PHARMACOLOGYCAL REVIEWS

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UDC: 615.37:616-018.74-008.6 **DOI: 10.18413/2313-8971-2017-3-3-135-156**

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LIPID DISTRESS-SYNDROME AND PROSPECTS OF ITS CORRECTION BY STATINES

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Abstract

Endothelial dysfunction in peritonitis: The formed concept of lipid distress syndrome (LDS) allows us to develop a working hypothesis on the key role of endothelial dysfunction in the aggressive development of atherosclerosis.

The role of vascular endothelium in atherosclerosis: The process of NO production from L-arginine through eNOS involving tetrahydrobiopterin (BH4) is discussed. With the degradation of BH4 along the free radical path, an "eNOS uncouplation" (uncoupled eNOS).

The clinical role of statins: Statins manifests itself by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA reductase). Many large, randomized clinical trials have shown that lipid-lowering strategies that include statins have an anti-atherogenic potential.

Pleiotropic effects of statins: Direct inhibition of small GTP-ase prenylation in vascular cells forms the essence of the hypothesis that explains the rapid pleiotropic effect of statins on the vascular wall, which does not depend on reducing lipid levels.

Endogenous antioxidant defense systems: Effects of stasms. Statins have a beneficial effect on the vasculature not only by suppressing the prooxidant enzyme, but also by increasing the intensity and activity of endogenous antioxidant systems.

The effect of statins on redox-sensitive transcritic pathways: One of the most important pathways is the NF-kB via the PI3K/Akt pathway.

Experimental evidence of endothelioprotective properties of statins in the modeling of endotoxin-induced pathology: The use of HMG-CoA reductase inhibitors in the background of the fashion modeling endotoxin-induced pathology, leads to the development of a dose-dependent endothelioprotective effect, which is expressed in the normalization of QED, as well as the normalization of biochemical markers of inflammation (C-reactive protein) and the level of pro-inflammatory drugs. At the same time, positive dynamics of the final products of NO and eNOS expression was detected.

Keywords: Statins, endothelial dysfunction, endotoxin-induced pathology, NF-kB and PI3K/Akt pathways.

Endothelial dysfunction in peritonitis

In recent years, works of VS Savlyev, VA Petukhov and co-authors put forward the concept of lipid distress syndrome (LDS) [1, 2, 3]. The concept was based on epidemiological studies, which indicate that in a remote period after an abdominal catastrophe in 10-20 years, patients develop atherosclerosis with catastrophic

consequences leading to the cardiovascular continuum [4]. The cause of arterial damage in persons who have undergone an abdominal catastrophe is not only endotoxin aggression, but also as a consequence of endothelial dysfunction with the further development of atherosclerosis and its complications [4, 5, 6, 7,].

In the opinion of the authors, endotoxin aggression accompanies the human body from early childhood, but clinically significant pathology develops only when endotoxin-binding and endotoxin-limiting organism systems are damaged [8]. In case of abdominal catastrophe, excess amounts of endotoxins enter the bloodstream to disrupt the adaptive capacity of these systems and multi-organ failure [9] It can be assumed that infectious diseases without adequate antibiotic therapy similarly deplete the antiendotoxin defense mechanisms, which primarily include high-density lipoproteins and lead to development endothelial dysfunction of atherosclerosis [10] It seems that endotoxemia is a starting point in the development of lorganorganic disorders with LDS. Further long-term endotoxinemia against the background of the dysbiosis of the gastrointestinal tract forms the conditions for the progression of endothelial dysfunction [11].

Researches of the last years confirmed a role of endothelial dysfunction in a pathogenesis of many cardiovascular diseases. Clinical implication of endothelial dysfunction is the perversion of reaction to influence of physiological or pharmacological incentives when normal vessels react dilatation. Gravity of atherosclerotic process always correlates with endothelial dysfunction, and standard therapy of cardiovascular diseases doesn't eliminate endothelial dysfunction, and keeps risk of development of complication in several times [3, 6, 11].

It is possible to believe, that the trigger of endothelial dysfunction is the Gram – липополисахарид. At the same time realization has the prescription mechanism at the low concentrations, and at high – macrophagic CD 14 the effect is complemented with other mechanisms enlarging permeability of an endothelium [5, 12].

Developing in the abdominal catastrophe, endothelial dysfunction can not be treated in isolation as soon as arteriolar vasculitis, an important role in the sequence of events plays the liver as the main target organ of LDS. Stimulated Kupfer cells reduce the synthesis of NO by 80-90%, causing local dysfunction of the hepatic vessels, followed by a powerful release of pro-inflammatory cytokines into the inflammatory bloodstream [13, 14]. At the same time, the concentration of TNF, C-reactive protein and other cytokines [15] and oxidized low-density lipoproteins significantly increase. The latter leads to a decrease in the synthesis of heparan and an increase in the size of the interendothelial gaps [16, 17, 18]. It is important to note that even a short-term increase in vascular permeability for macrophages with further endotoxin exposure significantly enhances endothelial dysfunction. At the same time, the protective role of high-density lipoproteins in limiting the activity of macrophages weakens [11, 19, 20]. At the same time, in addition to para- endothelial transport, the mechanism of transfer is accelerated by the co-endothelial mechanism and its activity is proportional to the level of endotoxemia [21].

The levels of P-selectin, interleukin 6 and others are the main markers of endothelial dysfunction [22, 23]. In clinical practice, a c-reactive protein is often used [24]. The quantitative determination of the latter correlates with Interleukin 1, Interleukin 6, TNF [25, 26].

C-reactive protein in its turn participates in the migration of monocytes to the atherosclerotic plaque and stimulates the formation of "foamy" cells by enhancing the capture of low-density lipoproteins by macrophages.

According to Savelyev V.S., Petukhov V. A., the information value S-reaktivnog about protein can SRB> the relation of "XC/LPNP"> LDL> XC> гомоцистеин> LP [9] is presented in the following form.

In this regard authors allocate several stages an endotoxin – the induced endothelial dysfunction. 1 stage – damage of a glycocalyx of an endothelium, 2 stage – permeability augmentation, 3 stage -damage, the last is fixed by emergence in a blood flow of the endotheliocytes circulating in a blood flow [12, 14, 18, 27, 28]

At early stages of atherosclerotic process, the formation of atherosclerotic and vasculitis is preceded by a thickening of the vascular wall.

