Cardiotonic drugs

Cardiotonic drugs are drugs, which increase cardiac contractile force during heart failure. Heart failure (HF) is a pathological state during which cardiac output is inadequate to provide the minute volume needed by the body or relatively normal minute volume and blood supply of the peripheral tissues is provided by the congested load of the heart.

Pathogenesis of HF

In 70 – 75% of the cases disorder of the cardiac systolic function is observed, which depends on the cardiac muscle shortening degree during systole and CO. CO or minute volume of the heart depends on the following hemodynamic 3 factors.

1. End diastolic volume of the ventricles, so called preload, which depends on the circulating blood volume, cardiac blood return, efficiency of the atrial contraction etc. According to the Frank-Starling relation, cardiac contractile force directly proportional to the end-diastolic fiber length of the ventricles. End-diastolic fiber length of the ventricles depends on the preload.
2. Inotropic state of the cardiac muscle, which depends on the tone of the sympathetic nervous system, heart rate, mass of the functioning cardiac muscle, degree of the coronary blood flow.
3. Intracardiac tension, which should form ventricles during contraction to overcome resistance against which the heart must pump blood (so called afterload). Afterload depends on the pressure in aorta and pulmonary arteries, mass of the functioning cardiac muscles, sizes of the ventricular cavities.

During systolic HF pumping function of the ventricles is markedly decreased, during systole ventricles can`t develop sufficient wall tension to pump out an appropriate volume of the blood.

In 25 – 30% of cases a reason for development of HF is a diastolic dysfunction of the ventricles. In this case there is a deterioration of diastolic relaxation or diastolic feeling of the ventricles.
Thus, during HF, deterioration of 3 important hemodynamic factors can be noticed.

a. decrease in cardiac output
b. increase in afterload
c. increase in preload

According to the above mentioned pathogenetic mechanisms of HF, the main goals of the treatment of HF are:

1. Increase in cardiac contraction force (cardiotonic drugs)
2. Reduction of preload and afterload (vasodilators, diuretics, ACE – inhibitors)
3. Regulation of neuro-humoral system and prevention of heart remodeling (β-adrenoblockers, ACE - inhibitors)

**Cardiotonic drugs**

**Classification of cardiotonic drugs:**

1. Cardiac glycosides /CGs/ – Strophanthine, Digoxin, Corglycon
2. Sympathomimetic drugs
   2.1 β-adrenomimetics – Prenalterol, Xamoterol
   2.2 Catecholamines and their derivatives – Dopamine, Dobutamine
3. Phosphodiesterase inhibitors
   3.1 Bipyridine derivatives – Amrinone, Milrinone
   3.2 Imidazole derivatives – Enoximone, Piroximone, Fenoximone
   3.3 Benzimidazole derivatives - Pimobendane
4. Cardiotonic drugs with other mechanism - Vesnarinone, Forskoline

**Demands for cardiotonic drugs are:**

1. Reduction of tachycardia.
2. Absence of increase in oxygen demand of myocardium.
3. Reduction of central venous pressure
4. Absence of action on AV node
5. Efficiency during oral rout of administration and long duration of action
Cardiac glycosides

CGs are drugs of plant origin, don’t contain nitrogen, increase contraction force of the myocardium, without an increase of oxygen demand.

In the medicine CGs were used in 500-1200 years as a vomiting drugs, in 1785 Uitering described and proved their usage.

CGs are derived from Digitalis purpurea, Strophanthus combe, Convallaria majalis and other plants.

Chemical structure of CGs

CGs contain non-sugar part (aglycon or genin) which is considered to be cyclopentanoperhydrophenantrene ring connected with 5-membered lactonic cycle (groups of cardenolids) or 6-membered nonsaturated lactonic cycle (groups of bufadienolids) and sugar part (glycon). The main CGs are considered to be cardenolids. Sugar part consists of widely spread sugars (D-glucose, D-fructose, D-xylose, L-rhamnose) and sugars which are specific and only in CGs (D-digitoxose, D-cymarose, D-oleandrose). The CGs, which contain specific sugar, are metabolized in the liver very slowly, so they have long period of action.

