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IMPLICATION OF ENDOTHELIAL DYSFUNCTION IN THE PATHOGENESIS OF CARDIOVASCULAR DISEASES

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ABSTRACT. Atherosclerosis represents the pathological background for a variety of cardiovascular diseases. The vascular endothelium regulates the arterial reactivity by secreting relaxing and contracting factors: nitric oxide, prostacyclin, endothelin-1 and angiotensin converting enzyme. Endothelial dysfunction is encountered in the early phases of atherogenesis. Its existence can be demonstrated in patients with risk factors for atherosclerosis (hypercholesterolemia, arterial hypertension). The endothelial function can be assessed by several noninvasive methods, the most popular being the ultrasonography of brachial artery.

Keywords: endothelial dysfunction, atherogenesis, nitric oxide, angiotensin, prostacyclin

INTRODUCTION

Atherosclerosis represents the pathological substrate for many cardiovascular diseases. The risk factors such as hypercholesterolemia, arterial hypertension, smoking, diabetes mellitus and obesity have been associated to its progression.

More precisely, a lot of evidences demonstrated a strong correlation between hypercholesterolemia and atherogenesis. Within this relationship, it was believed that oxidative changes of the LDL cholesterol deposited in the vessels walls were involved, followed by the take-up of the cholesterol by the scavenger cells (the macrophages). The foamy cells just formed liberate thereafter growth and inflammatory factors; thus, the atherosclerotic plate takes shape in the vascular wall. The atherosclerosis represents the major factor in the progression of coronary artery disease, and the thrombosis subsequent to the plaque rupture leads to acute clinical events (Bonetti P.O. et al., 2003).

It is well known that endothelial dysfunction plays the early pathogenic role in cardiovascular disease. After numerous clinical trials have been accomplished, it is now well known that the vascular endothelium is a multi-faced organ that controls vascular tonus, inflammation and hemostasis by liberating some vasoactive substances.

Several years ago, endothelium was known as a semi-permeable membrane that separated the vascular smooth muscle from the blood flow. Nowadays, it is known as a complex organ, with endocrine, autocrine, paracrine and regulatory functions and with anti-atherosclerotic role (Furchgott R.F. et al., 1980). It is well known that atherosclerosis development can be due to endothelial dysfunction.

Vascular endothelium activates not only as a selective barrier which controls permeability and transportation, but it is also strategically positioned, so as to detect hemodynamic forces and hormonal signals. Endothelium responds by liberating the vasoactive mediators and growth factors which modulate the tonus of the vascular smooth muscle, proliferation and inflammation and allows hemostasis by keeping the surface non-adhesive and anti-thrombotic (Ross R., 1999).

VASCULAR ENDOTHELIUM

Activated endothelial cells regulate basic vascular tonus and vascular reactivity, in physiological and pathological conditions, by answering to mechanic forces and to

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neurohormonal mediators, through the release of some vascular relaxing and constricting factors.

ENDOTHELIUM-DERIVED RELAXING FACTORS

Nitric oxide

Nitric oxide (NO) is largely spread in the body at the level of the smooth muscles, platelets, kidneys, nervous system and endothelium, where it plays a key role in regulating the vascular tonus. NO was originally described as a relaxing factor derived from endothelium, being released as an answer to the shear forces produced by the blood torrent and to the activation of various receptors. This is a gas without free radicals, which has in vivo the half time of few seconds and is able to cross biologic membranes. After its diffusion from endothelium to vascular smooth muscle cells it determines the increase of the intracellular concentration of GMPc by activating the guanylate-cyclase enzyme; all these reactions determine the smooth muscle cells to relax (Palmer R.M. et al., 1987).

