Effect of drugs on heart rhythm

The activity of the heart' is controlled by the autonomic nervous system via mediators. The mediator of the sympathetic nervous system is noradrenaline, the mediator of the parasympathetic nervous system is acetylcholine. Cardiac activity is also influenced by adrenaline from the adrenal gland. Acetylcholine depresses cardiac activity, while noradrenaline has an excitatory effect on the heart. The effect of mediators is mediated by specific receptors located on the cell membrane. Cardiac function depends on the presence of calcium in the extracellular space and in the endoplasmic reticulum.

Drugs that affect the rhythm (and other functions) of the heart pump include, but are not limited to, **cardioinhibitors**, **cardiotonics** and **antiarrhythmics**.

Cardioinhibitors

Cardioinhibitors' (heart-lowering drugs) exert negative chronotropic (by lowering heart rate) and inotropic (by lowering the contractility of the heart muscle) effects, leading to a reduction in cardiac output and blood pressure. These changes reduce cardiac activity and thus myocardial oxygen consumption. The mechanisms of action of these drugs also include a reduction in electrical conduction (negative dromotropic action).

The mechanical and metabolic effects of these drugs predispose them to the treatment of hypertension, angina and myocardial infarction. In addition, their effect on the electrical activity of the heart makes them suitable for the treatment of cardiac arrhythmias[1]. Some cardioinhibitors (especially certain β-blockers) are used in the treatment of heart failure.

Hypertension

Is caused by an increase in cardiac output or an increase in systemic vascular resistance. Cardioinhibitors reduce the heart rate and pulse volume, leading to decrease in cardiac output and thus a decrease in blood pressure.

Angina and myocardial infarction

Cardioinhibitors (by reducing heart rate, contractility and arterial pressure) reduce the work of the heart and its oxygen requirements. They can thus relieve the patient from anginal pain, which is most often due to lack of oxygen during heavy exertion. The importance in the treatment of myocardial infarction lies not only in the increase in the ratio of oxygen supply to oxygen demand, but also in the ability to inhibit postinfarction remodelling of cardiac tissue[1].

Cardiac Arrhythmias

Cardioinhibitors alter pacemakers activity and conduction of excitation through the heart, and are therefore useful in the treatment of arrhythmias caused by both abnormal pacemaking and abnormal conduction of excitation[1].

Heart Failure

Although it may seem paradoxical that cardioinhibitors would be used in heart failure, where the myocardium is functionally depressed, clinical studies have shown that certain cardioinhibitors have been shown to improve cardiac function in certain types of heart failure[1]. This effect may derive from their blocking the excessive sympathetic effects on the heart that damage the failing heart.

Classes of drugs and their general mechanisms of action

Clinically used cardioinhibitors can be divided into three groups: beta-blockers, calcium channel blockers, and centrally acting sympatholytics.

Beta-blockers (beta-adrenergic receptor antagonists)

Bind to **β-adrenergic receptors** in the conduction system and in the working myocardium. Both β-1 and β-2 adrenoceptors are found in the heart. However, β-1 adrenoceptors predominate in number and function. These receptors primarily bind noradrenaline released from sympathetic adrenergic nerve endings. In addition, they bind adrenaline and noradrenaline circulating in blood. β-blockers prevent binding of these ligands to the receptors by competing with them for the binding site. They reduce the effects of sympathetic (i.e., they are sympatholytics), which normally stimulate chronotropy, inotropy, and dromotropy. Their effect even increases if sympathetic activity is increased. Clinically used β-blockers are either **non-selective** (β-1 or β-2) blockers or relatively **selective'** β-1-

blockers (the relative selectivity may disappear at higher drug doses). Some of the β-blockers have additional effects beyond β-blocking. The third generation of &beta-blockers are agents that have additional vasodilator effects by acting on the α-adrenoceptors of blood vessels.

Some beta-blockers, after binding to the β-adrenoceptor, partially activate this receptor while preventing the binding of noradrenaline. Thus, these so-called **partial agonists** (partial &beta blockers) provide some background sympathetic activity even though they prevent normal or enhanced sympathetic effects. We refer to them as carriers of intrinsic sympathomimetic activity (***intrinsic sympathomimetic activity, ISA***). Some of the β-blockers also carry membrane stabilizing activity (*MSA*), which is also found in sodium channel blockers belonging to the antiarrhythmic drugs.

The β-adrenoceptors are coupled to **Gs-proteins** that activate **adenyl cyclase**. The increase in cAMP activates **cAMP-dependent protein kinases** (PK-A), which phosphorylate calcium channels, causing increased calcium flux into the cell. The increase in intracellular calcium during action potentials leads to increased calcium release from the sarcoplasmic reticulum, ultimately increasing inotropy (contractility). Gs-protein activation also leads to an increase in the frequency of cardiac contractions (chronotropy). PK-A protein kinases also phosphorylate parts of the sarcoplasmic reticulum, leading to increased calcium release through *ryanodine receptors* (ryanodine-sensitive calcium channels) associated with the sarcoplasmic reticulum. This provides more calcium for its binding to troponin-C, increasing inotropy. PK-A may further phosphorylate myosin light chains, which may contribute to the positive inotropic effect of β-adrenoceptor stimulation. They are used to treat hypertension, angina, myocardial infarction and arrhythmias[1].

Hypertension

The β-blockers lower arterial blood pressure by reducing cardiac output. They may thus represent an effective treatment for hypertension, especially when used together with diuretics[1]. Hypertension in some patients is caused by emotional stress, which activates the sympathetic nervous system, and in others by, for example, pheochromocytoma, which increases the level of circulating catecholamines. Even in these cases, treatment with β-blockers is successful. In addition, &beta-blockers inhibit the activity of the renin-angiotensin-aldosterone system. Acute treatment with &beta-blockers is not very effective in lowering blood pressure because of the compensatory increase in vascular resistance in the systemic circulation. The hypotensive effect of agents of this group is detectable within the first few days of treatment, but they achieve their full effect only after 2-3 weeks of administration[2].