This quantitative indicator received the name intimamedia thicknes a complex of the "erotic media" of KIM [2, 7, 29] Essential value in recent years had an opportunity of an intravital not invasive research by means of an US, a dopler and td. UZVR technique (ultrasound of high resolution) the offered D.S. Celermajer et al. on the humeral artery, the greatest distribution [7, 8]

Pharmacological correction of LDS syndrome in abdominal catastrophe according to Saveliev VS and Petukhov VA [9] should be reduced to two components: 1 – endotoxin binding therapy (enterosorbent, plant hepatoprotectors, probiotics of metabolic action 2 – endothelioprotection (quircetin-glucoronide of red leaves of grapes)

Based on the above, one can conclude that the formed concept of LDS syndrome as the consequence of abdominal catastrophe allows us to develop a working hypothesis on the key role of endothelial dysfunction in the aggressive development of atherosclerosis and its complications that lead to the cardiovascular continuum. This hypothesis is confirmed by numerous data on the dynamics of biochemical markers of endothelial dysfunction (C-reactive protein, pro-inflammatory cytokines, circulating endotheliocytes), as well as the results of instrumental studies of ultrasonic tomography with evaluation of the intima-media complex and endothelium-dependent vasodilatation.

At the same time, the following questions arise:

Any endotoxemia can induce endothelial dysfunction or caused exclusively by lipopolysaccharides of Gram negative bacteria as for peritonitis ?;

What experimental models besides peritonitis can be used for the development of endotoxin-induced endothelial dysfunction ?;

Which of the biochemical markers of endothelial dysfunction or their combination with functional studies most adequately quantify the development of endotoxin-induced endothelial dysfunction ?;

Separate discussion requires a strategy of pharmacological correction of endotoxin-inducing endothelial dysfunction and the prevention of aggressive development of atherosclerosis. We basically agree with the first part of endotoxin-binding therapy, especially in conditions of peritonitis and other conditions, accompanied by an infectious-toxic shock. However, the use of the term vegetable antioxidants as endothelial protectors from the standpoint of modern pharmacology is not sufficient. In this connection, in the following sections of the review, we propose to discuss the possibility of the pathogenetically justified use of HMG Co-A reductase inhibitors both in monotherapy and in combination with the donor NO L-arginine, nonselective and selective inhibitors of arginase and recombinant erythropoietin.

The role of vascular endothelium in atherosclerosis

As it known, endothelial dysfunction is currently considered as one of the key triggers in the development of the atherosclerotic process. Endothelial dysfunction is characterized by reduced availability of NO. This causes an increase in intracellular cyclic GMP, and induces vasodilation. In addition, NO also participates in the regulation of other processes, such as platelet aggregation and leukocyte adhesion, and plays an important role in vascular homeostasis [29]. The main enzymatic source of NO in the vascular wall is the endothelial synthetase of nitric oxide (eNOS), which is located mainly in endothelial cells. eNOS is a complex that uses L-arginine and molecular oxygen (O2) as a substrate for the production of NO and L-citrulline.

This is achieved by electron transfer using NADPH as a donor from the flavin reductase domain from one monodomain to the other where the active gemm-iron site [30, 31] is located. The presence of calmodulin, which activates calcium binding, increases the rate of electron flow. In place of the heme, electrons are used to reduce and activate O2, which in turn is used to produce NO through the two-step oxidation of L-arginine. This process requires the binding of the cofactor tetrahydrobiopterin (BH 4). The enzyme that limits the rate of biosynthesis of BH 4 is called cycloshydrolase guanosine triphosphate (GTPCH). When BH 4 is associated with eNOS, the enzyme is considered "linked" [3]. The adhesion of eNOS is important for the physiological function of the vascular endothelium. Degradation of BH 4 on the free radical path, especially with peroxynitrite (ONOO -), leads to a condition known as "uncoupling eNOS" of the enzyme. In the

absence of BH 4, the electron flux in eNOS is disrupted; this leads to the dissociation of a divalent-molecular oxygen complex, resulting in eNOS for converting O2 to superoxide (O2 -) radicals instead of producing NO [32]. O 2 – reacts with NO to form ONOO -, which can additionally oxidize to BH 4, creating a vicious circle of eNOS disconnection. As a result, the drop in NO production inhibits endothelium-dependent vasodilation, disrupts vascular homeostasis and leads to endothelial dysfunction [31]. In addition, ONOO – has a fixed role in the oxidation of low density lipoprotein (LDL), and is also responsible for the nitration of various cellular components. The accumulation of nitrated proteins is a potent marker of oxidative nitroergic cell damage. ONOO – and can induce cell apoptosis and necrosis even at high concentrations, further exacerbating endothelial dysfunction [33].

Endothelial dysfunction was established as an important predictor of future cardiovascular events, regardless of other risk factors. A number of studies have shown a link between impaired endothelium-dependent vasodilatation of the brachial artery and an increased risk of cardiovascular complications in patients undergoing vascular surgery [34], including in the absence of obstructive arteriosclerosis [35]. Recently, using meta-analysis, it was concluded that an increase in the diameter of the brachial artery during the cuff test is inversely associated with the risk of the cardiovascular continuum. At the same time, the risk is more pronounced in populations at high risk in the presence of traditional predisposing factors, and an increase in vasodilatation of the brachial artery by 1% leads to a 9% decrease in cardiovascular risk [36].

Oxidative stress and atherosclerosis. Modern understanding of the pathogenesis of cardiovascular diseases confirms the important role of free radicals (ROS) in atherogenesis [37]. Classical risk factors for atherosclerosis, such as diabetes mellitus, hypertension and smoking, are associated with increased production of ROS in the vascular wall [38]. One of the main factors in the development of the atherosclerotic process is the oxidation of lipoprotein molecules. First of all, the reaction of LDL + ROS leads to the formation of oxidized low density lipoproteins (oxLDL). This occurs primarily in the subendothelial space, rather than in the plasma, in which there are many antioxidant defense mechanisms [39, 40]. ROS-mediated dissociation of eNOS causes dysfunction of the endothelium layer, through the mechanisms presented earlier. The binding of oxLDL to a lectin-like receptor induces activation of redox, proinflammatory transcription pathways (eg, nuclear factor kappa B [NF-kB]) in endothelial cells. This induces the release of inflammatory cytokines (such as interleukin-6 (IL-6) and increases the expression of cell adhesion molecules (eg, vascular adhesion molecule 1 (VCAM-1).) As a result, circulating monocytes are attracted to the vascular endothelium, where they adhere to the increased expression of adhesion molecules and penetrate the subendothelial space. There they absorb (phagocytrate) oxLDL molecules, acquire microphage-like characteristics, and eventually turn into foamy cells. This further exacerbates the inflammatory processes triggered in the vascular wall and creates a vicious circle where more monocytes / macrophages are attracted to the subendothelial space. In addition, ROS inflammatory cytokines cause the migration of smooth muscle vascular cells in the intima. The accumulation of saturated lipid membranes of foam cells and the parallel migration / spread of smooth muscle cells ultimately lead to the formation of atherosclerotic plaques.

