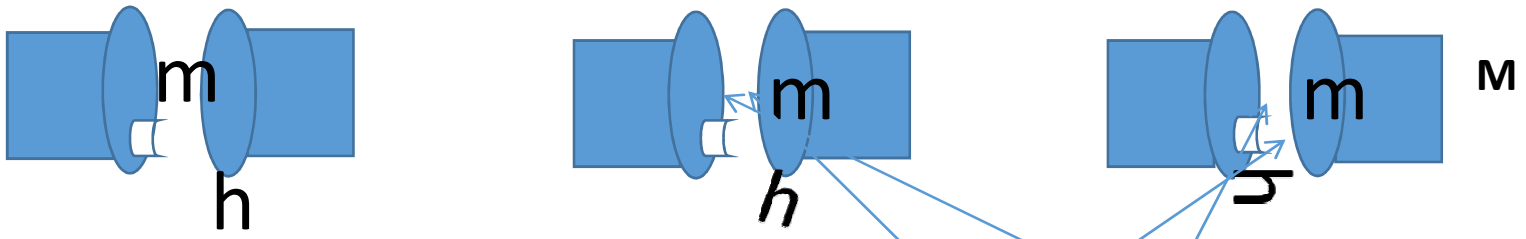
- Criterions of development of re-entry:
- 1. should be hypoxic or ischemic damage on the way of impulse conduction
- 2. should be an unidirectional block in the region of damage
- 3. After the impulses passed the barrier, the other branch of the re-entry should not be in refractory period
- The aim of therapy: 1. Blockade of unidirectional impulse conduction (bidirectional block), 2. Increase of refractory period to prevent re-entry impulse conduction

Antiarrhythmic drugs

Vaughan Williams – Singh – Henderson classification

Class	Drugs
Class I. drugs	Na+ channel blockers
IA	Prototype: Quinidine
IB	Prototype: Lidocaine
IC	Prototype: Flecainide
Class II. drugs	Beta receptor blockers
Class III. drugs	K+ channel blockers
Class IV. drugs	Ca2+ channel blockers
Class V. drugs	Bradycardia-inducing drugs

Antiarrhythmic drugs

- **Fast Na channels**
- Resting state Activated state Inactivated state **E**
- 

- **1. Drugs with high affinity to activated channels: Quinidine, lidocaine, flecainide**
- **2. Drugs with high affinity to inactivated channels: amiodarone, lidocaine, mexiletine, disopyramide**
- **In tachycardia: many activated channels – more time in activated state**
- **Ischemia: many inactivated channels (decrease of membr. pot.) more time in inactivated state**
- **Antiarrhythmic agents act more intensively and selectively in tissues of pathological state than in tissues of physiological state**

Antiarrhythmic drugs

- **Class IA drugs:**
- Moderate decrease in velocity of phase 0
- Prolongation of action potential duration
- Quinidine, procainamide, disopyramide
- **QUINIDINE (prototypic drug):**
- **PROCAINAMIDE, DISOPYRAMIDE**
- **Electrophysiological actions:**
- Reduction of pacemaker activity
- Prolongation of action potential duration and effective refractory period
- Decrease of conduction velocity

Antiarrhythmic drugs

- **QUINIDINE**

Side effects:

1. **Heart: cardiodepression(Ca2+ channel blockade), paradoxic tachycardia (atropine-like effects), proarrhythmic actions (QRS interval >50%)**
2. **Vessels: hypotension (alpha adrenoceptor inhibition). Incline to embolism (without previous anticoagulant therapy) in patients suffering with atrial fibrillation**
3. **Skeletal muscle: adynamia , myasthenia gravis-like symptoms (curariform effects)**
4. **Gastrointestinal: diarrhoe, vomiting, nausea**
5. **Cinchonism: headache, dizziness, tinnitus**
6. **Allergic reactions: skin eruptions, angioneurotic edema**

Therapeutical use: atrial and ventricular arrhytmias

Antiarrhythmic drugs

- **Class IB drugs:**
- No reduction in steepness of phase 0
- Decrease of action potential duration
- **LIDOCAINE (prototypic)**
- No action in supraventricular, but in ventricular arrhythmias. Its action can be manifested only in ischemic tissues.
- Ineffective in hypokalemia. K+ replacement!!!

