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Angiogenesis In Acute Coronary Syndrome: Mechanisms And The Role Of Biomarkers

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Abstract: The aim of the study was to identify the relationship between biomarkers of hypoxia, inflammation, and endothelial dysfunction in patients with acute coronary syndrome. The study included 62 male patients aged 24 to 50 years who were hospitalized for ACS.
Key markers associated with angiogenesis and hypoxia were studied: hypoxia-inducible factor-1 (HIF-1), vascular endothelial growth factor (VEGF), endothelin-1, von Willebrand factor, and xanthine oxidase activity. These biomarkers reflect the molecular mechanisms of angiogenesis and endothelial dysfunction.

Keywords: Angiogenesis; Acute coronary syndrome; Hypoxia; Hypoxia-inducible factor (HIF-1α); Vascular endothelial growth factor (VEGF-A); Endothelial dysfunction; Biomarkers; Inflammation; Atherosclerosis; Oxidative stress; Xanthine oxidase; Endothelin-1; Reactive oxygen species (ROS); Neovascularization; NF-kB pathway; Plaque destabilization.

INTRODUCTION:

Atherosclerosis as the basis for the development of acute coronary syndrome

Acute coronary syndrome develops as a result of an acute decrease in myocardial blood supply. The main cause of this condition is atherosclerosis, a multifocal, slowly progressive process affecting the intima of medium and large arteries [1].

This chronic metabolic and inflammatory process is characterized by the formation of plaques consisting of a cholesterol-rich core (atheroma) surrounded by a fibrous cap (sclerosis). Atherogenesis begins in early infancy and develops slowly over decades, gradually leading to the formation of lipid plaques. These plaques have a lipid core surrounded by a fibrous shell consisting of extracellular matrix proteins secreted by proliferating smooth muscle cells and myofibroblasts.

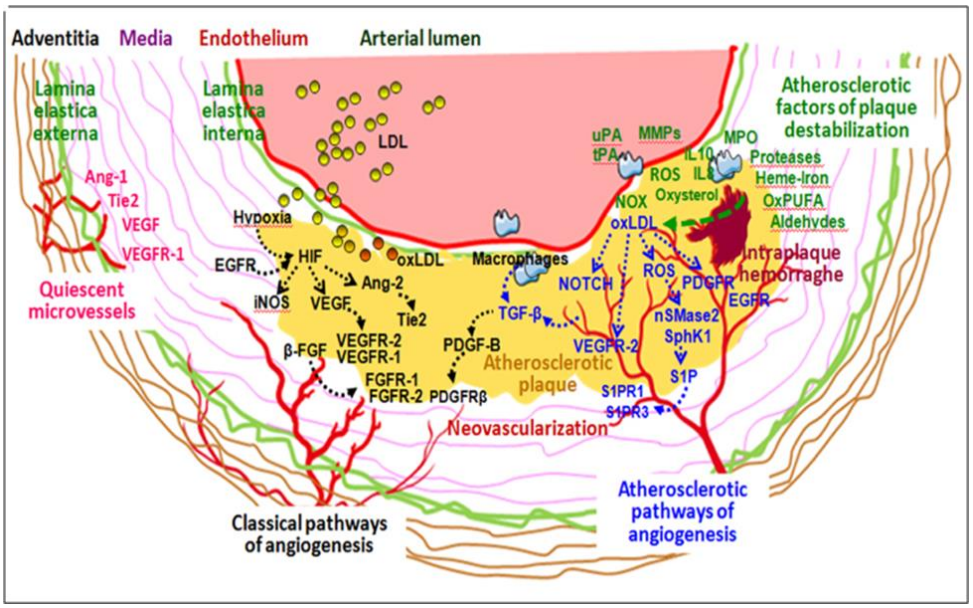

Fig. 1 Angiogenesis in an atherosclerotic plaque

Activated endothelium exhibits increased permeability, generates reactive oxygen species, and expresses inflammatory adhesion proteins and chemokines. Endothelial permeability allows plasma components to flow into the subendothelial region, where lipoproteins undergo various modifications, including oxidation. Leukocytes are attracted by chemokines and adhesion molecules, and monocytes are transformed into macrophage foam cells that form fatty streaks [1], [2]. Cholesterol deposition associated with local inflammatory response and secretion of pro-inflammatory cytokines contributes to the progression of atheromatous plaques [3].