Despite the obvious role of oxidative stress in the development of atherosclerosis, the actual causal relationship in the human body has not been conclusively proven. There is a question: – is the accumulation of ROS the cause of atherosclerosis or free radicals appear during its development [40]. Prove a causal relationship is difficult. Oxidative stress is widely studied in experimental models. Clinical studies have yielded results that are largely consistent with fundamental research. Thus, oxidative stress is now universally recognized as one of the key components of cardiovascular disease [39, 40].

Taking into account the participation of ROS in the pathogenesis of atherosclerosis, a therapeutic approach is designed logically to introduce biologically active antioxidant supplements such as ascorbic acid (vitamin C), alpha-tocopherol (vitamin E), and others. These compounds act as exogenous traps of free radicals and their use was considered a rational therapeutic

strategy for restoring the vascular oxidation-reduction balance and preventing cardiovascular diseases. Indeed, since 1994, more than 50 large randomized studies that used antioxidant vitamins in primary and secondary prevention of cardiovascular disease have been published, with disappointing results. The latest meta-analysis, based on the total population of nearly 300,000 participants, scattered across 50 randomized trials, concludes that there is no evidence to support the use of antioxidants for the prevention of cardiovascular disease [41].

The disappointing results of the use of antioxidant additives, in our opinion, should in no case be interpreted as invalidating the hypothesis of oxidative stress. For example, Patrignani et al. [42, 43, 44, 45] found that supplements with doses of vitamin E to 1200 mg / day did not affect the urinary concentration of 8-iso-PGF2a (a noninvasive marker of oxidative stress in vivo) in healthy smokers. In contrast, comparable doses of vitamin E significantly affect the level of 8-iso-PGF2a in clinical settings in patients with risk factors for cardiovascular disease. It is interesting that there is a linear correlation between the basal rate of excretion of 8-iso-PGF2a and changes in this index of lipid peroxidation depending on changes in the level of vitamin E in plasma. These results are consistent with the hypothesis that the basal rate of lipid peroxidation is the main factor determining response to the exogenous introduction of vitamin E.

The clinical role of statins: an effective lipid-lowering strategy

Statins are organic molecules, originally derived from fungi. They exhibit their effect by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA reductase) by competitive inhibition of substrate binding to the active site of the enzyme, due to their structural similarity to HMG-CoA [46, 47]. Inhibitors of HMG-CoA reductase is a rate-limiting enzyme in the biosynthesis of cholesterol. This enzyme converts HMG-CoA to mevalonate, which is then phosphorylated and converted to isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP). These molecules serve as isoprenoid precursors farnesyl pyrophosphate (FPP), which is converted to geranyl-geranium pyrophosphate (GGPP) and squalene. In hepatic cells, squalene forms the basis of ergosterol and subsequently the synthesis of cholesterol. Since a significant percentage of total cholesterol in the human body is endogenously produced, inhibition of HMG-CoA by statins leads to a subsequent decrease in cholesterol and, in particular, low-density lipoprotein [48].

Many large randomized clinical trials have shown that lipid-lowering strategies that include statins have an anti-atherogenic potential and reduce the risk of developing myocardial infarction and stroke. A 31% decrease in the number of coronary events in hypercholesterolemic patients after treatment with pravastatin (40 mg / day) [49, 50]. A recent review of the Cochrane database leads to the conclusion that statins reduce vascular complications and mortality from all causes in patients with no history of coronary artery disease [50]. Similarly, prolonged use of pravastatin in patients with ischemic disease demonstrates a significant reduction in coronary death from all causes in patients receiving pravastatin (40 mg / day [51]. In addition, in patients with CABG, aggressive lovelopidemic therapy of lovastatin + cholestyramine was more effective in compared with more conservative treatment [52]. As a result of these and other large-scale studies, statins are integral part of the drug therapy that recommended after major cardiovascular event. The latest WHO recommendations and the Russian guidelines recommend the initiation of statin therapy as a secondary prophylaxis in the presence of ischemic heart disease or other atherosclerotic vascular disease (class IA), with target LDL levels below 100 mg / dl, directed at least by reduction 30% of previous levels [53].

The pleiotropic effects of statins

Most of the early clinical trials of statins have been focused on correcting dyslipidemia in patients with CVD with high LDL cholesterol. However, an analysis of further studies reveals the beneficial effect of statin therapy in patients with CVD on newly diagnosed coronary heart disease or in patients who need revascularization, regardless of their LDL level [54, 55, 56, 57]. Similarly, post-factum analysis of the POST-CABG study shows a positive effect of intensive statin therapy on cardiovascular disease regardless of the decrease in lipid levels [55, 56, 57]. The concept, that statins can potentially have

effects beyond hypolipidemic capabilities is further enhanced by the verdict of the JUPITER trial in which non-lipidemic healthy subjects with high C-reactive protein levels (CRP) were randomized to receive rosuvastatin 20 mg / day or placebo [58] . The results of this study show that treatment with statins reduces the level of CRP and the frequency of major cardiovascular events. The effects of statins do not depend on LDL. This decrease in the level of C-reactive protein was termed "pleiotropic" and was the focus of extensive research in the last decade.

Direct pleiotropic effects of statins on vascular endothelial function in humans have been demonstrated by comparing the effects of various lipid-lowering strategies. In a randomized trial of patients with chronic heart failure for 4 weeks with simvastatin or ezetimibe (10 mg / day), statin showed a marked improvement in the results of the cuff test on the brachial artery compared with ezetimibe, despite a similar reduction in LDL levels [59, 60]. Similarly, in patients with dyslipidemia without cardiovascular disease, 40 mg / day of simvastatin improved cuff test results and the level of vascular Rho kinase was significantly higher than simvastatin 10 mg / day plus ezetimibe 10 mg / day [61]. Another recent meta-analysis, which examined the effects of statin therapy on cuff test results in diabetic patients, concluded that statins improve endothelial function, but only in patients who have no signs of severe endothelial dysfunction [62]. The latter highlights the role of prevention and modification of risk factors that can be realized with the use of statin therapy. Interesting, theat sudden cessation of treatment with simvastatin in patients with coronary heart disease leads to a significant reduction in the cuffing in the cuff sample in the first week after cessation of treatment, the effect does not correlate with an increase in rebound levels of LDL [63]. Conversely, in healthy people, the abrupt discontinuation of statin treatment also leads to a reduction in vasodilation in the cuff test on day 1 after discontinuation, which is restored to baseline within 1 week [63]. These results emphasize the potential of endothelium-protective pleiotropic effects of statins, as well as the need for an appropriate treatment regimen.

