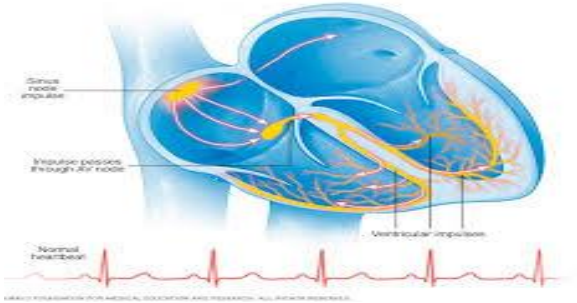
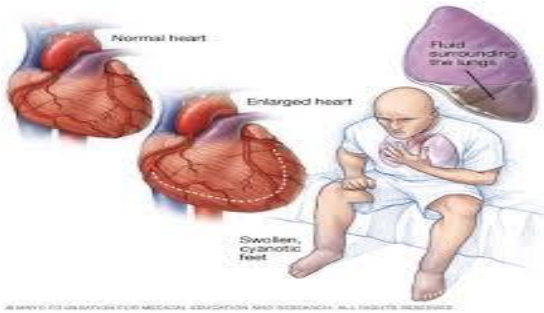




Clinical pharmacology of antiarrhythmic drugs and drugs used in heart failure.

Chianu Marin

Antiarrhythmic drugs - drugs from various pharmacological groups used to eliminate disturbances of cardiac rhythm

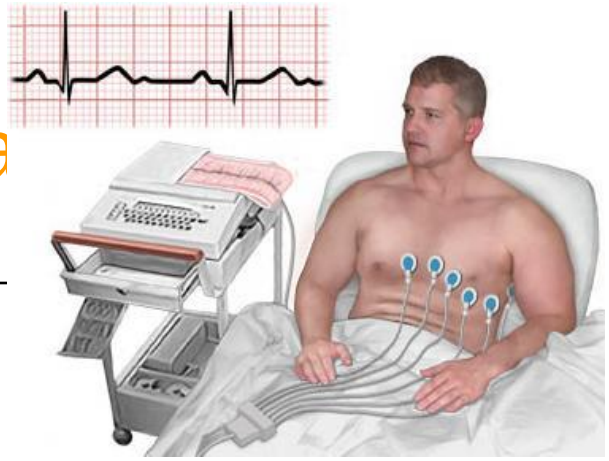
Clinically, dysrhythmias are classified according to:

- the site of origin of the abnormality—atrial, junctional or ventricular
- whether the rate is increased (tachycardia) or decreased (bradycardia).

Four basic phenomena underlie disturbances of cardiac rhythm:

1. Delayed after-depolarisation.
2. Re-entry.
3. Ectopic pacemaker activity.
4. Heart block.

Causes of the arrhythmia



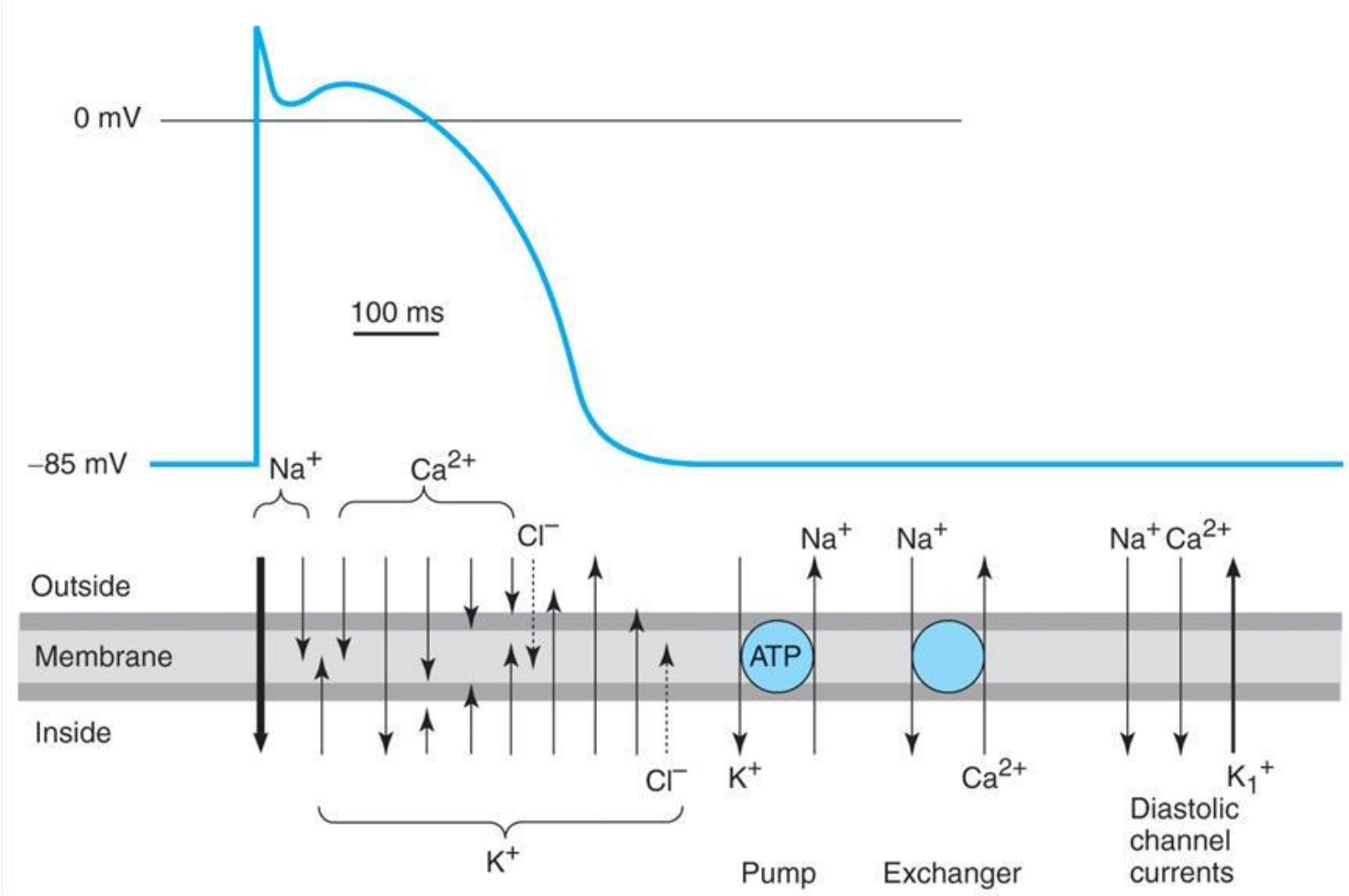
heart

- congenital heart defects and acquired)
- congenital anomalies (WPW syndrome)
- acute and chronic myocardial ischimia (heart attack)
- cardiac inflammatory disease;
- cardiac trauma, including cardiac surgery.

