FEATURES OF ENDOTHELIAL DYSFUNCTION AND CARDIAC REMODELING IN CORONARY HEART DISEASE

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Abstract

Currently, cardiovascular diseases are the most common cause of death in adults. Therefore, the search for a new molecular marker that can predict cardiovascular diseases is one of the highest priorities of medicine. VEGF and ET-1 are among the reliable predictors of cardiovascular disease. Our goal is to find out the relationship of VEGF and ET-1 biomarkers with the remodeling of the left ventricle of the heart in patients with coronary artery disease.

Keywords: endothelin 1, vascular endothelial growth factor; remodeling, left ventricle

Cardiovascular diseases (CVD) are the leading cause of death worldwide. It is estimated that 17.9 million people died from cardiovascular diseases in 2019, accounting for 32% of all deaths worldwide. 85% of these deaths were due to myocardial infarction and stroke [1]. Currently, coronary heart disease remains one of the most pressing problems of the internal medicine clinic, due to both the prevalence of cardiovascular diseases in the population and their contribution to the mortality structure. The interest in the treatment of cardiovascular diseases is determined by the widespread occurrence of coronary heart disease (CHD), its leading role in the causes of disability and mortality of the population, which gives the problem not only medical but also social significance [2-4]

By the beginning of the 21st century, the attention of clinicians focused on the role of endothelial dysfunction in the formation of coronary heart disease [1,5,6]. Endothelial dysfunction (DE) is an imbalance between the production of vasodilating, antiproliferative factors (NO, prostacyclin, tissue plasminogen activator, C-type natriuretic peptide, endothelial hyperpolarizing factor) on the one hand and vasoconstrictive, prothrombotic, proliferative factors (endothelin 1, superoxide anion, thromboxane A2, tissue activator inhibitor plasminogen) - on the other side. The leading role in the development of the latter belongs to a violation of the bioavailability of endothelium-produced nitric oxide (NO), activation of endothelin 1 and a decrease in vascular endothelial growth factor (VEGF). Inhibition of NO synthesis is considered as one of the main pathogenetic mechanisms of cardiovascular diseases [3,7,8,9]

Disruption of the structure and function of the endothelium in coronary heart disease has a significant effect on the tone and thrombogenicity of the vascular wall and the neurohormones produced by it can exacerbate vascular and cardiac remodeling [5, 10]

The search for possible new markers of vascular remodeling and DE development in CVD patients is of great interest. Considering the above, it is of interest to study the clinical, hemodynamic and humoral markers of the development of endothelial dysfunction during the course of the disease and remodeling processes in patients with coronary artery disease. The aim of the study was to study the relationship between myocardial and endothelial remodeling and the concentration of markers of endothelial dysfunction.

The study included 108 patients with coronary artery disease. The diagnosis was based on the clinical picture – clinical signs of angina pectoris of functional classes II-III, a history of myocardial infarction (MI) or electrocardiographic signs. The verification of the diagnosis was based on coronary angiography and coronary revascularization. Background diseases such as hypertension, type 2 diabetes mellitus, insulin resistance syndrome (according to the insulin resistance index in patients with glycemic levels within the reference standards), and hyperuricemia were recorded in all patients.