As mentioned earlier, isoprenoids FPP and GGPP are intermediate products of cholesterol biosynthesis, which is inhibited by statins. Protein prenylation is an important post-translational modification. The family of small GTP-as (Ras, Rho, Rac, etc.) is an important cellular target for prenylation. The addition of FPP or GGPP residues in proteins is crucial for lipid anchoring and activation of Rho and Rac [64]. Geraluleranization from Rho activates Rho-associated protein kinase (ROCK); Po / ROCK pathway is involved in the control of various cellular functions, including proliferation, cell migration, oxidation-reduction signaling and apoptosis [65, 66]. In addition, Rac is involved in the activation of the NADPH oxidase complex and thus plays an important role in regulating the generation of reactive oxygen species, as will be discussed in detail later.

Cholesterol biosynthesis is active not only in hepatocytes, where it was first described, but it is also important for the cellular homeostasis of vascular cells. Lipophilic statins (for example, atorvastatin and simvastatin) can passively diffuse through the lipid bilayer of the cell membrane and, therefore, can be assimilated by a large number of cells, and not only by hepatocytes (which also have such active transport mechanisms) [67]. Direct inhibition of small GTP-ase prenylation in vascular cells forms the essence of the hypothesis that explains the rapid pleiotropic effect of statins on the vascular wall, which does not depend on lowering lipid levels [67, 68].

Sources of free radicals as therapeutic targets of statins in the vascular wall. Cell redox imbalance, characterized by increased production and reduced utilization of ROS, is involved in many pathophysiological processes, including the development of cardiovascular diseases. Statins are probably the most effective and currently available pathway that inhibits prooxidant enzyme systems present in the vascular system and enhances antioxidant defense mechanisms. The effect of statins on the redox systems of the cell has been extensively studied in cell cultures in vitro. Nevertheless, the results obtained in experiments performed in such "model systems" do not necessarily reflect the processes in vivo and can not be applied to human diseases. A large number of experiments have been performed in human umbilical vein endothelial cells, which have significant functional differences compared

to arterial endothelial cells, which are directly related to the development of atherosclerosis.

The effect of statins on eNOS. The effect of statins on eNOS is well documented in the literature. It has been proven that pleiotropic effects of statins in the vasculature are at least partially mediated by changes in eNOS expression.

It was shown that geranylgearylation from GTPase Rho leads to a decrease in eNOS in the endothelial cell. Statin therapy is inhibited by GGPP formation and therefore leads to increased expression of eNOS, which was revised in the case of co-incubation with GGPP [69, 70]. Increased endogenous levels of LDLs also adversely affect the expression of mRNA in eNOS [71]. The mechanism by which statins increase the stability of eNOS mRNA is an increase in the eNOS mRNA of polyadenylation, due to changes in the cytoskeleton, after Rho inhibition [71]. In addition, the exposure of the H2O2 -induced, aging, smooth muscle cells to statins activates the phosphatidylinositide of the 3-kinase (PI3K) / Akt pathway and enhances the expression of eNOS [72]. More recently, eNOS mRNA has been identified as a target of micro-RNA-MIR-155, which is activated by inflammatory stimuli, such as tumor necrosis factor alpha (TNF). It is important to note, that this effect was weakened by simvastatin. The beneficial effect of statin was found when combined with megalonate or GGPP. Interestingly, the authors mimicked the effect by inhibiting RhoA, suggesting that the mevalonate / GGPP / RhoA pathway underlies the observed effects of simvastatin at the microRNA-155 level [73]. In animal experiments with diets induced by endothelial dysfunction, increased expression of eNOS mediated by statins leads to an improvement in endothelial function [74].

In addition to increasing the expression of eNOS at the transcriptional and post-transcriptional levels, statins cause an increase in eNOS activity at the post-translational level. eNOS has several sites of phosphorylation activation. The effect of fluvastatin on smooth-muscle cells of the human umbilical cord showed an increase in the phosphorylation of eNOS upon activation of Ser-633 and Ser-1177 genes via protein kinase A (PKA) – and PI3K / Akt-mediated pathway, respectively [75]. The statin-induced induction of eNOS phosphorylation by Ser-1177 is realized through the heat shock protein-90 [76]. On endothelial cell culture, it was shown that atorvastatin to increase eNOS phosphorylation by Ser-633 in adenosine monophosphate-activated protein kinase (AMPA) -mediated pathway [77]. In addition, in experiments on the mesenteric artery of rats incubated with simvastatin, it was found that the drug causes rapid AMPK-mediated phosphorylation of eNOS on Ser-1177 [78]. This leads to an improvement in endothelium-dependent vasodilation. The effect is removed both by inhibiting eNOS L-NAME and by joint incubation with mevalonate. In addition, statins also increase eNOS activity at the post-translational level by inducing its dissociation from caveolin-1. Caveolae are invaginations of the cytoplasmic membrane, formed mainly by the protein caveolin-1, which has the ability to bind eNOS and inhibit its enzymatic activity. Atorvastatin reduces the content of caveolin-1 and activates eNOS in endothelial cells, regardless of the presence or absence of LDL cholesterol [76]. This mechanism was also demonstrated in experiments on apolipoprotein E deficient mice, where rosuvastatin reduced caveolin-1 and improved cardiac function and blood pressure variability [79, 80].

Activation of eNOS does not necessarily result in an improvement in NO production. If there is significant dissociation of eNOS, then its phosphorylation causes induced activation to increase production of O 2 – instead of NO [81]. Nevertheless, cerivastatin or fluvastatin to prevent the dissociation of eNOS increase the expression and bioavailability of BH 4 in human umbilical cord endothelial cell culture [75, 82, 83]. In the experimental model of diabetes in laboratory animals, the administration of atorvastatin prevents the separation of NOS through the same mechanism [84]. Recently, in a randomized, double-blind, placebo-controlled clinical trial, it was demonstrated that on the 3rd day of treatment with atorvastatin (40 mg / d) in patients after coronary artery bypass grafting, the level of BH 4 and eNOS of the internal thoracic artery increased compared to the placebo group [85]. This is accompanied by an improvement in the results of the cuff test on the brachial artery. It is important that these effects are rapid and

independent of the lipid-lowering effect of atorvastatin. In experiments on isolated segments of the human thoracic artery, atorvastatin causes an increase in the expression of the GCH1 gene, encoding guanidine triphosphate cyclohydrolase followed by an increase in the level of total tetrahydrobiopterin. The effect was reversed by joint incubation with mevalonate [85].

