

REVIEWS

ARTICOLE DE SINTEZĂ

Exercise, angiogenesis and critical limb ischemia Activitatea fizică, angiogeneza și ischemia critică

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Abstract

Angiogenesis is formation of new blood vessels. This growth process is a complex process that involves multiple factors. Angiogenesis-related factors are: endogenous stimulators of angiogenesis (vascular endothelial growth factor VEGF; placental growth factor; angiopoietins; nitric oxide; basic fibroblast growth factor; angiotensin II; monocyte chemotactic protein 1; integrins; matrix metalloproteinases) and endogenous inhibitors of angiogenesis (angiostatin; endostatin; thrombospondin 1; soluble VEGFR1; tissue inhibitors of matrix metalloproteinases; platelet factor 4). Angiogenesis is present in adults in processes such as wound healing, formation of corpus luteum after ovulation, formation of new endometrium after menstruation and exercise remodelling. Many diseases are associated with chronic angiogenesis such as tumour growth, rheumatoid disease; chronic limb ischemia, arterial occlusive disease. Skeletal muscle is richly supplied with blood vessels: arteries, capillaries and veins. The amount of blood required by skeletal muscle is determined by cardiac and vascular factors, depending on its state of activity. Skeletal muscle circulation and blood flow are greatly increased during exercise.

Skeletal muscle requires approximately 20% of cardiac output in basal conditions and blood flow can increase 10 to 20 times during exercise. The distribution of blood volume that occurs during exercise, so that the active muscles receive the greatest proportion of cardiac output, results from: vasoconstriction of the arterioles (resistance vessels) supplying the metabolically less active areas of the body and vasodilatation of the arterioles supplying the metabolically more active skeletal muscle.

Numerous investigators have demonstrated the implication of oxidative stress in exercise and in critical illness. Moderate exercise is a pro-oxidant factor: a small amount of reactive oxygen species stimulates growth, vascular tonus and angiogenesis, but causes an increase of the endogenous antioxidant defenses. Stimulation of the angiogenesis is a new concept in the treatment of peripheral arterial disease and critical limb ischemia. Exercise hyperemia determines vascular remodeling in response to exercise and may help resolve a critical limb ischemia. In most patients with intermittent claudication, invasive procedures are not indicated, and physical exercise is the primary treatment strategy. Because most patients studied have mild to moderate claudication, little is known about the clinical benefits of exercise in critical limb ischemia. Exercise serves as a kinotherapy method and an alternative antioxidant strategy in patients with critical limb ischemia.

Key words: angiogenesis, exercise, limb ischemia.

Rezumat

Angiogeneza reprezintă formarea de noi vase. Acest proces de neoformare este complex și implică mai mulți factori. Factorii care influențează angiogeneza sunt următorii: factori stimulatori endogeni ai angiogenezei (factorul endotelial de creștere vasculară (VEGF); factorul de creștere placentar; angiopoietinele; oxidul nitric; factorul de creștere al fibroblaștilor; angiotensina II; proteina monocitară chemotactică 1; integrinele; metaloproteinazele) și factori inhibitori endogeni ai angiogenezei (angiostatina, endostatina; trombospondina 1; receptorul pentru VEGF 1; inhibitorii tisulari ai metaloproteinazelor; factorul plachetar 4). Angiogeneza este prezentă la adult în procese ca vindecarea plăgilor, formarea corpului luteal după ovulație, formarea noului endometru după menstruație și remodelarea prin exercițiul fizic. Multe boli se asociază cu angiogeneza cronică: creșterea tumorală, boala reumatoidă, ischemia critică, boala ocluzivă arterială. Mușchii striati au o vascularizație bogată, reprezentată de artere, capilare și vene. Cantitatea de sânge care ajunge la mușchii striati este influențată de factori cardiaci și vasculari, în funcție de starea acestuia de activitate. Debitul sanguin muscular este mult crescut în timpul activității. Mușchii striati au nevoie de aproximativ 20% din debitul cardiac în condiții bazale și fluxul sanguin crește de 10-20 de ori în timpul exercițiului fizic. Distribuția volumului sanguin în timpul exercițiului fizic, astfel încât mușchii să primească cantitatea optimă din debitul cardiac, este rezultatul vasoconstricției arteriolelor care irigă zone cu activitate metabolică scăzută și vasodilatației arteriolelor de la nivelul mușchilor striati.

