THE EFFICACY OF THE TREATMENT WITH ANGIOTENSIN II AT1 RECEPTOR BLOCKERS IN THE ENDOTHELIAL DYSFUNCTION

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Abstract: *Endothelial dysfunction plays a part in the initiation and progression of the atherosclerotic process. Sartans are efficient in the improvement of this dysfunction through the increase of the biodisponibility of the nitric oxide.*

Keywords: *AT1-receptor blockers, angiotensin, endothelial dysfunction, benefice*

Rezumat: *Disfuncţia endotelială are rol în iniţierea şi progresia procesului aterosclerotic. Sartanii sunt eficienţi în ameliorarea acestei disfuncţii prin creşterea biodisponibilităţii oxidului nitric.*

Cuvinte cheie: *blocanţi ai receptorilor AT_1, ai angiotensinei II, disfuncţie endotelială, beneficiu*

INTRODUCTION

The actual increase in the cardiovascular pathology is due to the extension of the metabolic diseases, especially of diabetes mellitus, very closely correlated to obesity and metabolic syndrome. The atherosclerotic cardiovascular disease is the main cause of morbidity and mortality in type II diabetes mellitus. The cardiovascular risk factors produce atherosclerosis by inducing the endothelial dysfunction.

The changes that appear before the atherosclerotic lesions are seen at the vascular endothelium, defining the endothelial dysfunction syndrome.

The functions of the vascular endothelium:

The vascular endothelium is a structure that covers the internal side of the vessel, realizing a selective barrier, being an organ with multiple and complex functions, most of them mediated by the synthesis of the nitric oxide. The vascular endothelium makes a monocellular layer at the interface between the circulating blood and the vascular subjacent layers.

The endothelial cell functions as a sensitive cell that records the hemodynamic and humoral signals. This cell also functions as a performing cell, having the capacity of integrating the signals and responding by the local generation of mediators, which modulate the vessel tonus and structure, including the cellular growth. (1,2) The most important functions of the vascular endothelium are:

- The regulation of the vascular tonus;
- Active transportation of the metabolites between the blood and tissues;
- The formation of a selective layer between the macromolecules and the blood cells, modulation of the leucocytes passing in the tissue;
- The maintenance of the thromboresitance of the vascular wall, the assurance of haemostasis;
- Mediation of the vascular remodelling processes;
- Synthesis and release of the lipoproteinlipasis – involved in the catabolism of the triglycerides in the blood;
- The endothelium is provided with receptors for hormones and chemical mediators and have the capacity of synthesising proteins, enzymes and cytokine;

The endothelial cells produce at least 3 vasodilatator substances: the nitric oxide (NO), the endothelium-derived hyperpolarizing factor (EDHF) and prostacyclin (PG12) and vasoconstrictor substances: the endothelins. (3)

The nitric oxide is produced by the endothelium, as a result of the blood flow and of the cross-sectional stress that activates the K+ ionic channels from the endothelial cells. (4)

The nitric oxide production is stimulated by the endogenous substances such as: acetylcholine, circulating hormones (catecholamines, vasopressins) histamine, bradykinin, some neuropeptides, substances released by thrombocytes (ADP, serotonin, thromboxane A2), thrombin.

These substances act on the specific receptors from the endothelium that are connected with the synthesis of the nitric oxide by coupling proteins (G-proteins).

The nitric oxide is formed in the vascular endothelium from L-arginina, by the action of an enzyme named – endothelial nitric oxide synthase (eNOS). The activation degree of this enzyme depends on the endothelial concentration of Ca+ and also on calmodulin. The released nitric oxide acts on the smooth muscular vascular cells, stimulating guanylate-cyclase and the production of the cyclic guanylate monophosphatic (cGMP), producing the relaxation of the smooth muscular cells. (5)

In the vascular lumen, the nitric oxide inhibits the aggregation of the platelet and leukocytes on the endothelium. Nitric oxide acts in a synergic manner with prostacyclin, inhibiting the platelet aggregation. The nitric oxide inhibits the fibrotic properties of the angiotensin II and of the endothelin I by the „down regulation„ of the receptors of these molecules. The nitric oxide also has an anti-inflammatory action, by inhibiting the NF-kappaB (NF-KB). (6)

At the level of the heart, the nitric oxide mediates the coronary vasodilatation and plays a part in the systolic and diastolic left ventricular function regulation.