There is another mediated mechanism by which statins can enhance eNOS activity, improve its communication and enhance metabolism or prevent ADMA effects. Endothelial cells exposed to ADMA exhibit an increased inflammatory response, which is markedly reduced by the action of simvastatin indirectly through the extracellular pathway of the kinase receptor [86]. Treatment of rats with spontaneous hypertension with rosuvastatin revealed a decrease in the level of circulating ADMA and a decrease in vascular oxidative stress, regardless of the decrease in cholesterol [87]. Similarly, in the rat model of pulmonary hypertension, rosuvastatin increases DDAH expression, and then decreases serum ADMA levels, while increasing eNOS phosphorylation through the PI3K / Akt pathway [88]. Nevertheless, the results of clinical studies were contradictory. Some randomized studies have shown that short-term statin therapy reduces the level of circulating ADMA in humans [89, 90, 91], while other studies have not been able to find such an effect [92, 93, 94]. These conflicting results might be related to differences in the characteristics of the patients examined. It is interesting to note that in a small randomized trial, simvastatin failed to improve endothelial function in patients with high ADMA levels, but managed to do this in combination with oral administration of L-arginine in patients with low ADMA [95].

The effect of statins on NADPH oxidases. NADPH oxidase is the most important source of ROS in the vasculature, both in isolated segments of the arteries, and in culture of human umbilical vein endotheliocytes. It catalyzes the conversion of O 2 into O 2 • – radicals, using NADPH as an electron donor. This membrane-bound enzyme complex; components that depend on the corresponding homologue of the membrane subunits: Nox1-5 and Duox1 or 2. Endothelial cells possess Nox2, nox4 and Nox5, while Nox1, nox4, and Nox5 were found in the umbilical cord endotheliocytes. Nox2 is a form of the enzyme present in phagocytes. It consists of two membrane-associated subunits, p22 phox and gp91 phox-Nox2 (which make up the complex with cytochrome b558), as well as four cytosolic subunits, p40 phox, p47 phox, p67 phox and RAC1 or 2, which upon stimulation are transformed with flavocytochrome b558, which can lead to the assembly and activation of the enzyme complex. The activity of Nox1 and Nox2 can be stimulated with angiotensin II, growth hormone and pro-inflammatory cytokines, via p47phox phosphorylation [96]. At the same time, Nox5 is in a state without a Ca-dependent stimulation [97]. Conversely, nox4 does not require ROS for activation [96]. It has been found that increased expression and activity of NADPH oxidase isoforms in the vasculature, together with increased production of ROS, contribute to the onset and maintenance of the atherosclerotic process. Nevertheless, it should be noted that recent studies have found a potentially useful role for the ROS-independent nox4 isoform in the vascular wall, by increasing vasodilation in the H 2 O 2 -mediated pathway [98].

A significant number of publications are devoted to the role of statins in inhibiting the activity of NADPH oxidase. As mentioned earlier, activation of ROS and its localization in the membrane is necessary for the activation of Nox1 and 2-complexes, which are widely distributed in vascular cells and are involved in the pathophysiology of atherosclerosis. The most important step in the activation of ROS is its geranylgernaliticim on geranyl-geranyl triphosphate through biosynthesis of cholesterol. Given that statins suppress both the formation of isoprenoids and geranyl-geranyl triphosphate, a large number of studies have attempted to determine whether inhibition of HMG-CoA reductase can lead to a decrease in the activity of NADPH oxidase.

In experiments on culture of human umbilical cord endotheliocytes, statin therapy reduced p22 phox mRNA and p47 phox protein levels [99]. Endotheliocytes of human umbilical arteries under the influence of atorvastatin reduce the expression of Nox1 in the membrane localization of Rac1, which leads to a decrease in the production of ROS [100]. Statins can also inhibit the generation of reactive oxygen species in

isolated segments of coronary arteries of pigs, reducing p22 phox levels of mRNA [101]. Thus, cerivastatin in human cord tissue culture of endotheliocytes induces the activation of LPO in the Rac1 region, followed by activation of NADPH oxidase and an increase O2 – [102]. The mechanism by which NADPH oxidase exerts its effect is the colocalization of the acid ceramic of sphingomyelinase with the formation of membrane adhesions in the cell membrane. Statin treatment prevents the formation of these membrane adhesions induced by low-density, oxidized lipids, and then reduces the generation of O 2 – [103].

The effects of statins on NADPH oxidase have also been studied in animal models simulating cardiovascular pathology. Thus, the administration of statins in rats suppressed the activity of NADPH oxidase by means of mevalonate-dependent activation of ROS. This resulted in improved vascular NO production and further improvement in endothelial function [104]. In experiments with the modeling of atherosclerosis in rabbits, fluvastatin prevented an increase in p22 phox and gp91 phox induced by a high fat content and improved endothelial function and reduced plaque size [105]. Similarly, simvastatin suppressed generation of reactive oxygen species and restored endothelial function in rats with modeling of diabetes mellitus [106]. In the normocholesterolemic model of hypertension in rats, statins reduced the expression of the p22 phox and Nox1 [100] gene, as well as the levels of the p22 phox protein of the angiotensin I receptors, and there by reduced the production of oxygen reactants and improved endothelial function [107]. In the experimental model of ischemic stroke in rats, atorvastatin prevented an increase in generation and NADPH oxidase activity of the ROS in, by reducing the gp91 phox levels of mRNA and P47 phox localized in the membrane [108]. On the other hand, statins prevent the development of endothelial dysfunction in mice through Rac1-mediated activation of NADPH oxidase [109].