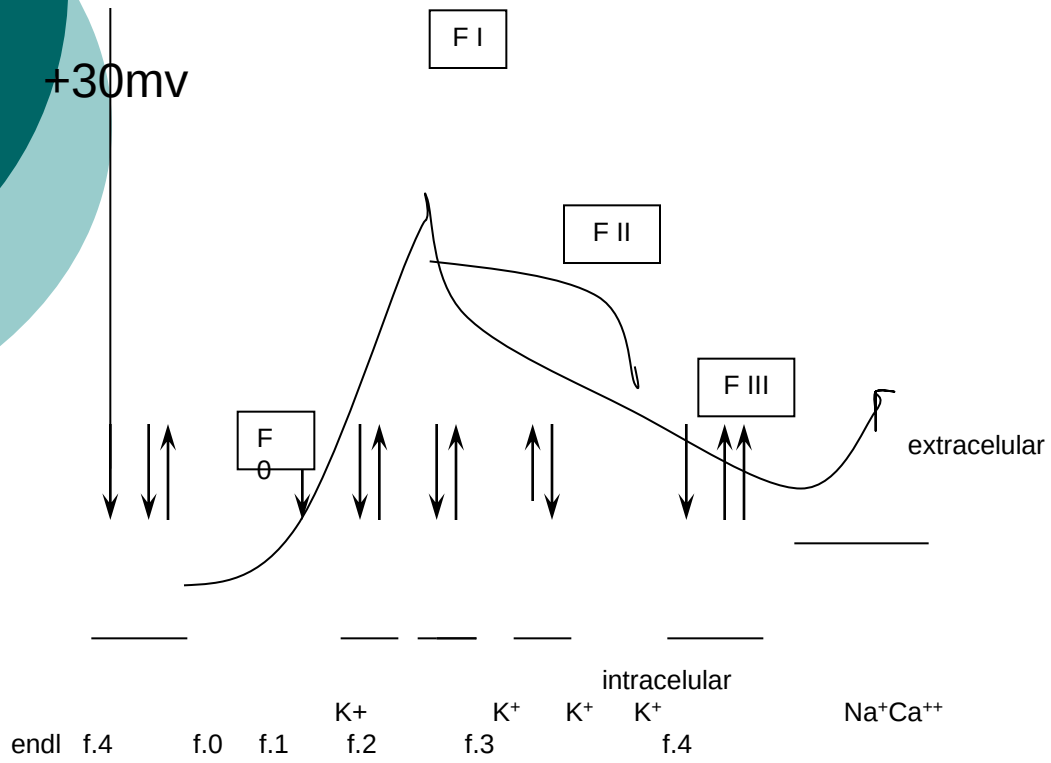
extracardiac

- fever;
- high blood pressure;
- electrolyte and acid-base disorders;
- poisoning by chemicals;
- cardiac digitalis poisoning, sympathomimetic, diuretics, psychotropic (tricyclic antidepressants phenothiazines, erythromycin etc.);
- disorders of innervation of heart;
- endocrine diseases (hyper- and hypothyroidism, primary aldosteronism, pheochromocytoma, etc.);
- infections and organic diseases (bronchopulmonary, digestive, CNS and peripheral diseases).

Phases of potential action and ionic changes



Transmembranar potential evolution (cell electrograma)



Classification of antiarrhythmic drug

(acording Williams with modification)

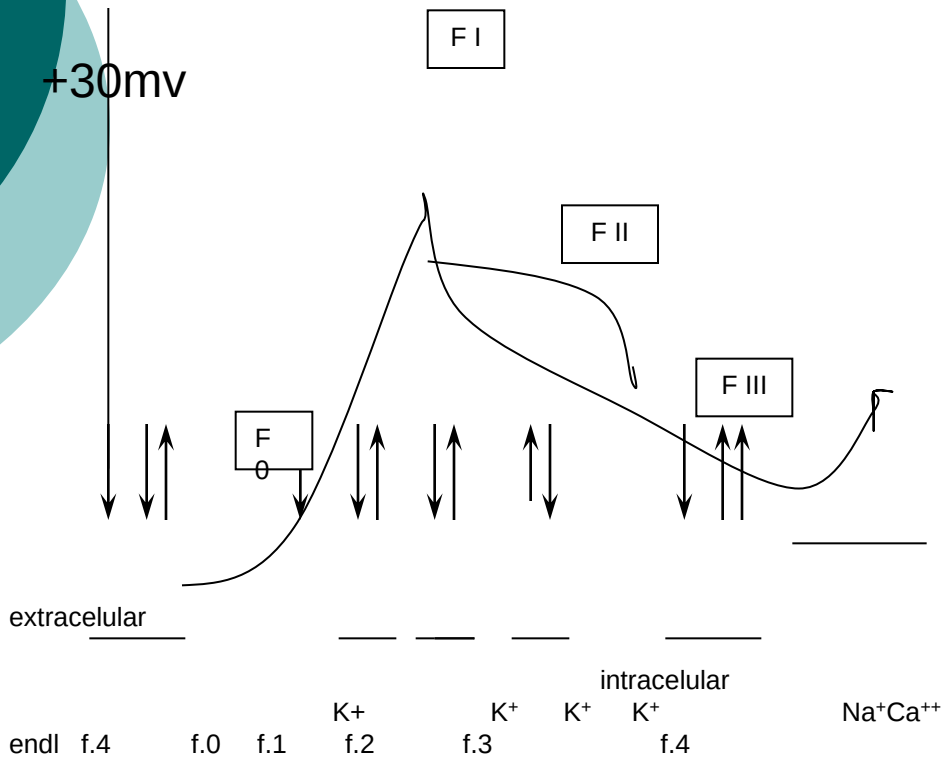
Class I: Na channel blockers (and K channels to some extent)

Subclass I A (time of restoration the Na channel blocate between 0,3 and - 1,5 sec.): **quinidine, procainamide, disopyramide, imipramine, ajmaline, lorajmaline, prajmalin**

Subclass I B (time of restoration the Na+channel blocate less < 0,3 sec.): **lidocaine, tocainid, mexiletine, phenytoin**

Subclass I C (time of restoration of the blocked Na+channel more > 1,5 sec): **flecainide, encainide, lorcainide, moracizine, propafenone.**

class I A (time of restoration the Na channel blocate between 0,3 and - 1,5 sec.):



MA: they inhibit Na+ influx (Ph 0 and 4);

Effects:

- ↓ diminish the polarization;
- they prolong repolarization and ERP,
- ↓automatism, excitability, conductibility, contractility,
- ↑cardiac rate - adrenolitic properties (↓AP);
- parasympatholitics properties;

class I A

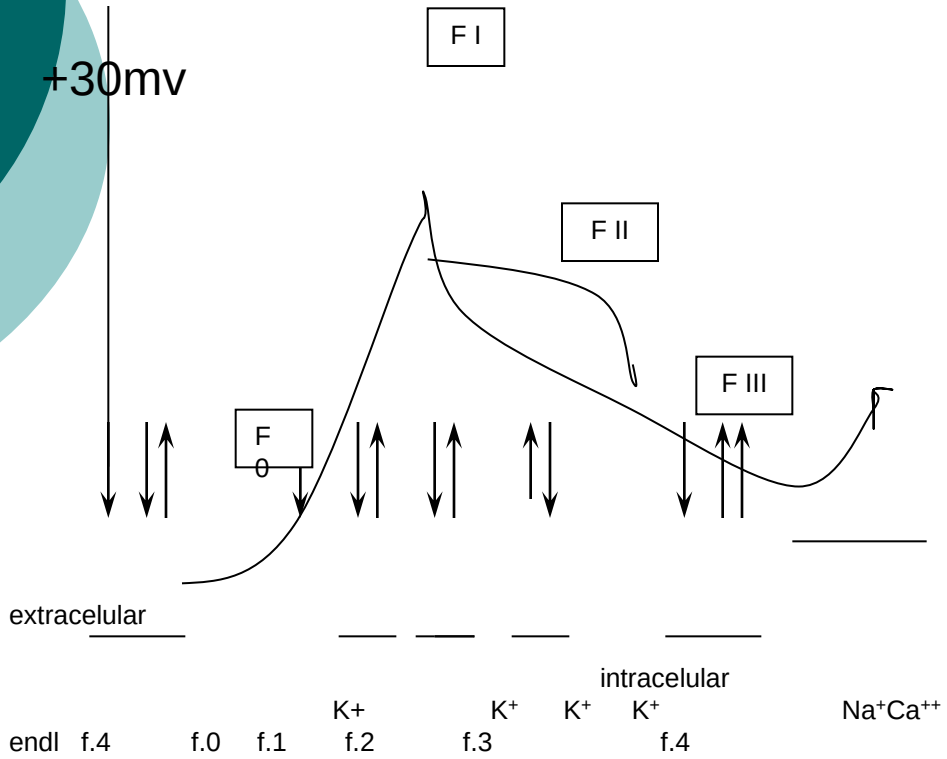
Indications:-to prevent and treatment of atrial and ventricular extrasystolia,

- supraventricular tachycardia,
- atrial fibrillation and flutter,
- ventricular tachycardia.