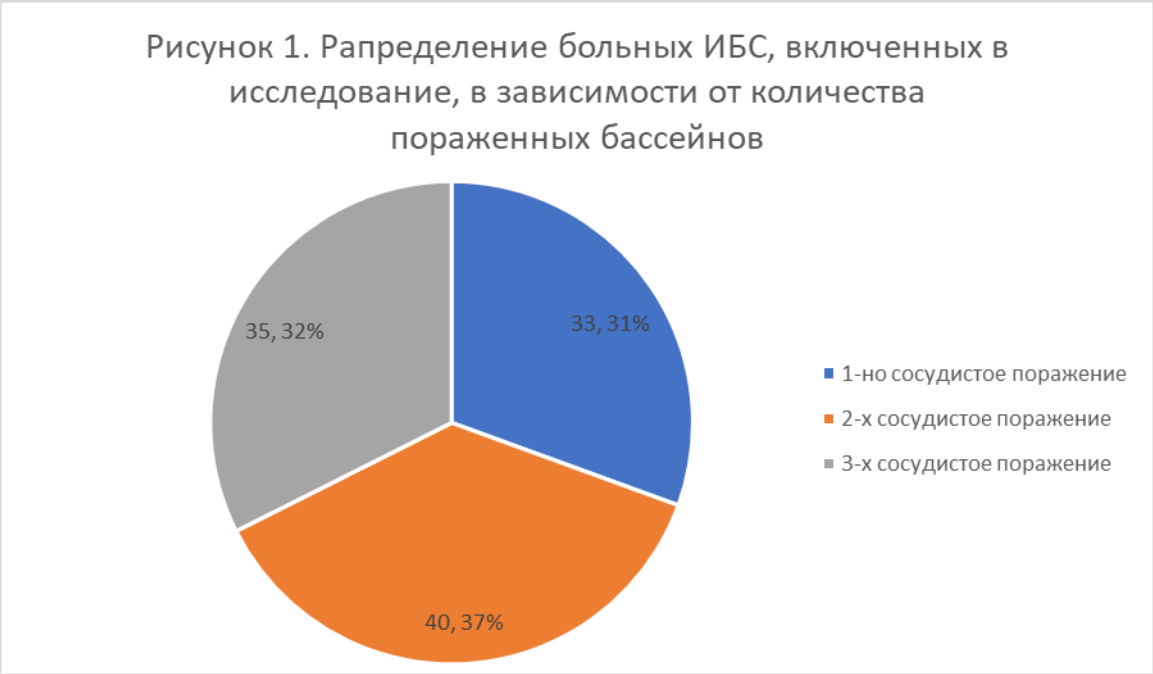
Criteria for inclusion in the study: 1) verified (coronarographically) coronary artery disease, stable course; 2) regular (at least 3 months before inclusion in the study) intake of basic therapy for coronary artery disease, including beta blockers, antiplatelet agents, statins, neprilysin receptor antagonists; 3) age of patients 25-70 years; 4) consent of patients to be included in the study.

Criteria for non-inclusion of patients in the study: 1) febrile state of any etiology; 2) malignant neoplasms; 3) destabilization of the course of coronary heart disease during the previous 2 months; 4) persistent form of atrial fibrillation; 5) terminal period of organ failure.

The average age of the patients was 55.94±1.29 years, height – 170.24±1.12cm, weight – 77.72±1.79kg. As a control group (KG), the study included 20 healthy volunteers without signs of damage to the cardiovascular system, of comparable age and anthropometric characteristics. 74 patients had a history of MI, including 18 patients with 2 and 10 patients with 3 MI.

All patients included in the study underwent diagnostic coronary angiography during the previous year.

According to the results of the study, all patients were distributed depending on the number of affected pools. 53 patients (49.07%) underwent CA stenting, 21 patients (19.44%) underwent surgical revascularization.



All patients included in the study received basic therapy for coronary heart disease (Table 1).

Table 1

Basic therapy of patients included in the study

Medications	number	Relative share (%)
B blocker	102	94,44%
Angiotensin converting enzyme inhibitors	32	29,63%
angiotensin receptor blockers	76	70,37%
sacubitril	51	47,22%
calcium channel blockers	28	25,93%
Antiplatelet	106	85,19%
anticoagulants	12	20,37%
Statins	99	91,67%

Note: Ace inhibitors are angiotensin converting enzyme inhibitors; ARBs are angiotensin receptor blockers, and BCC are slow calcium channel blockers.

During the study, all patients and persons with CG included in the study were examined, during which the structural and functional state of the myocardium (echocardiography - EchoCG) and the features of the functional state of the endothelium (endothelium-dependent vasodilation test, concentration of VEGF and ET-1) were studied.

