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CARDIO-VASOTOXIC EFFECT OF HEAVY METAL COMPOUNDS AND THEIR NANOPARTICLES (REVIEW)

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Introduction. Pathology of the cardiovascular system among the causes of morbidity and mortality in Ukraine occupies a prominent place. Many researchers rightly associate it with the influence of adverse factors of production and environment. Heavy metals and their compounds are included in the complex of «classica» risk factors for the development of heart and vascular disease. To date, it has been established that heavy metals in the form of ultrafine particles < 100 nm in size may be present in the air of the working area in some industries. The special physical and chemical properties inherent in these particles contribute to overcoming biological barriers and enhance the toxic effects of heavy metals. Thus, the study of the features and target organs of the toxic effects of heavy metal compounds and their nanoparticles as anthropogenic pollutants on the body of workers and the population in general is an urgent problem for occupational health and industrial toxicology.

The aim of the study – to study and summarize the data of world and national literature on the influence of heavy metal compounds, their nanoparticles (NPs) on the cardiovascular system, to establish the features and mechanisms of cardio-vasotoxic action, to determine further prospects in assessing the safety of nanotechnologies and nanomaterials.

Materials and methods of the study. The analytical review of modern scientific publications was carried out using the information databases Portalnano, PubMed and the Vernadsky National Library of Ukraine with the help of Internet resources.

Results. The article presents the literature data on the features and mechanisms of influence of heavy metal compounds on the cardiovascular system, as well as the results of the study of cardio-vasotoxic effects of metal nanoparticles. The data of experimental, clinical and epidemiological studies convincingly prove that heavy metals, such as lead, cadmium, iron, play an important and often leading role in the pathogenesis of cardiovascular diseases in workers, in particular the development of arterial hypertension, atherosclerosis, cerebrovascular pathology, peripheral vascular disease. At the same time, NPs metals have a greater cumulative and toxic activity against heart and vascular cells, which causes their death and dysfunction.

Conclusions. The data obtained allow us to conclude that the cardiotoxic effect of both heavy metals and their nanoparticles is based on two main mechanisms: the effect on the structure and integrity of the heart tissue and on the conducting system – the vascular endothelium. Metal compounds in the form of nanoparticles, in comparison with their micro- and ionic forms, are easier to overcome biobarriers, accumulate in the heart tissue, stimulate oxidative stress and cell apoptosis. The dominant mechanism in the development of cardiovascular diseases is their cyto- and genotoxic effect on cardiomyocytes and endothelial cells.

Key words: heavy metals, metal nanoparticles, cardiovascular system, toxicity

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Introduction

Cardiovascular system (CVS) pathology occupies a prominent place among the causes of morbidity and mortality. In the structure of CV diseases the main share belongs to arterial hypertension (AH) (41 %), coronary heart disease (CHD) (33 %), cerebrovascular diseases (15 %). According to the World Heart League, Ukraine ranks one of the first among European countries in terms of mortality from cardiovascular diseases. In recent decades, there is a tendency to early development of CVD pathology in young and middle-aged people, which causes significant socio-economic losses [1, 2].

Generally recognized risk factors for the development of cardiovascular disease (CVD) are physical inactivity, lipid metabolism disorders, stressful situations, unhealthy diet, overweight, bad habits (smoking, alcohol abuse). However, the progressive increase in cases of CVD, including among young people, many researchers associate with adverse occupational and environmental factors. It is established that the frequency of hypertension, coronary heart disease and their complications, including fatalities, is significantly higher among the population of cities with intense anthropogenic air pollution than in regions with relatively clean air [3].

Hazardous industrial and environmental pollutants include heavy metals and their compounds, which adversely affect the function of many organs and systems of the body, including the cardiovascular system. Recently, they have been included in the complex of «classical» risk factors for heart and vascular pathology. Experimental and clinical studies have proven the danger of developing long-term effects of heavy metals on the cardiovascular system in acute and chronic poisoning [4, 5].

The rapid development of nanotechnology and active synthesis of heavy metal nanoparticles (NPs), their wide application in various industries (electronics, energy, chemical and construction industries), medicine, veterinary medicine, agriculture contributes to direct human contact with them. The contact of workers with heavy metals NPs may occur at industries where metal NPs are synthesized and used, as well as at metallurgical, mining and electric welding industries, where under certain conditions condensation aerosol containing ultrafine particles smaller than 100 nm is formed. High levels of respirable nanoparticles in these industries can cause an increase in morbidity and mortality among workers due to pathology of the bronchopulmonary and cardiovascular systems [6, 7].

Thus, in addition to heavy metals in the usual form, their NPs can be dangerous. The danger that heavy metals NPs can pose is associated with special physicochemical properties that enhance their toxic effect. In particular, the small size of NPs (< 100 nm) contributes to increased bioavailability and overcoming biobarriers (blood-brain, histohematological, placental), facilitating transport into cells, binding to nucleic acids and proteins, penetration into organelles with functional changes. Increasing the chemical potential of NPs causes significant changes in the solubility of heavy metal compounds, their reaction and catalytic ability, stimulation of the synthesis of free radicals and reactive oxygen species, which causes damage to various biological structures. High cumulative ability of heavy metals NPs contributes to their accumulation in target organs and further slow elimination from the body [8, 9].