In physiological concentrations, the nitric oxide seems to have a positive inotropic effect, but in large concentrations, it reduces the heart contractility.

The nitric oxide can regulate the stretch of the muscular fibres, thus contributing to the increase of the cardiac function.

The endothelial dysfunction is defined as the reduction of the vasodilatator substances biodisponibility, especially of the nitric oxide and as the increase of the vasoconstrictor ones.

The main mediators involved in the pathogeny of the endothelial dysfunction are: nitric oxide, reactive oxygen species, the angiotensin converting enzyme, angiotensin II.

The increase and decrease of the nitric oxide concentration has major implications in the clinical pathology. The decrease of the nitric oxide concentration in the vascular endothelial was detected in the diabetes mellitus, hypercholesterolemia, hyperhomocysteinemia, in smokers, because of the reduction of the nitric oxide synthesis, or because of its excessive degradation.

The factors that reduce the nitric oxide biodisponibility are:

- The decrease of the nitric oxide synthase (eNOS) production;
- Blocking the cofactors necessary for the eNOS synthesis;
- The degradation or the excessive inactivation of the nitric oxide by the oxygen reactive species.

The biodisponibility reduction of the nitric oxide at heart level is associated with the increase of the ventricular filling pressure, accompanied by the ventricular remodelling and finally, by the cardiac insufficiency. (7,8,9)

The oxidative stress (OS) is defined as a disequilibrium between the excessive production of free oxygen radicals (FOR) and the body defence mechanisms, involved in the cardiovascular disease.

The increase of the oxidative stress associated to the cardiovascular risk factors leads to the inflammatory vascular lesions and to the increase of the endothelial cells permeability for LDL – cholesterol, with the oxidation of this one in the arterial intima. A series of factors of cellular growth are released, factors that stimulate the proliferation of the smooth muscular cells, producing excessive collagen with the formation of the atherom plaque. This phenomenon produces the arterial remodelling with the increase of the intimae-media thickness (IMT), the decrease of the arterial dispensability that is the arterial rigidity.

The angiotensin II represents the main mediator, with a central part in the endothelial dysfunction pathogeny. Through the activation of the AT1 receptor, it determines vasoconstriction, angiogenesis stimulation, increase of the oxidative stress generated by the reactive oxygen species, whose production is increased by stimulating the NADH-NADPH oxidase system from the endothelial cells, as well as the initiation of the inflammatory process, by the increase of the inflammatory molecular expressions. (10, 11)

The angiotensin II, by the increased production of superoxide, stimulates the interleukin 6 (IL-6), involved in the inflammatory process initiation and the development of the acute coronary syndromes. The interleukin 6 (IL-6) stimulates the acute-phase proteins (alpha 2 globulin, the C reactive protein), the increase of the prothrombin factors expressions (PAI-1), stimulates the release of the metalloprotease (MMPA-1, MMP-9), enzyme that produces the degradation of the cellular matrix and the instable plaque formation (12).

Angiotensin-converting enzyme (ACE) plays a key part in the pathogeny of the endothelial dysfunction. This is a zinc metalloprotease that can be found in a large quantity in tissues (arteries, brain, suprarenal glands, myocardium, kidneys etc) and in small quantity (below 10%) in plasma.

The main mechanisms by which the ACE acts at the level of the arterial endothelium are the following:

- Catalyzation of the synthesis of the angiotensin II from Angiotensin I;
- Degradation of bradykinin into an inactive peptide.

Lately, new treatment strategies have been developed, therapies that can ameliorate the endothelial dysfunction on the main pathogenetic links, improving the cardiovascular disease prognosis.

The Angiotensin AT1 Receptor Blockers represent a therapeutic class which increases the nitric oxide biodisponibility, by blocking the angiotensin II action, with the reduction of the oxidative stress factors. They activate the AT2 receptors, with the stimulation of the nitric oxide, via bradykinin.

Clinical and experimental studies have proved the efficacy of the angiotensin AT1 receptor blockers, by the improvement of the endothelial function in hypertensive, diabetic and ischemic patients.

CONCLUSIONS

- The endothelial dysfunction is important in the initiation and progression of the atherosclerotic process;
- The angiotensin II receptor blockers represent a therapy that can ameliorate the activities dependent on the nitric oxide from the vascular endothelium;
- The angiotensin II receptor blockers have proved their efficacy in ameliorating the endothelial

dysfunction, by increasing the nitric oxide biodisponibility in hypertensive, diabetic and ischemic patients.

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