



RESEARCH ARTICLE

# Morphological findings of arteriolar atherosclerosis and prognosis in patients undergoing artery bypass grafting in Armenia

Nona Kukurtchyan <sup>1</sup>, Gohar Karapetyan <sup>1</sup>, Arman Kocharyan <sup>1</sup>, Mher Voskanyan <sup>1</sup>, Mamicon Hovhannisyan <sup>1</sup>

<sup>1</sup> Best life Armenian-Japanese Medical Centre, Yerevan, RA



OPEN ACCESS

**PUBLISHED**

31 October 2025

**CITATION**

Kukurtchyan, N., Karapetyan, G., et al., 2025. Morphological findings of arteriolar atherosclerosis and prognosis in patients undergoing artery bypass grafting in Armenia. Medical Research Archives, [online] 13(10).

<https://doi.org/10.18103/mra.v13i10.7045>

**COPYRIGHT**

© 2025 European Society of Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**DOI**

<https://doi.org/10.18103/mra.v13i10.7045>

**ISSN**

2375-1924

## ABSTRACT

Cardiovascular disease remains the leading global cause of mortality and morbidity. Atherosclerotic alterations play a pivotal role not only in coronary vessels but also within the microcirculatory system, particularly affecting arterioles.

Right atrial appendage specimens from patients with coronary artery disease (CAD), obtained during cardiac surgical interventions, were processed using transmission electron microscopy (TEM), stained with Azure-2, and examined under a light microscope.

Morphological analysis revealed a marked increase in arteriolar formation via the intussusceptive angiogenesis mechanism. In certain patients, the number of de novo arterioles reached 4 points on a 5-point pathological vascular growth scale for intussusceptive angiogenesis. Coronary artery bypass grafting (CABG) is generally indicated for patients presenting with the most advanced forms of ischemic heart disease (IHD). Arteriolar atherosclerosis in CAD may represent one of the underlying mechanisms contributing to heart failure.

Early detection of such pathological changes may facilitate prognostication of disease progression, estimation of life expectancy, and the selection of optimal therapeutic strategies.

**Keywords:** CAD, atherosclerosis arteriole, intussusception growth, light optical microscopy.

## Introduction

Ischemic heart disease (IHD) remains a leading global cause of mortality and morbidity. Myocardial perfusion is maintained through an extensive vascular network comprising large epicardial coronary arteries, smaller arteries, arterioles, and capillaries. The microvascular network, consisting of arterioles and capillaries, plays a critical role in myocardial oxygen delivery. Atherosclerotic damage affects not only the major coronary vessels but also the primary microcirculatory elements—the arterioles.<sup>11,9</sup>

Coronary artery disease (CAD), characterized by plaque accumulation in the coronary arterial walls, gradually narrows the vascular lumen and contributes to impaired myocardial perfusion.<sup>12</sup> While CAD is often associated with large epicardial vessels, recent studies emphasize the crucial role of coronary microvascular dysfunction.<sup>11,9</sup> In IHD, coronary arterioles undergo morphological alterations due to reduced blood flow and oxygen supply. These resistance vessels, typically with diameters around 200  $\mu\text{m}$ , are key regulators of myocardial reperfusion.

Heterogeneity in the myocardial vascular network affects structural and functional parameters such as vessel diameter, length, connectivity, flow patterns, velocity, wall shear stress, and oxidative stress.<sup>22,21</sup>

Normally, arterioles have thin walls composed of endothelium, smooth muscle cells, and minimal connective tissue. Microvascular atherosclerosis leads to structural remodeling, including wall thickening, reduced elasticity, and impaired function. Coronary microcirculation disturbances are involved in multiple pathophysiological mechanisms of ischemia-reperfusion injury.<sup>1</sup> Knowledge of these mechanisms remains limited but is essential for understanding disease progression.<sup>22</sup>

Since atherosclerosis is a systemic process, its effects extend throughout the myocardium, including the right atrium. Cardiac surgical interventions, such as coronary artery bypass grafting (CABG), are employed to improve myocardial perfusion. Small fragments of the right atrial appendage, routinely obtained during cardiothoracic surgery, provide an opportunity to study myocardial arterioles using detailed histological methods.<sup>[18]</sup> These methods enable visualization of arteriolar morphology and assessment of the degree of atherosclerotic involvement.<sup>16,17</sup> Morphological analyses have demonstrated pathological growth of arterioles by intussusception type, highlighting the need for further morphological investigation.