Contraindications: arrhiythmias caused by the digitals, AV block, hyperkaliemia and hypokaliemia, in children, cardiac failure.

Pharmacokinetics: Good absorption from intestine and binding with albumines in 90%. **$T_{1/2}$-** procainamide 2-3 hours; dezopiramide -6 h, ajmaline-8 minutes. Metabolism in liver- formation of active metabolites. Elimination by the urine.

Subclass I B (time of restoration the Na+channel blocate less < 0,3 sec.): **lidocaine, tocainid, mexiletine, phenytoin**



MA: they inhibit Ca**2+** and Na+ influx (ph 4)

Eff:

↓ duration of potential of action,

not influence ERP,

↓automatism;

↑cardiac rate.

Subclass I B

lidocaine, tocainid, mexiletine, phenytoin

Indication: - acute myocardial infarction,
- intoxication with digitals;
- ventricular extrasystolia,
- ventricular tachycardia,
- ventricular fibrillation,

Phenytoin - in atrial and ventricular arrhithmia- by digitals.

Contraind: cardiac block, bradicardia, liver failure, epilepsia, parkinsonism, arterial hypotension.

Subclass I C

flecainide, encainide, lorcainide, moracizine, propafenone

(time of restoration of the blocked Na+channel more > 1,5 sec):

Eff: the same like IA**.**

Side effects: proarrhithmic effect therefore are indicated only in ventriculare tachyarrhithmia rezistent to other drugs.

Contraind: AV block, acute myocardial infarction, intoxication with digitals; liver and renal failure, COPD.

Class II: beta-adrenoblockers:

n/selective

SIA-: propranolol, nadolol, sotalol, timolol;

SIA+: oxprenolol, penbutolol, pindolol*,bopindolol

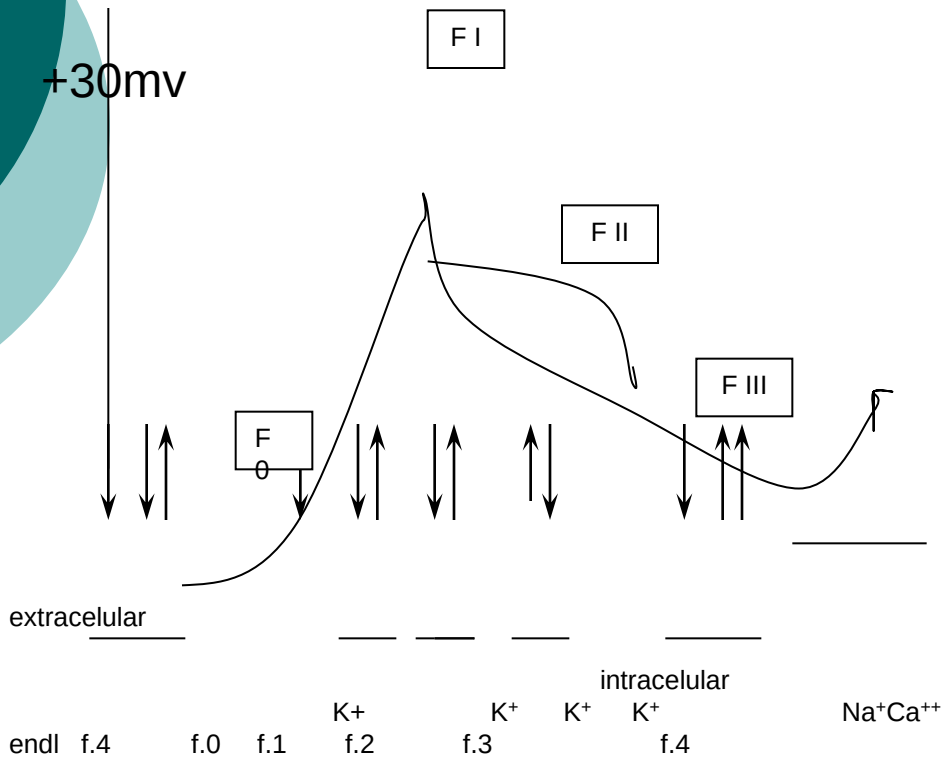
selective

SIA- : bisoprolol, esmolol, betaxolol;

SIA +: atenolol, metoprolol, talynolol,

acebutolol*, nebivolol*;

Class II: beta-adrenoblockers:



MA: They reduce sodium and calcium currents (ph 3-4);

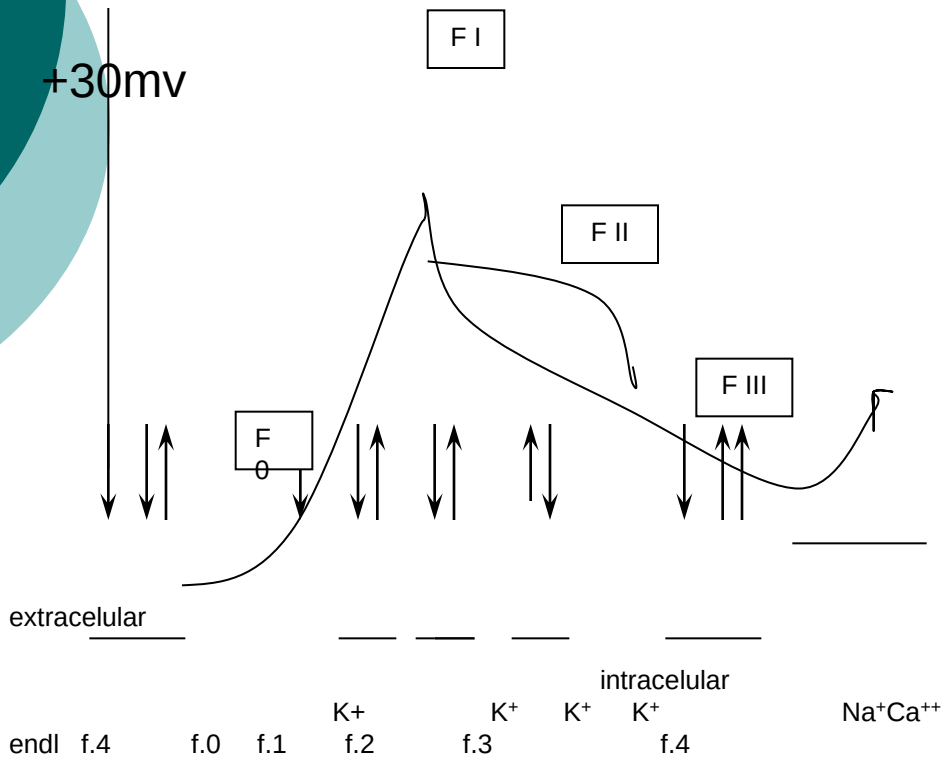
Effect -↓ automatism,
↓ excitability,
↓ conductibility,
↓ contractility,
↓ cardiac rate;

Class II: beta-adrenoblockers:

Ind: supraventricular tachyarrhythmias, ventricular arrhythmias after physical effort; Wolff - Parkinson- White syndrome.

