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THE USE OF VARIOUS MATERIALS AND METHODS FOR ASSESSMENT THE STATE OF THE ENDOTHELIUM IN SCIENTIFIC RESEARCH. REVIEW OF THE LITERATURE

I.M. Gayova, I.V. Tymkiv, M.V. Blyzniuk, V.E. Neyko

Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine:
The Chair of Propaedeutics of Internal Medicine Named After Professor M. Berezhnytskyi
ORCID ID: 0009-0007-5118-7820, e-mail: igayova@ifnmu.edu.ua;
ORCID ID: 0000-0002-1759-4576, e-mail: itymkiv@ifnmu.edu.ua;
ORCID ID: 0000-0002-0612-785X, e-mail: mblyzniuk@ifnmu.edu.ua;
ORCID ID: 0000-0002-6033-2387, e-mail: vnejko@ifnmu.edu.ua

Abstract. Endothelial functioning is one of the key topics of theoretical and practical medicine. Endothelial dysfunction (or endothelial dysfunction, ED) is understood as an imbalance of vasoconstriction/vasodilation, which occurs due to changes in the release of vasoactive biological substances (hormones, mediators, growth factors). The role of ED in hypertension, atherosclerosis, other vascular lesions is being studied. Methods for determining ED are divided into two groups: the first includes invasive and non-invasive methods for studying vascular tone in conditions of altered blood flow (this includes ultrasound, angiography), the second group is the study of the content, concentrations of circulating markers. Analysis of the literature showed that there are no new research methods in this matter yet. Atherosclerosis is a clinical manifestation of ED and the prevalence of this pathophysiological condition is extraordinary. There are numerous works where attempts are made to analyze the patterns of changes in the endothelium, and therefore vasoconstriction/vasodilation in various experiments: in animals and in humans; on vessels of different diameters; patients were chosen for all ages, healthy, with monopathology or with comorbid conditions. Dopplerography has proven a decrease in flow-dependent dilation as one of the reliable criteria for ED. Numerous works are devoted to the role of lipid peroxidation in the development of ED, among the markers of atherogenesis initiation are the products of free-radical oxidation of proteins in serum, the products of free-radical oxidation of proteins in lipoproteins, diene conjugates in platelets, malonic dialdehyde. Disturbances in the hemoglobin system due to activation of free-radical oxidation in red blood cells correlate with metabolic indicators such as glutathione peroxidase, superoxide dismutase, reduced glutathione, which are predictors of ED. An important role of nitric oxide (NO) in the regulation of the functional state of the endothelium has been proven, increased activity of NO-synthetase leads to an increase in the content of nitric oxide, which is confirmed by an increase in the level of its metabolites in the blood. Studies have established the relationship of the blood coagulation system and the state of the endothelium: an increase in the level of Willebrand factor reflects the state of the endothelium in patients with coronary artery disease. Insufficiency of sex hormones is named among the factors that provoke changes in the functioning of the endothelium. Conclusions on humoral factors: increased levels of adhesion molecules (VCAM-1S), insulin-like growth factor (IGF-1), aldosterone content in arterial hypertension confirm endothelial dysfunction. Using the radioimmune method, it is proved that in older people less vasodilators and more vasoconstrictors are synthesized by the endothelium. A separate group of studies is the study of ED patterns in various diseases, in particular, following data are available: endothelial dysfunction suggests a complicated course of chronic obstructive pulmonary disease against the background of coronary heart disease. Thus, damage to the endothelium by lipid peroxidation products, violation of the balanced synthesis of vasoactive factors by the endothelium worsens its protective properties, makes it sensitive to the effects of damaging factors, disrupts the wall homeostasis and promotes atherogenesis.

Keywords: endothelium, endothelial dysfunction, research methods, atherosclerosis, reactive hyperemia, vascular ultrasonography, lipid peroxidation, nitric oxide.

Pathological modification of the endothelium and disorder of its barrier-transport and regulatory functions are considered today as the main link of atherogenesis. Such endothelial changes are accompanied by an imbalance of vasocontriction/vasodilation and are designated by the term "endothelial dysfunction" (ED). For many years, the problems of structural and functional changes in blood vessels are relevant, studied in atherosclerosis, arterial hypertension, comorbid conditions.