Antiarrhythmic drugs

- **LIDOCAINE**
- **Enteral absorption and bioavailability is very poor!**
- **Overdose:**
- One of the least toxic antiarrhythmic agents, but cardiodepressive in congestive heart failure.
- CNS effects: tonic-clonic seizures. First aid: diazepam i.v.
- MEXILETINE (orally, less adverse react.,)
  PHENYTOIN (dig.intox.,open heart surg.,epil.pat.)

Antiarrhythmic drugs

- **Class IC drugs:**
- Strong reduction in steepness of phase 0.
- No change in action potential duration.
- Extraordinary proarrhythmic action. Increase the frequency of sudden cardiac death. Shorten the duration of life expectancy.
- They cause electric inhomogenity: shorten the action potential duration in His-Purkinje system, but not in the working myocardium. Incline to proarrhythmias.

Antiarrhythmic drugs

- **FLECAINAMIDE:** primarily in life-threatening ventricular tachycardia and paroxysmal atrial fibrillation.
- **PROPAFENONE:** its structure is similar to propranolol: slight beta blocking action (asthma!). Generally, it increases the frequency of sudden death. „Torsade de point" arrhythmias.
- Relatively safe in supraventricular rhythm disturbances. „Pocket drug" in paroxysmal atrial fibrillation!

Antiarrhythmic drugs

- **Class II. drugs: BETA ADRENERGIC RECEPTOR BLOCKERS**

Double action: inhibit the arrhythmogenic actions of increased catecholamine release + membrane stabilizing action

Do not shorten the duration of life and do not reduce the life expectancy contrary to the bulk of antiarrhythmic agents.

Therapeutical use: supraventricular and ventricular arrhythmias.

Antiarrhythmic drugs
2. Beta receptor blockers

- **BETA-ADRENERGIC RECEPTOR BLOCKERS**
- **1st generation (non-selective)**

Drug	Membr.stab. effect	ISA	Lipide sol.
Pindolol	+	+ + +	+
Timolol	-	+ -	+
Sotalol	-	-	+
Propranolol	+ +	-	+ +
Oxprenolol	+	+	+ +

Antiarrhythmic drugs
2. BETA RECEPTOR BLOCKERS

- 2nd generation (beta1 selective drugs)

Drug	Membr.stab. effect	ISA	Lipid solubility
Metoprolol	+ -	-	+ +
Atenolol	-	-	-
Esmolol	-	-	+ -
Bisoprolol	-	-	+ -

Antiarrhythmic drugs
2. Beta receptor blockers

- 3rd generation (vasodilatory beta blockers)

Drug	Lipid solubility	Mechanism of vasodilation
Labetalol	+ + +	Alpha-receptor blockade
Carvedilol	+	Alpha-receptor blockade
Nebivolol	+ -	NO production