Class III: prolong refractory period

amiodarone, ibutilide, dofetilide, sotalol, bretilium.



MA: (inh. eflux of K-f. 3
inh. influx of Na-f. 0
inh. influx of Ca
blocked β-AR

Eff: ↑ERP
↓automatism
↓ conductibility

bretylium is used

as a "chemical defibrillator" when arrhythmia is resistant to standard methods.

Class III: prolong refractory period

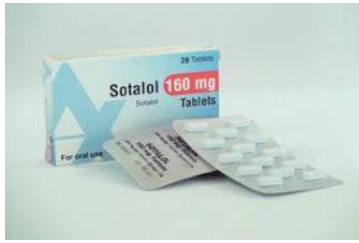
Ind: **amiodarone** in supraventricular and ventricular tachyarrhythmia,

angina pectoris;

- **sotalol** in supraventricular tachyarrhythmia.

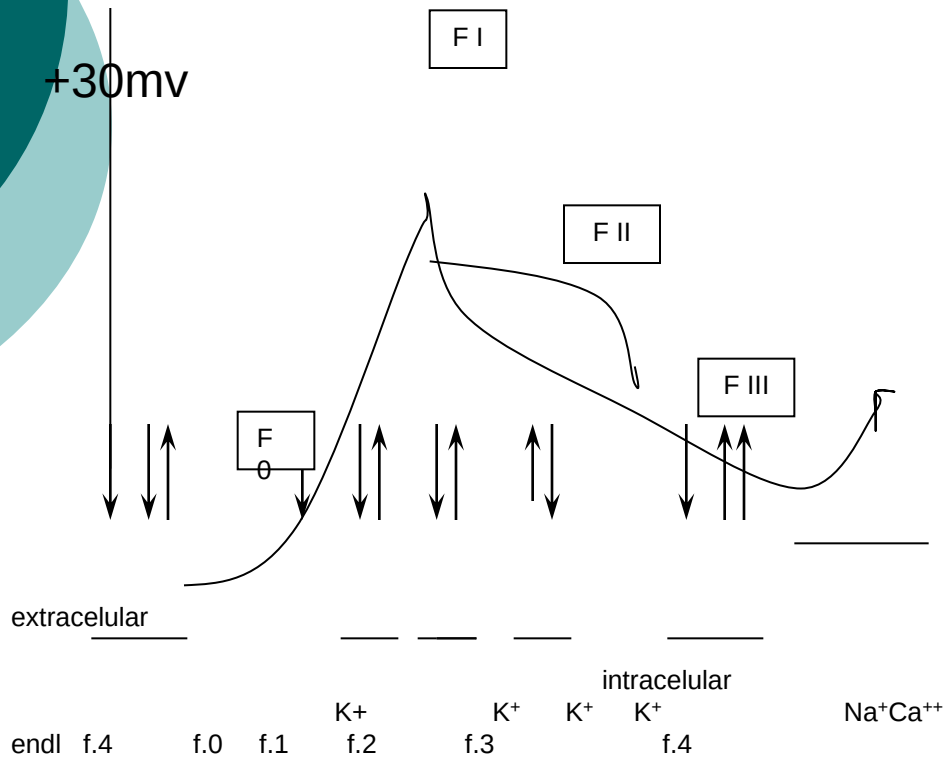
Contraind: bradicardia, AV block, thyroid diseases, pregnancy, insolation.

SE: pigment deposition in the cornea, thyroid dysfunction, pulmonary fibrosis, hepatocellular necrosis, photosensitivity, paresthesias, tremor.



Class IV. Calcium channel blockers:

Verapamil, galopamil, diltiazem, bepridil



MA: block slow responses of A-V conduction (ph 2,3-4) →↑ERP

Eff:

↓automatism,

↓excitability,

↓conductibility,

↓contractility,

↓cardiac rate;

Class IV. Calcium channel blockers:

Verapamil, galopamil, diltiazem, bepridil

Indications: Highly effective in treatment of

- supraventricular tachycardia,
- atrial fibrillation and flutter,
- ventricular extrasystolia.

Class V. different groups:

- **cardiac glycosides,**
- **adenosine,**
- **potassium drugs,**
- **magnesium sulfate**

Adenosine

Is a normal component of body.

MA: purinergic receptor agonist, which reduces adenylate cyclase activity→cAMP→↓ calcium influx.

- ↑Kalium eflux with membrane hyperpolarization in atrium, sinus and AV node.
- intravenous adenosine administration directly inhibits automatism of sinus node, atrioventricular conduction, myocardial contractility, prolongs the effective refractory period in atrioventricular node, but has little effect on sinusal node.

in high doses (6-12 mg) i/v.

Ind: - supraventricular tachycardia,

- ventricular tachycardia (rarely).

Potassium drugs

MA: similar acts that acetylcholine, but the effect is not removed by the atropine.

Eff: ↓automatism,
↓excitability,
↓conduction,

Ind: - arrhythmias produced by the digitals;
- arrhythmias in acute myocardial infarction.

SE: - paresthesias,
- AV block,
- disturbances of renal function

Magnesium sulfate

MA: of the antiarrhythmic action of the magnesium ions is not definitively clear, but is recognized their influence on Na+/ K+ATPase, sodium channels, potassium channels of calcium channels.

Ind: - arrhythmias produce by digitals;

- in period after the acute myocardial infarction,
- torsades de pointes in the conditions of normal plasma levels of magnesium.

Contraind: kiddney failure,

don' t assosiate with CNS inhibitors drugs and peripheral miorelaxants.

Cardiac glycosides

- **Inhibitors of sodium pump** (Na+ K+-ATPase) inotrop pozitive drugs
- - strophantine, corglicon,
- - digoxine,
- - digitoxine.

Cardiac gliycosides (CG)

Cardiac glycosides – of vegetal origine or semisynthetics derivates can to intenssify the contractility (force and speed contraction) of miocard in heart failure with pump defficiency.

- Classification of cardiac glycosides can be effectuated according to the following principles:
- - **speed of effect development;**
- - **duration of action;**
- - **cumulative capacity**;
- - **ways of administration**;
- - indications for administration.

I Inotropic - pozitive effect (CG)

- They ↑the force and speed of contraction → shorten the contr
- ↑ time of diastolic filling, the heart empties better, pression and thelediastolic volume ↓.
- These all ↑ myocardic tonus contribute to ↓ the heart diameter and neccesity in oxygen.

II. Chronotrop - negative effect

- Is manifested as bradicardia and has parasympathethic origin.
- Effect can be diminuated by atropine and is absent in patients with heart transplant.
- Clinic situation with ↑ of the sympathetic tonus and reduction of parasympathetic (fever, thyriotoxicosis) respond slowly to chronotrop - negative action of digitals. This case need combination with β-adrenoblockers.

III. dromotrop - negative effect

slowness of conduction through AV junction. Therefore potential of action develops more slowly, and have more duration, refractory period became longer due to ↑ vagale influence.

- Dromotrop - negative effect is used in: atrial flutter, atrial fibrillation; cardiac failure with tachiarrhythmia, supraventricular paroxistic tachicardia.
- **Is unfavorable** dromotrop negative action **:** in AV blocade, WPW syndrome (CG provoke transmision of impulse through accesory ways of conductivity, producing paroxystic tachycardia).