Genin provides pharmacodynamic activity of CGs, but glycone is responsible for pharmacokinetic properties. Polarity and, as a consequence solubility in lipids and water, is stipulated by the quantity of hydroxyl groups. See the picture 1

Classification of CGs

CGs are classified according to their level of polarity.

There are 3 groups:
1. Polar CGs (hydrophilic)- Strophanthine, Corglycone
2. With intermediate polarity - Digoxine, Celanide
3. Non polar CGs – Digitoxine, Gitoxine
Pharmacodynamics of CGs.

The main target of CGs is **Na+/K+ -ATPase**, which is membrane transporter, localized in outer part of sarcolemma and called sodium pump. This protein consists of α - and β – subunits. CGs bind to the sulphhydryl groups of **only phosphorylated form** of α – subunit. In this view an increased level of extracellular K+ ions leads to dephosphorylation of sulphhydryl groups, resulting in decrease of efficacy of CGs. Therapeutic concentrations CGs reversibly inhibit a phosphorylated form of Na+/K+ -ATP-ase in 35%.

**The cardiac effects of CGs are:**

1. Positive inotropic
2. Negative chronotropic
3. Negative dromotropic
4. Positive tonotropic
5. Positive bathmotropic effects
Mechanism of positive inotropic effect

As it’s known, during each depolarization Na\(^+\) and Ca\(^{2+}\) ions enter into the cardiomyocytes. Ca\(^{2+}\) ions enter through the L-type Ca\(^{2+}\) channels, bind to the ryanodine receptors (RyR) which are localized in sarcoplasmic reticulum and increase release of Ca\(^{2+}\) (induced Ca\(^{2+}\)) from the storage. When quantity of Ca\(^{2+}\) is increased in cytoplasm, it interacts with contractile proteins (when the concentration of free Ca\(^{2+}\) ions reaches 10\(^{-6}\) M they inhibit troponin-tropomyosine complex and cause removal of inhibitory effect of this complex on acto-myosin system and provides interaction between actin and myosine). Also Ca\(^{2+}\) ions provide energy, which actomyosine needs for interaction, as they stimulate myosine-ATPase.

During repolarization Ca\(^{2+}\) ions are removed from the cell with the following mechanisms:

1. 3Na\(^+\)/1Ca\(^{2+}\) transporter (NCX): This transporter brings into the cell 3 ions of Na\(^+\) and removes 1 Ca\(^{2+}\)-ion. It doesn’t use ATP-energy, its work depends on intracellular concentration of Na\(^+\) ions. The less is the concentration of intracellular Na\(^+\), the higher is intensity of the removal of Ca\(^{2+}\)-ions and vice versa, in a case of increase of concentration of intracellular Na\(^+\) ions, the intensity of the removal of Ca\(^{2+}\) is decreased even can be stopped.

2. Ca\(^{2+}\)-ATP-ase (SERCA2), which is located in sarcoplasmic reticulum, leading to restoration of Ca\(^{2+}\) in sarcoplasmic reticulum.

3. Ca\(^{2+}\)-ATP-ase, which is located in sarcolemma, removes Ca\(^{2+}\) from the cell.

Besides during repolarization the recovery of resting potential is due to the action of 3Na\(^+\)/2K\(^+\) -ATP-ase. This enzyme removes from the cell 3 ions of Na\(^+\) and and brings 2 ions of K\(^+\). This process is active and needs energy (picture 2)

CGs, binding to sarcolemma Na\(^+\)/K\(^+\) -ATP-ase, decrease the intensity of Na\(^+\) removal from the cell, increasing their concentration in the cell. Increase in intracellular concentration of Na\(^+\) leads to decrease in removal intensity of Ca\(^{2+}\) by the Na\(^+\)/Ca\(^{2+}\) transporter. Decrease of Ca\(^{2+}\) remove and entrance of Ca\(^{2+}\) into the cells during each depolarization causes accumulation of Ca\(^{2+}\) in cardiomyocytes. The accumulated calcium gradually stored in sarcoplasmic reticulum, so during the next depolarization release of calcium is increased which
enhance force of contraction. Therapeutic concentrations of CGs don’t have an action on sarcolemma and sarcoplasmic reticulum’s Ca\(^{2+}\)-ATP-ase

**Picture 2. Mechanism of action of CGs**

![Mechanism of action of CGs](image)

The other mechanisms of CGs positive inotropic effect.