Hypoxic and inflammatory conditions promote the release of angiogenic and inflammatory factors that stimulate sprouting angiogenesis from vasa vasorum [6]. This neovascularization allows nutrients to be delivered and promotes macrophage infiltration, thickening of the vessel walls, lipid deposition, inflammation, and progression of atherosclerotic lesions [7].

Angiogenesis is a dynamic process regulated by a delicate balance between angiogenic and angiostatic factors, which ultimately lead to an increase, stabilization, or decrease in the vascular network. A large number of factors, including hypoxic, hemodynamic, and metabolic parameters, may be involved in the regulation of angiogenesis in atherosclerotic areas [8].

Hypoxia is one of the most potent angiogenic stimuli, increasing the expression of various genes involved in angiogenesis , and erythropoiesis, ultimately leading to increased O_2 delivery and facilitating metabolic adaptation to hypoxia [9].

The transcription factor HIF (hypoxia-inducible factor) is a key regulator of the adaptive response to hypoxic conditions [10]. HIF-1α is regulated post-translationally via an O_2-dependent proteolytic pathway. Nuclear translocation of HIF-1α allows it to bind to HIF-1β and p300/BP, which activates hypoxia response elements (HREs) and induces the expression of target genes: VEGF, VEGFR, angiopoietin-2, and NO synthase [11,12].

VEGF-A is an endothelial-specific growth factor involved in the formation of the vascular network. Its expression increases during hypoxia, inflammation, and wound healing through transcriptional regulation mediated by HIF-1 and sp1 [13–15]. However, VEGF-A also increases endothelial permeability [16], expression of adhesive protein [17], and monocyte chemotactic protein-1 (MCP-1) [18,19], which promotes monocyte adhesion and migration [20].

METHODS

The study included 62 male patients aged 24 to 50 years who were hospitalized for acute coronary syndrome (ACS). The diagnosis of ACS was established based on generally accepted criteria [16]. All patients underwent a standard clinical examination, including collection of complaints, medical history, and objective status.

Demographic and clinical parameters were assessed: gender, age, presence of arterial hypertension >140/90 mmHg, use of antihypertensive drugs, abdominal obesity, smoking, hereditary predisposition, and lipid metabolism disorders.

All patients underwent clinical and biochemical blood tests, general urine analysis, and a 12-lead electrocardiogram. Laboratory tests were performed in a certified laboratory.

RESULTS

Atherosclerosis is a widespread disease that significantly increases the risk of serious vascular complications, including acute coronary syndrome, myocardial infarction, and cerebral infarction.

The anoxemia theory states that a mismatch between oxygen delivery and metabolic demands contributes to the progression of atherosclerosis. One of the key regulators of the cellular response to hypoxia is hypoxia-inducible factor-1 (HIF-1), which belongs to the helix-loop-helix family of proteins.

HIF-1 plays an important role in the development of atherosclerosis through its effects on endothelial cells, vascular smooth muscle cells (SMCs), and macrophages. Increased expression of HIF-1 leads to activation of VEGF, NO, POL, and AOS signaling pathways, which causes endothelial dysfunction, stimulates cell proliferation, angiogenesis, and inflammatory reactions.

Thus, HIF-1 is a key link in the initiation and regulation of angiogenesis in the progression of atherosclerosis.

Table

Blood serum parameters in patients with acute coronary syndrome

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

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

Hypoxia strongly affects the regulatory pathways of endothelial cells, leading to the activation of several transcription factors and the release of cytokines and growth factors. Several studies have evaluated how HIF regulates the functions of hypoxic endothelial cells.

Activation of HIF-1 allows cells to survive by adapting their energy metabolism, particularly through glycolysis. On the other hand, HIF-1 induces the expression of several angiogenic factors, including vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase, and platelet-derived growth factor. It is well known that HIF plays a crucial role in VEGF expression.