IV. Batmotrop pozitive effect

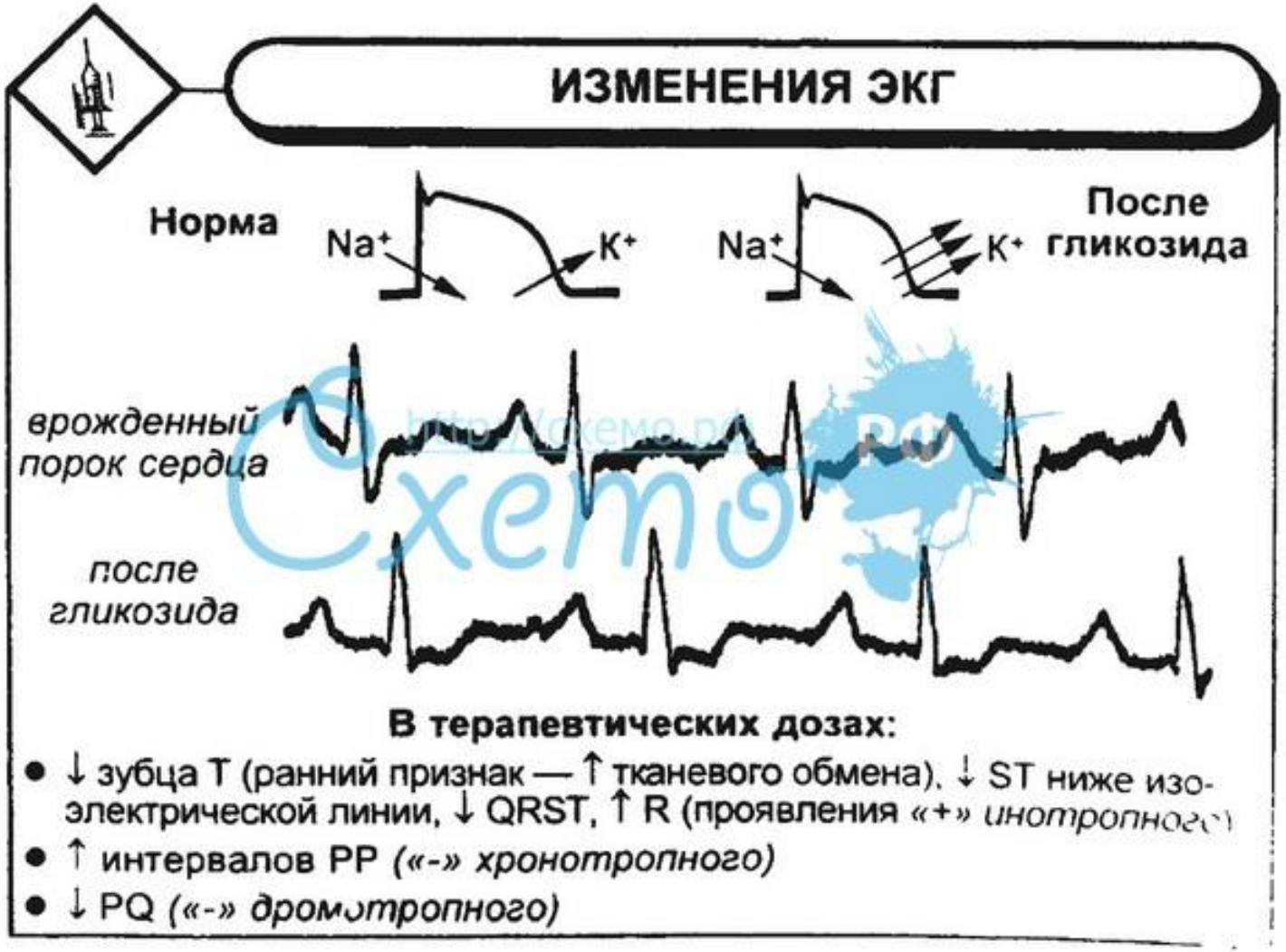
is undesirable and provokes ectopic automatism.

In atrium- therapeutic doses contribut to:

- ↓ duration of potential action;
- ↓ effective refractory period;
- ↑ of atria excitement.

This indirect action is mediated by acethylcholin, explans why digitalis can ↑ atrial fibrillation or flutter.

Interval PQ (not more than 0,2 sec) show about AV conductibility
Evolution wave T shows the intensity of coronary flux.
Amplitude R wave and duration of the QRS complex demonstrates inotropic - pozitive effect (systolic action).



Interaction of digoxine with other drugs

1. etacrinic acid	Hypokaliemie, hypomagneziemia
2. amiodarone	↑ D concentration by 69 % in blood
3. β-AB, chinidine	↑ D concentration by 100 %
4. Eritromicine	↑ D concentration by 116 %
5.Furosemide, glucoza	↑ D concentration by 60 %
6. Nifedipine	↑ D concentration by 45%
7. Tetracicline	↑ D concentration by 100 %
8. Verapamil	↑ D concentration by 41%
9. Sympathomimetics 10. Diuretics tiazide 11. Spironolactone	Arrhythmia Toxicity, bigiminia ↓ excretion by urine

B. ↓ digoxin effects

The drug	Causes
1. Alcohol, antiacids	↓ GI absorbtion
2. Colestiramine	↓ GI absorbtion, ↓ $T_{1/2}$ by 50%
3. Sodium nitroprusside	↑excretion by urine
4. Metoclopramida	↓ GI absorbtion
5. Neomicine	↓ GI absorbtion
6. Prednison	↑ metabolism

Bradiarrhythmia

- **Cardiostimulators**: dopamino- şi beta – adrenomimetics: dophamine, dobutamine, izoprenaline, dopexamine, epinephrine.
- **Phosphodiesterase inhibitors** : amrinone, milrinon, enoximon and methylxantines: aminophyilline, theophylline.
- **M-cholinoblockers:** atropine, scopolamine;
- **Calcium channel blockers:** nifedipine, amlodipine;
- **α-adrenoblockers:** prasosine, phentolamine.

Isoprenaline

- activation of adenylate cyclase and cAMP accumulation, the opening of Ca ++ channels and their intracellular influx, so increase conductivity, excitability and myocardial contractilyti.
  Compared with other sympathomimetic agents (epinephrine, norepinephrine, phenylephrine) isoprenaline does not increase blood pressure, angina type painless, no excite enhances the ectopic foci.

Isoprenaline

- As antiarrhythmic isoprenaline is used in:
- atrioventricular conduction disturbances,
- bradyarrhythmias sinus syndrome,
- prophylaxis accesses Adams – Stocs,
- syndrome of sinus node failure.

Cardiac glycosides. Modern cardiotonic drugs and other agents used in the treatment of congestive heart failure

Treatment of chronic heart insufficiency

- Heart glycosides
- Nonglycoside cardiotonic drugs
- Inhibitors of angiotensine transforming enzyme (IATE, IACE)
- Antagonists of angiotesine II receptors (ARA II)
- Diuretics
- Peripheral vasodilators
- Beta-adrenoblockers
- Drugs of metabolic action

CARDIOTONIC DRUGS

CARDIOTONIC DRUGS

HEART GLYCOSIDES

NONGLYCOSIDE CARDIOTONIC DRUGS (Dobutamin)