Angina and myocardial infarction

The antianginal effect of β-blockers is attributed to their depressant effect on heart rate, contractility and their hypotensive effects. β-blockers reduce cardiac work and thus the need for myocardial oxygen saturation (see above).

Cardiac Arrhythmias

The antiarrhythmic properties of β-blockers (class II antiarrhythmics) are related to their ability to inhibit the influence of sympathetic activity on cardiac activity. Sympathetic increases the frequency of excitations in the sinoatrial node, which increases sinus rhythm. It also increases the rate of impulse transmission to the ventricular myocardium and stimulates the generation of ectopic excitations. These sympathetic effects are mediated mainly through β-1-adrenoceptors. Therefore, β-blockers may reduce these effects, thereby reducing sinus rhythm, atrial conduction velocity (which may block reentry mechanisms), and inhibit abnormal pacemaker activity. The β-blockers also affect non-pacemaker action potentials by increasing action potential duration and relative refractory period. This effect may play a major role in preventing arrhythmias caused by the reentry phenomenon[1].

Heart Failure

The majority of heart failure patients suffer from systolic dysfunction, i.e., the contractile function of the heart is limited (i.e., loss of inotropy). Although it is not entirely clear by what mechanism β-blockers help in heart failure, it is certain that they improve cardiac function and reduce mortality[1].

Classes of β-blockers and specific drugs, clinical uses.

Class/Drug	HTN	Angina	Arrhy	IM	CHF	Comment
indiscriminate β-1/2						
carteolol	X					ISA; long-acting; also used in glaucoma
carvedilol	X				X	α-blocking effect
labetalol	X	X				ISA, α-blocking effect
nadolol	X	X	X	X		long acting
penbutolol	X	X				ISA
pindolol	X	X				ISA, MSA
propranolol	X	X	X	X		MSA; typical β-blocker
sotalol			X			even more effects
timolol	X	X	X	X		even more effects
β-1-selective						
acebutol	X	X	X			ISA
atenolol	X	X	X	X		
betaxolol	X	X	X			MSA
bisoprolol	X	X	X			
esmolol	X		X			particularly short effect
metoprolol	X	X	X	X	X	MSA

Abbreviations: HTN - hypertension, Arrhy - arrhythmia, IM - myocardial infarction, CHF - congestive heart failure, ISA - intrinsic sympathomimetic activity

Calcium-channel blockers (CCBs)

Bind to **L-type calcium channels** (slow calcium channels[2]) in the membrane of cardiomyocytes and nodal tissue. These channels are responsible for regulating calcium influx into the myocardial cell, which stimulates its contraction. In cardiac nodal tissue (SA and AV node), these channels have a role in pacemaker currents and the initial phase of action potential generation. Thus, by blocking the entry of calcium into the cell, these drugs act negatively inotropic (reduce the force of cardiac contraction), negatively chronotropic (reduce heart rate) and reduce the rate of impulse transmission through the cardiac conduction system (negatively dromotropic especially on the AV node). In vascular smooth muscle, they induce relaxation and a decrease in peripheral resistance with a decrease in blood pressure[2]. They are used in the treatment of hypertension, angina pectoris and arrhythmias.

Hypertension

By causing relaxation of smooth muscle in the vessel wall, CCBs reduce systemic vascular resistance, thereby lowering blood pressure. These drugs act mainly on arterial resistance vessels, with minimal effect on venous capacitance vessels[1].

Angina

The antianginal effects of CCBs are derived from their vasodilatory and cardiac action suppressing effects. Systemic vasodilatation reduces arterial pressure, leading to a reduction in ventricular afterload, thereby reducing oxygen demand. The more cardiac-selective CCBs (verapamil and diltiazem) reduce heart rate and myocardial contractility, making them (by virtue of reduced myocardial oxygen requirements) excellent anti-angiogenic drugs[1]. CCBs can also cause dilation of the coronary arteries, thus preventing their spasm (Prinzmetal's angina).

Cardiac Arrhythmias

The antiarrhythmic group of CCBs (class IV antiarrhythmics) act mainly by reducing the rate of conduction of the impulse and prolonging repolarization, especially in the atrioventricular node. Delayed AV node action helps to prevent the reentry mechanism that can cause supraventricular tachycardia.

Classes of calcium channel blockers

There are three classes of CCBs. They differ not only in their basic chemical structure but also in their relative selectivity for cardiac or vascular calcium channels. Most CCBs acting on vascular smooth muscle are **dihydropyridines**. Thus, they are mainly used to reduce vascular resistance and blood pressure, i.e., to treat hypertension. They are not used for the treatment of angina pectoris, because of their strong vasodilatory and pressure-lowering effect, which can lead to reflex cardiac stimulation (tachycardia and increased inotropy) leading to a dramatic increase in myocardial oxygen consumption. Dihydropyrimidines include the following specific drugs:

- ***amlodipine***;
- ***felodipine***;
- ***isradipine***;
- ***nikardipin***;
- ***nifedipine***;
- ***nimodipin***;
- ***nitrendipin***.

(Note: some newer agents such as amlodipine and isradipine are also referred to as second-generation dihydropyridines[2]*.)'*

Non-dihydropyridines' include two other classes of CCBs. ***Verapamil*** (phenylalkylamine class) is relatively selective for the myocardium and is less effective as a systemic vasodilator. This drug is very important in the treatment of angina and arrhythmias. ***Diltiazem*** (benzothiazepine class) represents an intermediate step between verapamil and dihydropyridines in terms of selectivity for vascular calcium channels. It reduces heart rate and has vasodilatory effects. By these mechanisms, it is able to lower blood pressure without causing the same degree of reflex cardiac stimulation as dihydropyridines[1].