## Materials and Methods

Small fragments of the right atrial appendage from 6 patients with CAD were obtained during routine cardiac surgical procedures. Biopsy specimens were immediately fixed in a cold mixture of paraformaldehyde and glutaraldehyde, followed by post-fixation in 1%  $\text{OsO}_4$ . The tissues were dehydrated in an ascending series of alcohols and acetone, then embedded in epoxy resin. Semithin epoxy slices with up to 1 micrometer thickness were prepared using an Ultracut Riechert. Sections were

stained with 1% solution of Azur II by special method<sup>18</sup> and examined under a light microscope using a 40 $\times$  objective lens combined with a 10 $\times$  ocular lens.

All obtained images of arterioles were analyzed and evaluated by 5 score scale of pathological growth of microvessels by intussusceptive type<sup>17</sup>.

All procedures involving human subjects were approved by the Institutional Review Board and Bioethical Committee of the Yerevan State Medical University, RRI, and conformed to the ethical guidelines and legal standards for research in accordance with the European Community Directives (2001/20/EC).

## The aim of Study

To investigate new morphological findings of arteriolar atherosclerosis in CAD patients, focusing on intussusceptive arteriogenesis (de novo formation) and the direction of these changes, with the goal of predicting potential complications.

## Results

On semithin epoxy sections stained with Azure-2, images of arterioles from the right atrial appendage were obtained. Six male patients with CAD, aged 48 to 65 years, were included in the study. To obtain a reliable representation of pathological changes in the arterioles, the entire biopsy material was utilized. Very small myocardial fragments of the atrial appendage were processed and embedded in epoxy resin, resulting in up to eight gelatin blocks.

The obtained images of arterioles were characteristic for each individual patient, showing both similarities and differences. The arterioles displayed variable lumen diameters, ranging from very large to small profiles. Wall thickness also varied, with some arterioles showing pronounced intussusceptive invaginations into the lumen. In certain cases, bridges connecting opposite arteriolar walls were observed, sometimes multiple in a single vessel.

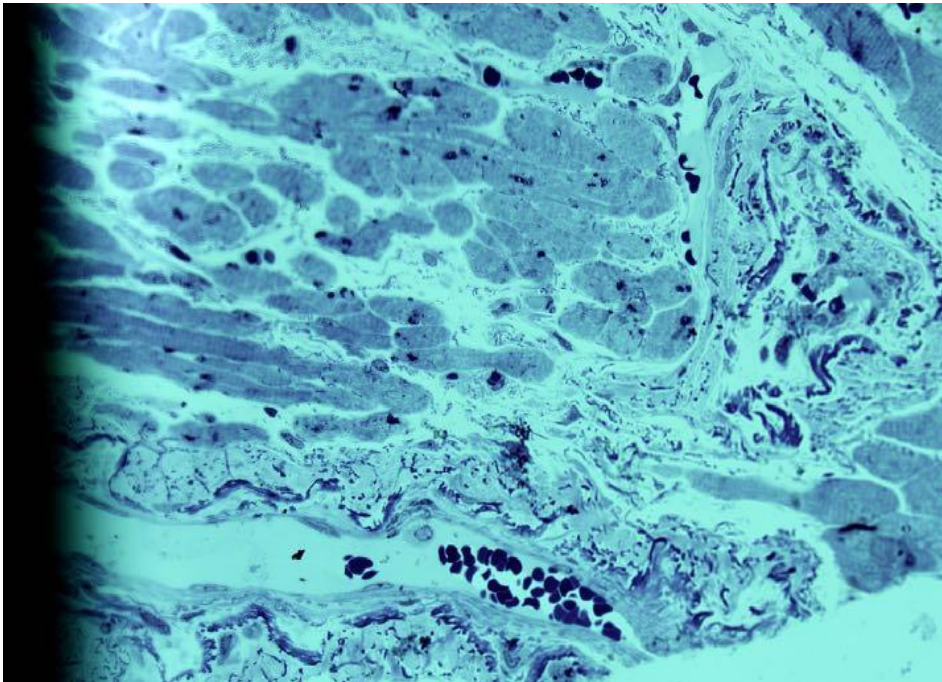
Atherosclerotic changes were particularly notable in larger arterioles. These vessels exhibited elongated lumens, significant wall thickening, and abundant smooth muscle cells. Some large arterioles showed up to two convolutions at different ends of the lumen. Evidence of newly forming arterioles was observed, including residual fragments indicating separation. Notably, the newly separated arterioles differed markedly in lumen size compared to the parent vessel. In some separated segments, chambers were present, indicating the formation of a new convoluted vessel. [fig 1]