NO is synthesized from L-arginine in the presence of NO synthetasis (NOS), and its conversion can be inhibited by analogues of L-arginine, such as NG monomethyl-L-arginine monoacetate (L-NMMA) (Palmer R.M. et al., 1988). NO continuous release determines the tonus of peripheral blood vessels and the systematic inhibition of NO synthesis, which causes the arterial pressure increase. Also, NO presents antithrombotic and antiproliferative effects, inhibits leukocyte adhesion and influences the myocardial contractility (Furchgott F.R. and Vanhoutte P.M., 1989).

Prostacyclin

Prostacyclin (PGI2) is liberated by endothelial cells as an answer to the shear forces, to hypoxia and to a variety of other substances which liberate NO and determine the increase of AMPc levels in the smooth muscle cells and platelets. In platelets, NO and PGI2 act synergically by inhibiting platelet aggregation, suggesting the need to activate both substances in order to perform complete antiplatelet activity (Moncada S. and Vade V.R. et al.,1989).

Endothelium-derived hyperpolarizing factor

The existence of an endothelium-derived hyperpolarizing factor (EDHF), with unknown structure, was suggested by the evidence that not all relaxing factors derived from endothelium in the coronary circulation are modulated by the inhibitors of L-arginine pathway (Richard V. et al., 1990).

ENDOTHELIUM-DERIVED CONSTRICTING FACTORS

Endothelin-1

It is well known that endothelin-1 (ET-1) is the most potent endogenous vasoconstrictor. There are three peptides having a similar structure, in the family of endothelins (ET-1, ET-2, ET-3), and they result from the action of the converting enzyme of endothelin on „the big endothelin", which has its origin in the big peptides, pro-endothelins, split by the endopeptidases (Ikegawa R. et al., 1991).

ET peptides are synthesized in the vascular endothelial cells and in the smooth muscle cells, but also in the neural, renal and pulmonary cells and in some circulating cells bearing the genes for endothelin (Inoue A. et al., 1989). The factors modulating the ET-1 expression are: shear forces, epinephrine, angiotensin II, thrombin, inflammatory cytokines (TNF-α, IL-1, IL-2), transforming growth factor β and hypoxia. ET-1 is metabolized by the neural endopeptidases, which split the natriuretic peptides, as well.

The manner by which ET-1 acts is more paracrine than endocrine, fact also reflected by its plasmatic levels of picomolar order. The infusion of an antagonist of ET-1 receptor in the brachial artery of a healthy individual causes vasodilatation; this indicates the fact that the ET-1 has a role to play in the maintenance of the basic vascular tonus (Heines W.G. and Webb D.J., 1994).

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Cyclooxygenase-derived vasoconstricting factor

In veins, ophthalmic and cerebral circulation, agonists such as arachidonic acid, acetylcholine, histamine and serotonin may produce endothelium-dependent vasoconstriction, mediated by thromboxane A2 or prostaglandin H2. The cyclooxygenase pathway is the source of super oxide anions which inactivate indirectly the NO and may cause direct vasoconstriction (Luscher T.F. and Vanhoutte P.M., 1990).

Angiotensin converting enzyme

Endothelin regulates the activity of the renin-angiotensin system. Angiotensin converting enzyme (ACE), which activates the transformation of the angiotensin I in angiotensin II, is expressed by the membranes of the endothelial cells. ACE is identical with kinase II, which splits bradykinin. We assume that other components of the renin-angiotensin system are produced by the endothelial cells, but this hypothesis is not demonstrated so far (Luscher T.F. and Vanhoutte P.M., 1990).

ENDOTHELIAL DYSFUNCTION

In physiologic conditions, endothelium regulates the release of vasoactive substances and balances some antagonic actions. Alteration of this balance may generate endothelial dysfunction, which is now known as the early event in the pathogenesis of various cardiovascular diseases. Some risk factors, including arterial hypertension and hypercholesterolemia, are characterized by endothelial dysfunction, representing a major risk factor for atherosclerosis.

Endothelial dysfunction in hypercholesterolemia

Research on animals has linked hypercholesterolemia to the alteration of endothelium dependent vasodilatation. The presence of vasodilating dysfunction was demonstrated before and after the development of atherosclerotic lesions, in the presence of hypercholesterolemia, both in humans and in animals (McLenachan J.N. et al., 1991).