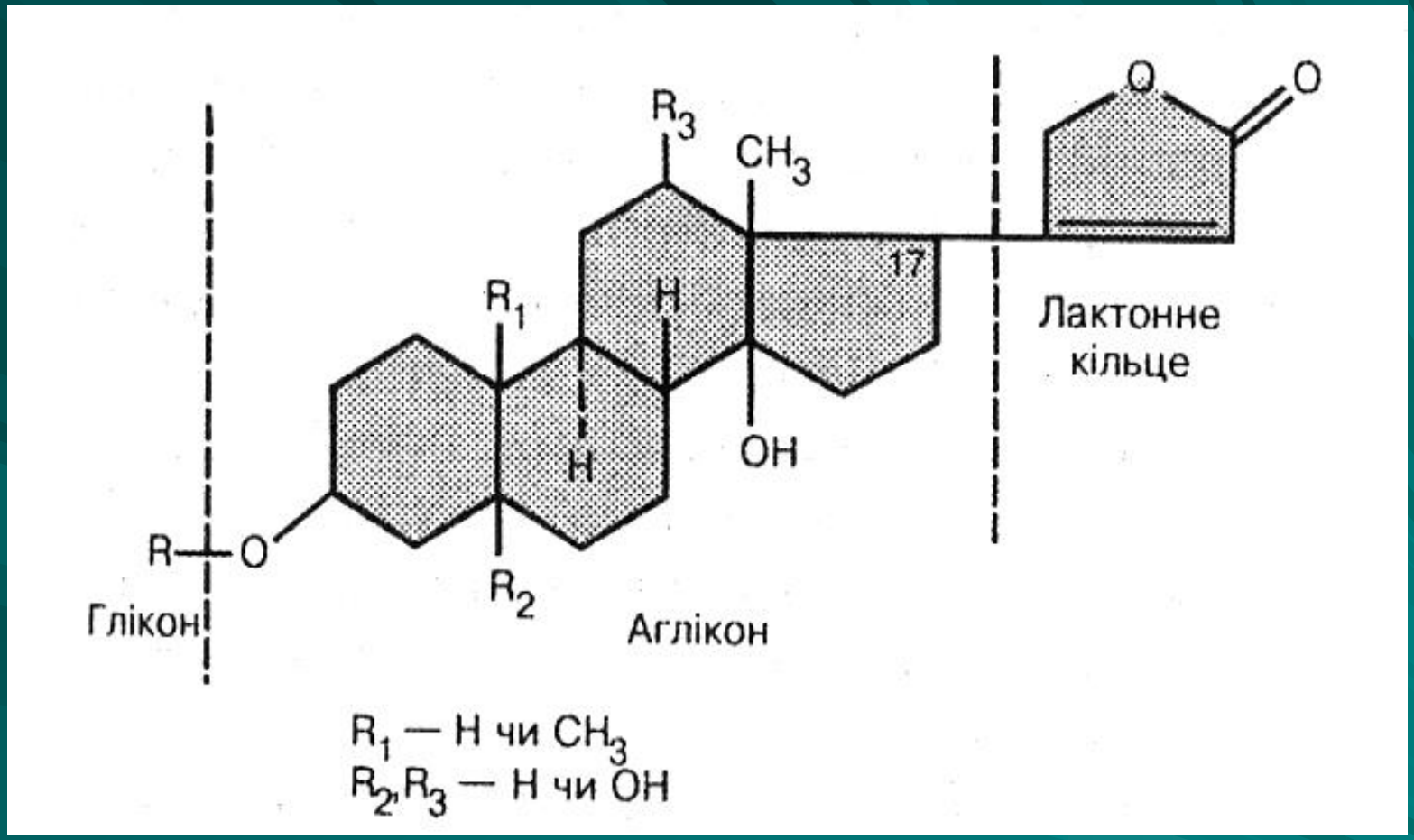
HEART GLYCOSIDES

Purple Foxglove

Foxglove

Lily of the valley

Lychnis



Chemical structure of heart glycosides

Pharmacodynamics

Cardiac action

Extracardiac action

Cardiac action

- Positive inotropic
- Positive bathmotropic
- Negative chronotropic
- Negative dromotropic

ECG changes under the influence of HG

- **Changes which correlate to positive innotropic action**

Narrowing QRS complex

Decreasing ST

T-blip – double-phased, negative

- **Changes which correlate to negative dromotropic action**

Prolongation of PQ interval

- **Changes which correlate to negative chronotropic action**

Increasing of RR interval

MECHANISM OF CARDIOTONIC (POSITIVE INOTROPIC) ACTION OG HG

HG

- **Promote increasing of Calcium ions concentration in myocardiocytes cytoplasm**
  Transport of Ca inside the cell

1. Stimulate exit of Ca from sarcoplasmic reticulum
2. Block K, Na-ATP-ase (braking repolarization)

- **Improve usage of macroergic substances by cells, decrease myocardium need in oxygen**
- **Increase tone of sympatic nervous system**

Extracardiac action of HG

- *Diuretic*
- *Sedative*
- *Stimulating influence on smooth muscles*

Pharmacokinetics of HG

Absorption of HG in gastro-intestinal tract

Digitoxin – 100 %

Digoxin – 60-80 %

Celanid – 15-40 %

Strophanthin – 3-5 %

Pharmacokinetics of HG

- **HG of short action (strophanthin, corglycon)**

- latent period – 5-10 min,
- action duration – 8-12 hours (corglycon), 1-3 days (strophanthin),
- slow intravenous introduction

- **HG of medium action duration (digpoxin, celanid)**

- latent period – 5-30 min. (i.v.), 30-60 min. (orally)
- action duration – 3-6 days
- slow intravenous, oral introduction

- **HG of long lasting action (digitoxin)**

- latent period – 4-12 hours
- action duration – 2-3 weeks
- oral introduction

INDICATIONS FOR INTRODUCTION OF HEART GLYCOSIDES

- They are drugs of choice for patients with systolic dysfunction of myocardium, accompanied by tachysystolic form of atria fibrilation
- Patients with III and IV FC (according to NYHA) of chronic heart insufficiency, in case of transferring of II FC into III FC
- Supraventricular tachycardia and tachyarrhythmia

Improving of disease currency, life quality, increasing of tolerance towards physical loads, but absence of influence on mortality level in patients with CHI

MECHANISM OF TREATMENT ACTION OF HG IN CASE OF HEART INSUFFICIENCY

- Increasing of systolic and minute volumes of heart activity
- Improving of circulation in lung and organic circulation circles, decreasing of CBV, excretion of surplus liquid from the organism
- Elimination of hypoxia and metabolic acidosis in tissues

The following manifestations testify about therapeutic action of HG:

1. Improving of general condition of the patient (decreasing of weakness, short breath, sleep normalization, disappearing of edema, cyanosis, etc.)
2. Tachycardia transforms into normo(brady)cardia
3. Increasing of diuresis
4. Typical changes in ECG

TREATMENT WITH HEART GLYCOSIDES – 2 stages

STARTING DIGITALIZATION (PERIOD OF SATURATION OF THE ORGANISM WITH THE DRUG)

The aim is to reach full dose of action in the organism of the patient (effective therapeutic dose) of HG

SUPPORTIVE THERAPY

The aim is to support the full dose in the organism of the patient

AVERAGE FULL DOSES OF ACTION OF HG

- Strophantin – 0,6-0,7 mg
- Celanid – 2 мг (i.v.), 5 mg (orally)
- Digoxin – 2 mg (i.v.), 3 mg (orally)
- Digitoxin – 2 mg

Real full doses of action in certain patients can differ from the average full dose of action for 50-200 %

Schemes of digitalization

- **Fast (1-2 days)**
- **Medium (3-4 days)**
- **Slow (more than 5 days)**

Nowadays rather often heart glycosides are administered from the beginning of treatment in supportive doses:

digoxin – 0,125-0,75 mg/day (digitalization lasts for 5-7 days),

digitoxin – 0,1-0,15 mg/day (digitalization lasts for 25-30 days)