To date, there is convincing evidence that small (nanoscale) particles are able to penetrate into various parts of the respiratory tract, transported through epithelial and endothelial cells into the circulatory and lymphatic systems, and ultimately

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accumulate in the bone marrow, lymph nodes, liver, spleen and heart [10].

There is enough data that synthesized NPs of silver, titanium, zinc, carbon and iron oxides can have cardiotoxic effects, the manifestations of which depend on the toxicity of the metal itself, as well as on the particle size [11–13].

In view of the above, the study of the peculiarities and target organs of the toxic effects of heavy metal compounds and their NPs as anthropogenic pollutants on the body of workers and the population is an urgent problem for occupational health and industrial toxicology today.

The aim of the study is to study and summarize the data of worldwide and national literature on the effect of heavy metal compounds and their NPs on the CVS, to establish the features and mechanisms of their cardio-vasotoxic action, to determine further prospects in assessing the hazards of nanomaterials.

Materials and methods of the study

The analytical review was carried out using Internet resources of abstract databases: Portalnano [http://www. portalnano. ru], PubMed [http://www. ncbi. nlm. nih. gov/pubmed], [http://www. nanomet. ru] and the Vernadsky National Library of Ukraine [http://www. ibis-nbuv.gov.ua] for the last 15 years.

Results of the study and their discussion

Commonly known risk factors for the development of cardiovascular pathology are physical inactivity, lipid metabolism disorders, insulin resistance, stress, irrational diet, overweight, bad habits (smoking, alcohol abuse). At the same time, the progressive increase in the incidence of cardiovascular disease, including among young people, due to atherosclerotic processes, many researchers associate with adverse industrial and environmental factors [3].

Of particular relevance is the problem of long-term effects of exogenous chemical compounds on the CVS. There is a direct dependence of the functional state of the circulatory system in workers on the length of work with harmful chemicals, as well as the mortality rate from cardiovascular diseases depending on the duration of exposure to xenobiotics. Thus, the frequency of arterial hypertension, coronary heart disease and their complications, including fatalities, is much higher among the population of cities with intense air pollution than in relatively clean non-industrial regions [1, 4].

Numerous clinical, hygienic and experimental studies indicate that the CVS, like any other body system, can become an open biological target for the damaging effects of chemicals with varying degrees of selectivity. These substances can have both indirect and direct toxic effects on the CVS (Figure 1) [5, 14].

Thus, clinical studies show that in systemic vascular pathology among young and middle-aged patients, arterial lesions have a special etiological basis – systemic damage to the arterial wall by xenobiotics, as well as its own pathohistological features that are not typical for atherosclerosis. Atherosclerotic changes are secondary – they are attached to existing changes as vasculitis or angiopathy. Analysis of the etiological factors of coronary heart disease and acute cerebrovascular disorders in young people has shown that this pathology develops mainly in people exposed to potentially hazardous chemicals on workplace. These are representatives of the following professions: drivers, tractor drivers, mechanics, welders, electric, television and radio installers, galvanizers, stampers,

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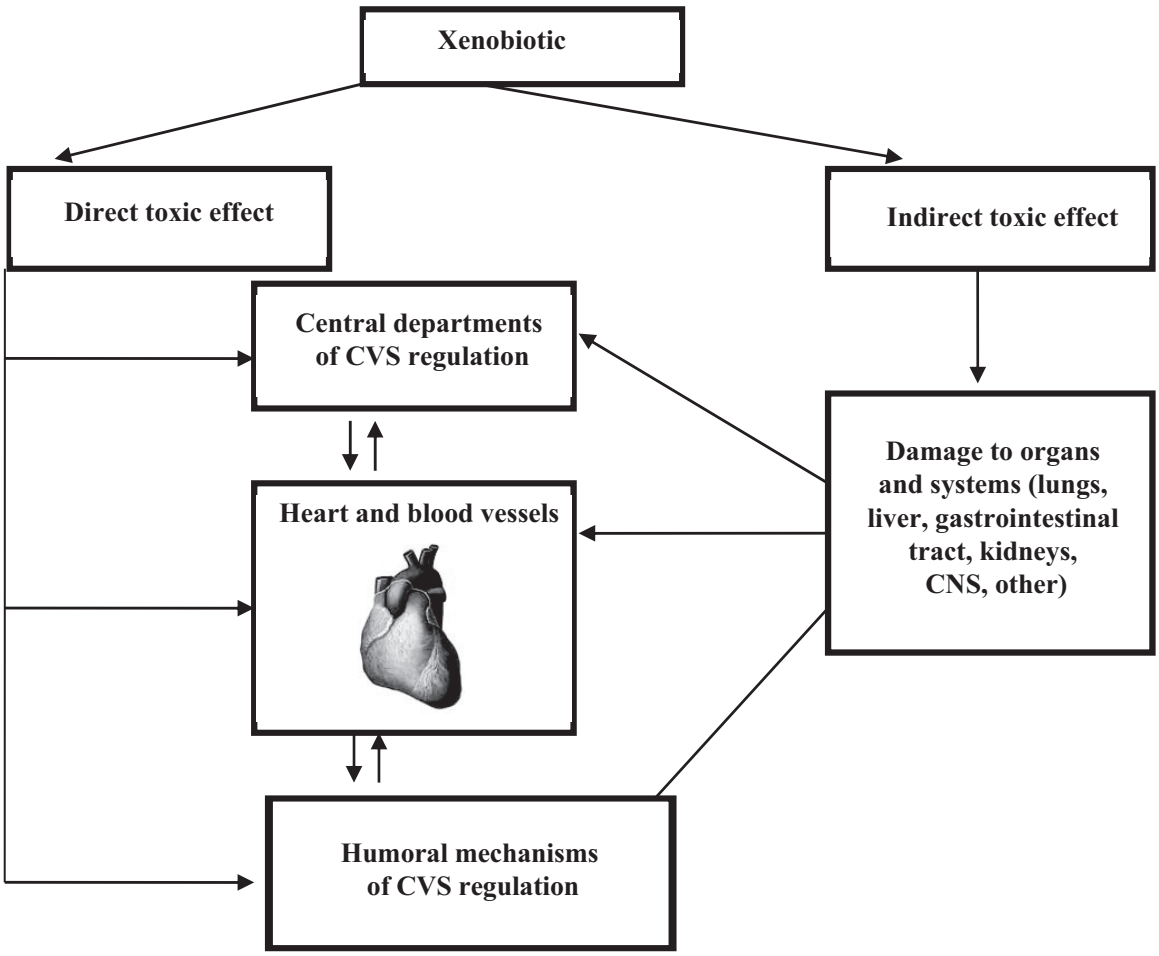