Increase of ET-1 action

Recent research suggested that endothelial dysfunction is due to the hyperproduction of ET-1. The increase of circulating and tissue levels of ET-1 was demonstrated in patients with hypercholesterolemia and coronary atherosclerosis. It was thought that the increase of LDL cholesterol had a role for the stimulation of gene expression (Yanagisawa M., 1994).

The role of the increased concentrations of ET-1 on atherogenesis and on endothelial injury may be caused by its effects related to the proliferation of fibroblasts and smooth muscle cells, which result from the stimulation of the synthesis of growth factor, increased expression of adhesion molecules, chemoattraction and properties of activated macrophages (Rizvi M.A. and Myers P.R., 1997).

Decrease of NO synthesis

The administration of L-arginine, substrate of NOS, lead to improvement of the endothelial function and of blood flow in experimental models of hypercholesterolemia, suggesting a deficiency of the substrate or alteration of the L-aringine metabolism. The direct effects of hypercholesterolemia on the NO pathway consist in the inhibition of the NOS expression by the oxidized LDL, determining the decrease of NO production (Rossitch E. Jr. and Alexander E., 1991).

Increase of NO inactivation

Native LDL (nLDL) and oxidized LDL (oxLDL) play a very important role in endothelial dysfunction from hypercholesterolemia (Ohara Y. et al., 1993). It was demonstrated that oxLDL determines endothelial injury and inhibits the release of NO and EDHF in vitro. It seems that the alteration of vascular relaxation depends on endothelium, suggesting that the involvement of oxygen free radicals in the NO distribution may be the decisive factor causing the

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decrease of NO bioactivity (Cooke J.P. and Dzau V.J., 1997).

ENDOTHELIAL DYSFUNCTION IN ARTERIAL HYPERTENSION

NO in arterial hypertension

In hypertensive patients, endothelium-dependent vasodilatation induced by acetylcholine is altered at the level of brachial circulation and in the coronary vascular bed, as there is a close connection between them (Anderson T.J. et al., 1995). NO production is diminished under basic conditions in patients suffering from essential arterial hypertension. The vasoconstricting reaction to L-NMMA, NO synthesis inhibitor, is significantly reduced in hypertensive patients as compared to non-hypertensives, while there are no differences concerning the reaction to noradrenalin, an endothelium independent vasoconstrictor (Forte P., et al. 1997).

Oxidative stress in hypertension

Oxidative stress plays a major role in the pathogenesis of hypertension. The superoxide anion (O2-), an oxygen radical, can release NO from peroxynitrite (ONOO-), with reduction in the bio-availability of NO at endothelial level. It may also act as vasoconstrictor (Kantusic Z.S. and Vanhoutte P.M., 1989).

The renin-angiotensin system plays a major role in arterial hypertension. Beside direct vasoconstricting effects of angiotensin II, there is an important interaction between angiotensin II, oxygen radicals and NO. Angiotensin II stimulates the generation of O2- by increasing the expression of the NADPH-oxidase gene and the activity of the NADPH-oxidase (Laursen J.B., et al., 1997). Besides, angiotensin II stimulates endothelin production at vascular wall level, action that induces vasoconstriction and determines the proliferation of smooth muscle cells (Moreau P. et al., 1997).

Endothelium-derived hyperpolarizing factor

It was proved the importance of a potassium channel depending on the calcium from endothelial and smooth muscle cells that is involved in the mediation of endothelium-dependent hyperpolarization. Endothelium-dependent hyperpolarization is a compensatory mechanism in patients with essential hypertension, who have a dysfunctional NO system (Takase H. et al., 1996).

