DIAGNOSTIC VALUE OF ENDOTHELIN 1 AND ENDOTHELI GROWTH FACTOR AND VALUE FOR DETERMINING THE THERAPEUTIC EFFECTIVENESS OF L-ARGININE ASPARTANE IN ISCHEMIC DISEASE.

Alyavi A.L., Toshev B.B.
State Institution "Republican Specialized Scientific and Practical Medical Center for Therapy and Medical Rehabilitation", Tashkent, Uzbekistan

Annotation. *Ischemic heart disease is the most common cause of death in the world. According to WHO, 740 million people die every year in the world, of which 13.2% die due to coronary heart disease.*

Keywords: *VEGF; ET-1; myocardial infarction; coronary heart disease; L-arginine aspartate; EZVD.*

Vascular endothelial growth factor (VEGF) was discovered as a signaling molecule that increases vascular permeability by breaking intercellular contacts [8]. VEGF-A induces myocardial angiogenesis and increases vascular permeability and CM proliferation [12]. CMs are not only producers, but also targets for VEGF-A. A rat model showed that VEGF-A inhibits apoptosis and activates the expression of genes involved in CM metabolism and contraction [14]. Under conditions of myocardial recovery, VEGF-A promotes stem cell migration via the PI3K/Akt pathway [6].

Cardiovascular disease (CVD) is the leading cause of death worldwide (Globalatlasoncardiovasculardiseasepreventionandcontrol.

Geneva: WorldHealthOrganization; 2011). An estimated 17.3 million people died from CVD in 2008, which accounted for 30% of all deaths in the world [4,8,11,14]. which is due both to the prevalence of cardiovascular diseases in the population and their contribution to the structure of mortality. 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 [1,13,24]. By the beginning of the XXI century. the attention of clinicians has focused on the role of endothelial dysfunction in the formation of CHD (BarstR., 2004; HumbertMetal, 2004; Belenkov Yu.N., 2010; Martynov A.I., 20011). Endothelial dysfunction (DE) is an imbalance between the production of vasodilatory, antiproliferative factors (NO, prostacyclin, tissue plasminogen activator, C-type natriuretic peptide, endothelial hyperpolarizing factor) on the one hand and vasoconstrictive, prothrombotic, proliferative factors (endothelin, superoxide anion, thromboxane A2, an inhibitor of tissue plasminogen activator) - on the other. The leading role in the development of the latter belongs to impaired bioavailability of endothelium-produced nitric oxide (NO), activation of endothelin 1, and a decrease in vascular endothelial growth factor [3,9,20]. Inhibition of NO synthesis is considered as one of the main pathogenetic mechanisms of cardiovascular diseases (Fischer D., Rossa S., Landmesser U. et al. 2016; Bauersachs J., Widder J. D. 2018). Under conditions of

inflammation and neoplasia, isolated VEGF-A can be released under the action of proteases, in particular metatalloproteinases, plasmin, urokinase-like plasminogen activator, elastase and tissue kallikrein. These proteases increase the activity of VEGF-A by influencing the clearance of the molecule, its activation and degradation, which activates angiogenesis, as a key component of carcinogenesis, and can also suppress VEGF-angiogenic effect [10].

In 1988, Yanagisawa et al. [24] identified a vasoconstrictor molecule, endothelin (ET), today called ET-1. ET-1 has a powerful long-term vasoconstrictor effect on the arteries. Two types of ET-converting enzymes (EPF 1 and EPP2) have been found that cleave the ET precursor (the so-called “big ET”) into active peptides [26].

The role of VEGF and ET-1 in the pathogenesis of CVD. Cardiovascular disease (CVD) is the most common cause of death in the adult population in the modern world [1]. The most common CVDs are coronary heart disease (CHD) and atherosclerosis [2]. CVD is associated with reduced quality of life and significant negative psychological, social, and economic impacts [1].

Myocardial infarction (MI) is the main manifestation of IHD, manifested by necrosis or apoptosis of the myocardium, causally associated with vascular occlusion of the coronary bed and leading to the development of heart failure with a negative prognosis [3]. MI is the main cause of death in patients with coronary artery disease [4].

Patients with coronary artery disease are characterized by an elevated serum level of VEGF-A, which correlates with the concentration of IL-18, a cytokine that induces VEGF-A expression [19]. This pattern allows us to consider the concentration of VEGF-A as a marker of revascularization in patients with coronary artery disease [7]. Therapeutic angiogenesis is used to improve myocardial reperfusion in IHD patients and to increase the myocardial microvascular network.

