Cardiac inhibitors

Cardioinhibitors (drugs that reduce heart function) have a negative chronotropic (by lowering heart rate) and inotropic (by lowering heart muscle contractility) effects, which leads to a reduction in cardiac output and blood pressure. These changes reduce cardiac activity and thus myocardial oxygen consumption. The mechanisms of effect of these drugs also include a reduction in electrical conduction (negative dromotropic action).

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

Hypertension

It is caused by an increase in cardiac output or an increase in systemic vascular resistance. Cardioinhibitors reduce heart rate and stroke volume, which leads to a decrease in cardiac output and thus to a decrease in blood pressure.

Angina pectoris and myocardial infarction

Cardiac inhibitors (by reducing heart rate, contractility and arterial pressure) reduce the heart's work and its oxygen requirements. In this way, they can relieve the patient from anginal pain, which most often arises due to lack of oxygen during heavy exertion. The importance in the treatment of myocardial infarction lies not only in increasing the ratio of oxygen supply to demand, but also in the ability to inhibit post-infarction remodeling of cardiac tissue

Cardiac arrhythmia

Cardioinhibitors alter pacemaker activity and impulse conduction through the heart. Therefore they are useful in the treatment of arrhythmias caused by both abnormal pacemaker activity and abnormal impulse conduction.

Heart Failure

Although it may seem paradoxical that cardioinhibitors are used in heart failure when the myocardium is functionally depressed, clinical studies have shown that certain cardioinhibitors have improved cardiac function in certain types of heart failure[1]. This effect can be deduced from their blocking of excessive sympathetic effects on the heart that damage the failing heart.

Drug classes and general mechanisms of their 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)

It binds to β-adrenergic receptors in the conduction system and in the working myocardium. There are both types in the heart: β-1 and β-2 adrenoreceptors. However, β-1 is predominant in number and function. These receptors primarily bind noradrenaline released from sympathetic adrenergic nerve endings. In addition, they bind adrenaline and noradrenaline circulating in the blood. β-blockers prevent the 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) that 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 be lost at higher drug doses). Some of the β-blockers have additional effects besides β-blocking. The third generation of β-blockers are substances that have additional vasodilator effects by acting on the α-adrenoceptors of blood vessels.

Some β-blockers, after binding to the β-adrenoceptor, partially activate this receptor while preventing the binding of noradrenaline. These so-called **partial agonists** (partial β-blockers) therefore provide a certain background for sympathetic activity even though they inhibit normal or enhanced sympathetic effects. We refer to them as **carriers of intrinsic sympathomimetic activity** (**ISA**). Some β-blockers also carry membrane stabilizing activity (**MSA**), which is also found in sodium channel blockers belonging to antiarrhythmics

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 and thus causing increased calcium flux into the cell. The increase in intracellular calcium during action potentials leads to increased calcium release from the sarcoplasmic reticulum, which ultimately increases inotropy (contractility). Gs-protein activation also leads to an increase in the frequency of heartbeats (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, which increases inotropy. PK-A can further phosphorylate myosin light chains, which may contribute to the positive inotropic effect of β-adrenoceptor stimulation. They are used to treat hypertension, angina pectoris, myocardial infarction and arrhythmias.

Hypertension

β-Blockers lower arterial blood pressure by reducing cardiac output. Thus, they can represent an effective treatment for hypertension, especially when used in combination with diuretics. Hypertension in some patients is caused by emotional stress, which activates the sympathetic nervous system, while in other cases, for example, pheochromocytoma, which increases the level of circulating catecholamines. Even in these cases, treatment with β-blockers is successful. In addition, β-blockers inhibit the activity of the renin-angiotensin-aldosterone system. Acute treatment with β-blockers is not very effective in lowering blood pressure due to the compensatory increase in vascular resistance in the systemic circulation. The hypotensive effect of agents of this group is detectable already during the first days of treatment, but they achieve their full effect only after 2-3 weeks of administration.