Frequently, arterioles with thickened walls consisted of multiple aligned lumens of different sizes, suggesting formation through bridging of opposite walls. [fig 2] In cases of single de novo arteriole formation, the pathological vascular growth score reached up to 3 -4 points.<sup>17</sup> In other patients, de novo arterioles exhibited variable lumen sizes, with multiple aligned or isolated lumens, sometimes associated with residual shared membranes. [fig 3] One arteriole showed chambers

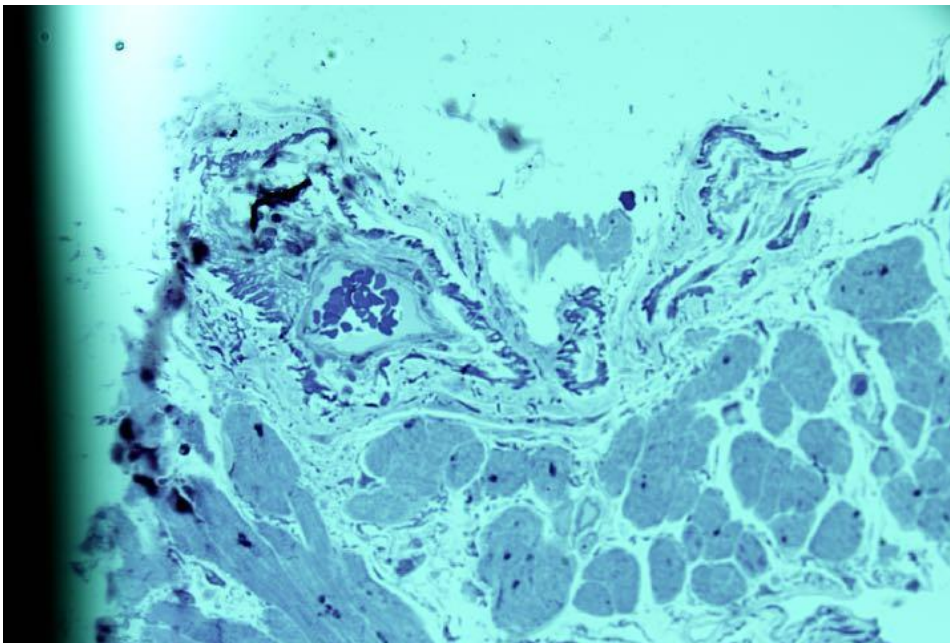
indicative of a separating convolution. Pathological arteriolar growth in this patient was also scored 4 due to increased de novo vessel formation.

The observed arteriolar growth sometimes resulted in highly irregular forms. Formation of pseudo-vessels

occurred through protrusion of one arteriolar wall into the lumen, and growing walls occasionally created new vessels with dual lumens. [fig 4] De novo formation from these vessels typically exhibited thickened walls and narrow lumen profiles.

