

# Clinical Significance Of Biomarkers Of The Angiogenic Process In Patients Who Have Suffered Acute Coronary Syndrome

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**Abstract:** In patients with acute coronary syndrome, a significant increase in the levels of the studied biomarkers was detected: hypoxia-induced factor-1 — 2.1 times, vascular endothelial growth factor (VEGF) — 1.8 times, endothelin-1 — 5.8 times, xanthine oxidase activity — 48%.

The data obtained indicate pronounced endothelial dysfunction and activation of angiogenic processes, which is of important prognostic and clinical significance in the management of patients with ACS.

**Keywords:** Acute coronary syndrome; Angiogenesis; Hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ); Vascular endothelial growth factor (VEGF-A); Endothelin-1; Xanthine oxidase; Endothelial dysfunction; Oxidative stress; Biomarkers; Atherosclerosis; Inflammation; Vasa vasorum; Reactive oxygen species (ROS); Hypoxia; Neovascularization; Cardiovascular disease; Clinical significance.

## INTRODUCTION:

Angiogenesis and its role in the progression of atherosclerosis and ACS

Neocapillaries in atherosclerotic plaques often have high permeability and can become a source of intraplaque hemorrhages. Such damage is associated with the accumulation of erythrocyte fragments, iron deposits, and the formation of foam cells and cholesterol crystals [4].

The angiogenic process in atherosclerosis can be initiated by hypoxia, which stimulates the expression and release of angiogenic factors (e.g., VEGF). When normoxia is restored, angiogenesis activity is suppressed [5]. Thus, activation or imbalance of the angiogenic process is a key link in the formation of atherosclerotic plaque instability and the development of acute coronary syndrome complications.

When O<sub>2</sub> supply is restored, HIF-1 $\alpha$  undergoes degradation, which reduces VEGF production and subsequent angiogenic signaling. Mitochondrial fatty acid metabolism in endothelial cells also participates in

the regulation of angiogenesis. Inhibition of carnitine palmitoyltransferase (CPT1A) leads to a decrease in fatty acid oxidation, depletion of cellular deoxyribonucleoside triphosphate reserves, and limitation of endothelial cell proliferation and vascular growth [21].

Reactive carbonyl compounds formed in the late stages of PUFA peroxidation, including malondialdehyde (MDA), are highly reactive, interact with cellular and extracellular components, and alter their biological properties [22]. These processes affect proliferation, migration, and angiogenesis.

Oxidative stress in atherosclerotic areas leads to the formation of oxidized lipoproteins and lipid peroxidation derivatives [23]. In advanced atherosclerotic plaques, intimal microhemorrhages release hemoglobin, heme, and iron, which contribute to the generation of free radicals and ROS (via the Fenton reaction), inactivate nitric oxide, and stimulate lipid peroxidation.

The aim of this study was to identify the relationship between biomarkers of hypoxia, inflammation, and endothelial dysfunction in patients with acute coronary syndrome.

## METHODS

In patients with acute coronary syndrome in the acute phase, the levels of the following biomarkers were determined:

- hypoxia-induced factor-1 (HIF-1),
- endothelin-1,
- vascular endothelial growth factor (VEGF),
- von Willebrand factor,
- xanthine oxidase activity.

To determine the concentrations of the studied biomarkers in blood serum, an immunoenzymatic method was used with kits from HUMAN.

Statistical data processing was performed using

Microsoft Excel and STATISTICA 6.0 software. Nonparametric methods were used to compare the mean values: the Mann–Whitney U test for two independent groups. Differences were considered significant at a significance level of  $P < 0.05$ .

## RESULTS

The results of the analysis showed that in the late stages of atherosclerosis, neoangiogenesis develops with the formation of vasa vasorum, in which HIF-1 plays a leading role. This factor regulates apoptosis and vessel formation by controlling the expression of VEGF, a key angiogenic mediator.

According to the data presented (Table 1), the quantitative content of HIF-1 $\alpha$  in the blood serum of patients with acute coronary syndrome was on average 2.1 times higher than in the control group. These results confirm the importance of HIF-1 as a biomarker of angiogenesis and the progression of atherosclerotic processes in ACS.