The aim of the study. Conduct a study of the scientific literature on the isolation of the most revalent methods for identifying and evaluating endothelial dysfunction.

During the investigation there was detected a considerable variety of the materials and methods in different authors and researching groups. To investigate a state of endothelium the experimental animals chose: the rabbits [1-2] and rats [3]; there were the patients: the young healthy and the old practically healthy persons [4-6], the patients with arterial hypertension [7-9], ischemic heart disease [10-13]; the patients with the combined diseases: COPD and ischemic heart disease [14-17]. A significant group of studies (experimental and clinical) was conducted to study the effect of lipid peroxidation, oxidadative stress on the development of endothelial dysfunction [18-21].

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The next step of the research was the analyses and conclusions' assessment for the state of endothelium at using different objects and methods of investigation.

In one of such multiply research the abdominal parts of aorta in the rabbits on the hypercholesterol diet were investigated [22]. By angiography it was established that in the group of study rabbits who had a hypercholesterol diet, starting from the 8th week of the study, an uneven narrowing of the abdominal aorta, less pronounced in the proximal end of this vessel, was even more pronounced from the 12th week of observation. Histological and morphological examination showed progression of damage to the internal elastic membrane, thickening of the aortic intima. In the control group (with normal nutrition) no such changes were detected.

Experimental studies have confirmed the well-known fact that before menopause, women have a lower risk of hypertension, coronary heart disease, and therefore cardiovascular disasters than their male peers. A study of the influence of sex hormones on the state of the vascular wall was conducted [23]. Mice deficient in endothelial nitric oxide synthetase (eNOS) and with gonadectomy that had been subcutaneously implanted with estradiol depot were examined. Compared with groups without gonadectomy and/or without additional estradiol administration. It was found that the combined effect of endothelial synthetase nitric oxide and estradiol had the maximum protective effect. In the absence of sex hormones, eNOS had a weak effect on vascular tone and exogenous estradiol had a powerful overprotective effect even in the absence of eNOS.

Influence of a few humoral factors on vasoregulatory function was investigated in the patients with the essential hypertension (EH) [7]. Using the method of dopplerography, the flow-dependent dilation of the brachial artery during the test with reactive hyperemia was checked. Using the immunoenzymatic method (IEMA) the level of the soluble vascular cella adhesion molecule (VCAM-1S) was controlled. Aldosterone and IGF-1 (Insulin-Like Growth Factor-1) contents were investigated with the method of radioimmunoassay. One of the humoral factors examined in the research was an aggregation ability of platelets induced by ADP. At the research of the flow-dependent dilation of the brachial artery during the test with reactive hyperemia, increase of the vessel's diameter d (ΔD) was equal 2 ± 7,46%, while in the control group, in the practically healthy persons - 12,0 ± 2,9%. Level of adhesion molecules (VCAM-1S) in the patients with AH was equal 713,9 ± 123,2 ng/ml and in the group of healthy persons - 590,8 ± 51,8 ng/ml. Aldosterone's content in the investigated group was 101,41 ± 50,17 ng/ml while in the control group - 42,7 ± 13,1617ng/ml. The scientists remarked in their conclusion that level of the adhesion molecules (VCAM-1S) and an aggregation ability of platelets induced by ADP to a greater degree correlate with impaired vasoregulatory function of the endothelium. In the patients with EH there was detected a real connection of increase in the blood IGF-1 (Insulin-Like Growth Factor-1), the adhesion molecules (VCAM-1S), aldosterone and an aggregation ability of platelets that was associated with marked violation of endothelium-dependent dilatation of the brachial artery.

Endothelial dysfunction was investigated as a possible predictor of complicated course of COPD on the background of ischemic heart disease [14]. There were examined the patients with combined cardiopulmonary pathology in dynamic with 2 years of interval. 4 groups of the patients were selected: the control, group of the patients with COPD, patients with ischemic heart disease (IHD) and the patients with COPD and IHD.

Non-invasive examination of the endothelial regulation of the vascular tone was conducted with high resolution ultrasound. Pressure was pumped in the cuff to get the level of systolic blood pressure increased by 50 mm Hg for 5 minutes. The brachial artery's (BA) diameter was estimated after 30, 60, 90 seconds and 5 minutes later. A nitroglycerin tablet sublingually was administered to the patients and 2 minutes later the brachial artery's diameter was checked again.