An EchoCG examination was performed using an Affiniti 50G ultrasound scanner. A convexic sensor with a frequency of 2-7.5MHz was used. The examination was carried out in the morning in the position of the patient on his left side and on his back, after a 10-minute rest. The examination included scanning using standard ultrasound windows and EchoCG positions. The study protocol included registration of parameters of the structural and functional state of the heart and features of intracardiac blood flow.

The concentration of VEGF was determined in blood serum by solid–phase enzyme immunoassay using a set of VEGF–ELISA-BEST reagents manufactured by Vector-Best CJSC (Russia) with a measuring range of 6.25-4000pg/ml, the reference norm in blood serum was 6.25-600pg/ml.

The concentration of ET-1 was determined in peripheral venous blood by enzyme immunoassay, the range of values was 0-10 mmol/L.

Endothelial function. The assessment of endothelium-dependent vasodilation was based on a change in the diameter of the brachial artery at the 5th second after arterial decompression during a 5-minute cuff test. The Affiniti 50G ultrasound scanner was used, equipped with a linear sensor with a frequency of 15 mhz. Statistical processing was carried out using the Student's confidence criterion for paired and unpaired values. Multiple comparisons were also performed using the Student's criterion, adjusted by the Bonferroni correction for multiple comparisons.

Research results. The study found that humoral markers of endothelial dysfunction were significantly increased in patients with coronary heart disease compared with the group of healthy volunteers (Table 2).

Thus, the concentration of VEGF in patients with coronary heart disease was increased by 11.09 times (p<0.001), ET-1 – by 10.33 times (p<0.001).

Correlation analysis revealed a strong positive relationship between VEGF concentration and the number of affected coronary basins (r=0.84, p<0.01), as well as an average positive relationship between ET-1 concentration and the number of affected basins (r=0.68, p<0.01) and between ET-1 concentration and VEGF concentration (r=0.68, p<0.01).

Table 2

Structural and functional state of the endothelium in patients with coronary artery disease and healthy individuals

Index	КГ (n=20)	ИБС (n=108)
VEGF, пг/мл	76,45±10,90	848,09±77,50***
ET-1, фмоль/л	0,22±0,02	2,27±0,15***
Arteria brachialis 0, мм	4,19±0,15	4,18±0,07
Arteria brachialis 1, мм	4,35±0,15	4,25±0,07
endothelium-dependent vasodilation, %	16,55±0,46	7,08±0,62**

Note: * - the reliability of the difference between the groups. One character – p<0.05, two characters - p<0.01, three characters - p<0.001.