The accumulation of HIF-1 heterodimeric complexes activates VEGF and genes necessary for cell metabolism in a low-oxygen environment. HIF-1 directly activates the transcription of VEGF and VEGF receptors (VEGFR) by binding to HRE.

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 and 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.

Atherosclerosis can be considered a chronic inflammatory disease affecting the arterial wall. Despite recent advances in the study of the pathogenesis of atherosclerosis, some pathogenic mechanisms have yet to be fully understood. Among these mechanisms is oxidative stress ( ), which is closely associated with the formation of foam cells and other key events in the development of atherosclerosis.

Two groups of enzymes are involved in the development of oxidative stress: prooxidants (including NADPH oxidases, xanthine oxidases, and endothelial nitric oxide synthase) and antioxidants (such as superoxide dismutase, catalases, and thioredoxins). Under normal conditions, prooxidant enzymes produce moderate concentrations of reactive oxygen species, which play an important role in cell function and can be completely utilized by antioxidant enzymes. Under pathological conditions, the activity of both prooxidant and antioxidant enzymes can be altered by numerous factors that may be relevant for the development of new treatments.

It should be noted that oxidative stress, the overproduction of reactive oxygen species (ROS), plays a crucial role in the pathogenesis of endothelial dysfunction. More recent data suggest that HIF-1 may be induced by free radicals, especially reactive oxygen species. Analysis of events preceding HIF-1α suggests a decisive role for ROS generation during hypoxia via mitochondria as an oxygen level sensor mechanism, and that ROS may be involved in HIF-1α changes.

Several systems producing reactive oxygen species are present in the vascular wall, including NADPH oxidase, xanthine oxidase, mitochondrial respiratory chain enzymes, and dysfunctional, uncoupled endothelial NO synthase (eNOS). It is noteworthy that there are cross-regulatory mechanisms between these pro-oxidant systems.

Xanthine oxidases are present in endothelial cells and blood and use molecular oxygen as an electron acceptor to generate hydrogen peroxide and superoxide anions. Interestingly, xanthine oxidases generate uric acid, high concentrations of which in the blood can lead to clinical manifestations of gout, which is associated with an increase in the frequency of events related to atherosclerosis. Elevated uric acid levels also trigger the formation of foam cells by stimulating the expression of the important CD-36 receptor, which is responsible for binding and absorbing oxidized LDL in macrophages.

As can be seen from the results of the study (Table 1), xanthine oxidase activity in the blood of subjects with acute coronary syndrome was increased by 48% relative to the control groups. Thus, the intensity and duration of reduced pO2 levels determine the nature of the resulting response of endothelial cells against the background of changes in the studied blood parameters in patients with acute coronary syndrome.

DISCUSSION

Activation of the NF-kB pathway in endothelial cells is an important factor in inflammation and is positively associated with HIF-1. This factor plays a key role in the proliferation and migration of smooth muscle cells, processes that contribute to atherogenesis. The formation of foam cells (lipid-laden macrophages) is also mediated by HIF-1 through the disruption of lipid metabolism pathways in macrophages.

Endothelial cells, as the first barrier in contact with blood, regulate vascular homeostasis, including antithrombotic functions, the recruitment of inflammatory mediators, and the control of vascular tone. These mechanisms are disrupted during hypoxia.

HIF-1α promotes cell adaptation to hypoxia by it reduces oxygen demand, induces mitochondrial autophagy, and regulates the expression of genes associated with angiogenesis, cell proliferation, survival, invasion, vascular tone, erythropoiesis, and metabolism. In addition, it increases the secretion of erythropoietin and growth factors that enhance angiogenesis and gas exchange in ischemic tissues.

The hypoxic microenvironment in the core of an atherosclerotic plaque plays a crucial role in its progression and destabilization. Experimental studies in animals and humans have shown a spatial correlation between HIF-1α and its targets in the central areas of the plaque. This is accompanied by cell migration, inflammation, and increased angiogenesis in the affected areas, which triggers atherosclerosis progression.