Figure 1. Scheme of organ-tissue tropism of chemical factors to the cardiovascular system [14]

metallurgists, steelmakers, smelters, miners, painters, as well as workers engaged in the chemical industry, printing and agriculture [4].

The main difficulty in studying the selective cardio-vasotoxic effects of chemicals is that all cells of the body contain the same set of cellular organelles and basic enzymes – molecular «targets» for the damaging effects of the chemical factor. Therefore, along with CVS, other organs and tissues are also damaged. The indirect tropism of harmful chemicals to the CVS causes its disruption through the impact on other organs, tissues and systems. At the same time, there is a more pronounced damage of anatomical and physiological structures of other organs, tissues and systems by the chemical substance, rather than the cardiovascular system. As a result, extracardiac and extravasal neurogenic and humoral factors are disorganized and the activity of the CVS is disturbed; that is, there is an indirect toxic effect on the CVS. This mechanism explains the frequent involvement of the CVS in pathology with pathogenetically «extracardiac» initial damage to the body by harmful chemicals, the so-called «parenchymal» poisons. The direct organ-tissue

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tropism of toxic chemical compounds to the CVS, in contrast to the indirect one, is characterized by the fact that its dominant pathogenetic «aggressiveness» does not go beyond its anatomical and physiological limits and regulation. An important role in the implementation of direct organ-tissue tropism of harmful substances to the CVS is played by the peculiarities of its topography, as well as through which organs and tissues this or that substance penetrates into the body and affects it. Blood vessels are an integral component of the anatomical and physiological organization of any organ and tissue of the body. If a chemical substance damages mainly the parenchyma of a particular organ, and not the vessels penetrating it, the latter with their histological structures are further involved in the pathological process. The formation of metabolites in this environment, which are transported to the centers of cardiovascular regulation, is not excluded. This involves not only central neural mechanisms, but also numerous chemo- and baroreceptor apparatus of blood vessels. The specific role of chemical factors in the development of CVS pathology, including occupational, is quite ambiguous. In some cases, they only accompany the main symptom complex directly related to this exposure, and in others – changes in the CVS occupy a leading place in clinical manifestations and determine the prognosis of the disease. Thus, the damage to the circulatory system is not isolated, but is a complex symptom complex of toxic effects of chemicals on the body [14].

The mechanism of cardio-vasotoxic action of xenobiotics (chemicals) is quite diverse. It may include disorders of the neurohumoral regulation of the cardiovascular system, tissue hypoxia, impaired activity of enzyme systems in the vascular wall and myocardium. In addition, the possibility of developing cardiovascular pathology in offspring due to the effect of chemicals on the genetic apparatus of parents and directly on the fetus (genetic, mutagenic, embryo- and teratogenic aspects of the effect of chemical compounds on the CVS) is not excluded [15, 16].

Thus, the existing results of experimental, clinical and epidemiological studies on the cardiovasotoxic effects of chemicals prove that xenobiotics play an important, and often a leading role in the pathogenesis of CVD, acting as a leading etiological factor. Chronic exposure to potentially hazardous chemicals entering the human body in doses and concentrations close to the maximum permissible concentrations of their content in water, atmospheric air and working zone air, as well as food leads to functional and morphological changes in the CVS system and affects the incidence of cardiovascular pathology.

The role of heavy metals in the pathogenesis of CVD

Among the potentially hazardous chemicals that pollute environmental objects (atmospheric air and working zone air, water, soils, food), heavy metals and their compounds form a significant group of xenobiotics, which, to some extent, determine the anthropogenic load on ecosystems and humans. Due to the growing scale of industrial production and use of heavy metals, their significant accumulation in the environment, high toxicity, accumulation in the human body, they can have a negative effect, even in relatively low doses [5,14].

