African Journal of
Medicine, Surgery and Public Health Research

ISSN : 3434-3567

Index: Harvard, Boston, Sydney University, Dimensions, Lens, ResearchGet Scilit, Semantic, Google Scholar, Base etc

https://doi.org/10.58578/AJMSPHR.v1i1.4013

Angiogenesis and Microcirculation in Ischemic Heart Disease

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Article Info:

Submitted:	Revised:	Accepted:	Published:
Sep 22, 2024	Oct 6, 2024	Oct 21, 2024	Oct 26, 2024

Abstract

Angiogenesis among the functional organ systems, the cardiovascular system is the paramount appearing system in the development of vertebrate embryo. However, different epigenetic and genetic mechanisms play important role in the development of vascular organ system. During embryonic life, the blood capillaries from endothelial tissues differentiate from mesodermal cells in the form of vasculo-genesis. Alteration of primary blood vessels into supplementary vascular system is believed to happen through a process known as angiogenesis. The process of angiogenesis happens naturally during pregnancy, wound healing, female menstrual cycle and important in tissue growth and repair. Different pathological conditions like diabetes, chronic kidney disease, cutaneous complications, cancer, neurodegenerative disorders, rheumatoid arthritis and age-related macular degeneration are considered by excessive angiogenesis in which vessels grow in unmannered and unrestricted pattern.

Keywords: Angiogenesis; Microcirculation; Ischemic heart disease

Introduction

Angiogenesis among the functional organ systems, the cardiovascular system is the paramount appearing system in the development of vertebrate embryo.Different epigenetic and genetic mechanisms play important role in the development of vascular organ system.During embryonic life, the blood capillaries from endothelial tissues differentiate from mesodermal cells in the form of vasculo-genesis.Thevasculo-genesis involves the differentiation of angioblasts into blood islets which further go into the formation of nascent capillary plexus.Thus the embryonic heart and embryonic vascular plexus are made in this way[1]. Different observations have specified that vasculo-genesis not limited to prompt embryogenesis, but may have a physiological role.The foremost proof supporting this opinion comes from:

- Newly evaluated mechanisms of vasculo-genesis in tumor growth
- Existence of endothelial precursors and endothelial cells [2].

With the commencement of embryonic circulation, the primary blood vessels modified into arteries and veins so as to improve functional vascular loop. Alteration of primary blood vessels into supplementary vascular system is believed to happen through a process known as angiogenesis[3]. During the whole embryonic life, vessel formation matures through transformation, pruning with vessel strips appearing and vanishing and relinking in new patterns throughout development. During the embryonic life, local perfusional modifications crop melodramatic variations in vascular pattern[4]. The process of angiogenesis happens naturally during pregnancy, wound healing, female menstrual cycle and important in tissue growth and repair.The angiogenesis being controlled process is dependent on an intricate equilibrium of both anti-antigenic and pro-angiogenic.The process of angiogenesis completed in arranged series which involves in interactions between vascular components, growth factors and extracellular matrix[5]. Angiogenesis is regulated by various 'classic' and 'non-classic' factors.Basic classic factors generally include cytokines and different growth factors like angiopoietins (Angs), fibroblast growth factor-2 (FGF-2), placental growth factor (PlGF), transforming growth factors (TGFs), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF).The various endogenous peptides fall in non-classic factors which are adiponectin, adrenomedullin (AM), angiotensin II (Ang II), endothelins (ETs), erythropoietin (Epo), granulocyte-macrophage colony stimulating factor (GM-CSF), granulocyte-colony stimulating factor

(G-CSF), interleukins, leptin, neuropeptide-Y, pituitary adenylatecyclase-activating polypeptide (PACAP), pro-adrenomedullin N-terminal 20 peptide (PAMP)[6]. Different pathological conditions like diabetes, chronic kidney disease, cutaneous complications, cancer, neurodegenerative disorders, rheumatoid arthritis and age-related macular degeneration (Figure1) are considered by excessive angiogenesis in which vessels grow in unmannered and unrestricted pattern.Furthermore, in different pathological situations growth factors also play significance role in the modulation of cellular differentiation, glucose metabolism, lipid metabolism and immune system[7-57].