The reaction by increase blood flow was calculated as a difference in BA diameters on the background of reactive hyperemia (RH) and the initial one. The reaction by nitroglycerin – as the difference of BA diameters on the second minute after nitroglycerine intake and the initial. The indicator of the growth deficit fraction of brachial artery was calculated as the reactions by nitroglycerin and by reactive hyperemia. The brachial artery reaction was considered as normal when its dilation on the background of reactive hyperemia was by 10% more than initial. The less degree of vasodilatation (vasoconstriction) was considered as pathological reaction.

The content of nitrous oxide in serum was made by the nitrites' concentration determination. Thickness of the intima-media complex compared in the patients of four groups. The increase of brachial artery diameter after the test with its compression was minimal in the patients with combined cardiopulmonary pathology (4,39±0,10mm) while in the control group the index was (4,68±0,9mm). The indicator of growth deficit fraction of brachial artery in the group of the patients with COPD and IHD was maximal (9,85 ± 0,79%) while in the group COPD (7,02 ± 0,35%) and in the group IHD (8,5 ± 0,61%). In control group the indicator was absent. Thickness of the intima-media complex was minimal in the control group (0,72 ± 0,03 mm) in the group with IHD it was (1,24 ± 0,03 mm) somewhat less than in the group with COPD and IHD (1,23 ± 0,04 mm). As the result of the conducted research, the conclusion was made that endothelial dysfunction predicts a complicated course of COPD on the background of ischemic heart disease.

To examine the nitric oxide's level in the vascular endothelium of the patients with diabetes the next research was made [4]. Lipidogram was administered to the patient; the intensity of free-radical oxidation of lipids was estimated according to the level of malonaldehyde; the level of nitric oxide detected using the summary content in plasma its stable metabolites – nitrites and nitrates; the nitrites' concentration was fixed using electrophotometry and Griss reaction; the endothelial function was checked according to its vascular motor activity, in the test with endothelium-dependent dilatation of the brachial artery using high-resolution ultrasound. The normal reaction of brachial artery was considered that one at which its diameter at the period of reactive hyperemia was increased by more than 8,5% from the initial.

The purpose of an investigation PERTINENT was to discover the mechanisms of antihypertensive medicines' influence on the humoral indexes of state of endothelium [10, 24]. In this research an influence of the

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inhibitor of ACE Perindopril on the endothelial function, in vitro, on the cellular level. In addition, the levels of angiotensin-2, bradykinin and the metabolites of nitrogen (nitrites, nitrates) were monitored in plasma. The research discovered that treatment with Perindopril causes the reliable decrease of angiotensin-2 level and increase of bradykinin's level (the natural phenomenon of renin-angiotensin system's block), the natural increase of the levels on nitric oxide metabolites' level by 17 %. The increase of nitric oxide metabolites was proved by the natural growth of endothelial synthetase of nitric oxide by 27 %. So, there were clinically proved the increase of nitric oxide's formation and the endothelial function's improvement due to the treatment with the ACE - inhibitor Perindopril.

The markers of the functional endothelial state and inflammation were studied in the patients with arterial hypertension [8]. Epadol (omega-3 polyunsaturated fatty acids) and the folic acid were administered to the patients. There were investigated the markers of the endothelial dysfunction: the Willebrand factor, the soluble adhesion molecules, homocysteine, C-reactive protein, interleukin-6, L-selectin. The immuno-enzymatic method was used. Non-invasive investigation of the functional state of endothelium was made using the tests with an reactive hyperemia.

Age changes of the endothelial vasodilators' and vasoconstrictors' levels were examined in plasma of the healthy young and old patients (60-74 years old) [5]. The functional state of endothelium was estimated by the method of dopplerography. The volume velocity of the skin blood flow was checked on the back surface of the forearm, in the beginning, after the formation of reactive hyperemia and after the subcutaneous adrenalin injection. The reactive hyperemia was created by compression of the shoulder's vessels for 3 minutes (pressure in the cuff was 50mm Hg more than level of systolic blood pressure). There were estimated a maximal volumetric velocity of blood flow and time of its achievement. Adrenaline hydrotartrate solution, in the dose 0,1ml was injected subcutaneously, 5mm above the sensor of the skin flow meter. There were detected a minimal volumetric velocity of blood flow of the skin, the time of its achievement after adrenaline injection and time to restore the values of the initial indicators. The levels of prostacyclin, prostaglandin E and $F_{2\alpha}$, thromboxane A_2 and angiotensin II in plasma were determined by the radioimmunoassay method. Endothelin content was measured by immunoenzymatic method using reagents Endothelin-1 ELISA system, NO_2 level was determined using the reagent Griss.