The toxic effect of heavy metals on the body is based on certain interrelated mechanisms, among which the leading role is played by the increased formation of active radicals with the activation of lipid peroxidation (LPO) and the development of oxidative stress, interaction with thiol groups of amino acids, proteins and low molecular weight

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thiols, with carboxyl and amine groups of amino acids, as well as competitive interaction with essential trace elements and the emergence of intracellular imbalance of the latter. The consequence of these processes with excessive intake of heavy metals in the body is a violation of homeostasis and the development of clinical manifestations of their toxic effects [16].

Among heavy metals as anthropogenic pollutants of the environment, a special place is occupied by lead and its compounds, which are characterized by high toxicity and ability to accumulate both in ecosystems and in humans and animals. The toxic effect of lead and its compounds is manifested primarily by damage to the nervous, cardiovascular systems, kidneys, porphyrin metabolism, blood system, especially hematopoiesis. Initial changes in the cardiovascular system are manifested by blood pressure (BP) lability with a clear tendency to arterial hypertension (AH) and increased vascular tone. It has been shown that the cardiotoxic effect of lead is realized both by indirect action on the cardiovascular system and directly by toxic effects on the heart and blood vessels. It has been established that lead in relatively small doses causes impaired iron utilization and accumulation of labile iron pool in mitochondria, impaired nitric oxide metabolism, which leads to its relative deficiency, resulting in the development of endothelial dysfunction. Direct membranotoxic effect of lead on cardiomyocytes is possible. Thus, prolonged contact with lead may be an independent etiological factor of hypertension. Today, there is little doubt that lead has a pathogenic effect on the circulatory system, acting as an etiological stimulus responsible for the development of cardiovascular pathology such as vasculitis, atherosclerosis, arteriosclerosis and, as a result, arterial hypertension. During prolonged lead intoxication, bradycardia develops and blood pressure rises. It was shown that among workers who had occupational contact with lead, electrocardiological signs of hypoxia, degenerative changes in the coronary arteries, proliferation of perivascular connective tissue, decreased tolerance to physical activity, impaired cardiovascular function on physical activity were detected. The results indicate the development of major cardiovascular diseases among young people exposed to lead compounds during lead smelting, foundry work, welding, cutting of metal structures, repair of automobile radiators and motor transport workers, which cannot be fully explained from the standpoint of the well-known theory of atherogenesis. At the same time, early pathomorphological changes in the vessels were observed in young people. Among workers who had contact with lead, electrocardiographic signs of hypoxia, degenerative changes in the coronary arteries, proliferation of perivascular connective tissue, impaired cardiovascular function on physical activity were found [16, 17].

Other scholars believe that the increase in blood pressure in lead poisoning is due to minor changes in calcium metabolism or impaired renal function. In addition, lead affects the metabolism of vitamin D [18].

The results of clinical and epidemiological studies show that prolonged contact with lead compounds leads to an increase in blood pressure and significantly increases the risk of hypertension and cardiovascular disease. The relationship between the level of lead in the human body and blood pressure, the risk of developing coronary heart disease, peripheral vascular disease has been noted. Thus, as a result of a 30-year study of the factors of hypertension development (The Normative Aging Study) it was found that an increase in bone lead content from 8 to 37 mg/g of bone dry matter is associated

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with a 1.5-fold increase in the risk of developing hypertension [19].

It has been shown that the cardio-vasotoxic effect of lead is realized through both direct and indirect effects on the heart and blood vessels. In relatively small doses, it causes impaired iron utilization and accumulation in mitochondria, impaired iron oxide metabolism, resulting in the development of endothelial dysfunction. Impaired contractile function of the heart muscle may be associated with the negative effect of lead on actin and myosin interaction with Ca^{2+} Mg^{2+} [20].

One of the long-term effects of lead intoxication on the CVS is the restructuring of the connective tissue of the aorta, capillaries and myocardium, which results in the damage of the elastic framework of blood vessels – the development of aortic dissection and aneurysm [2].

It has been shown in studies that an increase in lead content in the heart increases the activity of iNOS along with an increase in the production of lipid peroxidation (hydrogen peroxide, hydroxyl radical, superoxide anion) and lipid oxidation products (LOPs) (diene conjugates, TBA-active products). The increase in iNOS activity causes hyperproduction of NO, leads to significant formation of highly toxic peroxynitrite in the body, contributes to the emergence of a relative deficiency of nitric oxide due to its inactivation by reactive oxygen species. Violation of the normal ratio of dilator and constrictor vasoactive factors in the body leads to endothelial dysfunction, which is characterized by impaired functional activity of the endothelium and changes in vascular tone (mainly in the form of vasoconstriction) [21, 22].

Thus, the analyzed data led to the conclusion that prolonged exposure to lead may be an independent etiological factor in the development of hypertension, and endothelial dysfunction as the main mechanism of cardio-vasotoxic action of lead.

Among heavy metals, cadmium is also a priority global pollutant and hazardous toxicant. It has been shown that when ingested, cadmium and its compounds have a pronounced toxic effect, with the target organs being the lungs, liver, testes and bone tissue. At the same time, prolonged contact with cadmium compounds can stimulate the development of hypertension, coronary heart disease and peripheral vascular disease [23, 24].