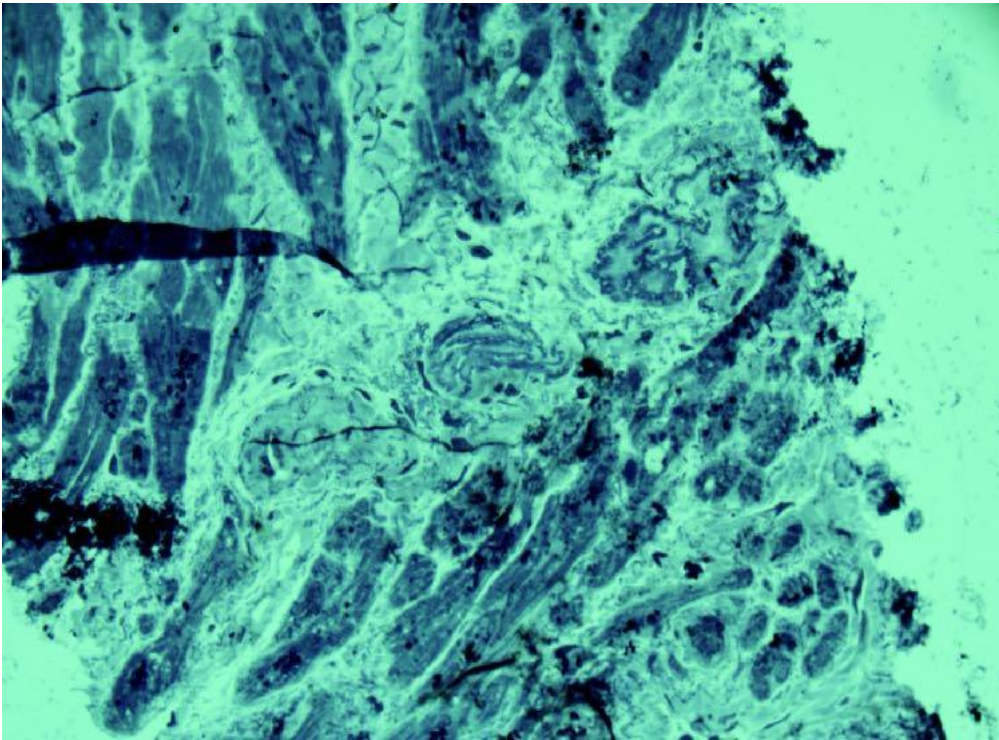


**Figure 1.** De novo formation in a large arteriole

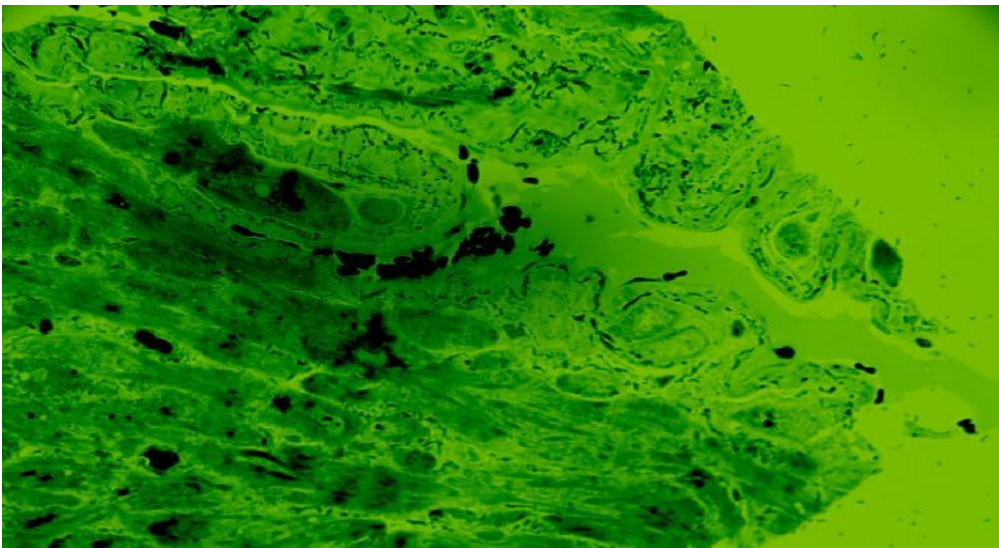


**Figure 2.** Several arterioles of varying lumen sizes.





**Figure 3.** Three closely positioned de novo arterioles.



**Figure 4.** Pseudo-arterioles within a parent arteriole.

## Discussion

In IHD, arterioles undergo morphological changes due to reduced blood pressure and compromised oxygen supply. These changes contribute to structural remodeling of the vessel walls, including increased thickness, hypertrophy, and fibrosis. In the early stages of CAD, structural changes in arterioles are often compensatory and are manifested as arteriolar dilation, a response to pathological processes, as indicated by our findings.

Beyond varying degrees of wall thickening, significant alterations were observed in arterioles consistent with intussusceptive arteriogenesis. [fig. 1-4] It could lead to microvascular dysfunction.

In recent decades, new terms such as coronary vasospasm, microvascular spasm, and microvascular angina have emerged, though their identification and clinical relevance remain poorly understood in daily practice.<sup>6,14,23,24</sup>

The observed arteriolar changes may also have clinical implications, contributing to manifestations of myocardial ischemia.

Microvascular dysfunction often undetected on routine coronary angiography, has emerged as a key determinant of prognosis acute and chronic coronary syndromes.

Patients with microvascular dysfunction are at higher risk of adverse cardiovascular events, such as recurrent myocardial infarction, heart failure, hospitalization and mortality. A notable phenomenon is the pathological growth of arterioles via intussusception.