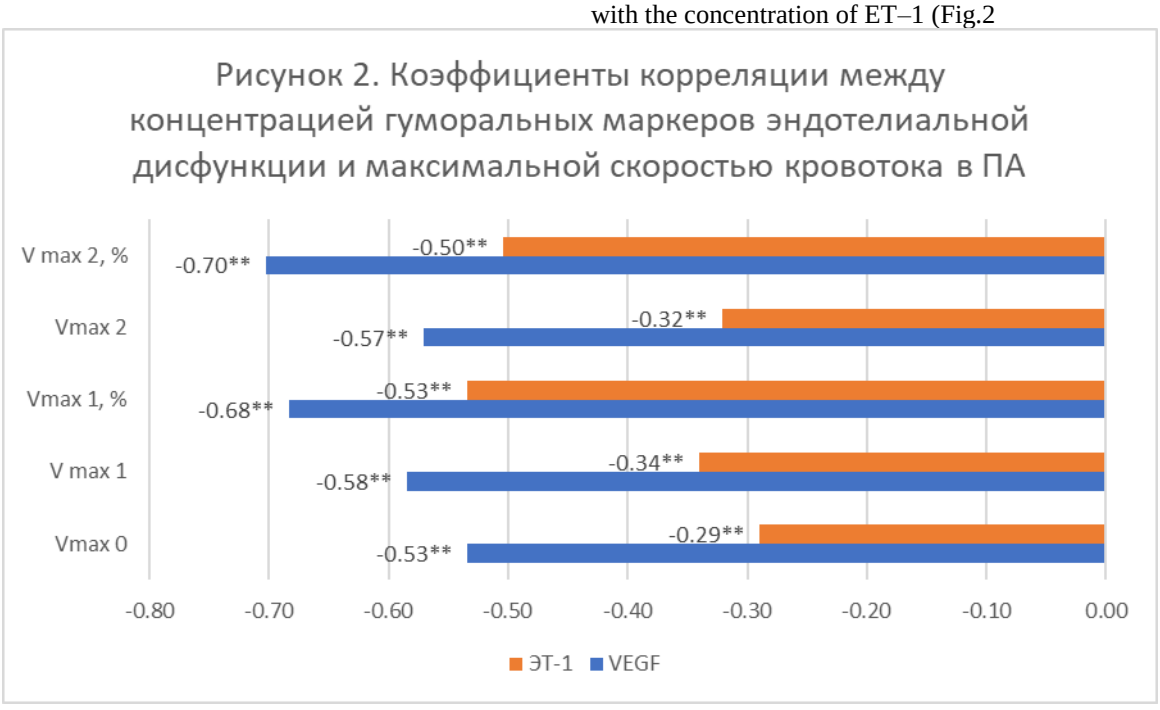
Functional vascular remodeling was also characterized by a 2.34-fold decrease in the degree of endothelium-dependent vasodilation compared with healthy individuals (p<0.001). In the group of patients with coronary heart disease, the majority of patients (55.55%) had insufficient ESRD (less than 10%), and 11.11% of patients had paradoxical vasoconstriction.

In patients with coronary artery disease, despite the development of endothelial dysfunction, the diameter of the PA did not differ from the diameter of the vessel in the group of healthy individuals, both initially and after 5-minute compression of the artery.

Correlation analysis showed that there is a significant negative relationship between the value of EDV and the concentration of markers of endothelial dysfunction: strong with a concentration of VEGF (r=-0.80, p<0.01) and moderate with a concentration of ET-1 (r=-0.61, p<0.01).

Analysis of the dynamics of maximum blood flow velocities in the PA revealed that at all stages of the study in patients with coronary artery disease, the maximum velocity was lower than in the group of healthy volunteers (1.21 times initially, 1.51 times on the 5th and 1.39 times on the 60th second of decompression), with a lower degree of speed increase after removal compressions: thus, the relative dynamics by the 5th second of decompression in the IHD group was 20.48±0.59% versus 51.25±3.48% in KG (dynamics 2.50 times less, p<0.001), by 60-1 seconds – 10.19±0.36% and 26.20±1.50%, respectively (2.57 times less, p<0.001).

Correlation analysis showed the presence of significant negative associations between the blood flow rate in the PA at all stages of the test with humoral markers of endothelial dysfunction, more pronounced with the concentration of VEGF and less pronounced with the concentration of ET–1 (Fig.2



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*Note: * - reliability of the correlation coefficient. One character – p<0.05, two characters – p<0.01.*

An EchoCG study revealed that in patients with coronary heart disease, dilation of all heart chambers was noted compared with CG (Table.4): the increase in LP in patients with coronary heart disease compared with CG was 59.27%, LV – by 37.86%, RV – by 31.56% and PP – by 49.18% (the reliability of intergroup differences for all indicators is p<0.001). The thickness of the MBP in patients with coronary heart disease was significantly higher (by 10.72%) compared with KG (p<0.01), reflecting myocardial hypertrophy in response to ischemic apoptosis. The thickness of the CSF in the groups did not differ. The predominance of dilation over hypertrophy led to a significant decrease in the OTC index in patients with coronary heart disease (by 14.74%, the significance of intergroup differences was p<0.01). Dilation of the heart cavities was accompanied by measurement of the geometry of the cavities, as LVH in patients with coronary heart disease increased by 18.88% (p<0.001).