**Table**  
**Blood serum indicators in patients with acute coronary syndrome**

| Indicators                       | Comparison group  | Main group         |
|----------------------------------|-------------------|--------------------|
| HIF-1 $\alpha$ , ng/mL           | 0.41 $\pm$ 0.04   | 0.86 $\pm$ 0.07*   |
| Endothelin-1 pg/mL               | 0.45 $\pm$ 0.03   | 2.82 $\pm$ 0.18    |
| VEGF-A, pg/mL                    | 106.34 $\pm$ 8.15 | 189.67 $\pm$ 9.86* |
| Activity von Willebrand factor % | 87.42 $\pm$ 6.15  | 119.28 $\pm$ 7.29* |
| Xanthine oxidase nmol/min/ml     | 3.27 $\pm$ 0.24   | 4.85 $\pm$ 0.38*   |

Note: \*- significance of differences  $P < 0.05$  relative to comparison groups

The results of the study indicate a 1.8-fold increase in the content of vascular endothelial growth factor in the blood compared to the control group.

The observed increased expression of HIF-1 and VEGF provides convincing evidence that endothelial cells proliferate and accelerate blood vessels under the influence of hypoxic stimuli in patients with acute coronary syndrome.

Analysis of the results presented in Table 1 showed a significant increase in the concentration of endothelin-1 in the blood serum of patients with acute coronary syndrome, on average 5.8 times higher than in the control group.

In this case, the increase in serum ET-1, in our opinion, indicates the activation of endothelial cells and the release of ET-1 into the intercellular space and blood. At the same time, ET-1 as a marker of endothelial dysfunction can be considered an independent risk factor for the development of cardiovascular pathology.

The possible role of HIF in the process of acute coronary syndrome is confirmed by the presence of intravascular angiogenesis and the involvement of several known HIF-sensitive genes, such as vascular endothelial growth factor-endothelin-1.

Endothelin-1 (ET-1) is a marker of endothelial dysfunction, which manifests itself in changes in vascular tone and damage to the vascular wall, leading to its thickening and vasoconstriction, which plays a certain role in the pathogenesis of atherosclerosis. ET-1, acting on ET-B receptors of endothelial and smooth muscle cells, stimulates the formation of nitric oxide, which counteracts vasoconstriction.

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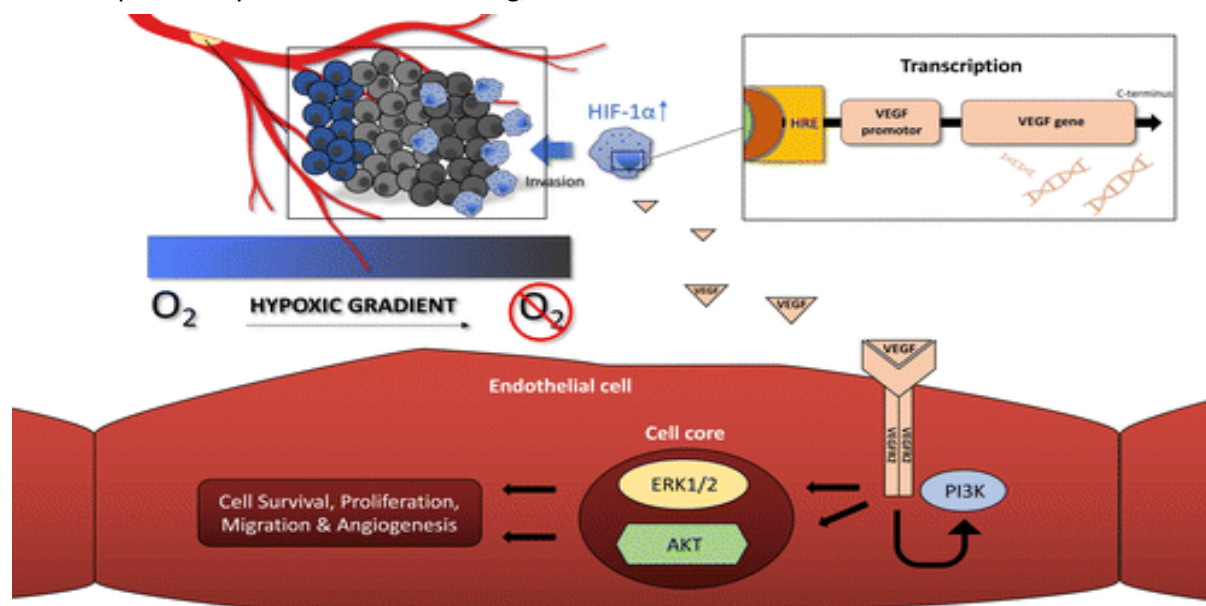
At the same time, ET-1 as a marker of endothelial dysfunction may be an independent risk factor for the development of cardiovascular pathology.