The cultivation of the cell lines obtained from patients demonstrated the relevance of the above observations to human physiology. Thus, treatment with statins reduced the level of gp91 phox in cultures of endotheliocytes of the internal thoracic arteries of a person obtained from patients undergoing aorto-coronary bypass grafting [110]. In a cross-over study, it was found that treatment with statins with hyperlipidemia leads to a decrease in the level of circulating gp91 phox, as well as markers of systemic oxidative stress [111]. The blockade of AT1 receptors in a randomized group of 49 patients with cholesterol-dependent oxidative stress after aorto-coronary bypass surgery compared with the placebo group showed that pravastatin (40 mg / day), irbesartan (150 mg / day), or both for 4- x weeks showed a significant positive effect [112]. Thus, statin therapy as well as combination therapy significantly increased eNOS expression and suppressed gp91 phox in the brachial artery during the cuff test, which indicates a synergistic effect on endothelial function, regardless of LDL-lowering effects [112]. Recently, it has been shown that short-term treatment with atorvastatin rapidly suppresses O2 – the formation and activity of NADPH oxidase in patients undergoing aortocoronary bypass irrespective of LDL-lowering effects [113]. This is also accompanied by a decrease in the plasma levels of malonic dialdehyde as a marker of systemic oxidative stress. In vitro incubation of human endotheliocytes with atorvastatin results in a decrease in p67 phox and ROS localization in the membrane. In this case, the effects were removed in the presence of mevalonate [113]. A similar mechanism of NADPH oxidase was found in human myocardiocytes [114].

Effect of statins on endothelial cells. As is known, endothelial cells synthesize prostacyclin (PGI 2) with the help of the enzyme PGI 2 – synthase. Its molecule, the precursor of prostaglandin H2, is itself synthesized from arachidonic acid by oxidation of fatty acids with cyclooxygenase. PGI 2 is an important vasodilator and an antithrombotic molecule that balances the effects of thromboxane A 2. Recently, it has been found that vascular PGI 2 can participate in the regulation of eNOS expression [115]. Di Francesco et al. [116] showed that inhibition of cyclooxygenase-2 induced by shift of heme oxygenase 1, results in the cessation of the effect of tumor necrosis factor in human endothelial cells [116]. Given that fluvastatin causes an increase in the expression of PGI 2 synthase and increases PGI 2 in human endothelial cells [117], this pathway can also

participate in the realization of vasoprotective effects of statins.

A statin-induced change in the activity of pro-oxidant enzymes may also partially explain the useful antithrombotic effects of statins, as evidenced by the reduced release of thromboxane A2 from the isolated rat aorta in the cyclooxygenase-2-mediated pathway [118]. Thus, the yield of 8-isoprostane is elevated in rat-resistant hypertensive rats. This is eliminated by the appointment of atorvastatin and improves endothelial function and restores the redox potential of the vascular wall [119]. Similarly, atorvastatin-induced modification of 5-lipoxygenase leads to a reduction in the vulnerability of plaques in rabbits [120].

Endogenous antioxidant defense systems: effects of statins. Due to the constant impact of ROS, almost all living cells possess several enzyme antioxidant defense systems that control the final availability of ROS. Superoxide dismutase (SOD) is an enzyme that catalyzes the conversion of O2 – to H2O 2. Catalase is an enzyme located in peroxis that decomposes H2O 2 in water and O2. Glutathione (GSH) is a tripeptide that acts as an important antioxidant of the limiting effect of H2O2; this is achieved by reducing the sulfhydryl groups in the cysteine residues of other proteins, thereby protecting these proteins from oxidative damage. It is catalyzed by glutathione-S-transferase, as well as glutathione peroxidase (GSH-PXS), which leads to the formation of glutathione disulfide (GSSG) from two GSH molecules; GSH can be replenished through the effects of glutathione reductase. The GSH / GSSG ratio is widely used as a cellular marker of oxidation-reduction processes. Paraoxonase is an enzyme involved in protecting against oxidation of the LDL molecule. Other antioxidant enzyme systems are also present in cells such as thioredoxins, peroxedoxins, and so on.

It has been shown that statins have a beneficial effect on the vasculature not only by suppressing the prooxidant enzyme, but also by increasing the intensity and activity of endogenous antioxidant systems, in experimental models and clinical studies. Symvastatin can partially restore the renal levels of all three major cellular antioxidant systems protection (SOD, GSH-Px and catalase) and reduce levels of biomarkers of oxidative damage in diabetic animals [121, 122]. In addition, an improvement in endothelial function was found by increasing the SOD level in rats chronically treated with the eNOS L-NFME inhibitor [123]. The beneficial effect of atorvastatin on reducing the size of plaques in animals on an atherogenic diet was observed against the background of an elevated level of circulating paraoxonase [124].

The effects of statins on catalase activity levels have been demonstrated in a number of studies. For example, endotheliocytes of aorta of rats and umbilical artery of a person show an increase in the levels of expression of genes and catalase proteins after treatment with atorvastatin [100]. The effect is mediated by PI3K / Akt by [125]. In addition, in animal models of hypertension and diabetes mellitus, statins increase the expression of aortic catalase [100, 125]. An increase in statin-induced catalase levels has also been demonstrated with an aneurysm of the human abdominal aorta [126].

The effect of statins on redox-sensitive transcritic pathways

It has been established that the main mechanism by which ROS production contributes to the development of atherosclerosis is the initiation of oxidation-reduction sensitive transcriptional pathways in the vascular endothelium. These pathways regulate the production of pro-inflammatory, pro-atherogenic cytokines and cellular components that enhance oxLDL and macrophage infiltration, as well as the proliferation and migration of smooth muscle cells to the intima. One of the most important oxidation-reduction pathways is the NF-kB pathway. NF-kB is a transcription factor that controls the expression of a large number of proinflammatory genes. In its non-activated form, NF-kB is in the cytosol bound to its inhibitor (IκBα). H2O2 was originally proposed as a candidate for direct activation of NF-kB [127]. Currently, it is understood that ROS have the ability to indirectly modulate the function of NF-kB [128]. Proinflammatory mediators, such as TNF; activate IκB kinases (IKK). This leads to its degradation, thereby freeing NF-kB molecules. Therefore, NF-kB is translocated to the nucleus and binds to its response elements, initiating the transcription of pro-atherogenic mediators, such as IL-6, TNFα, , adhesion

molecule VCAM-1 and intercellular adhesion molecule (ICAM) -1, and others. Another pro-inflammatory transcription factor that can be induced by ROS is a protein-1 activator (AP-1). Like NF-kB, AP-1 regulates the expression of genes involved in inflammatory processes, cell proliferation and apoptosis, and plays a role in the atherosclerotic process.

