TOSHKENT TIBBIYOT AKADEMIYASI
«YOSH OLIMLAR TIBBIYOT JURNALI»

TASHKENT MEDICAL ACADEMY
«MEDICAL JOURNAL OF YOUNG SCIENTISTS»

ТАШКЕНТСКАЯ МЕДИЦИНСКАЯ АКАДЕМИЯ
«МЕДИЦИНСКИЙ ЖУРНАЛ МОЛОДЫХ УЧЕНЫХ»

IXTISOSLASHUVI: «TIBBIYOT SOHASI»

ISSN 2181-3485

Mazkur hujjat Vazirlar Mahkamasining 2017 yil 15 sentabrdagi 728-son qarori bilan tasdiqlangan O'zbekiston Respublikasi Yagona interaktiv davlat xizmatlari portali to'g'risidagi nizomga muvofiq shakllantirilgan elektron hujjatning nusxasi hisoblanadi.

№ 3 (10), 2022

Jurnaldagi nashrlar O'zbekistonda va xorijda ilmiy darajalar uchun dissertatsiyalar himoya qilinganda chop etilgan ishlar deb hisoblanadi.

Ilgari hech qayerda chop etilmagan va boshqa nashrlarda chop etish uchun taqdim etilmagan maqolalar nashrga qabul qilinadi. Tahririyatga kelgan maqolalar ko'rib chiqiladi. Nashr mualliflari maqolalarda keltirilgan ma'lumotlarning to'g'riligi uchun javobgarlardir. Materiallardan foydalanganda jurnalga va maqola mualliflariga havola bo'lishi shart.

Materiallar mualliflik nashrida chop etiladi.

Публикации в журнале учитываются как опубликованные работы при защите диссертаций на соискание ученых степеней Узбекистана и зарубежья.

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Материалы публикуются в авторской редакции.

КЛИНИЧЕСКАЯ МЕДИЦИНА

ГИГИЕНА, САНИТАРИЯ И ЭПИДЕМИОЛОГИЯ

ЭКСПЕРИМЕНТАЛЬНАЯ БИОЛОГИЯ И МЕДИЦИНА

ДОКАЗАТЕЛЬНАЯ МЕДИЦИНА

УДК: 616.12-008.64-036.11-085

ENDOTHELIAL DYSFUNCTION IN ISCHEMIC HEART DISEASES

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Aim. To assess the role of disorders of vasodilating, vasoconstrictor and adhesive functions of the endothelium in the development of angina pectoris in patients with ischemic disease heart (CHD).

Material and methods. 93 patients with coronary heart disease were examined, 35 of them with functional class II (FC) angina pectoris, 30 with FC III, 28 with FC IV. The control group consisted of 23 healthy individuals. Bicycle ergometry, 24-hour ECG monitoring, and echocardiography were used to verify IHD. The vasodilating function of the endothelium was assessed by endothelium-dependent (EDVD) and endothelium-independent vasodilation (EIDVD) of the brachial artery; vasoconstrictor function - by the level of endothelin-1 (ET-1). The adhesive function of the endothelium was judged by the concentration of intercellular adhesion molecules JCAM-1, VCAM-1, and E-selectin.

Results. With angina pectoris II FC, the indicators of EDVD and EIDVD, the level of ET-1 and the content of intercellular molecules adhesions were within the normal range. As the FC of angina pectoris increased, the vasodilating function of the endothelium was inhibited, and the production of ET-1 and intercellular adhesion molecules increased. FC IV angina was characterized by overexpression of JCAM-1, VCAM-1, E-selectin, excessive secretion of ET-1 at low levels of EDVD and EIDVD.

Conclusion. The clinical course of coronary artery disease is associated with impaired vasodilating, vasoconstrictor and adhesive functions endothelium.

Key words: ischemic heart disease, angina pectoris, endothelial dysfunction, endothelium-dependent vasodilation, endothelin-1, adhesion molecules.

ДИСФУНКЦИЯ ЭНДОТЕЛИЯ ПРИ ИШЕМИЧЕСКОЙБОЛЕЗНИ СЕРДЦА

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Цель. Оценить роль нарушений вазодилатирующей, вазоконстрикторной и адгезивной функций эндотелия в развитии стенокардии у больных ишемической болезнью сердца (ИБС).