Morphological findings microvessels of patients with pulmonary artery valve stenosis<sup>15</sup> occurred pathological growth of microvessels by intussusception type, which indicate that such phenomena could take place at other heart diseases as well.

The group of Burry, including Djonov and Paten, initiated and developed the vessel intussusception concept in blood vessels<sup>10,11,19,20,25</sup>.

The term intussusception, related to angiogenesis and arteriogenesis, refers to the formation of new capillaries, arteries, and veins from pre-existing vessels—a concept well described since the 1990s, with mechanisms extensively investigated.<sup>2,7</sup>

Nevertheless, the mechanism of intussusception in skeletal muscle remains difficult to investigate, while no studies addressing cardiac tissue have been performed to date.

Recent studies on intussusceptive growth in skeletal muscle indicate that it is a slow process, influencing capillary remodeling; however, its implications for larger arteries remain less well understood.<sup>13</sup> The research primarily focused on the study of capillaries, whereas arterioles were not considered.

Experimental studies in skeletal muscle suggest that intussusceptive vessel growth during ischemia occurs gradually. In cardiac muscle, similar processes may contribute to structural adaptation, potentially affecting disease progression and responses to external stimuli, including hemodynamic stress.

The kinetics of new blood vessel formation and the functional capacities of newly formed vessels induced by VPV/VEGF or other cytokines in ischemic tissue have not been carefully investigated.<sup>3,5</sup> A role for intussusception

angiogenesis in rebuilding a vessel network, after ischemic muscle injury as unknown.<sup>8,25</sup>

Vascular growth is an important component of IHD pathophysiology. Impaired arteriolar function can exacerbate heart failure, as the heart is forced to work against increased vascular resistance. Understanding these microvascular changes is therefore essential for improving clinical management and therapeutic strategies in patients with CAD.

Morphological studies of the right atrial appendage myocardium during coronary artery bypass grafting allow the identification of atherosclerotic lesions of arterioles of the intussusception type. Furthermore, evaluation of pathological intussusceptive microvessel growth on a five-point scale enables prediction of subsequent atherosclerotic involvement of arterioles.<sup>17</sup> The atherosclerotic changes of arterioles assessed at 4 points in the present study indicate a severe vascular condition.

## Conclusion

Coronary artery bypass grafting (CABG) is indicated for patients with the most severe forms of ischemic heart disease (IHD), including those presenting emergently to clinical care. Arteriolar atherosclerosis in CAD may represent one of the underlying mechanisms contributing to heart failure. Timely detection of such microvascular changes can aid in predicting disease progression, estimating patient prognosis, and guiding appropriate pharmacological therapy.