Basically angiogenesis is of two types: splitting and sprouting. The longitudinal splitting of capillaries is supposed to a reaction to augmented sheer stress to capillaries lumen because of hyperanemia[59]. While the sprouting is the development of capillaries from bud capillaries happens due to stretch on capillaries due to overload[60]. The augmented blood flow during chronic stimulation causes vasodilation due to adenosine, ATP, nitric oxide (NO) and prostacyclin. The NO consecutively boosts expression of VEGF, the most prime angiogenic factor, responsible for differentiation of endothelial cells as well as smooth muscle cells, stimulation and proliferation [61, 62]. Sprouting angiogenesis is appreciated by rise in matrix metallo-proteinases(MMPs), essential for prominent VEGF levels and remodeling of extracellular matrix(59). Certainly, stress exercise encourages VEGF receptor 2 and VEGF production. It has been shown that after two week of overloaded rat muscles the elevated VEGF level return to normal at twenty-eight days in unload condition. Although endothelial NOS has no role on angiogenesis in overloaded rat model, the stress exercise augments angiogenesis in association with raised endothelial NOS and hypoxia induced factor-α (HIF1-α) protein levels[63]. The importance of VEGF is reflected by observation that VEGF catching obliterated angiogenesis in overloaded and stressed conditions[64]. The VEGF derived from myofiber is not mandatory for maintaining capillary bed as perceived in mice in association with myofiber related conditional VEGF[65].

Ischemic Diseases

In cardiovascular system, a group of diseases has known as ischemic diseases that originate mostly from insufficient oxygenation of cells like heart, peripheral muscles and brain.The chief pathophysiological course involved in the progression of ischemic diseases is

atherosclerosis[66]. Generally, the atherosclerosis is a progressive disease in which commonly large arteries are affected by buildup of lipids, fibrous material and inflammatory cells in the inner arterial walls results in the development of stenosis.The symptoms appear in case of significant stenosis are ischemic pain during exercise which represent as stable angina pectoris while pain at rest represent as unstable angina pectoris or chronic limb ischemia[67]. An insufficient blood supply to myocardium describes ischemic heart disease resulting in disturbance of oxygen supply and demand[68]. The main causes of ischemic heart diseases are atherosclerosis, thrombus or embolus. The coronary artery disease residue the primary reason of mortality globally[69]. Along with coronary artery disease aortic stenosis and hypertrophic cardiomyopathy can lead to ischemic myocardium damage(68). In Past era, different combinations like ACE inhibitors, antiplatelets agents and β-blockers provide optimal cure and prevention for coronary artery disease. Moreover, for the restoration of blood flow and relief to patients from ischemicepisodes' coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) adopted[70-72].

Conventional Treatment Strategies

The main purpose of treatment of ischemic diseases is the prevention of progression of diseases.Primary prevention include life style changes like sedentary lifestyle, overweigh, poor diet and smoking[67].Secondary prevention includes pharmacologically management of risk factors like hyperlipidemia, hyperglycemia and hypertension[73]. Though it has been reported that statins are helpful in decreasing the plaque size and improving the vascular endothelium function[74, 75]. Usually anticoagulants, exercise training and vasodilators can be used for relieving recurrent ischemic symptoms.Revascularization procedures like intravascular catheter-mediated thrombolysis, bypass surgery orthromboendarterectomy and percutaneous transluminal angioplasty are performed for improving blood circulation in ischemic patients[76, 77]. Yet, several patients cannot be managed with conservative revascularization plans due to poor health status. Furthermore, a considerable percentage of patients experiencing revascularization trials do not get benefits from therapy or sometimes. These trials have reinvigorated the researchers for new therapeutic approaches for treating ischemic diseases[67].