Материал и методы. Обследованы 93 больных ИБС, из них 35 - со стенокардией II функционального класса (ФК), 30 – III ФК, 28 – IV ФК. Контрольную группу составили 23 здоровых лиц. Для верификации ИБС использовали велоэргометрию, суточное мониторирование ЭКГ, эхокардиографию. Вазодилатирующую функцию эндотелия оценивали по эндотелийзависимой (ЭЗВД) и эндотелийнезависимой вазодилатации (ЭНЗВД) плечевой артерии; вазоконстрикторную функцию – по уровню эндотелина-1 (ЭТ-1). Об адгезивной функции эндотелия судили по концентрации молекул межклеточной адгезии – JCAM-1, VCAM-1 и Е-селектина.

Результаты. При стенокардии II ФК показатели ЭЗВД и ЭНЗВД, уровень ЭТ-1 и содержание молекул межклеточной адгезии были в пределах нормы. По мере возрастания ФК стенокардии отмечено угнетение вазодилатирующей функции эндотелия, повышение продукции ЭТ-1 и молекул межклеточной адгезии. Стенокардия IV ФК характеризовалась гиперэкспрессией JCAM-1, VCAM-1, Е-селектина, избыточной секрецией ЭТ-1 при низких показателях ЭЗВД и ЭНЗВД.

Заключение. Клиническое течение ИБС связано с нарушениями вазодилатирующей, вазоконстрикторной и адгезивной функций эндотелия.

Ключевые слова: ишемическая болезнь сердца, стенокардия, дисфункция эндотелия, эндотелийзависимая вазодилатация, эндотелин-1, молекулы адгезии.

YURAK ISHEMIK KASALLIGIDA ENDOTELIAL DISFUNKTSIYA

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Maqsad. Yurak ishemik kasalligida (YIK) bilan og'rigan bemorlarda stenokardiya rivojlanishida endoteliyning vazodilatatsiya, vazokonstriktor va adgeziv funktsiyalari buzilishining rolini baholash.

Materiallar va usullar. YIK bilan kasallangan 93 bemor tekshirildi, ulardan 35 tasi YIK II funktsional sinf, 30 tasi - III FS, 28 tasi – IV FS. Nazorat guruhi 23 sog'lom odamdan iborat. YIK verifikatsiyasi uchun veloergometriya, sutkaliklik EKG monitoringi, exokardiyografiyadan foydalanilgan. Endoteliyning vazodilatatsiya funktsiyasi elka arteriyasining endoteliyga bog'liq va endoteliyga bog'liq bo'lmagan vazodilatatsiya bilan baholandi; vazokonstriktor funktsiyasi – endotelin-1 darajasi bo'yicha, endoteliyning adgeziya funktsiyasi hujayralararo adgeziv molekulalari – JCAM-1, VCAM-1 va E-selektin kontsentratsiyasi bilan baholandi.

Natijalar. Stenokardiya II FS bilan endoteliyga bog'liq va bog'liq bo'lmagan vazodilatatsiya ko'rsatkichlari, ET-1 darajasi va hujayralararo adgeziya molekulalarining tarkibi normal diapazonda bo'lgan. Stenokardiya FS ortishi bilan endoteliyning vazodilatatsiya funktsiyasini pasayishi, ET-1 ishlab chiqarish va hujayralararo adgeziya molekulalarining ko'payishi qayd etildi. IV FS da JCAM-1, VCAM-1, E-selektinning giperekspressiyasi, endoteliyga bog'liq va bog'liq bo'lmagan vazodilatatsiya past darajalarida, ET-1 ning ortiqcha sekretsiyasi bilan ajralib turdi.

Xulosa. YIKning klinik kechishi endoteliyning vazodilatatsiya, vazokonstriktor va adgeziv funktsiyalarining buzilishi bilan bog'liq.

Kalit so'zlar: Yurak ishemik kasalligi, stenokardiya, endotelial disfunktsiya, endoteliyga bog'liq vazodilatatsiya, endotelin-1, adgeziya molekulalari.

ENDOTHELIAL DYSFUNCTION IN ISCHEMIC HEART DISEASES

Relevance. Ischemic heart disease (CHD) is the most widespread cardiovascular diseases with a high risk of cardiovascular attacs and death [1,2]. Experimental and clinical studies of recent decades show about the important role of the endothelial dysfunction in the development of atherosclerosis and ischemic heart disease arising from it [3,4].