Antiarrhythmic drugs

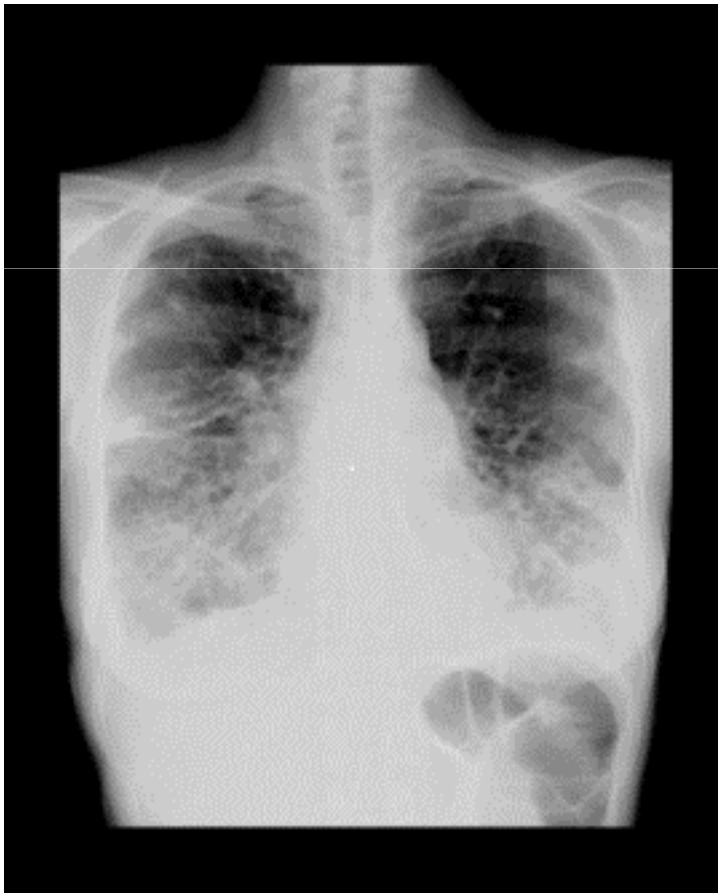
- **Class III. drugs: POTASSIUM CHANNEL BLOCKERS**
- **„MIXED" DRUGS:**
- **Amiodaron, Dronedaron**
- **Sotalol**
- **Bretylium**
- **„PURE" POTASSIUM CHANNEL BLOCKERS**
- **Ibutilid, Dofetilid: better profile of side effects, hopeful in treatment of atrial fibrillation**

Antiarrhythmic agents

- **AMIODARON**
- **The widest spectrum among antiarrhythmic agents.**
- **It is classificated mainly to Class III and I, but has also Class II and IV actions!**
- **Highly lipophylic. Onset of action is very slow in peroral application (1-3 months). Half-life is also very long (1-3 months).**
- **It can be effective in all types of arrhythmias. The arrhythmia-related death is decreased.**

Antiarrhythmic drugs

- **AMIODARON**
- Very frequent adverse
- reactions:
- 1. Pulmonary fibrosis
- (reversible) 15%