Numeroși cercetători au demonstrat implicarea stresului oxidativ în exercițiile fizice și în stadiile avansate ale diverselor afecțiuni. Exercițiile fizice moderate sunt factori pro-oxidanți: cantități scăzute din specii reactive ale oxigenului stimulează creșterea vasculară, tonusul și angiogeneza, dar determină și activarea mecanismelor antioxidante endogene. Stimularea angiogenezei este un nou concept în tratamentul bolii arteriale periferice și ischemiei critice. Hiperemia din timpul efortului fizic

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determină remodelarea vasculară și poate ajuta în tratamentul ischemiei critice. Pentru majoritatea pacienților cu claudicație intermitentă procedeele invazive nu sunt indicate, exercițiile fizice fiind incluse în strategia de tratament. Deoarece majoritatea studiilor au inclus pacienți cu claudicație ușoară sau moderată, sunt puține date despre beneficiul efortului fizic în ischemia critică. Kinetoterapia este considerată ca o metodă alternativă de scădere a stresului oxidativ în cazul pacienților cu ischemie critică.

Cuvinte cheie: angieneză, efort, ischemie critică.

Introduction

Angiogenesis is formation of new blood vessels. This growth process is a complex process that involves multiple factors (Folkman 2006).

Angiogenesis-related factors are: endogenous stimulators of angiogenesis (vascular endothelial growth factor VEGF; placental growth factor; angiopoietins; nitric oxide; basic fibroblast growth factor; angiotensin II; monocyte chemotactic protein 1; integrins; matrix metalloproteinases) and endogenous inhibitors of angiogenesis (angiostatin; endostatin; thrombospondin 1; soluble VEGFR1; tissue inhibitors of matrix metalloproteinases; platelet factor 4).

The factors involved in angiogenesis (Rissu, 1997; Folkman, 2006; Semenza, 2007; Egginton, 2008; Filip, 2009; Barrett et al., 2010) are described as follows:

a) Endogenous stimulators

- Vascular endothelial growth factor (VEGF)

Characteristics: a peptide in multiple isoforms (A-D); stimulation of mitogenesis of endothelial cells; VEGF receptors are tyrosine kinases (VEGF R₁, R₂, R₃); produced by endothelial cells, perivascular cells, skeletal muscle cells; regulation of production involves cytokines, growth factors, tumor suppressor factors, hypoglycemia, hypoxia.

Activities: vasculogenesis; lymph angiogenesis; capillary permeability; arteriolar vasodilatation.

- Placental growth factor (PIGF)

Characteristics: a member of VEGF family, PIGF receptor is R₁.

Activities: pathological angiogenesis in tumor growth arthritis; atherosclerosis.

- Angiopoietins (Angs)

Characteristics: stabilization of vessels; 2 isoforms: Ang 1 and Ang 2; Angs receptors are Tie 2.

Activities: modulating vessel development and remodeling; promotion of capillary growth in the presence of cleaved VEGF.

- Nitric oxide (NO), endothelium-derived relaxing factor

Characteristics: synthesized from arginine; produced in the nervous system, macrophages and other immune cells, endothelial cells; 3 isoforms of NO synthase (NOS1, NOS2, NOS3).

Activities: mediating the effects of VEGF; along with prostaglandins, it mediates VEGF-induced vasodilatation and vascular permeability; it maintains normal blood pressure; penile erection; cardiovascular regulation; dilator smooth muscle; regulation of renin secretion.

- Basic fibroblast growth factor (bFGF or FGF-2)

Characteristics: a cytokine; FGF receptors are FGFR₁ and FGFR₂; produced by satellite cells or from membrane stores on extracellular matrix degradation.

Activities: upregulation of NO production and

vasodilatation; angiogenesis; regulation of neuronal growth.

- Platelet-derived growth factor-BB (PDGF-BB) and transforming growth factor-β (TGFβ)

Characteristics: produced by endothelial cells and mural cells.