Epidemiological studies have revealed a positive correlation between the content of cadmium in urine and the development of diseases such as hypertension, peripheral arterial disease, stroke, heart failure. Authors [24] established the relationship between atherosclerosis and increased accumulation of cadmium in the body. In the pathogenesis of vasotoxic effects of cadmium, the leading role is played by the development of endothelial dysfunction, which causes a decrease in coronary blood flow. It has been shown that cadmium causes an increase in vascular wall permeability, which contributes to the accumulation of lipids in the wall, its infiltration by immune cells, and also causes an increase in the secretion of pro-inflammatory cytokines (IL-6, TNF-α) and antithrombolytic agents, modification of lipids due to their peroxidation, induces increased formation of intercellular (ICAM-1) and vascular adhesion molecules (VCAM-1) by endothelial cells and increases platelet and leukocyte adhesion to the vascular wall. As mentioned above, these mechanisms play a leading role in the pathogenesis of atherosclerosis.

It has been shown that cadmium causes ultrastructural changes in the myocardium due to oxidative damage of cardiomyocytes by LOPs, LOPs products, in addition, cadmium directly interacts with troponin C and myoglobin and disrupts the contractile function of the heart. The effect on the cardiac conduction system is due to blockade of

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Ca^{2+} – L-type channels, impaired potassium entry through the cell membrane, as well as blockade of fast Na^{+} – Purkinje fiber channels [25].

Thus, the above data allow us to conclude that the cardiotoxic effects of lead and cadmium are based on two main mechanisms: the effect on the structure and integrity of heart tissue and the effect on the conducting system which is the vascular endothelium.

Iron belongs to the vital chemical elements for all organisms. Being one of the essential metals, iron plays a key role in many intracellular biological processes. It can be classified as a system-forming element due to the complex interrelations of proteins involved in its metabolism with other body systems. However, in case of excessive intake of iron or disruption of the mechanisms of control over its intake, redistribution and utilization, it accumulates in organs and tissues, causes the development of metabolic syndrome, atherosclerosis, arterial hypertension, cardiomyopathy [26].

Features of the technological process in certain types of production (steelmaking, welding, iron ore mining, etc.) can contribute to the accumulation of iron, resulting in the development of clinical syndrome of secondary overload of the body or chronic iron intoxication). The results of clinical examination of welders revealed an increase in the incidence of diseases characteristic of chronic iron intoxication such as cardiomyopathy, coronary heart disease, chronic hepatitis, carbohydrate metabolism disorders and joint pathology [27].

When analyzing the results of prospective epidemiological studies conducted in Kuopio (Finland), within the framework of the well-known Program for the study of risk factors for coronary heart disease (KIHD – Kuopio Ischaemic Heart Disease Risk Factor Study, published in 1998), a clear dependence of the incidence of coronary heart disease on the increase in the body's iron load was noted. Moreover, this dependence was determined at such a load of iron in the body, which has not yet reached the level necessary for the manifestation of clinically expressed hemochromatosis [28].

It is known that excess iron in the body causes the development of oxidative stress and adversely affects the cardiovascular system. Increased iron content in the body and the associated disruption of free radical oxidation (ROS) processes is essential in the development of various pathological conditions, including atherosclerosis and its complications – myocardial infarction and stroke, degenerative changes in the nervous system (Parkinsonism, Alzheimer's disease, etc.), pneumosclerosis, hepatitis, diabetes mellitus, rheumatoid arthritis, cataracts, aging, mutagenesis, carcinogenesis, etc.

The role of iron in the development of cardiovascular disease has been confirmed by numerous epidemiological studies that have shown a positive correlation between excessive iron accumulation in the body and CVD. It has been demonstrated that serum ferritin levels directly correlate with the incidence and progression of atherosclerosis, which ultimately leads to CVD. This opinion was further confirmed by the lower incidence of coronary heart disease in patients with iron deficiency [31, 32].

Studies conducted by [33] confirm that the consumption of excess iron with food increases the risk of atherosclerosis, coronary artery disease in both men and women, especially in the elderly. According to other authors [34], men over 60 years of age are 3.5 times more likely to have cardiovascular diseases, and women of this age are 1.4 times more likely to have cardiovascular diseases when taking 50 mg of iron per month.

In recent years, new theories have emerged about the role of iron in the development of atherosclerosis. It is known that the most characteristic

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histological feature of an atheromatous plaque is a macrophage, or foam cell, loaded with cholesterol esters. In chronic inflammatory diseases, characteristic of the elderly, increases the formation of hepcidin, which closes the exit of iron from the cells, which accumulates in macrophages as a result of re-entry with serum iron transferrin, or from captured and destroyed old red blood cells. Such iron in its catalytically active form generates reactive oxygen species and induces lipid peroxidation, causing oxidative modification of low density lipoproteins, endothelial activation, smooth muscle proliferation and macrophage activation. Macrophages filled with highly reactive iron and heme are involved in the formation of atheromatous plaque, forming the so-called «foam cells», contribute to fibrosis and progression of the stages of its development with the subsequent possibility of plaque rupture. Degradation of extracellular hemoglobin due to hemorrhage into the plaque leads to the release of its hemoprosthetic groups into the bloodstream, promotes the production of free radicals and oxidative stress, actively participating in the development of atherosclerotic lesions [35]. All these processes are considered proatherogenic and are schematically presented in Figure 2.

When the body is overloaded with iron, it can penetrate into cardiomyocytes through both L-type and T-type calcium channels and increase the formation of toxic free radicals within the heart cells. These effects then weaken myofilament contraction, damage intracellular organelles, including mitochondria. In addition, iron can promote inflammatory fibrosis, which also impairs the contractility of the heart muscle [36, 37].