Side effects and contraindications

Dihydropyridine CCBs may cause congestion, headache, excessive hypotension, edemas and reflex tachycardia. In terms of activation of sympathetic reflexes and lack of direct effects on the heart muscle, they are not well suited to the treatment of angina[1]. Long-acting dihydropyridines have been shown to be safer antihypertensives due to reduced reflex responses. Cardioselective non-dihydropyridine CCBs may cause excessive bradycardia, impaired electrical conduction (AV node block) and reduced contractility. Therefore, they should not be used by patients with chronic bradycardia, cardiac conduction disturbances, or heart failure. CCBs (especially non-dihydropyridines) should also not be prescribed to patients being treated with β-blockers[1].

Centrally acting sympatholytics

Sympatholytics have a major role in the regulation of arterial blood pressure. It increases heart rate (positive chronotropic effect), myocardial contractility (positive inotropic effect), and the rate of conduction of excitation in the heart (positive dromotropic effect). The adrenergic sympathetic fibers that innervate the heart and blood vessels are postganglionic efferent nerve fibers. The cell bodies of these nerves are located in the prevertebral and paravertebral sympathetic ganglia. The preganglionic sympathetic fibers that lead to the ganglia from the spinal cord originate in the medulla oblongata of the brainstem. Here are located sympathetic excitatory neurons that have significant basal activity, which confers a certain tone to the heart under basal conditions. These neurons receive signals from other, vagal neurons of the nucleus tractus solitarii (receiving signals from peripheral baroreceptors and chemoreceptors) and from neurons in the hypothalamus. Together, this neuronal system regulates sympathetic (and parasympathetic) transmission to the heart and blood vessels. Sympatholytic drugs can block the sympathetic adrenergic system at three levels. The first, *peripheral sympatholytics* - antagonists of α and β-adrenoceptors - block the influence of noradrenaline on the effector organ (heart or blood vessels). The others are so-called **ganglion blockers**, which block impulse transmission in the sympathetic ganglia. The third group consists of drugs that block sympathetic activity within the brain. These are called **centrally acting sympatholytics**.

Centrally acting sympatholytics block sympathetic activity by binding and activating α2-adrenoceptors in the membrane of the cells of the medulla oblongata that regulate cardiac activity. This reduces the sympathetic effect on the heart and results in a decrease in cardiac output. These drugs are only used to treat hypertension[1].

Therapeutic indications

Centrally acting α2-adrenoceptor agonists are used to treat hypertension but are not used as first choice drugs due to their side effects when acting in the brain. They are usually prescribed in combination with diuretics to prevent fluid accumulation that would increase blood volume and thus reduce the effect of the drug. These drugs are suitable for patients with renal disease as they do not affect renal function[1].

Specific Medicines

Several different centrally acting antihypertensive drugs are used in clinical practice:

- ***clonidine***;
- ***guanabenz***;
- ***guanfacine***;
- ***α-methyldopa***.

Clonidine, guanabenz and guanfacine are structurally similar drugs and have identical antihypertensive effects. α-Methyldopa is a structural analogue of dopa and must first be converted to α-methynoradrenaline, which only acts as an agonist of α-2-adrenoceptors in the medulla oblongata and reduces sympathetic irritation. α-Methyldopa is the drug of choice for the treatment of hypertension in pregnancy, where its teratogenicity[1] has not been demonstrated.

Side effects and contraindications

Side effects of centrally acting sympatholytics include sedation, xerostomia, bradycardia, orthostatic hypotension, impotence, and nausea. Swelling may occur with prolonged therapy.

Cardiotonics

Cardiotonics (cardiostimulants) potentiate heart function by increasing heart rate (chronotropy) and myocardial contractility (inotropy), which increases cardiac output and arterial pressure. Many of them also have a positive dromotropic and lusitropic effect. Some of these drugs cause systemic vasodilation, while others have vasoconstrictive effects. The effects of these drugs on the heart muscle predispose them to use in heart failure, cardiogenic shock and hypotension[1]. In the treatment of heart failure, procedures that reduce the demands on myocardial function are preferred over cardiotonics- ie reduce afterload or preload, or both (diuretics, organic nitrates, calcium channel blockers, ACE inhibitors). [2]

Heart failure and cardiogenic shock

The main cause of heart failure and hypotension caused by acute heart failure (cardiogenic shock) is loss of myocardial contractility, which leads to reduced organ perfusion and hypotension. Cardiac function can be improved by reducing afterload, increasing preload (increased fluid volume) and increasing cardiac contraction. Cardiotonics work by this mechanism. Sympathomimetics or phosphodiesterase inhibitors are used for short-term therapy and may be harmful if used for a long time [1]. In contrast, cardiac glycosides (digitalis and others) are safe and effective in the long-term treatment of heart failure[1].

Circulatory shock

It is a form of shock caused by hypovolemia (for example in bleeding conditions) or vasodilation during infection (septic shock). Cardiotonics, especially sympathomimetics such as beta-agonists, are used to improve (ie increase) blood pressure. They are often used in conjunction with infusions and vasoconstrictor drugs.

General classes of drugs and their mechanisms of effect

Cardiotonics can be divided into four basic classes: beta-adrenoceptor agonists (beta-agonists), cardiac glycosides (digitalis and others), phosphodiesterase inhibitors and calcium sensitizers.