Activities: growing, maturation and capillary arterializations; regulation of extracellular matrix; regulation of neuronal growth.

- Angiotensin II (AT II)

Characteristics: AT1 and AT2 receptors, produced by angiotensin-converting enzyme (ACE) from inactive angiotensin I; 2 isoforms of ACE (somatic and germinal).

Activities: indirect electrical stimulation of angiogenesis; arteriolar constriction and a rise in systolic and diastolic blood pressure; increase in the secretion of aldosterone, vasopressin and ACTH; decrease of baroreflex sensitivity; AT₂R activation appears to be anti-angiogenic.

- Leptin

Characteristics: a hormone produced in fat cells.

Activities: promotion of VEGF; anti-anorexigenic.

- Monocyte chemotactic protein-1 (MCP-1)

Characteristics: secreted by bone marrow cells.

Activities: induced endothelial cell proliferation.

- Integrins

Characteristics: cell surface adhesion molecules.

Activities: mediated communication between endothelial cells and extracellular matrix; integrin α_vβ₃ responsible for angiogenesis.

- Matrix metalloproteinases (MMP_s)

Characteristics: Zn-dependent endopeptidases; numerous families with 28 members.

Activities: modulation of cell-cell and cell-matrix interactions; induced angiogenesis through bFGF, VEGF and TGFβ; MMP-3, MMP-7, MMP-9, MMP-12 have angiogenesis action: angiostatin, endostatin, are angiostatic factors; thrombospondin inhibits activation of MMP-2 and MMP-9.

- Ephrine

Characteristics: vasculogenesis of veins and arteries.

- IL-8

Characteristics: regulation of angiogenesis.

- Hepatic growth factor (HGF)

Characteristics: stimulation of mitogenesis.

b) Endogenous inhibitors

- Angiostatin

Characteristics: a proteolytic fragment derived from plasminogen via MMP; NOS increased activities of MMP which generate Zn.

Activities: antiangiogenic activity; inhibits cell growth; induces apoptosis of endothelial cells.

- Endostatin

Characteristics: a fragment from the C terminus of

collagen XVIII.

Activities: inhibits angiogenesis via action of endothelial cell proliferation; interferes with bFGF and VEGF; inhibits tumor growth.

- *Soluble vascular endothelial growth factor receptor (sVEGFR1)*

Characteristics: extracellular VEGF binding domain.

Activities: has selective endothelial cell expression; inhibits VEGF mediated effects.

- *Thrombospondin 1 (TSP-1)*

Characteristics: a large matrix glycoprotein produced by a wide variety of cells.

Activities: involves platelet aggregation; inhibits MMP_s; inhibits endothelial cell proliferation.

- *Tissue inhibitors of metalloproteinase (TIMP)*

Characteristics: 3 isoforms TIMP-1, TIMP-2, TIMP-3.

Activities: prevention of extracellular matrix turnover; timp-2 exerts antiangiogenic activity without MMP inhibition via integrin.

- *Platelet factor 4 (PF-4)*

Characteristics: a cytokine.

Activities: a strong inhibitor of angiogenesis; anti-heparin action.

- *Endothelial cell inhibitory factor (VEGI) vasostatin and calreticulin*

Activities: it inhibits the growth of endothelial cells.

- *Prolactin*

Characteristics: a hormone produced in the pituitary gland.

Activities: it inhibits bFGF and VEGF.

Angiogenesis is present in adults in processes such as wound healing, formation of corpus luteum after ovulation, formation of new endometrium after menstruation and exercise remodeling. Many diseases are associated with chronic angiogenesis such as tumor growth, rheumatoid disease or chronic limb ischemia, arterial occlusive disease. Skeletal muscle is richly supplied with blood vessels: arteries, capillaries and veins. The amount of blood required by skeletal muscle is determined by cardiac and vascular influences, depending on its state of activity.

Skeletal muscle circulation and blood flow are greatly increased during exercise (Bouchel, 2003).