Atherosclerosis is an inflammatory disease of the vascular wall with the formation of lipoprotein-containing zones (atherosclerotic plaques involving the intima and media of large and medium-sized arteries [9]. Neovascularization of an atherosclerotic plaque is associated with its instability and progression [22]. In the development of atherosclerosis, VEGF-A performs a double function [11]: on the one hand, it increases the expression of anti-apoptotic factors and nitric oxide in endothelial cells [12], on the other hand, it acts as a mitogen, promoting reendothelialization [15], prevents or restores endothelial damage, which can initiate atherogenesis [23]. VEGF-A promotes monocyte adhesion, transendothelial migration and activation [24], enhances endothelial permeability [25], expression of adhesive protein [26] and monocytic chemoattractant-1 [27].

This means that in human coronary arteries, VEGF-A and its receptors are not found in healthy vessels, but are found in endothelial cells of microcapillaries, macrophages and partially differentiated smooth muscle cells of segments with the presence of atherosclerotic lesions.

REFERENCES:

1. Elsky V.N., Vatutin N.T., Kalinkina N.V., Salakhova A.M. (2008) The role of endothelial dysfunction in the genesis of cardiovascular diseases. Journal. AMS of Ukraine, 14(1): 51–62.
2. Abbate A., Toldo S., Marchetti C., Kron J., Van Tassell B.W., Dinarello C.A. Interleukin-1 and the Inflammasome as Therapeutic Targets in Cardiovascular Disease. Circ. Res. 2020;126:1260–1280. doi: 10.1161/CIRCRESAHA.120.315937. [PMC free article]
3. Abhinand C.S., Raju R., Soumya S.J., Arya P.S., Sudhakaran P.R. VEGF-A/VEGFR2 signaling network in endothelial cells relevant to angiogenesis. J. Cell Commun. Signal. 2016;10:347–354. doi: 10.1007/s12079-016-0352-8. [PMC free article]
4. Abukar Y., May C.N., Ramchandra R. Role of endothelin-1 in mediating changes in cardiac sympathetic nerve activity in heart failure. Am. J. Physiol. Integr. Comp. Physiol. 2016;310:R94–R99. doi: 10.1152/ajpregu.00205.2015.
5. Afzal M.R., Samanta A., Shah Z.I., Jeevanantham V., Abdel-Latif A., Zuba-Surma E.K., Dawn B. Adult Bone Marrow Cell Therapy for Ischemic Heart Disease: Evidence and Insights From Randomized Controlled Trials. Circ. Res. 2015;117:558–575. doi: 10.1161/CIRCRESAHA.114.304792. [PMC free article]
6. Albrecht-Schgoer K., Schgoer W., Holfeld J., Theurl M., Wiedemann D., Steger C., Gupta R., Semsroth S., Fischer-Colbrie R., Beer A.G.E., et al. The angiogenic factor secretoneurin induces coronary angiogenesis in a model of myocardial infarction by stimulation of vascular endothelial growth factor signaling in endothelial cells. Circulation. 2012;126:2491–2501. doi: 10.1161/CIRCULATIONAHA.111.076950. [PMC free article]
7. Alexander S.P., Fabbro D., Kelly E., Marrion N., Peters J.A., Benson H.E., Faccenda E., Pawson A.J., Sharman J.L., Southan C., et al. The Concise Guide to PHARMACOLOGY 2015/16: Catalytic receptors. Br. J. Pharmacol. 2015;172:5979–6023. doi: 10.1111/bph.13353. [PMC freearticle]
8. Anand I., McMurray J., Cohn J.N., Konstam M.A., Notter T., Quitzau K., Ruschitzka F., Lüscher T.F. Long-term effects of darusentan on left-ventricular remodelling and clinical outcomes in the Endothelin A Receptor Antagonist Trial in Heart Failure (EARTH): Randomised, double-blind, placebo-controlled trial. Lancet. 2004;364:347–354. doi: 10.1016/S0140-6736(04)16723-8.
9. Ancey C., Corbi P., Froger J., Delwail A., Wijdenes J., Gascan H., Potreau D., Lecron J.-C. Secretion of IL-6, IL-11 and lif by human cardiomyocytes in primary culture. Cytokine. 2002;18:199–205. doi: 10.1006/cyto.2002.1033.
10. Anisimov A., Tvorogov D., Alitalo A., Leppänen V.-M., An Y., Han E.C., Orsenigo F., Gaál E.I., Holopainen T., Koh Y.J., et al. Vascular endothelial growth factor-angiopoietin chimera with improved properties for therapeutic angiogenesis. Circulation. 2013;127:424–434. doi: 10.1161/CIRCULATIONAHA.112.127472.
11. Antithrombotic Trialists' (ATT) Collaboration. Baigent C., Blackwell L., Collins R., Emberson J., Godwin J., Peto R., Buring J., Hennekens C., Kearney P., et al.