LV myocardial mass in patients with coronary artery disease was increased by 90.06% compared to KG (p<0.001). Thus, in the group of patients with coronary heart disease, the majority of patients (93 people – 86.11%) had LV hypertrophy (LVH, LVEF 110 g/m2 or more).

LV systolic function was characterized in patients with coronary heart disease by an increase in INRS, reflecting regional contractility disorders, compared with CG (by 53.09%, p<0.001), as well as a decrease in total systolic function, LVEF (-14.00% relative to CG, p<0.001).

The systolic function of the pancreas was characterized by a decrease in the FUP index, an analogue of the RV for the pancreas, calculated by area due to the complex geometry of the pancreatic cavity. The LVF in patients with coronary heart disease was 8.27% less than in KG (p<0.05).

Diastolic function revealed various variants of dysfunction in 100% of patients with coronary heart disease, while in KG diastolic dysfunction was observed only in 11 patients (10.97%, the significance of an intergroup difference in the frequency of various types of diastolic dysfunction between groups chi squared 4x2=57.67, p<0.001). Among the disorders of diastolic function, the variant of delayed relaxation prevailed.

The diastolic filling of the pancreas was also impaired in patients with coronary heart disease (59.26% of patients), while in representatives of KG the diastolic filling was normal (the reliability of the intergroup difference in the frequency of occurrence of various diastolic filling variants chi squared 2x4=23.70, p<0.001).

Impaired LV diastolic and systolic function in patients with coronary heart disease led to an increase in the average pressure in the LP cavity and in the LA system by 64.17% (p<0.001). In 80 patients of the CHD group (74.07%), the average pressure in the LA, determined by the ratio of acceleration time to expulsion time on the LA valve, exceeded the normal value (19 mmHg).

The study examined the Tei index, an integral index of myocardial functioning that characterizes the efficiency of the myocardium, that is, the time required for effective changes in intraventricular pressure. In patients with coronary heart disease, the Tei index was increased compared with the CG index (by 27.19% for LV, p<0.01, and 18.35% for RV, nd).

Table 4

Comparative characteristics of the structural and functional state of the myocardium in patients with coronary heart disease and healthy individuals

Index	КГ	Пациенты с ИБС
LA, ml/m2	26,90±1,75	42,84±0,87**
LVI, мл/м2	51,55±1,55	71,06±2,20*
EF LV, % (Simpson)	61,00±1,25	52,46±0,94*
LVMI, г/м2	87,20±2,52	165,73±4,93**
TW, отн ед	0,37±0,01	0,31±0,01*
IVS, мм	9,40±0,23	10,41±0,19*
PW LVT, мм	9,55±0,20	9,61±0,12
Sphericity index, отн ед	0,54±0,07	0,64±0,01*
Regional Myocardial Contractility, балл	1,00±0,00	1,53±0,04*
Tei LV, отн ед	0,60±0,01	0,77±0,06*
cpP PA, мм.рт.ст	14,85±0,27	24,38±0,68*
Tei RV, отн ед	0,63±0,01	0,75±0,06
RVI, см2/м2	19,70±0,54	25,91±0,70*
FC RV, %	48,40±1,53	44,40±0,63*
RAI, см2/м2	15,25±1,12	22,75±1,28*

Note: * - the reliability of the difference between the groups. One character – p<0.05, two characters - p<0.01, three characters - p<0.001.

Correlation analysis showed a significant relationship between the concentration of humoral factors of endothelial function VEGF and ET-1 and the characteristics of myocardial remodeling: a positive relationship with the volume of the chambers of the heart, LVEF, RMC, cpR LA and RVF, and a negative relationship with the thickness of the LVL, the value of TW, LVEF (Fig.2). The relationship is more reliable with a concentration of VEGF compared to ET-1 concentration.