- CG by themselves can increase the level of cytoplasmic Ca\(^{2+}\) ions, as they interact with ryanodine receptors directly and stimulate release of Ca\(^{2+}\) from sarcoplasmic reticulum. This mechanism is typical only for lipophilic CGs.
- The conformational changes of Na\(^+\)/K\(^+\)-ATPase, which is specific for only lipophilic CGs. Due to the conformational changes of this enzyme, lipophilic CGs change the
activity of Na⁺/K⁺-ATPase, as they destroy connection of phospholipids with the enzyme.

**Negative chronotropic effect (frequency of impulse generation in sinus node is decreased) and negative dromotropic effect (slowing down of impulse transmission from sinus node to the AV node).**

**The mechanisms of Negative chronotropic and dromotropic effects are:**

1. Direct inhibition of sinus node /only for negative chronotropic effect/
2. Stimulation of viscero-cardiac reflex due to sensitization of baroreceptors. Positive inotropic effect of CGs leads to strengthening of impulses which are coming from baroreceptors of reflexogenic zones (aortic arch, carotid sinus). As a result impulses, which are coming from baroreceptors, inhibit the activity of sympathetic system, stimulating vagal center. Besides CGs increase the sensitivity of baroreceptors toward different stimuli.
3. Stimulation of cardio-cardial reflex, due to sensitization of heart mechano- and chemoreceptors. Increase of heart contraction force, decrease in end-diastolic pressure of ventricles and amelioration of blood oxygen saturation leads to inhibition of brain sympathetic center and activation of vagal center.
4. Direct stimulation of vagal center
5. Increase of cholinergic neurotransmission due to release of Ach
6. Prolongation of effective refractory period in AV node (only for negative dromotropic effect)

Thus CGs in a case of therapeutic doses lead to primary parasympathomimetic effect. Because atriums comparing with ventricles have richer cholinergic innervation, this effect is prevailed in atriums and AV node, and is minimal in ventricles and Purkinje fibers. Due to negative chronotropic effect of CGs their cardiotonic effect **isn’t accompanied with increase of oxygen demand.** In the same concentrations all CGs have the same cardiotonic effect, but at the same time differ by the negative chronotropic effect. In this view Digitoxin, Digoxin and Celanide have maximal negative chronotropic effect.
In the absence of heart failure the negative chronotropic and dromotropic effects of CGs are slightly expressed.

3. **Positive tonotropic effect**

CGs lead to positive metabolic and hemodynamic changes in heart, increase concentration of Ca$^{2+}$. These effects increase tone of heart muscle.

4. **Positive bathmotropic effect (increase of heart excitability)**

Increase of intracellular Ca$^{2+}$ concentration by CGs leads to spontaneous diastolic depolarization, leading to decrease in excitation threshold of heart conductive system cells and development of different arrhythmmias.

In therapeutic doses of CGs there can be the following ECG findings: moderate prolongation of P-Q interval and decrease of S-T segment.

**Hemodynamic effects of CGs**

CGs have positive effects on hemodynamics:

1. Increase of cardiac output (in spite of bradycardia) due to increased stroke volume which by itself decreases activity of sympathetic nervous system, thus afterload also becomes reduced.
2. Normalization of arterial pressure due to decrease of renin-angiotensin-aldosterone system activity which decreases afterload.
3. Unloading (relief) of veins of big blood circulation, decrease of vein pressure, decrease of sympathetic nervous system, decrease of preload.
4. Decrease of pressure in small blood circulation, decrease of pulmonary oedema, increase of oxygen supply.
5. Increase of blood supply, improvement of rheological properties of blood.