Summarizing the literature data, it can be concluded that heavy metals (lead, cadmium, iron) can have a harmful effect on the heart and blood vessels both directly and indirectly with the involvement of other organs and systems. Understanding the mechanisms of implementation of cardio-vasotoxic effects of chemicals will allow to develop effective

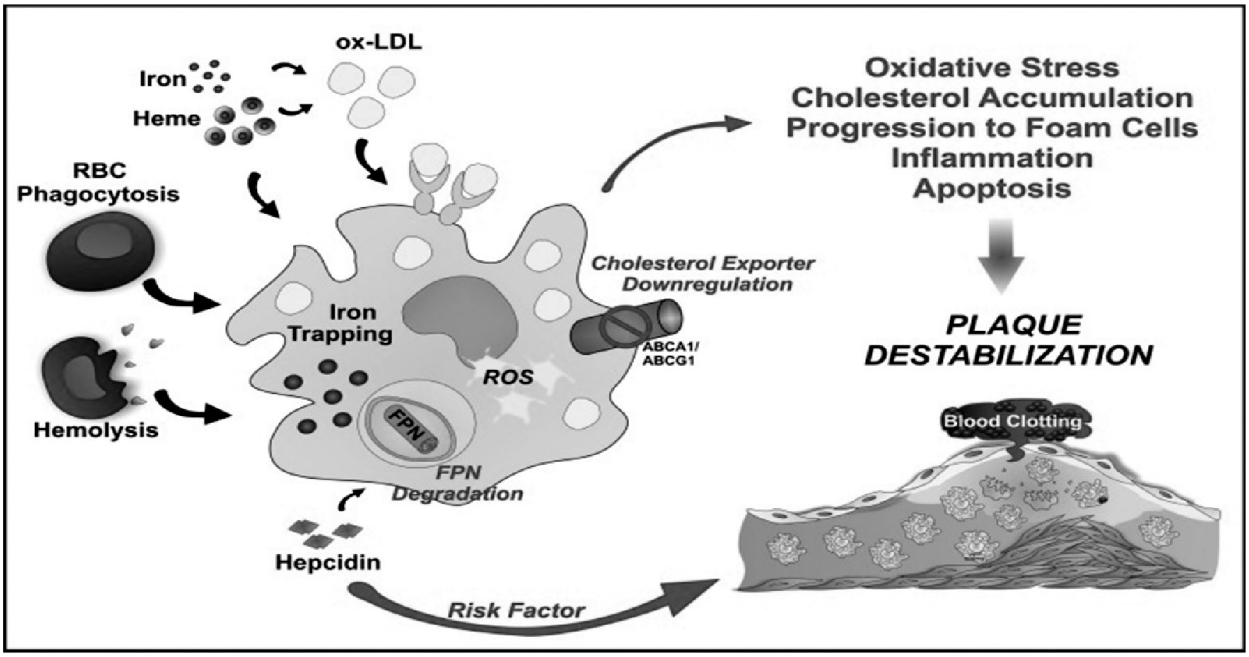

Figure 2. The presumed mechanism of atherosclerotic formation plaques (Front Pharmacol. 2014) [34]

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preventive, sanitary, hygienic, environmental, therapeutic measures to prevent the development of cardiovascular pathology of industrial and environmental genesis.

Cardiotoxic effect of metal nanoparticles

Recently, the relationship between exposure to heavy metal NPs and cardiovascular disease has been of particular concern. It is suggested that the heart is a specific target of nanoparticles. Scientific data confirming the effect of metal NPs on the cardiovascular system of the human body and experimental animals are currently limited.

The review [38] describes the effects and mechanisms of cardiotoxic effects of NPs of six metals and their oxides, which are actively used in various fields of human activity, in particular titanium oxide, zinc oxide, silver, carbon, silicon dioxide and iron oxide. A generalized scheme of cardiotoxicity of metal NPs, taking into account the mechanisms and specific biochemical markers of heart damage, is presented in Figure 3.

The experiment showed that exposure to silver NPs increased the synthesis of anions in the heart tissue of rats and stimulated oxidative stress with damage to cardiomyocytes [39, 40]. After subchronic (dermal) application of Ag NPs in guinea pigs, a slight accumulation of Ag in various organs, including the heart, was found. At the same time, deformation of cardiomyocytes was observed.