As a result, it was established that increase of volumetric velocity of skin blood flow, on the peak of reactive hyperemia, as well as the duration of hyperemia, when performing a cuff test, in the elderly persons are significantly smaller than in the young people. The increase of volumetric velocity in the group of the young was equal 5,3 ml/min (min·100g), in the group of the elderly – 3,2ml/min (min·100g) ($p<0,05$; $p<0,01$) in comparison with the young. The time of hyperemia (the cuff test) in the young was 125,3 ± 7,1 seconds, in the elderly - 93,2 ±5,2 seconds ($p< 0,05$). The reaction to adrenaline injection in elderly patients was much more considerable than in the young. Time to restore the initial volumetric velocity in the young group was equal 63,2 ± 4,1 seconds and at the same time in the elderly group - 78,3 ± 7,2 seconds ($p< 0,01$). Level of the vasoactive substances that synthesize in endothelium in the elderly patients was different significantly. Endothelin content in the young was 4,1 ± 0,2 pmol/l, in the elderly group - 6,2 ± 0,2 pmol/l ($p< 0,01$). The nitrous oxide in the young was 16,7±1,3 mmol/l, in the group with age 60-74 years old - 8,4 ± 1,1mmol/l ($p< 0,01$). The thromboxane A_2 in the young group was equal 265,1 ± 21,3 mmol/l, at the same time in the group of the elderly healthy persons - 396,4 ± 19,5 mmol/l. The conclusion that follows from the results of research: the changes of endothelial reactions with aging can be relate to the disorders of hormone synthetic function of endothelium depends on the age. Determination of the level of vasoactive substances that are synthesized in endothelium at different ages serves as confirmation of this hypothesis. Violation of the vascular wall homeostasis contributes to the atherosclerotic process. The results of research demonstrate that with aging the levels of endothelial relaxing factor (NO), prostacyclin, prostaglandin E are decreased significantly. At the same time, the levels of endothelin-1, thromboxane and angiotensin-II increase. One of the reasons of violation of synthesis of the endothelial vasodilators (NO) with aging – possibly there is a lack of the substrate-precursor of L-arginine. Experimentally was proved that injections of L-arginine to elderly animals increased the endothelium-dependent vasodilatation. So, in the aging organism there are physiological precursors for decreased synthesis of vasodilators. The same precursors can cause an excessive synthesis of vasoconstrictors.

The investigation examined lipid peroxidation connected with interaction of oxidation products with endothelium, that was considered as the initial damage causing the initiation of atherogenesis [11]. An assumption was made that a process of free-radical modification and destruction of proteins is a possible reason of the enzymes' inactivation at oxidant stress. The oxidant modification of proteins can be a reason of appearance of antigen characteristics in them and development of an autoimmune process to own proteins. To reply to the questions the patients with a progressing ischemic heart disease were chosen. There were investigating the products of free-radical oxidation of proteins in serum, the products of free-radical oxidation of proteins in lipoproteins of low density and lipoproteins of very low density, diene conjugates in platelets, malondialdehyde, catalase activity. The results of the investigation have proved that the products of free-radical oxidation of proteins are the markers of progress of ischemic heart disease. Damage of proteins in endothelium by the products of free-radical oxidation of lipids is one of the first steps of atherogenesis that leads to appearance of endothelial dysfunction.