**Effects of CGs on other organs-systems**

CGs can have effects also on other organs, including smooth muscles and CNS. Inhibition of Na$^+$/K$^+$-ATP-ase stimulate both spontaneous activity of neurons and smooth muscles.

**CNS:** Central effects include stimulation of vagus nerve center and chemoreceptors. CGs can cause hallucinations and disorders of color acceptance very rarely.
CGs can stimulate hypothalamus and also peripheral effects of estrogens. Thus very seldom gynecomastia can be observed.

**GIT:** anorexia, vomiting, nausea, diarrhea. Vomiting can be also due to stimulation of trigger zone.

**Urogenital tract:** Effects on kidneys are stipulated by improvement of their blood supply (due to positive inotropic effect) and stimulation of first urine formation. All these effects decrease blood volume and prevent development of peripheral oedema. Also CGs have antialdosterone effect which is provided by the following mechanisms:

- Inhibition of renin secretion,
- An improvement of liver blood supply which neutralizes aldosterone actively.
- As CGs have structural similarity with aldosterone, by negative feedback effect synthesis of aldosterone is decreased.

Antialdosterone action of CGs leads to the reduced production of antidiuretic hormone which brings to the less water and sodium reabsorption, diuretic action and potassium ion retention. Oedemas which are not connected with heart failure can not be treated by CGs.

**Pharmacokinetics of CGS**

The pharmacokinetic properties of CGs are connected with their polarity.

**Polar CGs differ from nonpolar CGs by the following pharmacokinetic properties.**

1. don`t form complexes with the blood plasma proteins
2. have rapid action
3. aren`t accumulated in body
4. have poor solubility in lipids, have good solubility in water.
5. have poor absorption from intestines
6. are excreted mainly by kidneys (nonpolar- mainly by bile)
7. are administered 4 times per day (nonpolar -1-2 times per day)
8. have small volume of distribution (whereas Vd for Digoxin is 6-8 L/Kg)
9. are administered mainly by parenteral rout (nonpolar -by enteral rout)

The food in stomach also can decrease the absorption of Digoxin and Digitalin.
All CGs are mainly accumulated in skeletal muscles, but not in fatty tissues, that’s why in exhausted patients concentration can be increased. Digoxin is mainly excreted in unchanged form by kidneys (by glomelural filtration). That’s why in patients with renal insufficiency the dosage should be decreased. 10% of popularity has intestinal bacteria - *Eubacterium lentum*, which metabolizes digoxin into nonactive metabolite, leading to decrease in its activity. In this view **Lanoxicaps** capsules have higher bioavailability.

**Intoxication by CGs.**

As CGs have narrow therapeutic index the frequency of CGs’ intoxication is very high

**Cardiac symptoms of intoxication**

Develops during inhibition of 60% of Na⁺/K⁺-ATP-ase. In this case the decreased intracellular level of potassium ions (hypokalihiestia) and also hypercalciemia are observed. As the Na⁺/K⁺-ATPase of heart conductive system is 2,5 time more sensitive toward CGs during intoxication cardiac signs are mainly observed as arrhythmias: ventricular extrasystoles, different degrees of atrioventricular conduction blockages.

**Extracardial symptoms of intoxication**

**Dyspeptic symptoms:**
1. Anorexia
2. Vomiting, nausea
3. Abdominal spastic pains, because of increase of vagus tone
4. Probability of development of intestine necrosis due to spasm of mesenteric vessels

**Neurological symptoms**
1. Headache, fatigue
2. Deliriums, convulsions
3. Micro-macropsia, xantopsia, all subjects are seen in yellow or green

**Treatment of CG intoxication.**

At first we should discontinue CGs.