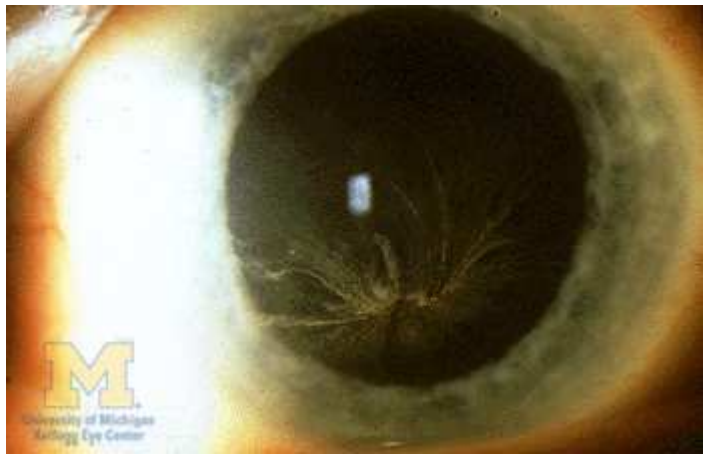


AMIODARON

- 2. Hypothyroidism
- cca. 5%

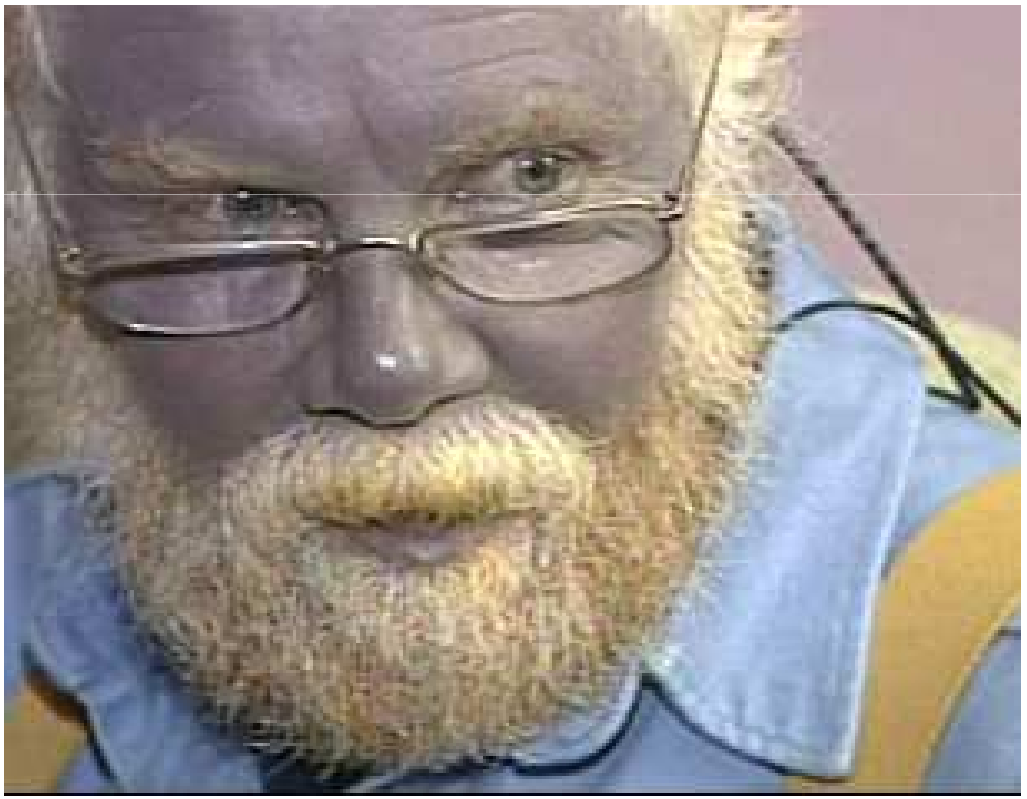
- 3. Hyperthyroidism
- cca. 1%

- 4. Cornea deposits 100%!



AMIODARON

5. Greyish-blue discoloration of skin cca. 10%



Antiarrhythmic drugs

- **SOTALOL**
- D-sotalol: pure K channel blocker
- L-sotalol: non selective beta blocker
- D-sotalol increased lethality of postinfarction patients by 5% (SWORD trial). Recently, only racemic form can be used!
- Useful in supraventricular and ventricular arrhythmias! „Torsade de point” can be occured!

Antiarrhythmic drugs

- **CLASS IV. DRUGS:**
- NON-DIHYDROPIRIDIN CALCIUM CHANNEL BLOCKERS
- VERAPAMIL ÉS DILTIAZEM
- In rhythm disturbances, where re-entry involves the AV junction. No ventricular actions.
- Therapeutic use: paroxysmal supraventricular tachycardia, atrial fibrillation (frequency control)

Antiarrhythmic drugs

- CLASS V. DRUGS:
- SELECTIVE BRADYCARDIA-INDUCING AGENTS.
- Novel type of antiarrhythmic agents. Inhibit the „funny current” (If) (they determine the steepness of slow diastolic depolarization) in sinuatrial node. No action on impulse conduction, contractility and contractile state of the vessels. Prototypic drug: IVABRADIN. As and antiarrhythmic can not be used, only in unjustified sinus sinus tachycardia. Primarily antianginal drug!

Antiarrhythmic agents

- NON-PHARMACOLOGICAL METHODS.
- According to great international trials: most of antiarrhythmic agents reduce the life expectancy in spite of the fact that they abolish arrhythmias!!! Therefore, recently cardiologists prefer various ablation methods.
- In a part of patients: combined drug+ablation treatment.

Antiarrhythmic drugs

- NEW HYPOTHESIS IN PATHOGENESIS OF ATRIAL FIBRILLATION
- Atrial fibrillation is inflammation. Anti-inflammatory drugs are necessary.
- Hopeful trials:
- Non-steroid anti-inflammatory drugs
- Statins
- Fish oil and omega-3-fatty acid containing substances.

Antiarrhythmic drugs

- Oxygen-derived free radicals are included in arrhythmogenesis. Therefore, use of antioxidant is rationale as adjuvant therapy.
- Vitamin C
- Beta-karotin
- Selenite
- Polyphenols