The role of statins as potential inhibitors of NF-kB has been investigated in cell cultures where NF-kB activity was induced by various factors. Atorvastatin prevented the induced TNFα and angiotensin II-induced activation of NF-kB and the subsequent release of inflammatory mediators. Effects were prevented by farnesyl pyrophosphate (FPP) and geranyl-geranyl pyrophosphate (GGPP) [129]. Fluvastatin also attenuated CRP-induced activation of NF-κB in endothelial cells [130] of smooth muscle cells of the umbilical vessels [131]. Simvastatin and atorvastatin reduced oxLDL-induced activation of NF-κB in the human coronary artery [132]. These statin-mediated effects have also been demonstrated in experimental models of cardiovascular disease. Thus, simvastatin reduced NF-KB activity in atherosclerotic plaques and circulating mononuclears in animals with an atherosclerotic diet, regardless of hypolipidemic effects [133]. Similarly, the administration of cerivastatin significantly reduced the activity of NF-kB in the hearts induced by angiotensin II and did not affect the level of cholesterol in the blood [134]. LDL-independent anti-inflammatory effects of statins have also been extensively studied in cellular models both at the forefront of atherosclerosis and inflammation induced by pathogenic microorganisms. In the culture of human umbilical cord endothelial cells, the inflammation induced by Chlamydia pnevmonalae was significantly lowered under the influence of cerivastatin. Similarly, the release of inflammatory mediators was reduced by suppressing the activation of NF-kB [135, 136]. Also, in the culture of portal vein endotheliocytes infected with cytomegalovirus, the effect of fluvastatin slowed the activation of NF-kB, which reduced viral replication [137].

The impact of statins on the pathway of NF-kB can play a decisive role in preventing monocyte infiltration, the formation of foam cells and the proliferation of smooth muscle cells of the vessels. Simvastatin dose-dependently inhibits the TNF-induced increase in ICAM and VCAM-1 in endotheliocyte culture of the portal vein due to decreased activation of NF-kB; this leads to a decrease in the interaction of monocytes with endothelial cells [138]. Importantly, in vitro pravastatin prevents the effect of human monocytes on LDL-induced activation of NF-kB and the subsequent expression of inflammatory mediators [139]. In addition, atorvastatin inhibits interleukin-18 induced migration of smooth muscle aortic cells and the inactivation of NF-kB [140].

Various hypotheses have been proposed to explain the ability of statins to reduce NF-kB activity. It has been shown that statins cause an increase in the expression of IκBα genes in endothelial cells, and also reduce the expression of NF-kB and decrease binding to smooth muscle cell proteins, which leads to a general decrease in NF-kB activity in vascular cells [141]. In addition, statins decrease ROS-mediated activation of NF-kB in monocytes by decreasing the activity of IkB kinase [142]. Phosphatidylisothiazidyl 3-kinase-independent pathway, which involves inhibition of the IkB kinase / Akt signaling pathway in human endotheliocytes [143].

The ability of statins to inhibit NF-kB signaling has also been found in clinical studies. In a small nonrandomized study, the appointment of pravastatin (40 mg / day) 3 months before the planned carotid artery prosthetics led to stabilization of the plaque in the carotid artery, as evidenced by a decrease in NF-kB activation lipids [144]. In an aneurysm of the abdominal aorta simvastatin suppresses the generation of active oxygen species and the activity of NF-kB [145]. In a randomized trial, treatment with atorvastatin (80 mg / day) for 1 month prior to surgery resulted in a decrease in NF-kB activation in circulating mononuclears in combination with a decrease in inflammatory gene expression and cellular plaque infiltration [146].

One of the main ways that is crucial for the cellular antioxidant response is the nuclear factor (erythroid origin 2 (Nrf2). In its non-activated form, Nrf2 is in the cytoplasm, binds to proteins callin 3 and endothelium-associated protein 1 (Keap1). cysteine residues that are sensitive to

changes in ROS because of their sulfhydryl group (-SH) .The oxidation of these -SH groups dissociates the callin3 / Keap1 complex from Nrf2, which translocates into the nucleus and initiates the transcription of genes encoding endogenous antioxidant defense proteins It has been shown that simvastatin is able to activate Nrf2 via the PI3K / Akt pathway and then suppress the generation of reactive oxygen species in primary embryonic fibroblasts of the mouse [147] .A similarly, fluvastatin significantly increased the Nrf2 nuclear translocation in smooth muscle cells of the coronary artery through the same intracellular pathway.This leads to increased activity of antioxidant enzymes and reduced production of ROS [148].

Thus, the use of statins is currently a key strategy for reducing cardiovascular risk, both in primary and secondary prevention. In addition to their hypolipidemic properties, statins also have a number of direct, or pleiotropic, effects on vascular function, suppressing atherogenesis, which in some cases may even lead to regression of atherosclerotic plaques. For the past decade, the vascular endothelium has been identified as one of the main targets for antiatherogenic / pleiotropic effects of statins. Statins have the ability to restore the physiological balance between NO and ROS in the vascular endothelium, through a series of LDL-dependent and -independent effects. They increase expression, and the enzymatic activity of eNOS, the main source of O 2 • – radicals in the human vascular endothelium, which leads to an increase in NO biosynthesis. At the same time, they suppress the activity of prooxidant enzymes (such as NADPH oxidases, unbound Enos, and others) and increase the effectiveness of endogenous antioxidant systems in the vascular endothelium, which leads to a net reduction in ROS. By restoring the balance between NO and ROS in the vascular endothelium, statins also control the activation of the inflammatory processes of the vessels, and prevent the proliferation / migration of smooth muscle cells and lead to suppression of atherogenesis.

At the same time, there are several unresolved issues that need to be understood regarding the biological role of statins.

1. Their indirect influence requires study. For example, by changing the biology of perivascular fat tissue, which has a paracrine effect on the vascular wall.

2. The role of statin therapy in the pathogenesis of vascular disease and especially in atherosclerosis is clear. Statins are now involved in all therapeutic strategies in primary and secondary prevention of the cardiovascular system. They stabilize atherosclerotic plaques and improve survival (3). However, it is difficult to imagine that these effects are mediated primarily because of their direct or indirect "antioxidant capacity." Further studies are needed to study the efficacy of statins in other cardiovascular diseases with a large involvement of ROS in their pathogenesis. The last in full priory refers to endotoxin-induced pathologies. This would further expand their broad clinical application.

3. Finally, the ability of statins to exert a biological effect on the vascular endothelium, regardless of their primary pharmacological action, can serve as a "pharmacological model" for the development of new antioxidant strategies that aim to control the intracellular balance between production / elimination. These smart strategies should aim to imitate the pleiotropic effects of statins on the vascular endothelium.