## DISCUSSION

Under conditions of hypoxia arising in acute coronary syndrome, the activation of HIF-1 $\alpha$  and HIF-2 $\alpha$ , as well as related molecules (nitric oxide, endothelial NO synthase), leads to a cascade of molecular changes. This is accompanied by vascular remodeling, the

growth of new capillaries, and, in chronic hypoxia, fibrosis and tissue scarring.

Such processes have direct clinical significance. Increased expression of HIF-dependent factors, including VEGF, endothelin-1, erythropoietin, and inflammatory mediators, are considered potential biomarkers of atherosclerosis progression and plaque instability.



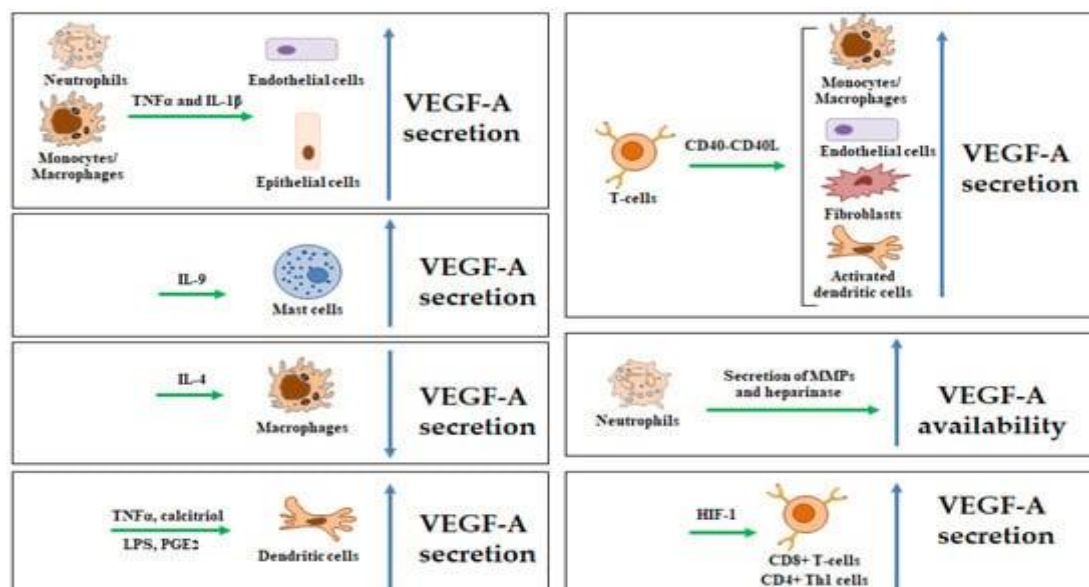
**Figure 1. HIF-dependent VEGF secretion in macrophages**

In patients with acute coronary syndrome, the detection of elevated concentrations of these molecules in blood serum can serve as an additional diagnostic tool. For example, an increase in endothelin-1 levels reflects endothelial dysfunction and correlates with the risk of cardiovascular complications.

Thus, monitoring biomarkers of the angiogenic process allows not only a better understanding of the pathogenesis of ischemic events, but also the prediction of disease progression and the optimization of therapeutic approaches.

The formation and organization of blood vessels occurs through two processes, defined as vasculogenesis and angiogenesis. Vasculogenesis is the development of a capillary network through the differentiation of pluripotent mesenchymal cells into hemangioblasts, while angiogenesis refers to the process by which new blood vessels develop from existing ones [28]. The importance of vasculogenesis and angiogenesis is related to their homeostatic role in

supplying oxygen and nutrients to tissues and organs, while also removing waste metabolites. Thus, vasculogenesis and angiogenesis are critical points in physiological processes such as embryonic development, growth, hematopoiesis, tissue remodeling, and wound healing, as well as pathological conditions such as cancer, inflammation, atherosclerosis, or diabetic retinopathy [29]. These processes are coordinated both by interactions between different types of cells of endothelial and non-endothelial origin and by cellular responses to angiogenic or antiangiogenic factors [30]. The vascular endothelial growth factor (VEGF) family of factors ( ) includes central mediators in the processes of vasculogenesis and angiogenesis. Since 1983, with the isolation of vascular permeability factor VPF/VEGF-A [31], the most studied member of the family, the role of various VEGF and their receptors has been thoroughly characterized in both physiological and pathological angiogenesis [32].