Endothelial dysfunction belongs to the early brand frames of vascular disorders and seems to be a significant factor in the development of atherothrombosis; it is characterized by an imbalance of vasodilating and vasoconstrictor substances, increased expression of intercellular adhesion molecules [5–7].

The main substance producedendothelium is a natural vasodilator - nitric oxide (NO). NO reduces the adhesion of blood cells to the vascular wall, inhibits the proliferation of vascular smooth muscle cells, and prevents the release of tissue factors that increase the likelihood of thrombosis [5]. The most important of the vasoconstrictors is endothelin-1 (ET-1), which contributes to atherosclerotic vascular damage, the development of pulmonary and systemic hypertension, and ischemic damage to the heart and brain [6]. Early signs of endothelial activity include increased expression of selectins (E-selectin, P-selectin) and intercellular adhesion molecules (JCAM-1, VCAM-1), which is directly related to the process of atherosclerotic vascular damage [7]. It is believed that they stimulate the adhesion of macrophages and their migration into the vascular endothelium.

Purpose of the study- assessment of the role of disorders of vasodilating, vasoconstrictor and adhesive functions of the endothelium in the development of angina pectoris in patients with coronary artery disease.

Material and methods

The study included93 IHD patients with stable angina pectoris (all men, mean age 53.2±4.2 years). 35 patients were diagnosed with angina II functional class (FC), 30 - III FC, 28 - IV FC. Most patients with angina II (66.7%), III (77.8%) and IV FC (84.6%) had previously suffered a myocardial infarction. IHD was diagnosed on the basis of clinical and instrumental data. Attention was paid to the typical clinical signs of angina pectoris, the specificity of changes in ECG parameters at rest and during exercise on a bicycle ergometer (VEM), during daily ECG monitoring, and echocardiography (ECHOCG) data.

Patients with grade III hypertension, complex disorders heart rate and chronic heart failure III-IV FC (NYHA), severe diseases of the liver, kidneys, lungs, blood, endocrine organs requiring correction were not included in the study. Basic therapy for IHD included antiplatelet agents, beta blockers, calcium antagonists, statins, nitrates, angiotensin converting enzyme inhibitors. The control group included 23 healthy male volunteers (mean age 49.9±6.1 years) who underwent VEM (to rule out latent coronary insufficiency), echocardiography (to rule out myocardial and valvular lesions), duplex scanning carotid arteries (to exclude atherosclerosis of non-coronary localization), the study of blood lipids.

To characterize immune inflammatory responsesions determined the level of pro-inflammatory cytokinesns (IL-1β, IL-6, TNF-α) in serum by enzyme immunoassay using test systems of OOO Proteinovy Kontour (St. Petersburg).

The vasoregulatory function of the endothelium was assessed using ultrasoundhigh resolution system ACUSON 128 XP/10 (USA), equipped with a linear transducer with a frequency of 7 MHz [14]. Endothelium-dependent vasodilation (EDVD) of the brachial artery was studied in the 2D ultrasound scanning mode during the test with reactive hyperemia and in response to sublingual intake of 500 μg of nitroglycerin (EIVD). The adhesive function of the endothelium was judged by the concentration of intercellular adhesion molecules (JCAM-1, VCAM-1, E-selectin), which were studied by enzyme immunoassay using test systems from Bender Med systems (Austria).

Statistical data processing was carried out with using Microsoft Excel programs 7.0 and statistics for Windows 6.0. Data were presented as mean value and standard error (M±m). The $p<0.05$ level was considered statistically significant.

Results and discussion

Indicators of EDVD and EIDVD in angina pectoris II FC on were within the control values, but significantly decreased with an increase in the FC of angina pectoris (table). With angina pectoris III FC, the level of EDVD was 17.3% less than in healthy individuals; EIDVD after sublingual administration of nitroglycerin had only a downward trend. The minimum parameters of EDVD and EIDVD are set for severe angina (IV FC). Thus, the level of EDVD of the brachial artery in angina FC IV was significantly reduced and significantly differed not only from the control (36.2%; $p<0.001$), but also from the values characteristic of angina II (29%; $p<0.01$) and III FC (22.9%; $p<0.05$). The EIDVD indicator was significantly lower than the control values (24.5%; $p<0.05$) and the data of angina II FC (19.2%; $p<0.05$). The content of a powerful vasoconstrictor, ET-1, in angina pectoris II FC was within the normal range, but as the severity of angina pectoris increased, its concentration in the blood increased. Even with angina III FC, the level of ET-1 increased by 33.3% ($p<0.01$). The highest parameters of ET-1 were found in angina IV FC; its values significantly exceeded not only the values in healthy individuals (by 66.6%; $p<0.001$), but also the indicators for angina II FC (by 56.8%; $p<0.01$).