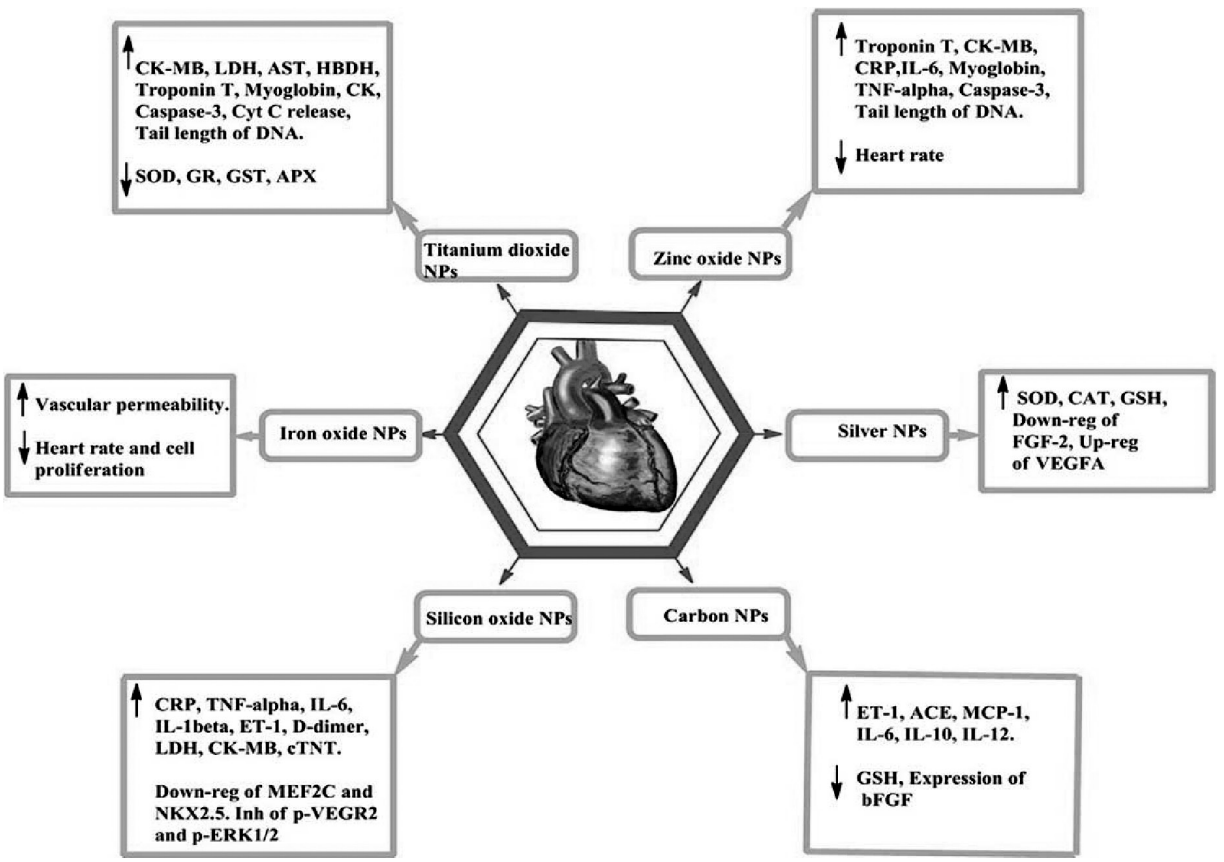

Figure 3. Cardiotoxic effects and mechanisms of cardiotoxicity of metal nanoparticles and their oxides
Note. ↑ – indicates an increase, and ↓ – a decrease in indicators [38].

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Fibroblast growth factor-2 (FGF-2) in the heart contributed to the emergence of pathological conditions such as hypertrophy, atherosclerosis and ischemia/reperfusion (I/R) [41].

Prolonged oral administration of colloidal solutions of gold NPs 2 nm in size to adult mice caused toxic changes in the heart, which were manifested in all tissue components of the myocardium, the most pronounced at a dose of 10 μg/ml after 7 days of observation. Morphological changes of the vessel wall of the microcirculatory bed were observed. In the endothelium of capillaries dystrophic changes were found in the cities of accumulation of gold NPs, an increase in the number of microvilli, a sharp activation of pinocytosis. The authors explain the direct changes in the cytoplasm and nucleus of cardiomyocytes by the toxic effects of NPs. Dystrophic changes in cardiomyocytes were more pronounced on the 28th day of the experiment, which can lead to cardiac dysfunction [42].

DNA damage, damage and apoptosis of heart cells, as well as an increase in the level of biomarkers of cardiomyocyte damage – troponin T, CPK-MB and myoglobin – were observed after oral administration of ZnO to rats. In addition, an increase in serum levels of inflammatory biomarkers, including: TNF-α, IL-6, and C-reactive protein (CRP), the induction of which may play a fundamental role in cardiac toxicity due to exposure to NPs ZnO [43]. Other authors have shown that under the exposure of ZnO NPs in the culture of cardiac myocytes, an increase in the level of TNF-α and ROS synthesis was determined, which leads to DNA damage. Increased synthesis of TNF-α can lead to the activation of other cytokines, such as IL-6, which is known as the main stimulator of C-reactive protein production – a marker of inflammation [44]. ZnO NPs can cause cardiotoxic effects due to the stimulation of systemic inflammation (increased TNF-α levels), disruption of calcium homeostasis, which can lead to the accumulation of Ca^{2+} in the cytosol [45]. This phenomenon is associated with myocardial damage. It was found that ZnO NPs caused an increase in troponin and CK-MB, as well as an increase in caspase-3 activity and DNA fragmentation of heart cells, which are signs of damage and death of cardiomyocytes [46].