HG according to level of positive inotropic action

strophantin > celanid > digoxin > digitoxin

according to level of negative chronotropic action

digitoxin > digoxin > celanid > strophantin

Contraindications for administration of HG

1. Absolute contraindication – intoxication with HG

2. Other contraindications

- diastolic dysfunction of myocardium
- sinus tachycardia based on thyrotoxicosis, anemia, increased temperature, hypoxia
- insufficiency of aortal valves, isolated mitral stenosis, diffuse myocarditis

Intoxication with heart glycosides

Cardiac symptoms

Worsening of contractive action of myocardium, increasing of circulation insufficiency

Disturbance of heart rhythm

Extracardiac symptoms

Gastro-intestinal
Neurological and psychical
Eye symptoms
Disturbance of kidney function
Allergic reactions
Gynecomastia

Treatment of intoxication

Immediate quitting of HG introduction

Acceleration of HG excretion from GI tract

Correction of hypopotassiumemia

Introduction of unitiol

Treatment of arrhythmia

Oxygen therapy

Factors which promote development INTOXICATION WITH HEART GLYCOZIDES

- **Digitoxin** is a choice drug when HI is combined with **kidney insufficiency**, but contraindicated if liver is damaged (it is metabolized by liver)
- **Digoxin** is not contraindicated even in case of **liver cirrhosis** (it is not metabolized in liver), but contraindicated in case of kidney insufficiency (it is excreted by kidneys)

Intoxication with heart gkycozides

Cardiac symptoms

Worsening of contractive function of myocardium, increasing of circulation insufficiency – relapse of HI (18-26 %)

Disturbance of heart rhythm

(90-95 %, y 65 % - single symptom of intoxication)

- tachyarrhythmia (increasing of automatism)
- blockades
- combined disorders of rhythm

Intoxication with heart glycosides

Extracardiac symptoms

Gastro-intestinal (40-50 %)

Neurological and psychical(25 %)

Eye symptoms (65 %)

Worsening of kidneys function

Treatment of intoxication with heart glycosides

- Immediate quitting of HG introduction
- Correction of hypopotassiumemia (KCl, panangin)
- Introduction of unitiol (1 ml of 5 % solution / kg of weight i.m. 2-3-5 times per day)
- Clearing of GI tract (vaseline oil, cholestyramin, magnesium sulfate)
- Treatment of arrhythmias (anaprilin, verapamil, difenin, lidokain, atropine)
- Na EDTA (trilon B), Na citrate
- Calcitrin
- Antibodies towards digoxin (Digibind)
- Oxygen therapy

NONGLYCOSIDE CARDITONIC DRUGS

- Xantins, derivatives of isoquinoline (ethophiline)
- Pyridines, and bipyridines (amrinon, milrinon)
- Derivatives of imidazole (vardax)
- Derivatives of piperidine (buquineran, carbazeran)
- Polypeptides (glucagon)
- Carboxyl antibiotics (lasolacid, calcimycin)
- Derivatives of other chemical groups: L-carnitin, heptaminol, creatinol-o-phosphate, trapidil, etc.

NONGLYCOSIDE CARDIOTONIC DRUGS

- Dobutamin – beta$_1$-adrenomimetic - in case of acute and chronic heart insufficiency – intravenously dropping – 2,5-5-10 mcg/(kg.min); in case of constant infusion tolerance develops after 3-4 days; in case of increasing of dose – heart arrhythmias
- Amrinon, milrinon – inhibitors of phosphodiesterase – for temporary improvement of patient's condition in terminal stage of HI

INHIBITORS OF ANGIOTENSINE TRASFORMING ENZYME (IATE)

Captopril, enalapril, ramipril, lysinorpil

In case of HI they brake pathological consequences of activation of renin-angiotesine system by inhibiting ATE:

- **production of angiotensine II** decreases (vasoconstrictor, inductor of aldosterone, norepinephrine, endothelin secretion, myocardium hypertrophy)
- **Accumulation of bradikin** (inductor of prostacycline and nitrogen oxide synthesis)

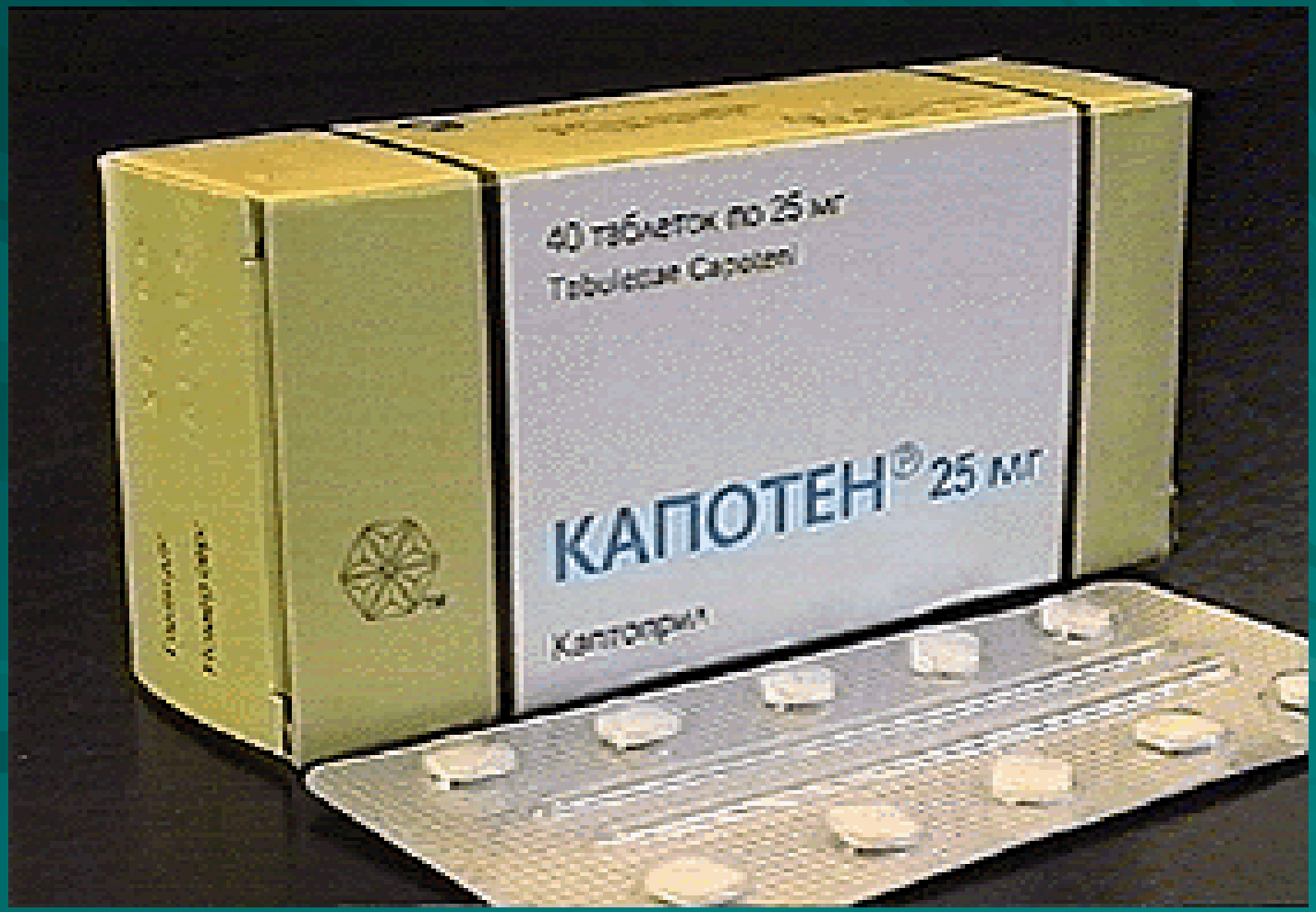
INHIBITORS OF ANGIOTESINE TRANSFORMING ENZYME (IATE)