Correlation analysis revealed inverse relationships between ET-1 and EVD ($r=-0.51$; $p<0.05$).

Thus, the severe course of angina pectoris (FC IV) is characterized by excessive production of ET-1 against the background of sharply disturbed flow-dependent vasodilation and EIDVD induced by nitroglycerin.

In angina pectoris II FC, JCAM-1 values did not differ from the control. As the severity of angina progressed, a distinct increase

in JCAM-1 levels was noted. In angina III FC, the concentration of this molecule exceeded that in the control (27%; $p<0.05$). The maximum levels of JCAM-1 were found in angina pectoris IV FC; they significantly exceeded the data in healthy people and patients with angina II FC.

Correlation analysis established relationships between JCAM-1 and TNF-α ($r=0.39$; $p<0.05$).

The level of the vascular adhesion molecule VCAM-1 in angina pectoris II FC tended to increase, and in angina pectoris III FC it significantly increased compared to the control (by 25%; $p<0.05$). The highest levels of VCAM-1 were found in angina pectoris IV FC, its values were significantly higher than both control data and parameters of angina II FC (by 22.9%; $p<0.05$). Correlation analysis revealed relationships between the concentration of VCAM-1 and the level of pro-inflammatory cytokines IL-1β ($r=0.44$; $p<0.05$) and TNF-α ($r=0.47$; $p<0.05$).

In the study of the content of E-selectin, active molecule specific only for activated endothelium, it was found that an increase in the severity angina pectoris is accompanied by its increased expression. In angina pectoris II FC, there was a tendency to increase the concentration of E-selectin, and in angina pectoris III FC a significant increase in its level by 31.3% was registered compared with the control. In severe angina (IV FC), the level of E-selectin significantly exceeded that in the control and in patients with angina II FC. Correlation analysis revealed close relationships between the level of E-selectin and the concentrations of VCAM-1 ($r=0.64$; $p<0.01$) and JCAM-1 ($r=0.59$; $p<0.01$).

There were moderate inverse relationships between left ventricular myocardial mass and EDVD ($r=-0.33$; $p<0.05$); direct relationships of myocardial mass were determined with the level of ET-1 and E-selectin ($r=0.38$; 0.41; $p<0.05$).

Thus, the severe course of angina pectoris in patients with coronary artery disease is associated with hyperexpression of intercellular adhesion molecules, which develops against the background of inhibition of EDVD and EIDVD and increased production of ET-1.

Clinical results studies indicate early endothelial dysfunction that contributes to the development of atherosclerosis and related diseases [3–8]. One of the main manifestations of endothelial dysfunction is a decrease in the production of substances belonging to the class of vasodilators, in particular, the endothelium relaxing factor, NO, and, as a result, a violation of the ability of blood vessels to expand and provide an increase in blood flow.

Most authors associate the violation of EDVD with the suppression of the synthesis of endothelial relaxing factor (NO) [5]. Therefore, one of the main mechanisms for the development of endothelial dysfunction in patients with coronary artery disease may be a decrease in the synthesis, release, or increased breakdown of NO [15].

Powerful vasoconstrictor and a predictor of endothelial dysfunction are ET-1, the formation of which occurs in endothelial cells, as well as on the surface of smooth muscle cells [6,16]. ET-1 acts in a paracrine manner on vascular smooth muscle receptors, causing their contraction and growth, and in an autocrine-paracrine manner on endothelial cells, causing the production of vasorelaxants and growth-stimulating factors - NO and prostacyclin. ET-1 is one of the most important regulators of the state of the vascular endothelium. In our study, it was found that the concentration of ET-1 increased as the FC of angina pectoris increased: the maximum values of ET-1 were recorded in angina pectoris IV FC. Correlation analysis determined inverse relationships between EDVD and ET-1 level.