One of the factors that initiates atherosclerosis and promotes its progression is considered today the Willebrand factor [12]. At mechanical damage of carotid artery endothelium there was discovered the same increase of expression of the WF as after balloon angioplasty. The WF is synthesized in megakaryocytes from which platelets are released; at the same time, the factor is synthesized in endothelium as well. This WF creates a complex with the VIII factor of blood coagulation. This complex makes the VIII factor stable to participate as a cofactor for a thrombus formation. The WF has two groups of the active centers, the first for the connection with collagen and glycosaminoglycans of the subendothelial matrix, another for the

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connection with the receptors of platelets. The platelets attach to the altered endothelium with their receptors GP-I-b, the endothelium changes due to the interaction of WF and microfibrils of sub endothelium. The WF becomes a kind of bridge between the platelets and the subendothelial. The WF was investigated in the patients with different degrees of atherosclerosis in coronary arteries. In the conclusions there is a statement that the greater is the prevalence of atherosclerosis in coronary arteries in the patients with ischemic heart disease, the higher is level of WF. The patients with IHD and the signs of destroyed atherosclerotic plaque level of WF is increased. In the patients with IHD and diabetes, dyslipidemia of II-b, II-a types, in the smokers the WF is higher than in the patients without these disorders. The changes of the level of WF reflect a state of the endothelium in the patients with IHD. The WF in the patients with the endothelial dysfunction is elevated on average of 53,7 %, after the compression of brachial artery, in the patients with the preserved endothelial function its content is decreased on average of 29,3 %.

The processes of an oxidant stress and its influence on the structural – functional state of erythrocytes and endothelium were examined in the patients with post-infarction cardiosclerosis, during aorto-coronary bypass operations [25]. The main indices of the metabolism of free radicals there were detected: the glutathione peroxidase, superoxide dismutase, reduced glutathione, binreductase (ferricyanide reductase activity, FRA), methemoglobin, MetHb and membrane-bound hemoglobin, MbHb. The intensiveness of free-radical oxidation in the erythrocytes' membranes was estimated by the content of malondialdehyde. Activation of free-radical oxidation in the erythrocytes was stimulated by the disorders in the system of hemoglobin: a pronounced decrease of FRA, a pronounced increase of MetHb and MbHb. As a result of these changes, the system of secondary generation of reactive oxygen species emerged, that strengthened the processes of free-radical oxidation in erythrocytes. Formation of toxic compounds, peroxynitrites and nitrates associated with hyperproduction of reactive oxygen species can act as the leading factors of damage of lipid-protein structures during the formation of oxidant stress. This mechanism is possible at the period of reperfusion of myocardium that develops at such complications of aorta-coronary bypass as acute coronary syndrome, disorders of rhythm and acute cardiac insufficiency. To prevent and to adjust the oxidant stress at the surgery of aorta-coronary bypass the effective antioxidants should be prescribed with a complex treatment.

Conclusions.

Electronic and histochemical methods detected the changes of the landscape of endothelium by changing the morphology of endotheliocytes.

Dopplerography has proven a decrease in flow-dependent dilation as one of the reliable criteria for endothelial dysfunction. This method is one of the most often used to study ED.

Activation of lipid peroxidation, as a probable cause of the initiation of atherogenesis, was indicated by an increase in the chemiluminescence intensity from the surface of the affected endothelium, a decrease in the activity of catalase and glutathione reductase. Among the indicators of lipid peroxidation, as proven markers of atherogenesis initiation, are the products of free-radical oxidation of proteins in serum, the products of free-radical oxidation of proteins in lipoproteins, diene conjugates in platelets, malonic dialdehyde.

With hyperproduction of reactive oxygen species is connected the toxic complexes formation such as peroxynitrites and nitrates that can be the leading damaging factors for lipid-protein structures at formation of oxidant stress.

Activation of free radical oxidation in red blood cells, as one of the causes of endothelial dysfunction, has been proven by abnormalities in the hemoglobin system (levels of methemoglobin, membrane-bound hemoglobin). The main predictors of endothelial dysfunction are glutathione peroxidase, superoxide dismutase, reduced glutathione, ferricyanide reductase activity.

It has been proven that a sufficient quantity of sex hormones has a vasoprotective effect.

There was proved an important role of nitric oxide (NO) for regulation of functional state of endothelium, the increased activity of NO-synthetase is the reason of nitric oxide content that is confirmed by the increased level of its metabolites in the blood.

The influence of humoral factors on ED has been established: the aggregation ability of platelets induced by ADP in patients on arterial hypertension is 5 times higher than in healthy individuals. Levels of adhesion molecules (VCAM-1S), insulin-like growth factor (IGF-1) and aldosterone content are elevated in hypertension and attest to ED.