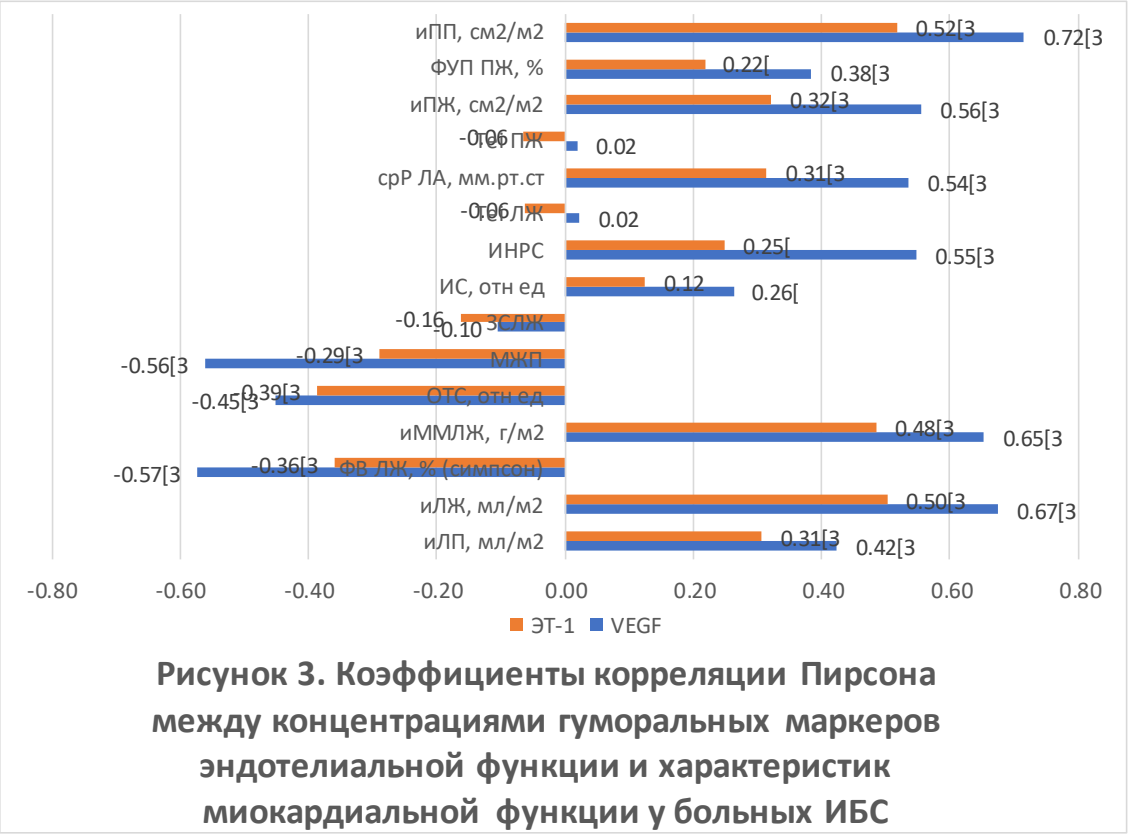

Рисунок 3. Коэффициенты корреляции Пирсона между концентрациями гуморальных маркеров эндотелиальной функции и характеристик миокардиальной функции у больных ИБС

*Note: * - reliability of the correlation coefficient. One character – p<0.05, two characters – p<0.01.*

Thus, the results of our study showed that coronary heart disease is associated with a marked decrease in the degree of EDVD in 56% of patients, and in 11% of patients with paradoxical vasoconstriction.

It was revealed that ischemic myocardial remodeling is characterized by dilation of the heart cavities, spherical deformation of the LV cavity, thinning of the walls, an increase in LVEF and an increase in the time to achieve an effective pressure gradient between the chambers (Tei). Structural and functional remodeling of the myocardium is accompanied by a decrease in regional and global contractility of the left and right ventricles, as well as a violation of active diastolic relaxation, and the formation of postcapillary pulmonary hypertension.