Endothelin

Beside the growth of the arterial pressure, ET-1 induces myocardial and vascular hypertrophy, that are independent risk factors for the cardiovascular morbidity and mortality. In patients with arterial hypertension, the thickening of carotid artery wall and left ventricle mass are correlated with the reduction of endothelium-dependent vasodilation. Increased plasmatic levels of ET-1 were reported in patients with essential arterial hypertension (Ghiadoni L. et al., 1998; Perticone F. et al., 1999).

Assessment methods

Quantitative coronary angiography may be used for the examination of vascular diameter changes as a reaction to intracoronary infusion of endothelium-dependent vasodilators, like acetylcholine. In healthy vessels, acetylcholine determines an immediate vasodilating reaction, mediated by NO; in patients with endothelial dysfunction, this effect is diminished or determines paradox vasoconstriction.

The endothelial function at the coronary microcirculation level may be assessed by intracoronary ultrasound, method that measures the coronary blood flow as a reaction to pharmacologic or physiologic stimuli. Non-invasive tests to assess coronary function include Doppler echocardiography, positron emission tomography and contrast-enhanced magnetic resonance imaging.

Brachial artery ultrasonography is widely used as a non-invasive technique to assess the endothelial function. The occlusion of the brachial artery for five minutes determines reactive hyperemia after the sleeve is taken from the arm; the growth of the shear forces determines vasodilation mediated by flow and dependent on endothelium. The endothelial

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dysfunction determined by this technique is correlated with the measurements of the coronary endothelial dysfunction (Anderson T.J. et al., 1995).

The peripheral vascular resistance can be determined by impendence plethysmography (Mather K.J. et al., 2001). This technique examines the changes of the blood flow at the forearm level (brachial artery) as a reaction to direct intra-artery administration of agonists. A series of circulating markers of the endothelial dysfunction and vascular inflammation have been studied recently, out of which we name soluble cell adhesion molecules (CAMs) and C reactive protein (CRP).

CAMs are expressed on the surface of endothelial cells and leucocytes as a reaction to endothelial dysfunction. The three main classes of CAMs include selectins (P-selectin, L-selectin and E-selectin) (Furchgott R.F. and Zawadzki J.V., 1980; Moncada S. and Higgs A., 1993), beta-2 integrins (CD11/CD18) and immunoglobulins (ICAM-1, VCAM-1 and PECAM-1). CAMs lead a complex process implying the enrolment of leukocytes, adhesion and transmigration in the subintimal space. Plasmatic levels of CAMs have been examined as surrogate markers of the endothelial dysfunction. In patients with cardiovascular risk, increased levels of CAMs were noted, predicting the occurrence of cardiovascular disease. A series of recent proofs suggests that atherosclerosis represents a chronic inflammatory process and inflammation markers (like CRP) may represent an additional method for the global assessment of the cardiovascular risk. Numerous large scale studies showed that plasmatic levels of CRP represent an important independent predictor for the endothelial dysfunction, subsequent myocardial dysfunction, stroke, peripheral artery disease and cardiovascular death (Ridker P.M. et al., 2001).

Pharmacological modulation of endothelial function

Endothelium-dependent coronary artery vasodilation, mainly determined by the NO released from endothelium, is altered in atherosclerosis and represents a prognostic factor in patients with coronary artery disease (Murakami T. et al., 1998).

Hypolipidemic therapies determined the substantial reduction of cardiovascular mortality and morbidity. The administration of statins showed significant improvement of the endothelial function at the forearm level (Treasure C.B. et al., 1995). Beside beneficial effects implying lipid reduction, statins seem to have protective anti-oxidizing effects. Statins increase NOS expression, considerably reduced in patients with atherosclerotic vascular disease.

ACE inhibitors may improve the endothelial function in patients with coronary artery disease, as well as endothelium-dependent vasomotricity in patients with arterial hypertension and heart failure. Some ACE inhibitors increase NOS expression, as well.

There are new betablockers that release NO and determine vasodilation in relation to their concentration, action prevented by removing the endothelium (Gao Y.S. et al., 1991).

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