- Increase duration and improve quality of life of patients with HI
- Increase tolerance towards physical loads
- Decrease risk of recurring MI
- Brake development of miocardium hypertrophy

CAPTOPRIL (CAPOTEN)

- Dose titration: from 6,25-12,5 mg per day to 12,5-50 mg 3 times a day until appearance of effect
- Side effects: dry cough (can be decreased by nonsteroid antiinflammatory), considerable decreasing of AP, worsening of kidneys' function, hyperpotassiumemia, tachycardia, neutropenia, aphtose stomatitis
- Contraindicated in case of bilateral stenosis of kidney arteries, should not be combined with potassium drugs

CAPTOPRIL (CAPOTEN)



ANTAGONISTS OF ANGIOTESINE II RECEPTOS (ARA II)

LOSARTAN (cosaar)

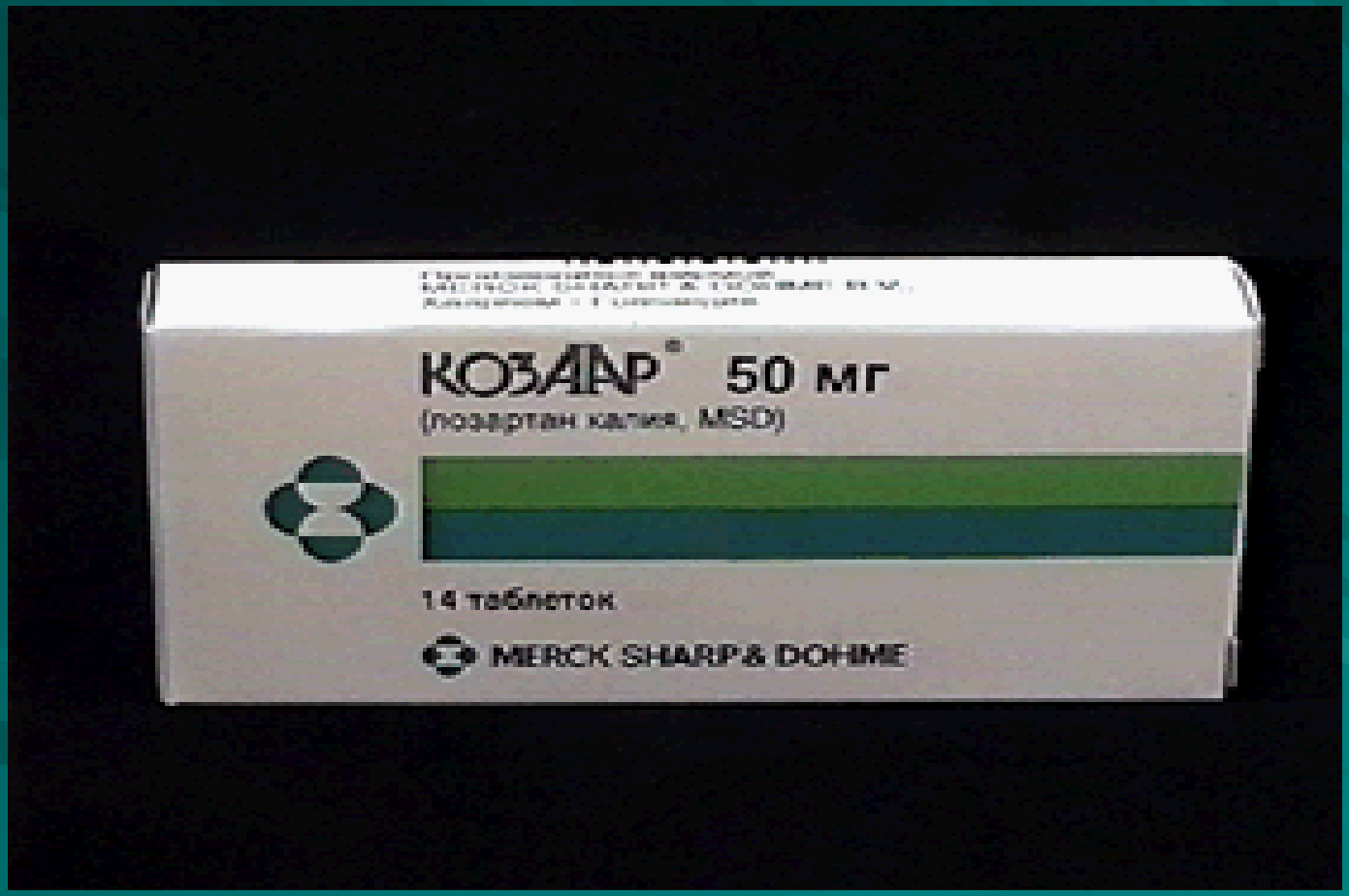
Blocks receptors of angiotensine II

Decreases mortality of patients with HI on 50 %

Breaks development of myocardium hypertrophy

It is approved to combine IATE with ARA II

Losartan (cosaar)



DIURETICS

Dichlotiazide, hyhrotone (oxodoline), clopamide (brinaldix)

Furosemid, etacrine acid

Spironolacton

improve currency of the disease, increase tolerance of patients towards physical loads,

spironolacton decreases quantity of relapses and mortality

PERIPHERAL VASODILATORS

- **Arterial:** hydralasin, calcium ions antagonists, minoxydil
- **Venous:** nitrates, molsidomin
- **Of mixed action** (influence on tone of arterioles and venules): sodium nitropruside, prasosine, inhibitors of ATE, ARA II

Isosorbide dinitrate (30-160 mg/day) +

hydralasin (50-300 mg/day) – for patients which have contraindications towards administration of IATE

PERIPHERAL VASODILATORS

Unfavorable action in case of HI:

They activate sympatic-adrenalsystem and intermediately renin-aldosterone system

BETA-ADRENOBLOCKERS

Carvedili, methoprolol, bisoprolol

They decrease mortality, improve disease currency and quality of patients' lives in case of stagnant HI

Mechanism of treatment action in case of HI

- Renewing of quantity and sensitivity of beta-adrenoreceptors in heart, which leads to increasing of systolic volume after 8-10 weeks of regular administration (paradox of beta-adrenoblockade)
- Prevent calcium overload of myocardium, improve coronary blood circulation
- Decrease production of renin
- Prevent arrhythmias
- Carvedilol – alpha$_1$-adrenoblocking and antioxidant action

BETA-ADRENOBLOCKERS

Scheme of administration of beta-adrenoblockers in case of HI

The treatment is started from a small dose

(3,175-6,25 carvedilol), every 2-4 weeks it is doubled until obtaining the effect (usually develops after 2-3 months).

Average effective doses:

carvedilol – 50 mg

metoprolol – 100 mg

bisoprolol – 5 mg

Administration of beta-blockers is possible only in case of constant condition of the patient, before development of stabile improvement of condition temporary worsening may develop

DRUGS OF METABOLIC ACTION

- Vitamins: E, C, B group
- Ryboxin
- Mildronate
- Phosphaden, ATP
- Creatinphosphate
- Potassium orotate, anabolic steroids

Drugs manifest cardiocytoprotective action, improve energetic metabolism in myocardium

Atp-long 0.01
(Drugs of metabolic influence)

PECULIARITIES OF TREATMENT OF DIASTOLIC DISFUNCTION OF MYOCARDIUM

Indicated:

IATE, ARA II,

Beta-adrenoblockers, calcium ions antagonists

Contraindicated:

Nitrates, diuretics, heart glycosides

Thank you all