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THE EFFECT OF PULMONARY FIBROSIS CAUSED BY NITROGEN DIOXIDE ON THE MORPHOLOGICAL PARAMETERS OF THE WALLS OF THE ESOPHAGUS AND THEIR CORRECTION

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Abstract: This article is devoted to the study of changes in digestive function in people with pulmonary fibrosis. In addition, in this work, residual changes in the morphology of the esophagus caused by stressful situations were studied, that is, morphological changes in the esophageal wall at different stages of pulmonary fibrosis.

Key words: pulmonary fibrosis, esophageal wall, histological, morphometric, histochemical and immunocytochemical methods.

It is known that nitric oxide is an autocrine and paracrine mediator capable of influencing metabolic processes in cells. OA, as a powerful endogenous vasodilator, participates in the regulation of systemic and pulmonary vascular resistance and blood coagulation. It functions in the central and autonomic nervous system. According to the efferent nerves, this agent regulates the activity of the respiratory system, gastrointestinal tract and genitourinary system. OA suppresses the proliferation of vascular smooth muscle cells, a decrease in its activity causes vasoconstriction and thrombosis. The reaction of OA with oxygen is accompanied by the formation of stable end products - nitrite and nitrate, which are indirect markers of OA concentration in the body. In response to physical and chemical stimulation, the formation of OA in the vascular endothelium increases under the influence of acetylcholine, bradykinin, 5-hydroxytryptamine, and adenylic nucleotides. The participation of OA synthase in vascular regulation is associated with a vasodilating effect. The concentration of cGMP increases in smooth muscle cells, which reduces the level of intracellular calcium. This leads to relaxation of the cell and causes vasodilation. The OA signal can be mimicked by organic nitrates, which are used to treat angina pectoris, myocardial infarction and heart failure. In addition to the role of a vasodilator, OA performs the function of a neurotransmitter and plays an important role in the long-term potentiation of neuronal memory, inhibits the adhesion of shaped blood elements to the endothelium, inhibits platelet aggregation and secretion. In hypertension, the function of the endothelium of the resistive arteries suffers, the regulatory effect of OA on vascular tone and platelet adhesion to the endothelium decreases. The effect of angiotensin converting enzyme (ACE) inhibitors is closely related to the function of OA. ACE is known to be key in the formation of angiotensin II (AT-II). ACE biosynthesis and AT-II levels are controlled by the glucocotticoid receptor mechanism. Glucocorticoids also inhibit the transcription of OA synthase. The functional relationship of AT-II with the vascular relaxing factor was found. It has been shown to activate endothelial OA synthase. ACE inhibitors increase the OA content in the coronary arteries and aorta. Cytokine-activated macrophages produce high concentrations of OA, which exhibit direct cytotoxic and immunogenic effects. Under the influence of OA, a sharp vasodilation occurs, vascular permeability increases, edema forms and the development of an

inflammatory reaction. In this case, OA combines with superoxide, forms peroxynitrite anion, which induces DNA damage and mutation, and participates in the implementation of oxidative stress (OS). The pathogenetic mechanism of OS is characterized by a decrease in ATP levels, an increase in the content of hypoxanthine, xanthi oxidase. In hypoxic conditions, when blood flow is restored, oxygen and calcium flow occurs, which increases the synthesis of free radicals. OA synthase in an oxidant medium accelerates their formation and generates lipid peroxides. These events trigger further expression of OA synthase, adhesive molecules and the release of platelet activation factor, leukotrienes, thromboxane A2 and other inflammatory process inducers (VP). Neutrophils are activated, adhere to the endothelium, generate superoxide anions and OA, thereby inducing tissue necrosis. Consequently, OA, being one of the key links in the pathophysiology of OS, plays an important role in the pathogenesis of many extreme conditions, including septic shock. It has a protective antibacterial effect, includes stable vasodilation, hypotension.

