

**MECHANISMS OF DRUGS THAT AFFECT THE VASCULAR SYSTEM OF THE HEART****Ziyayeva Muazzam Kupaysinovna**

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**Annotation:** Cardiovascular drug, any agent that affects the function of the heart and blood vessels. Drugs that act on the cardiovascular system are among the most widely used in medicine. Examples of disorders in which such drugs may be useful include hypertension (high blood pressure), angina pectoris (chest pain resulting from inadequate blood flow through the coronary arteries to the heart muscle), heart failure (inadequate output of the heart muscle in relation to the needs of the rest of the body), and arrhythmias (disturbances of cardiac rhythm).

**Key words:** Drug, cardiovascular dgur, blood, body, symptoms.

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When insufficient blood reaches the heart, waste products accumulate in the heart muscle and irritate local nerve endings, causing a deep sensation of heaviness, squeezing, or burning that is most prominent behind or beneath the breastbone and over the heart and stomach. In some instances, the sensation may radiate into the shoulders, the neck, the jaw, or the arms on one or both sides of the body. A feeling of constriction or suffocation often accompanies the discomfort, though there is seldom actual difficulty in breathing. Symptoms usually subside within five minutes. In acute cases (e.g., unstable angina or acute coronary syndrome), the skin becomes pale and the pulse is weak. Although symptoms may be mild in some cases, the peculiar qualities of angina pectoris may induce anxiety.

Attacks of angina can be precipitated by walking or more strenuous exertion; by anger, fear, or other stressful emotional states; by exercise after a large meal; or by exposure to cold or wind. Attacks are apt to recur following less or no exertion as coronary heart disease worsens. Angina pectoris is rare in persons under middle age and tends to be more common in men than in women. Men and women sometimes experience different symptoms; women, for example, may experience nausea or vomiting, feel sharp pain rather than pressure in the chest, or have symptoms of increased duration. Differences in the characteristics of angina are attributed to differences in the underlying conditions that precipitate angina; for example, coronary artery disease frequently is associated with angina in men, whereas coronary microvascular disease is a common cause of angina in women.

**Effects on heart function**

Drugs affect the function of the heart in three main ways. They can affect the force of contraction of the heart muscle (inotropic effects); they can affect the frequency of the heartbeat, or heart rate (chronotropic effects); or they can affect the regularity of the heartbeat (rhythmic effects).

## Contractions

Inotropic agents are drugs that influence the force of contraction of cardiac muscle and thereby affect cardiac output. Drugs have a positive inotropic effect if they increase the force of the heart's contraction. The cardiac glycosides, substances that occur in the leaves of the foxglove (***Digitalis purpurea***) and other plants, are the most important group of inotropic agents. Although they have been used for many purposes throughout history, the effectiveness of cardiac glycosides in heart disease was established in 1785 by English physician William Withering, who successfully used an extract of foxglove leaves to treat heart failure. The two compounds most often used therapeutically are digoxin and digitoxin.

Cardiac glycosides, however, have disadvantageous side effects. These include a tendency to block conduction of the electrical impulse that causes contraction as it passes from the atria to the ventricles of the heart (heart block). Cardiac glycosides also have a tendency to produce an abnormal cardiac rhythm by causing electrical impulses to be generated at points in the heart other than the normal pacemaker region, the cells that rhythmically maintain the heartbeat. These irregular impulses result in ectopic heartbeats, which are out of sequence with the normal cardiac rhythm. Occasional ectopic beats are harmless, but if this process continues to a complete disorganization of the cardiac rhythm (ventricular fibrillation), the pumping action of the heart is stopped, and death occurs within minutes unless resuscitation is performed. Because the margin of safety between the therapeutic and the toxic doses of glycosides is relatively narrow, they must be used carefully.

Cardiac glycosides are believed to increase the force of cardiac muscle contraction by binding to and inhibiting the action of a membrane enzyme that extrudes sodium ions from the cell interior. These drugs also enhance the release of calcium from internal stores, resulting in a rise in intracellular calcium. This subsequently increases the force of contraction, since intracellular calcium ions are responsible for initiating the shortening of muscle cells.

The disturbances of rhythm that may be caused by cardiac glycosides result partly from the depolarization and partly from the increase in intracellular calcium. Because these rhythm disturbances are caused by the same underlying mechanism that causes the beneficial effect, there is no likelihood of finding a cardiac glycoside with a significantly better margin of safety. Apart from their cardiac actions, these glycosides tend to cause nausea and loss of appetite. Because digoxin and digitoxin have long plasma half-lives (two and seven days, respectively), they are liable to accumulate in the body. Treatment with either of these drugs must involve careful monitoring to avoid the adverse effects that may result from their slow buildup in the body. The second type of inotropic agents that increase the force of cardiac muscle contraction includes dobutamine. Administered intravenously in moderate doses, dobutamine will increase contractility without affecting blood pressure or heart rate.

## Heart rate

The heart rate is controlled by the opposing actions of sympathetic and parasympathetic nerves and by the action of epinephrine released from the adrenal gland. Norepinephrine, released by sympathetic nerves in the heart, and epinephrine, released by the adrenal gland, increase the heart rate, whereas acetylcholine, released from parasympathetic nerves, decreases it. A

competitive antagonist that acts to inhibit the stimulating action of norepinephrine on the heart is propranolol, which slows the heart and is often used to treat anginal attacks and disturbances of cardiac rhythm. Atropine blocks acetylcholine receptors and is used during anesthesia to prevent excessive cardiac slowing.

