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The Importance of Oxidative Stress in the Development of Chronic Kidney Disease in the Context of Chronic Heart Failure

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Annotation: The review article presents current research data on the important role of oxidative stress in the pathogenesis of chronic kidney disease against the background of chronic heart failure as well as modern approaches to eliminate the effects of exposure to active oxygen forms and/or preventing their excessive initiation. We described the markers of oxidative stress and the modern methods of determination of the free radical oxidation and antioxidant products in various tissues.

Keywords: oxidative stress, chronic kidney disease, chronic heart failure, antioxidant system, superoxide dismutase.

Currently, a lot of data has been collected on the role of oxidative stress as a leading factor in the pathogenesis of many diseases, including chronic kidney diseases. Oxidative stress is the damage to various organs and tissues by active forms of oxygen at the cellular level, which occurs as a result of an imbalance in the functional activity of prooxidant and antioxidant systems. This process may be the result of insufficient antioxidant protection and excessive formation of free radicals caused by disruption of endogenous antioxidant production. Oxidative stress occurs as a result of a disruption in the balance between oxidation and the antioxidant system, with the predominance of the former, and consequently, cell damage is observed [1,2,3].

In the mechanism of development of chronic kidney disease (CKD) against the background of chronic heart failure (CHF), hemodynamic disorders, neurohumoral activation, endothelial dysfunction, atherosclerosis, an increase in inflammatory cytokines, oxidative stress, embolism of renal vessels, and other factors play an important role[1].

Of the factors listed above, oxidative stress plays an important role in the occurrence and development of kidney damage in CHF. Malonic dialdehyde is a reliable marker for determining

oxidative stress and is used for monitoring the diagnosis and treatment of a number of diseases, including CHF and CKD.

Oxidative stress occurs when the formation of active forms of oxygen in the body predominates over its metabolic processes or when the antioxidant defense mechanism weakens. They are relatively small molecules, containing superoxide, hydroxyl, peroxide, alkoxide oxygen radicals, as well as non-radical hydrogen peroxide. Active forms of oxygen multiply as residual products in a number of cellular processes. The activity of the mitochondrial respiratory chain in aerobiosis is responsible for the production of most of the active forms of oxygen.

In addition, the transmembrane proteins of nicotinamidadenindinucleotide phosphate (NAD (F) N) oxidase (NOX) in a large number of subunits play an important role in the formation of active forms of oxygen. Of the seven oxidase families, only four (NOX1, NOX2, NOX4, and NOX5) are excreted from the cardiovascular system. NOX2 and NOX4 are the main isoforms present in cardiomyocytes. Several cytosol subunits (p47phox, p67phox, p40phox and Rac1) are involved for NOX2 activation, and they are mainly bound to flavorocytochrome to induce the superoxide anion. The activation of NOX4 primarily participates in the formation of H2O2. It is located in the endoplasmic reticulum and in the perinuclear regions of cardiomyocytes. There are also opinions about its mitochondrial location[3].

High levels of oxygen radicals suppress the activity of mitochondrial enzymes and cause DNA damage, interacting with DNA repair enzymes and transcription factors, leading to cell death. The suppression of the activity of the endothelial nitric oxide factor, which causes vascular relaxation, is a secondary effect of the active forms of oxygen. The oxygen superoxide anion acts on NO, forming a strong oxidizing and nitrosing agent, peroxynitrite, which eliminates its effective effect. The latter cause oxidative stress, causing the oxidation of lipids, DNA, and proteins[4].

Additionally, active forms of oxygen enhance their self-production, forming a negative ring and consequently activating the permeability of mitochondrial pores, resulting in mitochondrial dysfunction and their further increase [5].

For normal heart function, a regular supply of high levels of adenosine triphosphoric acid (ATP) is required. It is known that mitochondria are the main source of ATP, and therefore there is a strong connection between them and the heart [6].

Experiments on animals have shown that in CHF, oxidative stress and cardiac damage increase due to the disruption of several pathways. During the exacerbation of heart failure, ATP retention in the myocardium decreases by 60-70% compared to the norm[7]. This decrease is associated with a slowdown in mitochondrial oxidative metabolism, leading to increased absorption of compensatory glucose and enhanced glycolysis [8].

Changes in energy sources in cells also lead to changes in ATP release from them. Even with an increase in glycolysis in CHF, the heart's energy needs are not met due to low ATP production compared to fatty acid oxidation. A decrease in oxidative metabolism causes the accumulation of free fatty acids in cardiomyocytes, and a constant self-sustaining mechanism arises, oxidative stress increases, which begins to have an extremely negative effect on the heart. The production of active forms of oxygen in the kidneys is enhanced in response to the production of a number of systems, including angiotensin-II and aldosterone, and affects several physiological processes [9].

While angiotensin-II primarily affects renal tubular epithelial cells, aldosterone has the property of damaging podocytes [10]. NOX enzymes are the main source of active forms of oxygen in smooth cells of the vessels of the renal cortex and brain lobes [11]. When stimulated with angiotensin-II and aldosterone, the cytosol of NAD (F) N-oxidase penetrates the mitochondrial membrane, enhancing the production of active forms of oxygen.

The decisive mechanism for regulating blood flow in the flag of active forms of oxygen is the reaction of the oxygen superoxide anion with nitric oxide, as a result of which its relaxing effect on afferent arterioles is limited [12].

In physiological processes, nitric oxide stabilizes endothelial activity, leading to dilation of afferent arterioles and, as a consequence, increased renal blood flow, weakening of tubulo-glomerular rebinding, increased natriuresis, and the release of low concentrations of active forms of oxygen[13]. In the process of high oxidative stress, the oxygen superoxide anion reacts with nitrogen oxide to form peroxynitrite (OHOO-). The accumulation of peroxynitrite in the body leads to a cascade reaction, causing narrowing and dysfunction of vessels, inflammation, and changes in the kidneys. The above-mentioned complex processes in the body of patients with CHF (angiotensin-II, aldosterone, water-electrolyte imbalance, the effect of oxidative stress on cells, heart, and kidneys) ultimately have a mutually reinforcing effect, leading to the development and progression of cardiorenal syndrome. The antioxidant system of superoxide dismutase has the opposite effect on the above-described processes of oxidative stress in the human body. The superoxide dismutase family belongs to the first group of enzymes that modulate oxidative stress. In the human cardiovascular system, active extracellular superoxide dismutase is considered its dominant isoform, constituting approximately 70%[14].

In previous observations, it was established that the activity of superoxide dismutase in patients with CHF is associated with endothelial activity. In addition, it was shown that oxidative stress participates in the occurrence of cardiac remodeling through a number of mechanisms. Experiments on mice have proven that superoxide dismutase protects the heart from oxidative stress and ventricular remodeling[15].

Conclusion. However, in a small number of studies, the direct participation of superoxide dismutase in left ventricular remodeling was studied in a small number of patients in the terminal stage of heart failure. However, data obtained in large population studies on the relationship between superoxide dismutase and the transition of left ventricular remodeling to CHF are insufficient. Therefore, the study of works in this area is of scientific and practical importance.

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