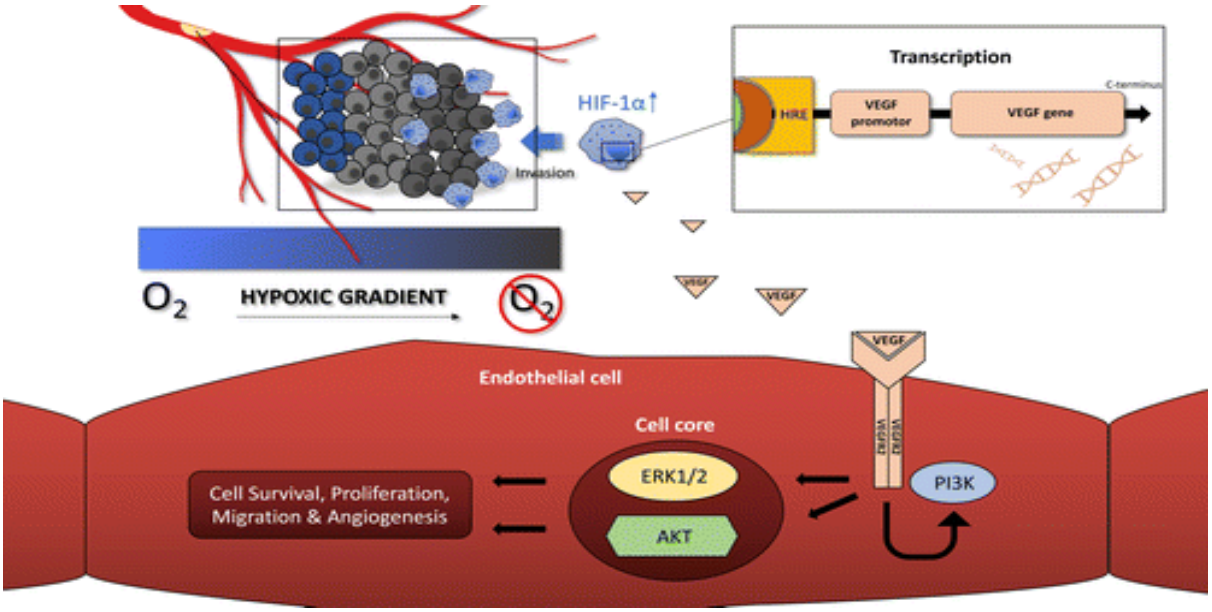

Fig. 2 HIF-dependent VEGF secretion in macrophages

The formation and organization of blood vessels occur through two processes known 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 as suppliers of oxygen and nutrients to tissues and organs, as well as the removal of 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 family of vascular endothelial growth factors (VEGF) 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].