Aspirin in the primary and secondary prevention of vascular disease: Collaborative meta-analysis of individual participant data from randomised trials. Lancet Lond. Engl. 2009;373:1849–1860. doi: 10.1016/S0140-6736(09)60503-1. [PMC free article]

12. Aoyagi T., Matsui T. The Cardiomyocyte as a Source of Cytokines in Cardiac Injury. J. Cell Sci. Ther. 2011;2012 doi: 10.4172/2157-7013.S5-003. [PMC free article]

13. Arai H., Hori S., Aramori I., Ohkubo H., Nakanishi S. Cloning and expression of a cDNA encoding an endothelin receptor. Nature. 1990;348:730–732. doi: 10.1038/348730a0.

14. Arrillaga-Romany I., Norden A.D. Antiangiogenic therapies for glioblastoma. CNS Oncol. 2014;3:349–358. doi: 10.2217/cns.14.31. [PMC free article]

15. Arsic N., Zentilin L., Zacchigna S., Santoro D., Stanta G., Salvi A., Sinagra G., Giacca M. Induction of functional neovascularization by combined VEGF and angiopoietin-1 gene transfer using AAV vectors. Mol. Ther. J. Am. Soc. Gene Ther. 2003;7:450–459. doi: 10.1016/S1525-0016(03)00034-0.

16. Asahara T., Chen D., Tsurumi Y., Kearney M., Rossow S., Passeri J., Symes J.F., Isner J.M. Accelerated restitution of endothelial integrity and endothelium-dependent function after phVEGF165 gene transfer. Circulation. 1996;94:3291–3302. doi: 10.1161/01.CIR.94.12.3291.

17. Azimi-Nezhad M. Vascular endothelial growth factor from embryonic status to cardiovascular pathology. Rep. Biochem. Mol. Biol. 2014;2:59–69. [PMC free article] [PubMed] [Google Scholar]

18. Badimon L., Suades R., Crespo J., Padro T., Chiva-Blanch G. Diet, microparticles and atherothrombosis. Front. Biosci. LandmarkEd. 2018;23:432–457. doi: 10.2741/4598.

19. Banquet S., Gomez E., Nicol L., Edwards-Lévy F., Henry J.-P., Cao R., Schapman D., Dautreaux B., Lallemand F., Bauer F., et al. Arteriogenic therapy by intramyocardial sustained delivery of a novel growth factor combination prevents chronic heart failure. Circulation. 2011;124:1059–1069. doi: 10.1161/CIRCULATIONAHA.110.010264.

20. Barleon B., Sozzani S., Zhou D., Weich H.A., Mantovani A., Marmé D. Migration of human monocytes in response to vascular endothelial growth factor (VEGF) is mediated via the VEGF receptor flt-1. Blood. 1996;87:3336–3343. doi: 10.1182/blood.V87.8.3336.bloodjournal8783336.

21. Barton M., Yanagisawa M. Endothelin: 30 years from discovery to therapy. Hypertension. 2019;74:1232–1265. doi: 10.1161/HYPERTENSIONAHA.119.12105.

22. Beck H., Plate K.H. Angiogenesis after cerebral ischemia. ActaNeuropathol. (Berl.) 2009;117:481–496. doi: 10.1007/s00401-009-0483-6.

23. Bohm F., Jensen J., Svane B., Settergren M., Pernow J. Intracoronary endothelin receptor blockade improves endothelial function in patients with coronary artery disease. Can. J. Physiol. Pharmacol. 2008;86:745–751. doi: 10.1139/Y08-081.

24. Bohm F., Pernow J. The importance of endothelin-1 for vascular dysfunction in cardiovascular disease. Cardiovasc. Res. 2007;76:8–18. doi: 10.1016/j.cardiores.2007.06.004.

25. Borgers M., Voipio-Pulkki L.-M., Izumo S. Apoptosis. Cardiovasc. Res. 2000;45: 525–527. doi: 10.1016/S0008-6363(99)00404-6.

26. Borgeson D.D., Grantham J.A., Williamson E.E., Luchner A., Redfield M.M., Opgenorth T.J., Burnett J.C. Chronic Oral Endothelin Type A Receptor Antagonism in Experimental Heart Failure. Hypertension. 1998;31:766–770. doi: 10.1161/01.HYP.31.3.766.

27. Camaré C., Pucelle M., Nègre-Salvayre A., Salvayre R. Angiogenesis in the atherosclerotic plaque. Redox Biol. 2017;12:18–34. doi: 10.1016/j.redox.2017.01.007. [PMC free article]

28. Campia U., Tesauro M., Di Daniele N., Cardillo C. The vascular endothelin system in obesity and type 2 diabetes: Pathophysiology and therapeutic implications. LifeSci. 2014;118:149–155. doi: 10.1016/j.lfs.2014.02.028.