Angina pectoris a 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 arrhythmia

The antiarrhythmic properties of β-blockers (class II antiarrhythmics) are related to their ability to inhibit the effect of sympathetic activity on cardiac activity. The sympathetic nervous system 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, the rate of atrial conduction (which may block reentry mechanisms), and inhibit abnormal pacemaker activity. 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.

Heart Failure

The majority of heart failure patients suffer from systolic dysfunction, i.e., there is limited contractile function of the heart (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.

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

Class / Cure	HTN	Angina	Arrhy	IM	CHF	Comment
Non-selective β-1/2						
karteolol	X					ISA; long acting; also used in glaucoma
karvedilol	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; a typical β-blocker
sotalol			X			other effects
timolol	X	X	X	X		other 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			especially short effect
metoprolol	X	X	X	X	X	MSA

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

Calcium-channel blockers (CCB)

They bind to L-type calcium channels (slow calcium channels) 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 play a role in pacemaker currents and the initial phase of action potential generation. 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. They are used in the treatment of hypertension, angina pectoris and arrhythmias.

Hypertension

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

Angina pectoris

The antianginal effects of CCBs are derived from their vasodilatory and cardiac suppressive effects. Systemic vasodilatation reduces arterial pressure, which leads to a reduction in ventricular afterload, thereby reducing oxygen demand. The more heart-selective CCBs (verapamil and diltiazem) reduce the frequency of cardiac contractions and myocardial contractility, making them (based on the reduction of myocardial oxygen requirements) excellent anti-angiogenic drugs. CCBs can also cause dilation of the coronary arteries, thus preventing their spasm (Prinzmetal's angina).

Cardiac arrhythmia

The antiarrhythmic CCB group (class IV antiarrhythmics) acts 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.

Calcium channel blocker classes

There are three classes of CCBs, differing 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. They are mainly used to reduce vascular resistance and blood pressure, i.e. to treat hypertension. They are not used to treat 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:

- ***amlodipin***;
- ***felodipin***;
- ***isradipin***;
- ***nikardipin***;
- ***nifedipin***;
- ***nimodipin***;
- ***nitrendipin***.

(note: some newer agents such as amlodipine or isradipine are also called second-generation dihydropyridines)

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 pectoris and arrhythmias. **Diltiazem** (benzothiazepine class) is an intermediate step between verapamil and dihydropyridines in terms of selectivity for vascular calcium channels. It lowers 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.

Side effects and contraindications

Dihydropyrinidine CCBs can cause congestion, headache, excessive hypotension, edema, and reflex tachycardia. In terms of activation of sympathetic reflexes and lack of direct effects on the heart muscle, they are not very suitable for the treatment of angina pectoris. 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 decreased contractility. Therefore, they should not be used by patients with chronic bradycardia, cardiac conduction defects or heart failure. CCBs (especially non-dihydropyridines) should also not be prescribed to patients treated with β-blockers

Centrally acting sympatholytics

The sympathetic nervous system has a major role in the regulation of arterial blood pressure. It increases heart rate (positively chronotropic effect), myocardial contractility (positively inotropic) and the rate of conduction of impulse in the heart (positively 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 spinal ganglia originate in the medulla oblongata of the brainstem. There 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. First, **peripheral sympatholytics** - α- and β-adrenoceptor antagonists - block the effect of norepinephrine on the effector organ (heart or blood vessels). The second are so-called ganglion blockers, which block impulse transmission of impulses in the sympathetic ganglia. The third group then 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.

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 kidney disease as they do not affect renal function

Specific drugs

Several different centrally acting antihypertensive drugs are used in clinical practice

- ***clonidine***;
- ***guanabenz***;
- ***guanfacin***;
- ***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 α-2-adrenoceptor agonist 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 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.

References

Related articles

- Cardiotonics
- Antiarrhytmics
- Antihypertensives

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