**Figure 2. Mechanisms of VEGF-A expression regulation mediated by immune cells.**

VEGF-A protects endothelial cells by inducing the expression of anti-apoptotic proteins and NO production, promotes re-endothelialization, and prevents damage to the vascular wall. However, it also increases endothelial permeability, stimulates the expression of adhesive proteins and MCP-1, which enhances monocyte adhesion and their migration through the endothelium. Moreover, VEGF-A can induce proatherogenic changes in lipoproteins.

In coronary arteries, VEGF and its receptors are absent in normal areas but are actively expressed in atherosclerotic plaques, especially in non-vascular endothelial cells, macrophages, and partially differentiated smooth muscle cells.

Angiogenesis in atherosclerotic lesions is realized through classical mechanisms, but under the influence of pathological stimuli, it acquires a persistent and destabilizing character. Local hypoxia activates HIF-1 $\alpha$  and VEGF, which triggers angiogenic signaling. When oxygen supply is restored, VEGF decreases, and in its absence, persistent activation leads to the formation of unstable and leaky neovessels. This is clinically significant, as persistent pathological angiogenesis contributes to destabilization of atherosclerotic plaques and progression of coronary syndrome.

The hypoxic inflammatory environment causes monocytes to be attracted to the site of ischemia, their differentiation into macrophages, and accumulation in the hypoxic epicenter, which exacerbates oxygen deficiency. These processes are clinically significant because they enhance inflammation, lipid accumulation, and progression of vascular wall damage.

In the early stages of atherogenesis, hypoxia promotes the formation of foam cells through the uptake of

lipoproteins by macrophages and stimulates the secretion of pro-inflammatory mediators. Lipid droplets in macrophages can act as mediators of inflammation, and angiogenesis in the deep layers of plaques supports the chronic pathological process. These mechanisms determine the importance of HIF, VEGF, and other factors as clinically important biomarkers associated with the destabilization of atherosclerotic plaques and the risk of complications in patients after ACS.

A complex system of lipid efflux pathways, including ATP-binding cassette transporters (ABC transporters), scavenger receptors, and high-density lipoprotein, is regulated by inflammation and hypoxia. HIF-1 $\alpha$  has been shown to be an important regulator of ABCA1, directly stimulating the promoter region and increasing gene expression.

This is clinically significant because dysregulation of HIF-1 $\alpha$  leads to decreased glycolysis, reduced cellular ATP levels, and impaired myeloid aggregation and bactericidal function. Such changes reflect not only the progression of atherosclerotic lesions, but also a high risk of complications in patients who have had acute coronary syndrome.

An important enzymatic source of superoxide anion (O<sub>2</sub><sup>-</sup>) radicals and H<sub>2</sub>O<sub>2</sub> in cells is xanthine oxidoreductase, which under physiological conditions is predominantly in the xanthine dehydrogenase form and can reversibly or irreversibly convert to xanthine oxidase as a result of the formation of disulfide bonds between cysteine residues Cys535 and Cys992 [5]. The xanthine oxidase reaction contributes to the formation of a highly reactive OH radical, which arises as a result of further reduction of H<sub>2</sub>O<sub>2</sub> and is a powerful inducer of lipid peroxidation (LPO). The main physiological function of the enzyme is to participate in purine



catabolism, with the xanthine dehydrogenase form using mainly NAD<sup>+</sup> as an electron acceptor, while the oxidase form uses molecular oxygen. At the same time, xanthine oxidoreductase is the only metabolic source of uric acid, an important antioxidant in extracellular fluids, and an increase in its activity under oxidative stress conditions can play a dual role [51].

## CONCLUSIONS

1. In our opinion, a 5.8-fold increase in serum ET-1 indicates the activation of endothelial cells and the release of endothelin-1 into the intercellular space and blood.

2. The intensity and duration of reduced pO<sub>2</sub> levels determine the nature of the resulting response of endothelial cells against the background of changes in the studied blood parameters, accompanied by a 48% increase in blood xanthine oxidase activity in patients with acute coronary syndrome.

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