Beta-agonists

These are sympathomimetics that bind to cardiac β-adrenoreceptors. Activation of β-1 and β-2 adrenergic receptors leads to an increase in heart rate and contractility, which increases cardiac output. Their activation also has a positive dromo- and lusitropic effect. These drugs are indicated for both acute and refractory heart failure and circulatory shock. B-Adrenoceptor agonists bind to β-receptors in the heart and smooth muscle. They also have effects in tissues other than the heart, especially in the smooth muscle of the bronchi (relaxation), liver (stimulating glycogenolysis) and kidney (stimulating renin release). They therefore cause cardiac pacing (increased heart rate, contractility, rate of transfer, relaxation) and systemic vasodilation. An increase in arterial pressure may occur, but not necessarily, as a decrease in vascular resistance interferes with an increase in cardiac output. Thus, the final effect on blood pressure depends on the relative effect on cardiac or vascular receptors [1]. β-agonists cause β-receptor down-regulation, which limits their use to short-term. As they are catecholamines (and have low bioavailability), they must be administered by intravenous infusion[1].

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The principle of operation of β-adrenergic receptors - see above.
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Specific drugs and their therapeutic use

The table shows several different β-agonists that are used clinically to treat heart failure and circulatory shock. These are either natural catecholamines or their analogues. Almost all have a certain degree of α-agonist activity. For some of these drugs, receptor selectivity is highly dose dependent.

β-agonists

Medicine	Receptor selectivity	Clinical use	Comment
Adrenaline	β-1 = β-2> α-1 = α-2	Anaphylactic shock; cardiogenic shock; cardiac arrest;	Low doses cause cardiac pacing and vasodilation. It has a vasoconstrictive effect at high doses.
Noradrenaline	β-1 = α-1 > β-2 = α-2	Severe hypotension; septic shock	Reflex bradycardia masks the direct stimulatory effects on the SA node.
Dopamine	β-1 = β-2 > α-1	Acute heart failure, cardiogenic shock and acute renal failure	Biosynthetic precursor of noradrenaline, stimulates its release. At low doses, it stimulates the heart and reduces systemic vascular resistance. It has a vasodilating effect at high concentrations.
Dobutamine	β-1 > β-2 > α-1	Biosynthetic precursor of noradrenaline, stimulates its release. At low doses, it stimulates the heart and reduces systemic vascular resistance. It has a vasodilating effect at high concentrations.	The effect is cardiac pacing with weak vasodilation.
Isoproterenol	β-1 = β-2	Bradycardia and AV block.	The effect is cardiac pacing and vasodilation with little change in pressure.

Side effects and contraindications

The main side effect of β-agonists is cardiac arrhythmias. Because they increase myocardial oxygen demand, they can accelerate the development of angina pectoris in patients with coronary artery disease. They can also cause headache and tremors[1].

Cardiac glycosides (digitalis)

They have been used for more than 200 years to treat heart failure. They represent a family of compounds derived from the plant *Digitalis purpurea* (foxglove). These drugs inhibit Na + / K + ATPase in cardiac sarcolemma, leading to an increase in intracellular calcium through the Na + / Ca 2+ -exchange system. The increase in intracellular calcium subsequently stimulates the release of additional calcium from the sarcoplasmic reticulum, its binding to troponin C, which increases contractility.

Due to the long half-life of digitalis, this fact should be considered when dosing. It should be administered for several days to reach its therapeutic plasma level (0.5-1.5 ng / ml[1]).. Digitalis has a relatively narrow therapeutic window. Plasma concentrations higher than 2.0 ng / ml can be toxic [1]. Digitalis toxicity is manifested by (sometimes life-threatening) cardiac arrhythmias. Digibind (immune mechanism) or potassium supply are used to reduce digitalis levels (especially if toxicity is associated with hypokalemia).

Therapeutic use:

Heart failure

Digitalis compounds have cardiotonic effects and are used in heart failure. Although new and more effective drugs are already available, digitalis is still widely used. Clinical studies in patients with heart failure have shown that digoxin, when used in combination with diuretics and vasodilators, increases cardiac output and ejection fraction and reduces filling and capillary wedge pressures [1]. This reduces congestion in the lungs and the risk of edema. Heart rate changes slightly. These effects are expected with a drug that increases inotropy.

Atrial fibrillation a flutter

Atrial fibrillation a atrial flutter lead to an accelerated ventricular rate that can affect their filling (reducing their filling time). Digoxin and other drugs in this group are useful in reducing the ventricular rate, which was initiated by the increased rate of atrial contractions. The mechanism of this beneficial action of digoxin is its parasympathomimetic effect. Activation of the vagus can reduce the rate of conduction through the atrioventricular node to the point that some impulses are blocked. A smaller number of pulses is then fed to the chambers and the frequency of the chamber contractions decreases. In addition, digoxin increases the relative refractory period in the AV node.

Specific drugs from the group of glycosides

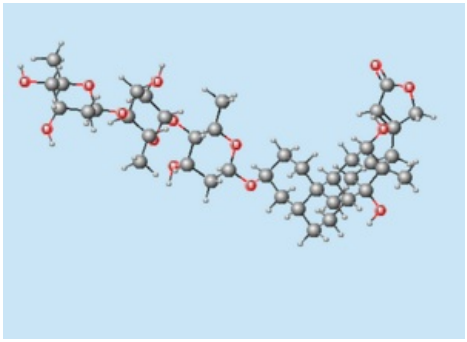
Drug	Oral absorption	Half time (hours)	Elimination
Digoxin	75 %	40	kidneys
Digitoxin	>90 %	160	liver
Oubain	0 %	20	kidneys

Note: Oubain is no longer used today. [2]

Side effects and contraindications

The most significant side effect of digitalis is cardiac arrhythmias, especially atrial tachycardia and atrioventricular block. The drug is contraindicated in patients with hypokalemia, AV block or Wolff-Parkinson-White syndrome. Impaired renal function leads to increased plasma concentrations of digitoxin as it is eliminated by the kidneys.