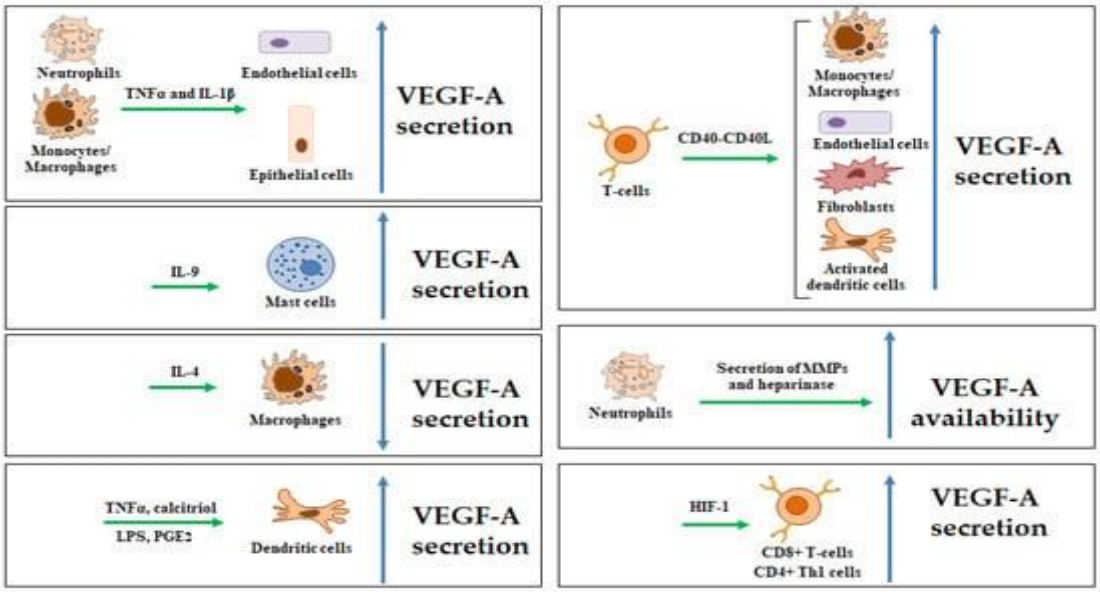

Fig. 3. Mechanisms of VEGF-A expression regulation mediated by immune cells.

As can be seen from the figure, hypoxia can induce T cells to secrete VEGF-A via HIF-1. VEGF-A is secreted by cells of epithelial and mesenchymal origin, and its expression is mainly modulated by hypoxia. In addition, immune factors and inflammatory mediators such as PDGF-BB, EGF, TGF-β1, IL-1β, and TNF-α can also induce VEGF-A expression.

IL-9 stimulates human mast cells to secrete VEGF-A, enhancing inflammatory processes, while IL-4 can inhibit VEGF-A secretion and simultaneously activate antiangiogenic mechanisms via soluble VEGFR-1. Thus, VEGF-A expression increases significantly during hypoxia, inflammation, wound healing, and other pathological processes, making it a central regulator of angiogenesis.

VEGF-A is a potent inducer of vascular growth, essential for embryonic development and vital for normal vascular function. However, its role in atherosclerosis is dual: it can have both protective and damaging effects.

When HIF is activated, cell metabolism adapts by reducing oxygen consumption by mitochondria and inducing mitochondrial autophagy, while erythropoietin is secreted to improve oxygen supply. Upregulation and release of growth factors enhances vascular neogenesis and improves gas exchange in tissues affected by hypoxia.

The hypoxic environment activates a cascade of molecular signals that promote angiogenesis: monocyte migration, their transformation into macrophages, and the activation of angiogenic proteins are enhanced, which ultimately triggers the process of neovascularization. Thus, HIF and associated growth factors are key biomarkers and regulators of angiogenic processes in acute coronary syndrome.

As macrophages and vascular smooth muscle cells absorb lipids, foamy cells form and the intimal layer thickens. The proliferation of neovascularization leads to destabilization of the atherosclerotic lesion and ultimately to plaque rupture.

Hypoxic areas of atherosclerotic plaques lined with macrophages are a source of local angiogenic activity. Macrophages, under low oxygen conditions, enhance the expression of HIF-regulated genes, leading to tissue remodeling, neovascularization, and progression of the pathological process.

Physiological concentrations of reactive oxygen species participate in cellular metabolism and signal transduction, as well as in the regulation of various cellular functions, such as proliferation, migration, and angiogenesis. In contrast, oxidative stress (an excess of reactive oxygen species (ROS) resulting from an imbalance between ROS production and degradation) can lead to cellular dysfunction, accelerated aging, and apoptosis [48]. Moderate concentrations of extracellular ROS trigger the expression of angiogenic

factors. For example, ROS generated during arterial damage can enhance local VEGF expression [49]. In addition, intracellular ROS formed in endothelial cells upon stimulation by growth factors, inflammatory cytokines, or oxLDL can trigger angiogenic signaling pathways, including p38MAPK, ERK1/2, NF-kappaB, and the nSMase2/SK1 pathway. Antioxidants block this signaling and the angiogenic response [50].

CONCLUSIONS

1. Hypoxia-induced factor is the main element in the induction of angiogenesis, and its content in blood serum is increased on average by 2.1 times in patients suffering from acute coronary syndrome compared to the control groups.

2. Endothelial cells proliferate and accelerate blood vessels under the influence of hypoxic stimuli, which is reflected in a 1.8-fold increase in the content of vascular endothelial growth factor.

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