Angiogenic Factors for IHD

In an ischemic myocardium a lot of proangiogenic factors provoked. But the VEGF as well as FGF families are better studied growth factors in the development of angiogenesis subsequent MI (Table1).

Table 1. Different Growth factors with their effects on angiogenesis

Growth Factor	Mode of Action	References
Vascular Endothelial Growth Factor (VEGF)	- Promotes cardiac vascularization and function. - Triggers vasculogenesis by stimulating endothelial cell proliferation and vascular permeability. - Has antiapoptotic, antioxidative, cardioprotective, and cytoprotective effects.	[78–80]
Placental Growth Factor (PGF)	Overexpression linked to increased cardiac hypertrophy and capillary density.	[81]
Platelet-Derived Growth Factor (PDGF)	- Plays a role in cardiac fibrosis progression. - Important in heart and vessel development.	[82]
Basic Fibroblast Growth Factor (bFGF)	Has pro-angiogenic effects in ischemic heart conditions in both humans and animals (e.g., dogs, mice, pigs, rabbits).	[83–86]
Epidermal Growth Factor (EGF)	Stimulates endothelial cell growth and promotes angiogenic activities.	[87]
Hepatocyte Growth Factor (HGF)	- Prevents apoptosis and stimulates endothelial cell proliferation, supporting vasculogenesis in heart and skeletal muscle. - Upregulates VEGF expression in the heart.	[88–91]

Concept of Angiogenic Therapy

The importance of angiogenesis in tissue regeneration and growth clearly elaborate the angiogenic therapy that is encouraging growth of blood vessel as therapeutically for dealing ischemic heart diseases[67]. The main purpose of angiogenic therapy is to promote blood vessel growth in deprived areas of vascularization and encourage tissue function and recovery. Blood vessel growth prompted by three ways: angiogenesis, arterio-genesis and vasculo-genesis.Angiogenesis by definition is the progression of capillary vessel growth and proceed by:

- Sprouting angiogenesis;
- Extension of preexisting capillaries; or through
- Splitting angiogenesis[92-94].

Arterio-genesis by definition is the phenomenon of collateral arteries growth through which pre-existing arterioles expand and modify into larger vessels that sidestep the arterial occlusion[95, 96]. Arterio-genesis is commenced by shear-stress-mediated mechanisms and blood pressure, while angiogenesis is generated through hypoxia results in fabrication of vascular growth factors in the ischemic areas.The angiogenesis and arterio-genesis both occur endogenously on almost all types of diseases.According to Rissanen et al., (2005), both angiogenesis and arterio-genesis might be valuable throughout the process of angiogenictherapies[92]. The pre angiogenic agents are responsible for the stimulation of vascular growth and can be administered exogenously. The pro angiogenic agents are members of vascular endothelial growth factor (VEGF-A165 and VEGF-D), fibroblast growth factor family (FGF2 and FGF-4), platelet-derived growth factor family (PDGF-BB), angiopoetins (notably ANG-1), hepatocyte growth factor (HGF), hypoxiainducible factor family (HIF-1α), insulin-like growth factors (IGFs) and nitric oxide synthase (NOS)[97-107].

Conclusion

The process of angiogenesis happens naturally during pregnancy, wound healing, female menstrual cycle and important in tissue growth and repair.Vasculo-genesis is not limited to prompt embryogenesis, but may have a physiological role like vasculo-genesis in tumor growth as well as existence of endothelial precursors and endothelial cells. In an ischemic myocardium a lot of pro-angiogenic factors provoked but the VEGF as well as FGF families are better studied growth factors in the development of angiogenesis subsequent MI. The importance of angiogenesis in tissue regeneration and growth clearly elaborate the angiogenic therapy that is encouraging growth of blood vessel as therapeutically for dealing ischemic heart diseases.

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