Phosphodiesterase inhibitors



Digoxin

These are drugs that inhibit the enzyme(**cAMP-dependent phosphodiesterase, PDE**) responsible for reducing cAMP. This leads to an increase in cAMP levels, which has a positive inotropic and chronotropic effect in the heart. cAMP is the second messenger in the pathway initiated by the binding of catecholamines to beta1-adrenergic receptors coupled to Gs-proteins. This is followed by activation of the adenyl cyclase and the formation of cAMP. cAMP (by reaction with other intracellular messengers) increases contractility, heart rate and conduction velocity.

These drugs are used to treat acute and refractory heart failure, but not chronic heart failure. The drugs used target cAMP-dependent phosphodiesterase (PDE3) isoform 3 [1].

Therapeutic indication

The pacing and vasodilatory properties of PDE3 inhibitors predispose them to the treatment of heart failure. Artery dilation reduces the afterload of a failing ventricle and leads to an increase in ejection fraction and organ perfusion. Reduction of afterload leads to a secondary decrease in preload, which increases the mechanical efficiency of the dilated heart and reduces the oxygen requirements of the failing myocardium. The pacing effect of these drugs increases inotropy, which leads to an increase in heart rate and ejection fraction. However, tachycardia is also the result, so drugs are dosed to minimize the positive chronotropic effect. Baroreceptor reflex,which occurs in response to hypotension, may also contribute to tachycardia. Clinical trials have shown that long-term therapy with PDE3 inhibitors increases the mortality of heart failure patients. These drugs are very useful in the treatment of acute decompensated heart failure[1]. They are always used together with other drugs such as diuretics, ACE inhibitors, β-blockers or digitalis.

Specific drugs

PDE3 inhibitors are **milrinone** a **amrinone** (possibly emoximone and piroximone[2]). (PDE5 inhibitors are used to treat erectile dysfunction).

Side effects and contraindications PDE3 inhibitors

The most common and at the same time most serious side effect of PDE3 inhibitors are ventricular arrhythmias, some of which can reach life-threatening proportions. Some patients may experience headaches and low blood pressure[1].

Calcium sensitizers

They represent the latest class of cardiostimulants. These drugs increase the sensitivity of troponin-C to calcium, so more calcium binds to it, which increases the contractility of the heart. These drugs are currently undergoing clinical trials for possible use in heart failure [1]. These include, for example, some phosphodiesterase III inhibitors (sulmazol, imobendan, levosimendal) [2].

References

External links

- Kardiotonika (česká wikipedie)

References

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2. HYNIE, Sixtus. *Pharmacology in a nutshell.* 2. edition. Prague : Triton, 2001. ISBN 80-7254-181-1. **Cite error:**

Invalid <ref> tag; name "Hynie" defined multiple times with different content

</noinclude> **Cardiotonics** (cardiac pacing drugs) potentiate cardiac function by increasing heart rate (chronotropy) and myocardial contractility (inotropy), which increases cardiac output and arterial pressure. Many of them also exert positive dromotropic and lusitropic effects. Some of these drugs cause systemic vasodilation, while others have vasoconstrictive effects. The effects of these drugs on cardiac muscle predispose them to use in heart failure, cardiogenic shock, and hypotension[1].

Pharmacotherapy for arrhythmias depends on the type of arrhythmia, its duration, severity and the condition of the heart muscle. Arrhythmias are divided into tachyarrhythmias and bradyarrhythmias.

Mechanisms of tachyarrhythmias may be increased excitability, increased automaticity or reentry. Diagnosis of the mechanism of arrhythmia origin determines the treatment - reduction of excitability and automaticity, treatment of ischemia.[2]

Therapeutic uses

The main goal of antiarrhythmic treatment is **restoration of normal heart rhythm and conduction**; possibly at least to prevent more severe to fatal arrhythmias. They decrease or increase the rate of conduction of the impulse, alter the excitability of the heart cells, and suppress abnormal automotion.

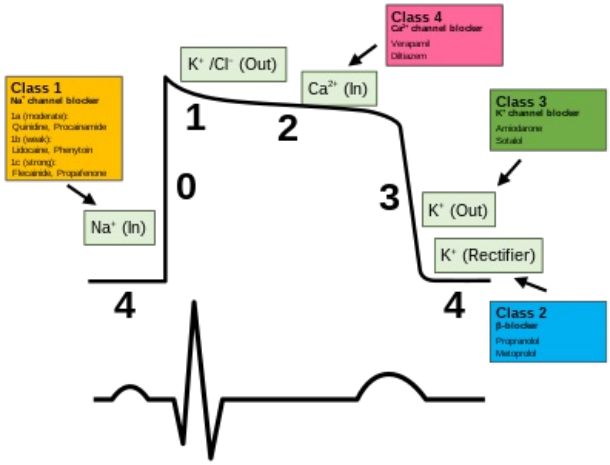
All antiarrhythmics alter membrane conductance by the following mechanisms:

- **Blockade of fast sodium channels**. These channels determine the rate of membrane depolarization during the action potential, which may help to eliminate tachyarrhythmias caused by the reentry mechanism.
- **By affecting the course of action potentials** and in particular the **relative refractory period**'. By prolonging the relative refractory period, tachycardias can often be eliminated. Tyto léky ovlivňují **draselné kanály** a oddalují fázi repolarizace.
- **Blokádou pomalých kalciových kanálů**. Tyto léky snižují sinusovou frekvenci zpomalováním depolarizace pacemakerových buněk. Rovněž snižují rychlost vedení vzruchu AV uzlem.
- **Blokádou aktivity sympatiku**, která může být rovněž příčinou vzniku arytmií, proto léky blokující β_1–adrenergní receptory jsou užívány k potlačení tohoto vlivu sympatiku na srdce. Jelikož jsou β-adrenoceptory spřažené s iontovými kanály, β-blokátory nepřímo mění i tok iontů přes membránu, zejména kalcia a draslíku.
- V případě AV blokády se někdy používají léky **inhibující vagové vlivy** (například atropin, antagonista muskarinového receptoru). AV blokáda se může objevit během léčby β-blokátory.Template:Doplňte zdroj
- V některých případech je komorová frekvence nepřiměřená, jelikož je iniciována síňovým flutterem či fibrilací síní. Vzhledem k tomu, že je velice důležité zamezit komorové tachykardii, léky se často používají ke **zpomalení vedení vzruchu AV uzlem**. K tomuto se často používají blokátory kalciových kanálů a β-blokátory. For the same reason, the parasympathomimetic effect of digitalis can also be exploited.<ref name="Schroeter">{{Citation

Antiarytmika mají často **proarytmický efekt**, proto je vhodné je užívat pouze u symptomatických arytmií, zhoršujících kvalitu života nebo prognózu nemocného.[2]

Třídy léčiv používaných k terapii arytmií[1]

1. **Třída I – Blokátory rychlých sodíkových kanálů** – kardioverze fibrilace síní aj.
   1. Ia – blokáda Na^+ kanálů – chinidin,
   2. Ib – blokáda Na^+ kanálů – lidokain, trimekain, fenytoin
   3. Ic – blokáda Na^+ kanálů – propafenon, flekainid
2. **Třída II – β-blokátory** (viz výše) – kontrola komorové odpovědi při supraventrikulární tachykardii,
3. **Třída III – Blokátory draselných kanálů** (např. amiodaron) – supraventrikulární i komorová tachykardie,
4. **Třída IV – Blokátory vápníkových kanálů** (verapamil, diltiazem) – pouze supraventrikulární tachyarytmie.
5. **Další**:
   1. ***adenosin***,
   2. ***doplnění elektrolytů*** (soli hořčíku a draslíku),
   3. ***srdeční glykosidy*** (digitalis),
   4. ***atropin*** (antagonista muskarinového receptoru),
   5. ***bradines*** (SA node blockers)[2].



Působení antiarytmik na iontový přesun v převodním systému, ovlivnění refrakterní fáze

Class Ia angiarrhythmics

Sodium channel blockade class Ia antiarrhythmics prolong action potential duration and slightly prolong repolarization[3].

Quinidine

For pharmacological cardioversion of atrial fibrillation and flutter. Has many adverse effects.

Procainamide

Used to treat ventricular and supraventricular arrhythmias.

Disopyramide

For the treatment of tachyarrhythmias, especially after a heart attack.

Class Ib angiarrhythmics

They block the sodium channel but have little effect on the rate of action potential rise. They shorten repolarization time[3].

Lidocaine, trimecaine

Mainly used in the treatment of ventricular tachycardia.

Antiarrhythmics class Ic

They block the sodium channel, significantly slowing the rate of action potential onset and conduction of excitation. Repolarization time is little affected by them[3].

Propafenone

Used to treat atrial fibrillation and ventricular tachycardia.

Class I antiarrhythmics are not commonly used today, except for propafenone and flecainide (both class Ic)[2].

Class-II-antiarrhythmics

These are β-adrenergic blockers. They reduce calcium channel phosphorylation. They negatively affect the frequency of spontaneous depolarization in the SA and AV node. They do not affect repolarization time[3].

Class III angiarrhythmics

They block potassium channels, prolong the action potential, and depress sympathetic action. Prolong atrial, conduction system and ventricular refractoriness[2]. They are used in atrial fibrillation and ventricular tachycardia.

Amiodarone

It has a slow onset of action and an extremely long elimination half-life (up to 100 days), so we must monitor its plasma levels. It is the most effective antiarrhythmic agent in suppressing ventricular and supraventricular tachycardias. It is indicated after acute myocardial infarctionTemplate:Source, in high risk of sudden cardiac death and impaired left ventricular systolic function. Amiodarone has an undesirable negatively inotropic effect, requiring cautious use in heart failure. However, it is also the only antiarrhythmic that reduces the risk of atrial fibrillation (e.g., again in heart failure)[2]. It has numerous side effects, **mainly thyroid disorders** (hypothyroidism, rarely hyperthyroidism), bradycardia, pulmonary fibrosis, hepatotoxicity and corneal deposits.

Sotalol

Prolongs action potential duration and slows the repolarization phase. Its use is limited due to its lower antiarrhythmic action[2].

Class IV antiarrhythmics

Calcium channel blockers **verapamil'** and **diltiazem'** inhibit conduction in the AV node. They do not affect the time of repolarization. They are mainly used in supraventricular tachycardias[3].

Adenosin

Adenosine acts by stimulating potassium channels. It is administered intravenously for its short action. It decreases sinus node autonomation and slows down atrial conduction. Slows the ventricular response in supraventricular arrhythmias (it is the drug of first choice). It can also be given in pregnancy.

Bradines[2]

Bradins act selectively in the sinus node where they slow down spontaneous diastolic depolarization. Their effect is only to slow the heart rate.

The main indication for bradins is angina pectoris.