The immediate manipulations are:
1. Usage of physical antagonists (activated carbon or cholestiramine)
2. Prevention of hypokalihistia (panangin or “polar” mixture)
3. Prevention of hypercalciemia (administration of substances which can form complexes: like citrate of sodium, disodium salt of ethylenediaminotetraacetic acid.
4. Antiarrhythmic drugs: administration -lidocaine, beta-blockers
5. Chemical inactivation of blood CGs by the substances which are donators of sulfhydryl groups (unithyol I/M or I/V administration of special antibodies against digoxine and digitoxine `Fab-fragments)
6. When drug treatment is not useful an electroimpulsive therapy.

**Indications**

1. Acute heart failure /which isn`t accompanied with myocardial infarction/, chronic systolic or mixed failure. In this case positive inotropic effect of CGs is used.
2. Paroxysmal supraventricular tachiarrhymtias, fibrillation, flutter of atriums (independently with HF)
3. Prevention HF development (severe pneumonias, different types of intoxications, reumacarditis)

In acute HF the polarized CGs are preferable, in chronic HF – CGs with intermediate polarity.

**Non glycoside cardiotonic drugs**

2. **Sympathomimetic drugs**

**Dopamine** is an endogenous catecholamine.

**Pharmacodynamics.**

Pharmacological and hemodynamic effects of Dopamine are dose-dependent.

**In low doses** (2mcg/kg/min), Dopamine stimulates dopamine receptors D₁>D₂ (cAMP – dependent relaxation) and presynaptic D₂ receptors (decrease of NE release and adrenergic stimulation), dilate the vessels. These receptors are prevalent in mesenterial and renal arteries. In the same doses i/v injection of Dopamine improves renal blood flow and glomerular filtration rate. Also dopamine has direct effects on epithelial cells of renal tubules and through this mechanism also increases urination.
In the middle doses (2-5 mcg/kg/min), Dopamine directly stimulates $\beta_1$-adrenoreceptors increasing cardiac output and stroke volume.

In higher doses (5-15 mcg/kg/min) Dopamine stimulates presynaptic $\beta_2$-adrenoreceptors and increases NE release from presynaptic endings. Through this mechanism tachycardia is developed, sometimes even arrhythmias.

In very high doses (in 15 mcg/kg/min) Dopamine stimulates $\alpha_1$-adrenoreceptors and causes constriction of peripheral arteries and veins, also vessels of kidney. These doses are not used during HF because afterload of heart becomes increased, which worsens HF.

Pharmacokinetics. Dopamine is used only i/v. Effect is maintained 10 min, as it’s neutralized by MAO very quickly. It’s eliminated through the kidney.

Side effects. Tachycardia (compared to Dobutamine it’s more significant), arrhythmias, worsening of peripheral arterial diseases, nausea, vomiting. In higher doses probable stomach bleedings, impairment of peripheral blood supply, even gangrene development. In asthmatic patients it can provoke bronchial asthma attacks. Treatment with dopamine should last not more than 2-3 days, as it causes tolerance /tachyphylaxis/.

Indications:

1. Resistant HF,
2. Cardiogenic shock or acute myocardial infarction,
3. Traumatic, toxic, postoperative, hypovolemic shock.

Dobutamine

Pharmacodynamics: Dobutamine has a selective $\beta_1$-adrenomimetic action. I/V injection of Dobutamine increases stroke volume of the heart. Also peripheral resistance and resistance of vessels of small blood circulation become decreased, renal and coronary blood flow is improved, excretion of sodium ions and water becomes stimulated.

Pharmacokinetics. Half life period of Dobutamine is about 2-3 min as it’s inactivated by MAO. During 2-3 days tolerance is developed.

Side effects. Tachycardia, arrhythmias, retrosternal pains, hypertension, vomiting, nausea, phlebitis in the place of injection.
Indications:
1. Acute HF conditioned by the acute myocardial infarction
2. Aggravation of chronic HF
3. Cardiogenic shock
4. Surgical interventions of the heart
5. Bleeding
6. Sepsis

β-Adrenomimetics

Prenalterol and Xamoterol are selective β1-adrenomimetics, increase heart stroke volume and oxygen demand, have also moderate diuretic effect.

The above mentioned 2 drugs haven`t clinical practice, because by increasing heart oxygen demand, increase heart energetic processes, exhausting heart.