It is known that the functional activity of the endothelium largely depends on cellular adhesion molecules. [7,17,18], the overexpression of which on the membranes of endothelial cells reflects the process of endothelial activation. Adhesion molecules play an important role in the intercellular interaction of endothelial cells, monocytes, smooth muscle cells and platelets, as well as in the interaction of leukocytes, platelets and fibroblasts with the extracellular matrix.

It has now been established that endothelial cells express E-selectin, JCAM-1 and VCAM-1 [17,18-20]. Their activity is modulated by the proinflammatory cytokines IL-1□ and TNF-□, which induce the expression of E-

selectin and VCAM-1, and increase the production of JCAM-1. E-selectin is an endothelial leukocyte adhesive molecule; its synthesis is strictly specific for endothelial cells [17,18]. JCAM-1 is expressed on various types of endothelial cells, epithelial cells, fibroblasts, and tissue macrophages stimulated by T-lymphocytes [19]. JCAM-1 is poorly detected on resting endothelium, and VCAM-1 is simply absent. Upon activation of the endothelium, the expression of these molecules rapidly increases.

Thus, a number of intercellular adhesion molecules (JCAM-1, VCAM-1, E-selectin) is of endothelial origin, which allows us to consider them as indicators characterizing the adhesive function of the endothelium.

When assessing the content of JCAM-1 in patients with coronary artery depending on the severity of angina pectoris, it was found that in angina pectoris II FC, its level did not differ from the control and with the progression of angina pectoris, its overexpression, which reaches a maximum at angina IV FC. The results obtained are consistent with the data of [21], which showed an increase in the concentration of JCAM-1 in patients with coronary artery disease. We found that severe angina (FC IV) is also associated with increased production of the vascular adhesion molecule, VCAM-1, which is consistent with the results of the study [22], which shows the relationship between VCAM-1 indicators and the prevalence of coronary atherosclerosis (according to coronary angiography) and the thickness of the carotid intima-media complex. In addition, in experimental atherosclerosis, VCAM-1 expression precedes sub endothelial monocyte accumulation, suggesting a significant role for VCAM-1 in the early stages of vascular injury. LDL or oxidized LDL may be responsible for the induction of VCAM-1 [23].

In our previous studies, activation of immune-inflammatory responses in patients with coronary artery disease, which is associated with the severity of the course diseases [24]. In severe angina pectoris, on increased expression of pro-inflammatory cytokins TNF-α, IL-1β, IL-6, which are known to induce the synthesis of intercellular adhesion molecules [17]. Correlation analysis established the relationship of E-selectin, JCAM-1 and VCAM-1 with the levels of TNF-α and IL-1β, found correlation between the parameters of the functional state of the endothelium and myocardium.

Thus, the results obtained witnessas a significant violation of the EDVD with hyperexpression of ET-1, and an increase in the adhesiveness of the endothelium, which confirms a pronounced dysfunctionendothelium in severe and high FC of stable angina pectoris. The established patterns of changes in the vasodilating, vasoconstrictor and adhesive functions of the endothelium in patients with coronary artery disease with different course of angina pectoris, apparently, indicate the pathogenetic role of impaired humoral and vasoregulatory response of the endothelium in the formation and clinical course of coronary artery disease.

Conclusions

With stable angina II FC, the indicators of EDVD and EIDVD and the level of ET-1 are within the normal range. Severe course of angina pectoris (FC IV) is characterized by excessive production of ET-1 and a significant suppression of the vasodilating function of the endothelium. The content of intercellular adhesion molecules in angina pectoris II FC did not differ from the control, and in angina pectoris high FC (IV) hyperexpression of JCAM-1, VCAM-1 and E-selectin was registered. Correlation analysis, conducted in patients with severe angina pectoris, found relationships between indicators of the functional state of the endothelium and myocardium.

Thus, the clinical course of coronary artery disease is interconnected with disorders vasodilatory function of the endothelium, increased production of ET-1, overexpression of intercellular adhesion molecules JCAM-1, VCAM-1 and E-selectin.

Literature:

1. Celermajer DS, Sorensen KE, Gooch VM et al. Non-invasive detectionof endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992;340:1111-5.