Summary of classes of antiarrhythmic drugs[1]

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Class IA: atrial fibrillation, flutter; supraventricular & ventricular tachyarrhythmias

quinidine'	anticholinergic (moderate)	cinchonism (visual disturbances, tinnitus, headache); nausea; potentiates digitalis toxicity
procainamide'	anticholinergic (weak); relatively short half-life	lupus-like syndrome in 25-30% of patients
disopryamide'	anticholinergic (strong)	negative inotropic effect

Class IB: ventricular (ventricular) tachyarrhythmias (VT)

lidocaine'	IV only; VT and PVCs	high efficacy in ischemic myocardium
mexiletine'	orally active lidocaine analogue	high efficacy in ischaemic myocardium
phenytoin	digitalis-induced arrhythmias	

1. {{Citation In the treatment of cardiac insufficiency, procedures that reduce the demands on myocardial function - i.e., reduction of afterload or preload, or both (diuretics, organic nitrates, calcium channel blockers, ACE inhibitors) - are now preferred over cardiotonics.<ref name="Hynie">{{Citation

Heart failure and cardiogenic shock

The main cause of heart failure and hypotension caused by acute heart failure (cardiogenic shock) is loss of myocardial contractility, leading to reduced organ perfusion and hypotension. Cardiac function may improve by reducing afterload, increasing preload (increased fluid volume) and increasing cardiac contractility. It is by this mechanism that cardiotonics work. Sympathomimetics, or phosphodiesterase inhibitors, are used for short-term therapy, and can be harmful if used long-term. On the other hand, cardiac glycosides (digitalis and others) are safe and effective in the long-term treatment of heart failure.

Circulatory shock

This is a form of shock caused by hypovolaemia (e.g. in haemorrhagic conditions) or vasodilatation in infection (septic shock). Cardiotonics, especially sympathomimetics such as beta-agonists, are used to improve (i.e. raise) blood pressure. They are often used concomitantly with infusions and vasoconstrictor drugs.

Classes of drugs and their general mechanisms of action

Cardiotonics can be divided into four basic classes: beta-adrenoceptor agonists (beta-agonists), cardiac glycosides (digitalis and others), phosphodiesterase inhibitors, and calcium sensitizers.

Beta-agonists

These are sympathomimetics that bind to cardiac β-adrenoceptors. Activation of β-1 and β-2 adrenergic receptors leads to an increase in heart rate and contractility, which increases cardiac output. Their activation also exerts positive dromo- and lusitropic effects. These drugs are indicated in acute and refractory heart failure and in circulatory shock. The &beta-adrenoceptor agonists bind to &beta-receptors in the heart and smooth muscle. They also have effects in tissues other than the heart, particularly in the smooth muscle of the bronchial (relaxation), liver (stimulating glycogenolysis) and renal (stimulating reninu release). Thus, they cause cardiac stimulation (increased heart rate, contractility, rate of conduction, relaxation) and systemic vasodilation. There may be a rise in arterial pressure, but not necessarily because the decrease in vascular resistance cancels each other out with the increase in cardiac output. Thus, the ultimate effect on blood pressure depends on the relative influence on cardiac or vascular receptors. The β-agonists cause β-receptor down-regulation, which limits their use to the short term. Since they are catecholamines (and have low bioavailability) they must be administered by intravenous infusion.See above for the principle of β-adrenergic receptors.

Specific drugs and their therapeutic uses

The table shows several different β-agonists that are clinically used to treat heart failure and circulatory shock. These are either natural catecholamines or their analogues. Almost all have some degree of α-agonist efficacy. For some of these drugs, receptor selectivity is highly dose-dependent.

&beta-agonists

Drugs	Receptor selectivity	Clinical use	Commentary
'**Adrenaline**'	β-1 = β-2 > α-1 = α-2	Anaphylactic shock; cardiogenic shock; cardiac arrest	Low doses cause cardiac stimulation and vasodilation. In high doses, vasoconstrictive.
'**Noradrenaline**'	β-1 = α-1 > β-2 = α-2	Severe hypotension; septic shock	Reflex bradycardia masks direct stimulatory effects on the SA node.
'**Dopamine**'	β-1 = β-2 > α-1	Acute heart failure, cardiogenic shock and acute renal failure	Biosynthetic precursor of noradrenaline, stimulates its release. In low doses, stimulates the heart and reduces systemic vascular resistance. In high concentrations, it is vasodilating.
Dobutamine'	β-1 > β-2 > α-1	Acute heart failure;cardiogenic shock; refractory heart failure	The net effect is cardiac stimulation with weak vasodilation.
Isoproterenol'	β-1 = β-2	Bradycardia and AV block.	The net effect is cardiac pacing and vasodilation with little change in pressure.

Side effects and contraindications

The main side effect of β-agonists is cardiac arrhythmia. Because they increase the oxygen demand for the myocardium, they may precipitate the development of angina in patients with coronary artery disease. They may also cause headache and tremor.

Srdeční glykosidy (digitalis)

🔎 *For more information see Heart glykosides.*

Užívají se již více než 200 let k léčbě srdečního selhání. Představují rodinu sloučenin odvozených z rostliny *Digitalis purpurea* (náprstník). Tato léčiva inhibují Na^+/K^+ ATPázu srdeční sarkolemy, což vede ke zvýšení množství intracelulárního vápníku přes Na^+/Ca^{2+}-výměníkový systém. Zvýšení nitrobuněčného kalcia následně stimuluje uvolňování dalšího vápníku ze sarkoplasmatického retikula, jeho vazbu na troponin C, což zvyšuje kontraktilitu.