Comprehensive studies, which included the use of biochemical, cytogenetic and morphological methods, revealed the negative effect of NPs of iron, copper, zinc oxides at a concentration of 0.05–5.0 mg/kg when administered orally to laboratory animals as dietary supplements. It was found that iron NPs damages myocardial cell membranes, contributing to an increase in serum AST and CK activity, with a pronounced effect observed when administered at concentrations of 0.05 mg/kg and 5.0 mg/kg. The introduction of copper NPs causes the development of pathological processes in the liver, which is manifested by an increase in the activity of AKT, GGT and an increase in the level of bilirubin in the blood serum. Metal oxide NPs at concentrations of 1.25 mg/kg and 2.5 mg/kg had a toxic effect on hepatocytes and myocardial cells, which was similar to the isolated effect of copper NPs and iron NPs. It was shown that the toxic effect of NPs is manifested by the activation of inflammatory processes, organ hemorrhage, dystrophy, necrosis and the appearance of micronuclei in cells [47].

Experimental studies have been carried out to assess the toxicity of iron oxide NPs for medical and industrial use [48]. It was found that after subcutaneous injection, superparamagnetic iron oxide NPs were distributed in the heart, lungs, kidneys, liver and spleen. Due to the generation of ROS, iron oxides lead to oxidative effects, causing cytoskeleton

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disruption, decreased proliferation and cell death in these organs.

Studies of the effect of ferromagnetic fluid on the vascular system and blood coagulation system using phantom systems for intravenous administration of drugs have shown that magnetite penetrates from the lumen of the vessels through the pores in the vascular wall into the intercellular space, then through the cell membrane into the cell, where it is localized on cell organelles for some time. According to the results of coagulogram, it was found that intravenous administration of magnetite at a dose of 80 mg/kg of body weight causes a shift of the coagulation system towards hypercoagulation. At a dose of 125 mg/kg of weight there is a «breakdown» of the hemostasis system and the development of disseminated intravascular coagulation syndrome. It was found that inhalation exposure of 0.8 and 20.0 mg/kg 22 and 280 nm iron oxide NPs caused induction of reactive oxygen species in cells, hyperemia, hyperplasia and fibrosis of lung tissue of rats, as well as disruption of the blood coagulation system [49].

Seong Cheol Hong et al. [50] report an increased vascular permeability after exposure to NPs iron oxide and a slight change in the viability of heart cells and their genetic content. It was also investigated that the direct effect of iron oxide NPs on human aortic endothelial cells (HAEC) and possible indirect effects on monocytes (U937 cells) *in vitro* [51]. During the study, HAEC and U937 cells were exposed to 22 nm Fe_2O_3 and 43 nm Fe_3O_4 (at concentrations of 2, 20, 100 mg/ml). The obtained results indicate that HAEC cells showed cytoplasmic vacuolization, activation of mitochondrial respiration and death. Activation of nitric oxide (NO) synthesis was determined in HAEC cells, which coincided with an increase in the activity of NO synthase. Adhesion of monocytes to HAEC was significantly enhanced. Enhanced expression of intracellular adhesion molecule-1 (ICAM-1) and interleukin-8 (IL-8), which is considered as an early stage of atherosclerosis, was detected. The authors concluded that iron oxide NPs (Fe_2O_3 and Fe_3O_4) can cause inflammation and dysfunction of the endothelial system in three ways: NPs interact directly with the endothelial monolayer; NPs are phagocytosed by monocytes and then dissolved, thus affecting endothelial cells as free iron ions; NPs are phagocytosed by monocytes, and stimulate oxidative stress.

Since endothelial inflammation is crucial for the development of cardiovascular pathology, the effect of metal oxides NPs on human aortic endothelial cells (HAEC line) was studied [52]. HAEC cells were incubated for 1–8 hours with different concentrations (0.001–50 μg/ml) of Fe_2O_3 NPs, ZnO NPs, and then measured the levels of mRNA and protein of three inflammatory markers: intracellular adhesion molecule-1, interleukin-8 and chemotactic monocyte protein-1. The data obtained indicate that the delivery of NPs to the surface of HAECs and their uptake by cells directly correlates with the concentration of particles in the cell culture medium. Fe_2O_3 nanoparticles did not stimulate an inflammatory response in HAECs at any of the concentrations tested; whereas ZnO NPs induced a pronounced inflammatory response above a threshold concentration of 10 μg/ml. At the highest concentration, ZnO NPs resulted in significant cell death. These results demonstrate that inflammation in HAECs after acute exposure to metal oxide nanoparticles depends on the particle composition.

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Conclusions

1. Clinical and epidemiological studies convincingly prove that heavy metals – lead, cadmium and iron – play an important role in the pathogenesis of cardiovascular diseases in people exposed to them in the workplace, in particular the development of hypertension, atherosclerosis, cerebrovascular pathology, peripheral vascular disease.
2. The results of experimental *in vivo* and *in vitro* studies indicate that the cardiotoxic effect of heavy metals is realized both by indirect action on the cardiovascular system and directly by toxic effects on the heart and blood vessels (endothelial dysfunction). The toxic effect of heavy metals is based on interrelated mechanisms, among which the leading role is played by the increased formation of active radicals with the activation of lipid peroxidation and the development of oxidative stress.
3. It has been established that lead and cadmium compounds as well as iron oxides NPs, in comparison with their micro- and ionic forms, are easier to overcome biobarriers, accumulate in the heart tissue, stimulate oxidative stress and apoptosis of cardiomyocytes. The dominant mechanism in the development of cardiovascular diseases under the influence of metal nanoparticles is their cyto- and genotoxic effect on cardiomyocytes and endothelial cells.

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