In patients with coronary artery disease with myocardial remodeling, the concentration of VEGF and ET-1 is more than 10 times higher than the values typical for healthy individuals. The concentration of VEGF and ET-1 in venous blood correlates with the severity of pathological myocardial remodeling and the degree of EDV impairment.

Factors associated with LV systolic dysfunction in patients with coronary heart disease are LV remodeling and dilation, three-vessel damage to the coronary bed, VEGF concentration in venous blood above 654 pg/ml, ET-1 concentration in venous blood above 1.95fmol/l.

References:

1. Gutiérrez E, Flammer AJ, Lerman LO, Elízaga J, Lerman A, Fernández-Avilés F. Endothelial dysfunction over the course of coronary artery disease. Eur Heart J. 2013 Nov;34(41):3175-81. doi: 10.1093/eurheartj/eht351. Epub 2013 Sep 7. PMID: 24014385; PMCID: PMC3814514.

2. Allbritton-King Jules D. , García-Cardeña Guillermo Endothelial cell dysfunction in cardiac disease: driver or consequence? Frontiers in Cell and Developmental Biology. 11. 2023. https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2023.1278166. doi:10.3389/fcell.2023.1278166

3. Drera, A.; Rodella, L.; Brangi, E.; Riccardi, M.; Vizzardi, E. Endothelial Dysfunction in Heart Failure: What Is Its Role? *J. Clin. Med.* 2024, *13*, 2534. https://doi.org/10.3390/jcm13092534

4. Jun-ei Obata, Takeo Horikoshi, Takamitsu Nakamura, Kiyotaka Kugiyama, Sustained endothelial dysfunction in the infarct-related coronary artery is associated with left ventricular adverse remodeling in survivors of ST-segment elevation myocardial infarction, Journal of Cardiology, Volume 75, Issue 3, 2020, Pages 261-269, ISSN 0914-5087, https://doi.org/10.1016/j.jjcc.2019.08.001. (https://www.sciencedirect.com/science/article/pii/S0914450871930245X)

5. Lee Bockus, Francis Kim - Coronary endothelial dysfunction: from pathogenesis to clinical implications: Open Heart 2022;9:e002200.

6. Medina-Leyte, D.J.; Zepeda-García, O.; Domínguez-Pérez, M.; González-Garrido, A.; Villarreal-Molina, T.; Jacobo-Albavera, L. Endothelial Dysfunction, Inflammation and Coronary Artery Disease: Potential Biomarkers and Promising Therapeutical Approaches. *Int. J. Mol. Sci.* 2021, *22*, 3850. https://doi.org/10.3390/ijms22083850

7. Pepin, Mark E. et al. The Role of Endothelial Cells in Atherosclerosis The American Journal of Pathology, Volume 194, Issue 4, 499 – 509

8. Widlansky, M, Gokce, N, Keaney, J. et al. The clinical implications of endothelial dysfunction. *JACC*. 2003 Oct, 42 (7) 1149–1160.https://doi.org/10.1016/S0735-1097(03)00994-X

9. Стаценко М.Е., Гузенко Д.С., Дудченко Г.П., Верле О.В. Состояние микроциркуляторного русла и его влияние на ремоделирование миокарда левого желудочка у пациентов с артериальной гипертонией и облитерирующим атеросклерозом артерий нижних конечностей. *Южно-Российский журнал терапевтической практики*. 2024;5(4):32-38. https://doi.org/10.21886/2712-8156-2024-5-4-32-38

10. Пахтусов Н.Н., Юсупова А.О., Привалова Е.В., Хабарова Н.В., Беленков Ю.Н. Эндотелиальная дисфункция и воспаление у пациентов с ишемической болезнью сердца и необструктивным поражением коронарных артерий. *Кардиология*. 2021;61(1):52-
58. https://doi.org/10.18087/cardio.2021.1.n1423