## References

1. Alfary A, Kabach M.J, Nieves J., Pino J., Chait R., "Microvascular Coronary artery disease." USE/US Cardiology Review 2017.
2. Burry P.H., Hlushchuk R., Djonov V., 'Intussusceptive angiogenesis its significance. Dev. Dyn. 2004, 231; 474-488. Doi:10.1002/dvdy.20184.
3. Camiei P.G., Crea F. "Coronary microvascular disfunction". N. Egl. Med.2007, 356, 830-40. Doi:10.1056/NFJ Mra 061889
4. Chen H., Kasseb Ch.S. 'Microstructure- Based Biochemical of Coronary Arteries in Health and Disease' J. Biomech, 2016; 49(12); 2548-2559: Doi:10.1016/j.biomech. 2016.03.023.
5. Chilian W. M. 'Coronary Microcirculation in Health and Disease. Summary of an NHLBI Workshop. Circulation 1997; 95, 522-528. Doi. Org:/10.1161/01.CIR 95.2.522.
6. Del Buono M. G., Montone R.A., Camilli M. Et al. 'Coronary microvascular dysfunction across the spectrum of cardiovascular disease. J AM. Coll Cardiol. 2021, 78, 1352-1371.
7. Djonov V, Baum O, Burry P.H. Vascular Remodeling by intussusceptive angiogenesis, j. Cell Tissue Res. 2003, 314(1); 107-117. Doi: 10.1007/S00441-003-0784-3.
8. Egginton S., Zhou A.L., Brown M.D., Hudlicka D. 'Unorthodox angiogenesis in skeletal muscle' cardiovascular. Res. 2001; 49; 634-646.
9. Fonseka D.A., Antunes R.E., Doulce D., Cotrin D. The morphology, Physiology and Pathohistology of Coronary microcirculation. Open access peer-reviewed chapter oct. 2016. Doi: 10.5772/64537.
10. Gianni-Barera, Tzani M, Fontanellar C, Hebery M, Djonov V, Hlushchuk R., Banfi A. 'VEGF over expression in skeletal muscle induces angiogenesis by intussusception rather than sprouting' Angiogenesis 2013, 16, 123-136. Doi: 10.1007/9 10456-012-93049
11. Gianni-Barera R., Butsch K.A., Uccelli A., Gertelli A., Valente P., Bartolomeo M., Groppa E., Bargen M. G., Heberer M, Schafer D., Gurske L, Djonov V, Vallmar B, Banfi A. "PDGF-BB regulating sprouting angiogenesis in skeletal muscle by limiting VEGF-induced endothelial proliferation". Angiogenesis, 2018; 21; 883-900.
12. Jivorny R., Taqueti, Marclo F, Dicarli; Coronary microvascular disease. Pathogenic mechanisms and Therapeutic Options. J. Am. Coll Cardiol, 2018, N27; 72(21); 2625-2641. Doi; 10.1016/j.jacc. 2018.09.042.
13. John-Michael Azpino. "Low-flow intussusceptive and metastable VEGF, Sigma Link launch angiogenesis ischemic muscle" Science advances. Nov.2021, Vol 7, issue 48. Doi:10.1126/Sciadv.abg9509
14. Juan Carlos Kaskietal et al., Reappraised of Ischemic Heart Disease. Circulation 2018 Ana 138(4); 1463-1480. Doi; 10.1161/Circulation Ana, 118.03.1373
15. Kukurtchyan N.S., Karapetyan G.R., Heart microvessels research at ischemic heart disease at open heart surgery' EJBPT, 2021, 8(8): 71-75.
16. Kukurtchyan N.S., Karapetyan G.R., Case report visualisation and Evaluation study of some patients with coronary artery bypass grafting 2024, European Society of Medicine. Medical research archives. 2024; 12/3. Doi org: /10.18103/mra.v.12
17. Kukurtchyan N., Karapetyan.G., Kocharyan A., Voskanyan M., Hovhannisyan M., Farsyan N, Sahakyan I., Tumasyan N., 'Microvessels Atherosclerosis study and Evaluation of some patients with coronary artery disease at open heart surgery in Armenia. The European Society of Medicine. Medical Research Archives, Volum 13 Issue 1, 2025.
18. Kukurtchyan N.S., Karapetyan G.R., Patent 2844A. Rep Armenia. Staining method of histological material.
19. L. Dear-Flosy, R. Cutiesver, S Cayso, Mp Gassia, M. Gonzales-Comes, L. Dear-Flores, R Sanchez, J.M. Carrasco, J. F. Madrid. 'Intussusceptive angiogenesis and antepart intussusceptive lymphangiogenesis " Histol. Histopathology 2022, oct., 35(10)1083-1103.
20. Mentzez S.I., Konerding M.A. 'Intussusception angiogenesis expansion and remodeling of microvascular network' Angiogenesis 2014; 17, 499-509.
21. Pries A. R., Regin B. 'Coronary microcirculatory pathophysiology' j. Eur. Heart 2017; 38; 478-488. Doi; 10.1093/eurheart j/ehv 760.
22. Pries A.R, Coronary Microcirculation in Ischemic Heart Disease. PubMed Curr Pharm Des., 2018.
23. Sorrob O., Van Der Wow, Chadler S., Ohanyan V., Tuni J.D., Chilian W.M., Mecus D., Bender S.B., Duncker D.J. 'Experimental animal model of coronary microvascular dysfunction' Cardiovascular research 2020; 116(4); 756-787. Doi.org:10.1093/CV2/cvas002
24. Sucator V., Novos, Rubino N., Di Agestino A, Erolos Novo G., 'Prognosis in patients with microvascular angina. A clinical follow up' j. Cardiovascular. Med 2019, 20, 794-795. Doi: 10.2459/j.CM000000000 0000842.
25. Zhou A., Egginton S., Hudlicka O., Brown M.D. 'Internal division of capillaries in rat skeletal muscle in response to chronic vasodilation treatment with alphas-antagonist pargyline'. Cell. Tissue Res 1992; 293; 293-303.