Vzhledem k dlouhému poločasu rozpadu digitalisu, je třeba tento fakt zvažovat při dávkování. Je třeba jej podávat několik dní, abychom dosáhli jeho terapeutické hladiny v plasmě (0,5-1,5 ng/ml). Digitalis má poměrně úzké terapeutické okno. Plazmatické koncentrace vyšší než 2,0 ng/ml mohou působit toxicky. Digitalisová toxicita se projevuje (někdy až život ohrožujícími) srdečními arytmiemi. Ke snížení hladin digitalisu se používá Digibind (imunitní mechanismus) nebo dodání draslíku (zejména souvisí-li toxicita s hypokalemií).

Terapeutické použití:

Srdeční selhání

Digitalis compounds have cardiotonic effects and are used in heart failure. Although new and more effective drugs are now available, digitalis is still widely used. Clinical studies of patients with heart failure have shown that digoxin, when taken with diuretics and vasodilators, increases cardiac output and ejection fraction and reduces filling pressures and pulmonary capillary wedging pressures. This reduces congestion in the lungs and the risk of edema. The heart rate changes slightly. These effects are expected for a drug that increases inotropy.

Atrial Fibrillation and Flutter

Atrial fibrillation and atrial flutter lead to an accelerated ventricular rate that can affect their filling (decrease their filling time). Digoxin and other drugs in this group are useful in reducing the ventricular rate that has been initiated by increased atrial contraction rate. The mechanism of this beneficial action of digoxin lies in its parasympathomimetic effect. Activation of the vagus can reduce the rate of conduction of the impulse through the atrioventricular node to the extent that some impulses are blocked. Consequently, fewer impulses are delivered to the ventricles and the frequency of ventricular contraction decreases. In addition, digoxin increases the relative refractory period in the AV node.

Specific cardiac glycoside drugs

Drug	Oral absorption	Half-life (hours)	Elimination
Digoxin	75 %	40	kidneys
Digitoxin'	>90 %	160	liver
Oubain'	0 %	20	kidneys

Note: Oubain is no longer in use today.

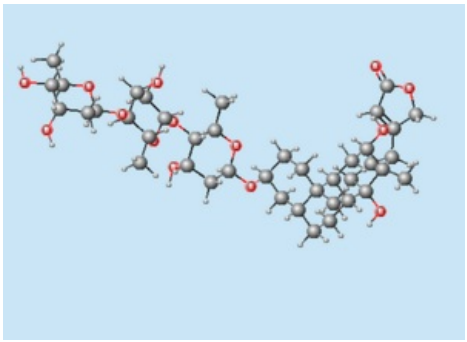
Side effects and contraindications

The most significant side effect of digitalis is cardiac arrhythmia, especially atrial tachycardia and atrioventricular blockade. The drug is contraindicated in patients suffering from hypokalaemia, AV blockade or Wolff-Parkinson-White syndrome. Renal impairment leads to an increase in the plasma concentration of digitoxin as it is eliminated by the kidneys.

Phosphodiesterase Inhibitors

These are drugs that inhibit the enzyme (*cAMP-dependent phosphodiesterase, PDE*) responsible for lowering cAMP. This leads to an increase in the concentration of cAMP, which has a positive inotropic and chronotropic effect in the heart. CAMP is the second messenger in the pathway initiated by the binding of catecholamines to beta1-adrenergic receptors coupled to Gs-proteins. This is followed by activation of adenyl cyclase and the formation of cAMP. cAMP (by reacting with other intracellular messengers) increases contractility, heart rate, and rate of conduction of excitation.

These drugs are used to treat acute and refractory heart failure, but not chronic heart failure. The drugs used target the isoform 3 of cAMP-dependent phosphodiesterase (PDE3).



Digoxin

Therapeutic indications

The cardiostimulatory and vasodilatory properties of PDE3 inhibitors predispose them to the treatment of heart failure. Arterial dilation reduces afterload of the failing ventricle and leads to increased ejection fraction and organ perfusion. Reduction of afterload leads to a secondary decrease in preload, which increases the mechanical efficiency of the dilated heart and reduces the oxygen requirements of the failing myocardium. The pacing effect of these drugs increases inotropy, leading to an increase in heart volume and ejection fraction. However, tachycardia also results, so the drugs are dosed to minimize the positive chronotropic effect. The baroreceptor reflex, which occurs in response to hypotension, may also contribute to tachycardia. Clinical trials have shown that long-term therapy with PDE3 inhibitors increases mortality in heart failure patients. These drugs are very useful in the treatment of acute decompensated heart failure. They are always used together with other drugs such as diuretics, ACE inhibitors, β-blockers or digitalis.

Specific Medications

Of the PDE3 inhibitors, these are **milrinone** and **amrinone** (ev. emoximone and piroximone). (PDE5 inhibitors are used to treat erectile dysfunction).

Side effects and contraindications of PDE3 inhibitors

The most common and most serious side effect of PDE3 inhibitors is ventricular arrhythmias, some of which can take on life-threatening proportions. Some patients may experience headaches and low blood pressure.

Calcium sensitizers

They represent the newest class of pacemakers. These drugs increase the sensitivity of troponin-C for calcium so that more calcium binds to it, increasing the contractility of the heart. These drugs are currently undergoing clinical testing for possible use in heart failure. Examples include some phosphodiesterase III inhibitors (sulmazole, imobendan, levosimendal).

Antiarrhythmics

Antiarrhythmics' (also antidysrhythmics) are drugs used to treat heart rhythm disorders, and in some cases prevent them. They affect cardiac contractility and hemodynamics<ref name="Hynie">HYNIE, Sixtus. *Pharmacology in a nutshell.* 2. edition. Prague : Triton, 2001. pp. 248 - 252. ISBN 80-7254-181-1.

2. BULTAS, Jan. Course *Pharmacotherapy of cardiovascular diseases*. 3rd Faculty of Medicine, Charles University, 2010
3. **Cite error: Invalid <ref> tag; no text was provided for refs named `Hynie`**