Known endogenous factors involved in angiogenesis during exercise (Rissu, 1997; Gavin et al., 2004; Egginton, 2008):

a) *Stimulators*

- *VEGF*

Mechanism: inhibition of endogenous hypoxia-inducible factor (HIF-1 α).

- *Angs*

Mechanism: promotion of capillary growth in the presence of elevated VEGF.

- *NO*

Mechanism: it may regulate TSP-1 activity.

- *bFGF*

Mechanism: increased mitogenic activity in stimulated muscle; role played in angiogenesis and exercise-induced collateralization in muscle.

- *PDGF-BB and FGF β*

Mechanism: possible role in functional hyperemia.

- *MMP_s*

Mechanism: role in regulating matrix remodeling and vascular sprouting.

b) *Inhibitors*

- *Endostatin*

Mechanism: role in the capillary network in skeletal muscle.

- *PF-4*

Mechanism: interfering with FGF-2 signaling via a heparan-sulfate-dependent mechanism.

Numerous investigators have demonstrated the implication of oxidative stress in exercise and in critical illness. Moderate exercise is a pro-oxidant factor: a small amount of reactive oxygen species stimulates growth, vascular tonus and angiogenesis, but causes an increase of endogenous antioxidant defenses. Stimulation of angiogenesis is a new concept in the treatment of peripheral arterial disease and critical limb ischemia. Exercise hyperemia determines vascular remodeling in response to exercise and may help resolve a critical limb ischemia.

Physical activity in critical limb ischemia

A number of previous prospective studies have demonstrated the benefits of exercising for patients with claudication (initial stage of peripheral arterial disease). Because most of the studies included patients with mild to moderate claudication, there are few data available on the impact of exercising on patients with critical ischemia (final stage of peripheral arterial disease) (Stewart et al., 2002).

Controlled physical exercise can be indicated as an adjuvant of the revascularization process in patients with debilitating claudication and critical ischemia. Studies in patients with critical ischemia treated by angioplasty followed by physical therapy supervised by a kinethotherapist have shown that the maximal walking distance was longer than that walked by patients with angioplasty but no rehabilitation therapy (Kruidenier et al., 2011). In addition, in patients treated with bypass revascularization the maximal walking distance was 175% greater when the bypass procedure was followed by exercise training (vs a 4% increase in the distance after bypass revascularization alone) (Badger et al., 2007). Although not all patients included were suffering from critical ischemia, the exercise program seemed to be beneficial in the management of critical ischemia.

Indications of physical exercise for rehabilitating patients with critical ischemia

In most centers, rehabilitation is considered the first goal in patients with peripheral arterial disease. Given the high prevalence of the disease, prescribing physical exercise to all patients is not possible. Recommendations are to propose a rehabilitating program to symptomatic patients, with difficult to control cardiovascular risk factors, coronary disease and high risk of (socially) debilitating disease (***, 2010). These patients usually have atherosclerotic disease with multiple affected territories: coronary, cerebral and lower limbs. Supervised exercises improve the evolution in the entire cardiovascular system with additional beneficial effects: lowering blood pressure, improving lipid profile,

glycemic control in diabetic patients and reducing obesity (Stewart et al., 2002). The magnitude and duration of these effects are still in research.

When it comes to critical ischemia, saving the limb through revascularization is the first priority. Exercise training is used to facilitate functional rehabilitation and also as secondary prevention in a multidisciplinary approach (Lundgren et al., 1989).

Exercise therapy is an important part of peripheral arterial disease management.

The limited availability of qualified therapists and the financial barriers in the healthcare system are the main reasons why exercise training is not widely used (Lauret et al., 2012).

In most patients with intermittent claudication, invasive procedures are not indicated and physical exercise is the primary treatment strategy (van Royen et al., 2001). Because most patients studied have mild to moderate claudication, little is known about the clinical benefits of exercise in critical limb ischemia.

Conclusions

1. NO is an important factor in ischemia-induced angiogenesis

2. Exercise serves as a kinetotherapy method and an alternative antioxidant strategy in patients with critical limb ischemia.

3. Comorbidities (associated diseases) perceived as contraindications, including coronary disease, are in fact additional indications to include patients in the exercise training program.

Conflicts of interest

Nothing to declare.

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