3. Phosphodiesterase inhibitors (PDI)

These drugs are Amrinone, Milrinone, Enoximone, Piroximone, Fenoximone, Pimobendane etc.

Pharmacodynamics. 7 types of phosphodiesterases (PD) are studied. These drugs block the third type of PD, which provides hydrolyses of cGMP-dependent cAMP. Due to these drugs, accumulation of cAMP is mentioned, which is activator of calcium channels in sarcolemma and sarcoplasmatic reticulum and increases calcium ions quantity in myofibrils. Derivatives of bipyridins amrinone (INOKOR) and milrinone (KOROTROP) have no effects on heart rate, they increase force of contraction, dilate resistant and capacitive vessels and decrease pre- and afterload. Also they stimulate lipolysis, inhibit aggregation of thrombocytes and production of cytokins. Milrinone is 10 times more active than amrinone.

Pharmacokinetics

These drugs can be administered both per os and i/v injections. Half-life period of amrinone is 2-3 hours, of milrinone is 30-60 min, but in HF effects can be prolonged by 2 times.
Side effects: Amrinone compared to milrinone has more side effects like vomiting, nausea, arrhythmias, toxic damage of hepatocytes and cells of bone marrow. In some cases it can cause severe thrombocytopenia. Also it was described that the long-term usage of PDI increases mortality in 2 times. That’s why it is not recommended to use these drugs for the long time.

Indications
1. Chronic heart failure, when classical treatment is non effective.
2. Acute cardiac insufficiency
   Benzimidazole derivative - Pimobendane, besides inhibition of PDE, increases also actomyosine sensitivity toward Ca2+ ions.

4. Cardiotonics with the different action mechanism

Vesnarinone induces opening of potential dependent Na and Ca channels, prolongs action of potential in heart muscle cells. It mainly inhibits PD III in heart and kidneys. It has positive inotropic effect, decreases heart rate and has antiarrhythmic and week vasodilating effects.

List of drugs

**Strophanthin** 0,05%-1ml ampouls for injections

**Digoxin** /generic, Lanoxicaps, Lanoxin/ 0.125, 0.25 mg tablets; 0.05, 0.1, 0.2 mg capsules; 0.1, 0.25 mg/ml for injections

**Dobutamine** (generic, Dobutrex) 12.5 mg/ml 20ml flacons

**Dopamine** (generic, Intropin) 40 mg/ml 5 ml ampouls

**Milrinone** (generic, Primacor) 1 mg/ml for i/v injections; 200 mkg/ml, for i/v injections droply

**Amrinone** 20 ml ampules, for i/v injections
Sample of tests

Mention the drugs which are cardiac glycosides:
1. cardiac glycosides
2. sympathomimetics
3. ACE-inhibitors
4. inhibitors of phosphodiesterase enzyme
5. nitrates
a) 1,2,4  b) 2,3,4  c) 1,2,5 d) all  e) 1,2,3

Polarized glycosides are:
1. Strophanthine
2. Digitoxine
3. Celanide
4. Convalatoxin
5. Gitoxin
a) 1,2  b) 2,3,4  c) 1,2,5 d) all  e) 1,4

Which properties belong to amrinon?
1. increase of force of construction of heart
2. decrease of force of construction of heart
3. decrease of pre- and afterload
4. inhibition of PhDE III enzyme
5. inhibition of PhDE II enzyme
a) 1,3,4  b) 2,3,4  c) 1,2,5 d) all  e) 1,2,3

Treatment of cardiac failure include:
1. increase of force of construction of heart
2. decrease of preload
3. increase of afterload
4. regulation of cardiac rhythm
5. treatment of anemia
   a) 1,2,4  b) 2,3,4  c) 1,2,4,5 d) all  e) 1,2,3

Therapeutic doses of cardiac glycosides inhibit:
   a) Na⁺/K⁺ - ATP-ase enzyme
   b) Ca²⁺ - channels
   c) K⁺ - channels
   d) Ca²⁺ – dependent ATP-ase
   e) Na⁺ - channels