Experimental evidence of endothelioprotective properties of statins in the modeling of endotoxin-induced pathology

The use of simvastatin HMG-CoA reductase inhibitors (2.2, 4.3 and 8.5 mg / kg), atorvastatin (1.1, 2.2 and 4, 3 mg / kg), rosuvastatin (2.2, 4.3 and 8.5 mg / kg) and nanoparticulated rosuvastatin (3, 6.3 and 11.6 mg / kg) against the background of endotoxin-induced pathology modeling leads to the development of a dose-dependent endothelioprotective effect, expressed in the normalization of QED, the prevention of increased adrenoreactivity and exhaustion myocardial reserve, as well as the normalization of biochemical markers of inflammation (C-reactive protein) and the level of pro-inflammatory cytokines. At the same time, positive dynamics of the final products of NO and eNOS expression was detected. It is noteworthy that the most effective was the nanoparticulated form of rosuvastatin, which supports the hypothesis of a change in the volume of distribution of the drug. Parallel to this, there was a decrease in hypertrophy of myocardiocytes and

a normalization of the morphological picture of the endothelium of small vessels of the kidneys.

Use of monotherapy with donor NO L-arginine (70 and 200 mg / kg), non-selective inhibitor of arginase BEC (5 and 10 mg / kg), selective inhibitor of arginase 2 Arginazine (1 and 3 mg / kg) and recombinant darbepoetin (50 and 500 μg / kg) in the modeling of endothelial dysfunction of the pathology revealed their high activity, expressed in preventing the increase in QED, adrenoreactivity, preservation of myocardial reserve and normalization of biochemical markers values (Total NO, eNOS expression, C-reactive protein, IL-6, TNF). In this case, the drugs had a dose-dependent effect and were approximately equally effective.

Use of combined use of L-arginine (200 mg / kg) with inhibitors of HMG-CoA reductase by simvastatin (8.5 mg / kg), atorvastatin (4.3 mg / kg), rosuvastatin (8.5 mg / kg) and nanoparticulated rosuvastatin (11.6 mg / kg) against the background of endotoxin-induced pathology modeling proved to be so effective that the values of QED, adrenoreactivity, conservation of myocardial reserve and biochemical markers (Total NO, eNOS expression, C-reactive protein, IL -6, TNF) did not differ from the indices of intact animals. The combined use of L-arginine and statins in the modeling of L-NAME-induced pathology also revealed a pronounced additive endothelial and cardioprotective effect, manifested in a decrease in QED, prevention of a decrease in NOx concentration, and an improvement in myocardial contractility in performing adrenoreactivity and load tests resistance. reduction of hypertrophy of myocardiocytes and normalization of the morphological picture of the endothelium of small vessels of the kidneys.

Combined use of non-selective inhibitor of arginase BEC (10 mg/kg) with simvastatin (8.5 mg/kg), atorvastatin (4.3 mg/kg), rosuvastatin (8.5 mg/kg) and nanoparticulated rosuvastatin (11, 6 mg/kg) did not show a positive pharmacodynamic interaction both in the modeling of endotoxin-induced and L-NAME-induced pathologies.

Combined use of the selective inhibitor Arginase 2 Argazine (3 mg/kg) with simvastatin (8.5 mg / kg), atorvastatin (4.3 mg / kg), rosuvastatin (8.5 mg/kg) and nanoparticulated rosuvastatin (11, 6 mg/kg) showed ectothelial and cardioprotective effect, which is expressed in preventing the increase in QED, adrenoreactivity, preservation of myocardial reserve and normalization of biochemical markers values (Total NO, eNOS expression, C-reactive protein, IL-6, TNF). At the same time, combined therapy revealed the additive effect of drugs. A similar dynamics was observed with L-NAME-induced pathology.

Use of concomitant use of recombinant darbepoetin (500 mcg / kg) with simvastatin (8.5 mg / kg), atorvastatin (4.3 mg / kg), rosuvastatin (8.5 mg / kg) and nanoparticulated rosuvastatin (11.6 mg / kg) on the background of modeling endotoxin-induced pathology exhibits ectothelial and cardioprotective effects. At the same time, combined therapy revealed the additive effect of drugs. Similar dynamics was observed in L-NAME-induced pathology, which was reflected in a decrease in the endothelial dysfunction coefficient, prevention of NOx concentration decrease, and improvement of myocardial contractility in performing functional tests and reducing myocardiocyte hypertrophy.

Vector analysis of the additive effects of the combined use of simvastatin, atorvastatin and rosuvastatin inhibitors and nanoparticulated rosuvastatin with L-arginine, arginase inhibitors-BEC and Arginazine and darbepoietin showed that, with endotoxin-induced pathology, the highest probabilistic percent of additions turned out to be in combinations of rosuvastatin with "Arginazine" (3 mg / kg) and dabropoietin (500 μg / kg), respectively, 31.9 ± 2.8 and 30.2 ± 2.9%.

Thus, the foregoing indicates that the problem of pharmacological correction of endotoxin-induced pathology and its components of endothelial dysfunction and multiple organ failure does not have a pathogenetically grounded pharmacological correction strategy. One of the possible ways is the use of drugs in the mechanism of action of which the principles of pharmacological pre- and post-conditioning, restriction of the activation cascades of LPO, NF-kB and the release of pro-inflammatory cytokines, as well as an increase in the level of ADMA and TNF-induced increase in ICAM are laid. It seems that for the role of "drugs of choice" in this situation the most meaningfully claim statins, including nanaparticulated dosage forms. At the same time, the potential of L-arginine endothelioprotective

agents, nonselective and selective inhibitors of arginase 2 and darbopoetin is not fully disclosed. In this case, the approaches to experimental research in this direction should be formed taking into account the possibilities of a complex comparative evaluation of the dose-dependent anti-inflammatory effects of HMG-CoA reductase inhibitors, their cardioprotective effects in coronary-occlusive infarction, endothelioprotective effects in endotoxin-induced endothelial dysfunction in both monotherapy and in combination with drugs possessing endothelioprotective effects of various mechanisms of action. As a control of endothelioprotective activity, a well-developed model of L-NAME-induced deficiency of nitric oxide can be used in our laboratory. At the same time, taking into account the special role of the processes of "low gradation inflammation" in the development of endotoxin-induced endothelial dysfunction, it is necessary to control the level of inflammatory markers and the dynamics of morphological changes in the "target organs" of the myocardium and microvessels of the kidneys.

Conflicts of interest

The authors have no conflict of interest to declare.

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Received: July, 13, 2017
Accepted: August, 30, 2017
Available online: September, 30, 2017