2. Cooke JP Role of nitric oxide in progressionand regression of atherosclerosis. West J Med 2016; 164:419-26.

3. Davignon J., Ganz P. Role of endothelial dysfunction in atherosclero-sis. Circulation 2014;109(23 Suppl 1):III27-32.

4. Dupuis J., Tardif JC, Cernacek P., Throux P. Cholesterol reduction rapidly improves endothelial function after acute coronarysyndromes. The RECIFE (reduction of cholesterol in ischemia and function of theendothelium trial.circulation. 1999;99(25):3227-33.

5. Gearing A., Newman W. Circulation adhesion molecules in disease. Immunol Today 1993;14:506-16.

6. Harrison DG Cellular and molecular mechanisms of endothelial cell dysfunction. J Clin Invest 1997;100:2153-7.

7. Hwang SJ, Ballantyne CB, Sharrett AR et al. Circulating adhesionmolecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: the AtherosclerosisriskIn Communities (ARIC) study. Circulation 1997; 96:4219-25.

8. Kovalev I.A., MartsinkevichG.I., Suslova T.E., Sokolov A.A. Disendothelial function in persons with atherosclerosis burdened heredity. Cardiology 2014;(1):39-42.

9. Landmesser U., Hornig B., Drexler H. Endothelial function: a critical determinant in atherosclerosis? Circulation 2014; 109:27-33.

10. Libby P., Ross R. Cytokinesand growth regulatory molecules. In: Fuster V., Ross R., Topol EJ, eds. atherosclerosis and coronary artery disease. Vol. I. Philadelphia: Lippincott-Raven, 2016. p.585-94.

11. Lutai M.I. Rupture of an atherosclerotic plaque and its clinicalskye consequences.Can a coronary catastrophe be prevented? Ukr cardiol journal 2020;(5):45-9.

12. Marui N., Offermann MK, Swerlick R. et al. Vascular cell adhesion molecule-1 (VCAM-1) gene transcription and expression age regulated through an antioxidant – sensive mechanism in human vascular endothelial cells. J Clin Invest 1993;92:1866-74.

13. Oganov R.G., Maslennikova G.Ya. Prevention of cardiovasculardiseases - a real way to improve the demographic situationin Russia. Cardiology 2017;(1):4-7.

14. Oliveira GH Novel serologic markersof cardiovascular risk. Curr Atheroscler Rep 2018 5;7:148-54.

15. Pataraia S.A., Preobrazhensky D.V., Sidorenko B.A., Masenko V.P.Biochemistry and physiology of the endothelin family. Cardiology2020;(6):78-85.

16. Price DT, Loscalzo J. Cellular adhesion molecules and atherogenesis.Am J Med. 1999;107:85-97.

17. Rich S., McLaughlin VV Endothelial receptor blockers incardiovasculardisease. Circulation 2018;108:2184-90.

18. Soboleva G.N., Pogorelova O.A., Kuznetsova T.V. etc. Influence shaftsartan, extended-release fluvastatin and their combinations on blood pressure, lipid levelsChanges and function of the endothelium in patients with hypertension. Cardiology 2007;(11):9-13.

19. Sitnikova M.Yu., Maksimova T.A., Khmelnitskaya K.A. etc. Nekoother indicators of the state of the endothelium in patients with ischemicheart disease complicated by heart failure.Collection of scientific papers dedicated to the 100th anniversary of the Department of Faculty Therapy named after Academician G.F. Lang. St. Petersburg: St. Petersburg State Medical University; 2000. S. 241-6.

20. Teerlink JR Endothelins: pathophysiology and treatment implicationin chronic heart failure. Current Heart Failure Reports 2015; 2:191-7.

21. The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Guidelines on the management of stab-le angina pectoris: executive summary. Eur Heart J 2016;27:1341-81.

22. Vanhoutte PM Endothelial control of vasomotor function: from healthto coronary disease. Circ J 2003;67:572-5.

23. Volkov V.I., Serik S.A. Pro-inflammatory cytokines and solutionpossible adhesion molecule-1 in IHD. Cardiology 2002;(9):12-6.

24. Zakirova N.E., Khafizov N.Kh., Karamova I.M., Zakirova A.N., Oganov R.G. Immunoinflammatory responses in ischemic diseasehearts. Rational Pharmacoter Cardiol 2017;(2):16-9.