There are a number of drugs that are useful in treating abnormalities in heart rate. Reentrant rhythm and ectopic pacemakers cause abnormally high heart rates (tachycardia), and they require treatment with drugs that slow the heart and reduce the electrical excitability of the muscle cells. Reentrant rhythms can be eliminated by increasing the refractory period of the cells, which is the interval following transmission of an electrical impulse during which the cell cannot be reexcited by another impulse. Increasing the refractory period has the effect of reducing the frequency at which impulses can be transmitted.

Quinidine, procainamide, lidocaine, and phenytoin exert their antiarrhythmic effects by reducing electrical excitability. Quinidine and procainamide have the disadvantage that they reduce the force of contraction of the heart and tend to lower blood pressure. They are also liable to cause side effects such as nausea and skin rashes. Lidocaine, which is also used as a local anesthetic, has a very short duration of action and must be given intravenously; its main use is in the prevention of ventricular arrhythmias following acute occlusion (blockage) of a coronary artery.

An important factor tending to exacerbate ectopic pacemakers is the release of norepinephrine from sympathetic nerves. Norepinephrine acts on beta-adrenoceptors in the heart to increase its rate, which strongly increases the tendency for ectopic pacemakers to develop. Beta-adrenoceptor-blocking drugs (e.g., propranolol), commonly known as beta-blockers, are widely used to control these types of arrhythmia because they slow the actions of the heart. They also tend to reduce the force of contraction of the heart, which can be a disadvantage, and they produce various other unwanted effects.

In the mid-1970s the calcium channel blockers, another type of antiarrhythmic drug, were introduced. Verapamil and diltiazem are important examples of this class of drugs. They reduce the influx of calcium ions through the cell membrane, which normally occurs when the cell is depolarized. This movement of calcium ions across the membrane appears to be important in the genesis of reentrant rhythms and ectopic heartbeats. Inhibiting the influx of calcium ions is effective in controlling many types of arrhythmia. Since calcium entry is essential for initiating the contraction of heart muscle cells, calcium channel blockers tend to impair muscle contractility. Since calcium entry is also important in the contraction of blood vessel smooth muscle, these drugs cause vasodilation and tend to lower arterial blood pressure.

All the antiarrhythmic drugs discussed so far impair the conduction of the impulse for contraction from atria to ventricles and therefore can cause heart block. Antiarrhythmic drugs should be used carefully to avoid the various hazards and side effects that they may produce. Heart block causes a pathological slowing of the heart and is not usually treated with drugs, although beta-adrenoceptor agonists such as isoproterenol are sometimes used in emergencies. An artificial electrical pacemaker device is usually fitted to provide effective long-term control.

### Drugs affecting the blood vessels

Drugs affect blood vessels by altering the state of contraction of the smooth muscle in the vessel wall, altering its diameter and thereby regulating the volume of blood flow. Such drugs are classified as vasoconstrictors when they cause the smooth muscle lining to contract and vasodilators when they cause it to relax. Drugs may act directly on the smooth muscle cells, or they may act indirectly—for example, by altering the activity of nerves of the autonomic nervous system that regulate vasoconstriction or vasodilation. Another type of indirect mechanism is the action of vasodilator substances that work by releasing a smooth muscle relaxant substance from the cells lining the interior of the vessel. Some drugs mainly affect arteries, which control the resistance to blood flow in the vascular system, an important determinant of the arterial blood pressure; others mainly affect the veins, which control the pressure of blood flowing back to the heart and hence the cardiac output (i.e., the volume of blood pumped out by the heart per minute).

Apart from the actions of the autonomic nervous system, several other physiological mechanisms regulate vascular smooth muscle. Of particular pharmacological importance are the renin-angiotensin system and locally acting vasodilator substances, such as histamine, bradykinin, prostaglandins, and nitric oxide.

Renin is an enzyme that is released into the bloodstream by the kidney when the blood pressure falls. It acts on a plasma protein to produce a peptide, angiotensin I, which consists of a chain of 10 amino acids. This in turn is acted on by angiotensin converting enzyme (ACE) to produce an eight-amino-acid peptide, angiotensin II (a potent vasoconstrictor), which raises the blood pressure. ACE inhibitors, which block the formation of angiotensin II, are used in treating hypertension, which is produced by excessive constriction of the small arteries. Drugs that block the binding of angiotensin II to its receptor can also be used.

Other drugs used in the treatment of hypertension include methyldopa and clonidine, which work at the level of the central nervous system; adrenoceptor-blocking drugs (e.g., propranolol, which lowers blood pressure by reducing the cardiac output, and prazosin, which blocks the vasoconstrictor action of norepinephrine); calcium channel blockers (e.g., nifedipine); and nitrates (e.g., nitroglycerin tablets). Hypotensive drugs, particularly nitroglycerine tablets and calcium channel blockers, are often used to relieve angina pectoris. Angina often is the result of partial occlusion of the coronary vessels by fatty deposits (atheroma) or blood clots. Hypotensive drugs reduce arterial blood pressure and cardiac output and thereby lower the work and oxygen consumption of the heart. They also have some effect on the coronary vessels themselves, and many direct blood toward the regions in which the flow is impaired.

Most antihypertensive drugs have a variety of unwanted effects, such as drowsiness, dizziness on standing (due to an excessive postural fall in arterial pressure), impotence, and allergic reactions. Though often fairly minor, side effects are a serious problem because of the long-term nature of antihypertensive therapy, and better drugs are constantly being sought.

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