Studies have established the relationship of the blood coagulation system and the state of the endothelium: changes in the level of Willebrand factor reflect the state of the endothelium in patients with coronary artery disease (in patients with ED the level of WF is increased).

In elderly healthy persons the endothelium synthesizes less vasodilators and more vasoconstrictors (proven by the radioimmune method).

Damage of endothelium by the products of lipid peroxidation, disorder of the balanced synthesis of vasoactive factors in endothelium impair its protective properties making it sensitive to the influence of damaging factors, destroying wall hemostasis and promotes atherogenesis.

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ВИКОРИСТАННЯ РІЗНИХ МАТЕРІАЛІВ ТА МЕТОДІВ ДЛЯ ОЦІНКИ СТАНУ ЕНДОТЕЛІЮ В НАУКОВИХ ДОСЛІДЖЕННЯХ (ОГЛЯД ЛІТЕРАТУРИ)

І.М. Гайова, І.В. Тимків, М.В. Близнюк, В.Є. Нейко

Івано-Франківський національний медичний університет, Івано-Франківськ, Україна:
Кафедра пропедевтики внутрішньої медицини імені професора М.М. Бережницького
ORCID ID: 0009-0007-5118-7820,
e-mail: igayova@ifnmu.edu.ua;
ORCID ID: 0000-0002-1759-4576,

ISSN 2521-1455 (Print)
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e-mail: itymkiv@ifnmu.edu.ua;
ORCID ID: 0000-0002-0612-785X,
e-mail: mblyzniuk@ifnmu.edu.ua;
ORCID ID: 0000-0002-6033-2387,
e-mail: vnejko@ifnmu.edu.ua

Резюме. Ендотеліальна дисфункція є однією з ключових тем теоретичної та практичної медицини. Під ендотеліальною дисфункцією (ЕД) розуміють дисбаланс вазоконстрикції/вазодилатації, що відбувається за рахунок змін у виділенні вазоактивних біологічних субстанцій. Вивчається роль ЕД при гіпертензії, атеросклерозі та інших ураженнях судин. Методи визначення ЕД поділяють на дві групи: перша включає інвазивні та неінвазивні методики вивчення тонусу судин в умовах зміненого кровотоку (сюди відносять ультразвукові дослідження, ангіографії), друга група – це вивчення вмісту, концентрацій циркулючих маркерів. Атеросклероз є клінічним проявом ЕД і поширеність цього патофізіологічного стану надзвичайна. Є численні роботи, де проведені спроби проаналізувати закономірності змін в ендотелії, а значить і вазоконстрикції/вазодилатації в різних експериментах: у тварин і у людини; на судинах різного діаметру; пацієнтів обирали для будь-якого віку, здорових, з монопатологією або з коморбідними станами. Допплерографія довела зниження потоково-залежного розширення як один з надійних критеріїв ЕД. Численні роботи присвячені ролі перекисного окислення ліпідів у розвитку ЕД, серед маркерів ініціації атерогенезу - продукти вільнорадикального окиснення білків у сироватці крові, продукти вільнорадикального окиснення білків у ліпопротеїнах, дієнові кон'югати у тромбоцитах, малоновий диальдегід. Підтверджено важливу роль оксиду азоту в регуляції функціонального стану ендотелію. Недостатність статевих гормонів названа серед факторів, що провокують зміни у функціонуванні ендотелію. Обгрунтовано, що підвищення рівня адгезії молекул (VCAM-1S), інсуліноподібний фактор росту (IGF-1), вміст альдостерону при артеріальній гіпертензії підтверджують ендотеліальну дисфункцію. Таким чином, пошкодження ендотелію продуктами перекисного окислення ліпідів, порушення збалансованого синтезу вазоактивних факторів ендотелієм погіршує його захисні властивості, робить його чутливим до впливу вражаючих факторів, порушує гомеостаз стінки і сприяє атерогенезу.

Ключові слова: ендотелій, ендотеліальна дисфункція, методи досліджень, атеросклероз, реактивна гіперемія, ультрасонографія судин, перекисне окислення ліпідів, оксид азоту.

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