In septic shock, a significant increase in serum concentrations of nitrite and nitrate was found, which positively correlated with the content of endotoxin in the blood and negatively with hemodynamic disorders. The inflammatory response is closely correlated with the level of OA end products, which plays an important role in the release of IL-1, 6, 8 and other VP inducers. The determination of OA in the blood of patients with rheumatoid arthritis and systemic lupus erythematosus, characterized by a pronounced inflammatory reaction, indicates a significant increase in its level compared with the control. The levels of OA, IL-6, and TNFa are significantly higher in the active phase of VP than in remission. An increase in OA levels may be one of the causes of spontaneous bleeding in uremia, since it inhibits platelet aggregation and adhesion, and inhibition of OA synthase in chronic renal failure completely normalizes the parameters of the blood coagulation system. In the treatment of diseases characterized by an excess of OA in the blood, drugs that inhibit the activity of OA synthase are included in complex therapy. L-arginine analogues have been clinically used. Glucocorticoids inhibit the transcription of OA synthase and reduce the content of the final metabolites of OA in the blood, which determines their high therapeutic activity in conditions characterized by hyperproduction of OA.

Exogenous sources of NO are a powerful way to replenish NO when the body cannot produce enough for normal biological functions. Some endogenous compounds can act as NO donors or cause NO-like reactions in vivo. Nitroglycerin and amyl nitrite serve as vasodilators, since they are converted into nitric oxide in the body. The vasodilating antihypertensive drug minoxidil contains a fragment of NO and can act as an agonist of NO. Similarly, Sildenafil citrate, commonly known by the trade name Viagra, stimulates erection primarily by enhancing signal transmission along the nitric oxide pathway. Prominent examples are S-nitrosothiols, some organic nitrates, nitrosylated metal complexes, dinitrosyl iron complexes (DNIC) and even nitrite anions (NO2-) High salt intake reduces NO production in patients with essential hypertension, although bioavailability remains unregulated.

Dietary nitrate is also an important source of nitric oxide in mammals. Green leafy vegetables and some root vegetables (for example, beets) contain high concentrations of nitrates. When eaten and absorbed into the bloodstream, nitrate is concentrated in saliva (about 10 times) and reduced to nitrite on the surface of the tongue using a biofilm of synanthropic facultative anaerobic bacteria. This nitrite is ingested and reacts with acid and reducing substances in the stomach (such as ascorbate) to form high concentrations of nitric oxide. It is believed that the purpose of this mechanism of NO formation is both to sterilize ingested food (to prevent food poisoning) and to maintain blood flow in the gastric mucosa.

The nitrate-nitrite-nitric oxide pathway increases the level of nitric oxide by consistently reducing the content of dietary nitrates obtained from plant products.[13] It has been shown that nitrate-rich vegetables, in particular leafy greens such as spinach and arugula, as well as beetroot, increase cardioprotective levels of nitric oxide with a corresponding decrease in blood pressure in people with prehypertension..In order for the body to produce nitric oxide via the nitrate-nitrite-oxide pathway, the reduction of nitrate to nitrite (using

nitrate reductase, a bacterial enzyme) occurs in the mouth by commensal bacteria, which is an obligatory and necessary step. Monitoring the state of nitric oxide using saliva analysis detects the bioconversion of plant-derived nitrate into nitric oxide. Increased saliva levels indicate diets rich in leafy vegetables, which are often present in antihypertensive diets such as the DASH diet. Oral antiseptic mouthwash eliminates the effects of dietary nitrates that lower blood pressure by destroying nitrate-reducing bacteria.

A related mechanism is believed to protect the skin from fungal infections when nitrates in sweat are reduced to nitrites by cutaneous commensal organisms and then to NO on a slightly acidic skin surface. Alternatively, nitrite anions on skin exposed to the sun can be photolysed to free radicals of nitric oxide under the action of UVA in sunlight.[19] This mechanism can cause significant changes in the systemic circulation in humans and be used for therapeutic purposes.

The induced nitric oxide synthesis pathway (iNOS) in phagocytes can generate large amounts of NO, which triggers apoptosis and kills other cells. In vitro studies show that phagocyte-dependent generation of NO in concentrations exceeding 400-500 nM triggers apoptosis in nearby cells and that this effect can act similarly to specialized mediators promoting resorption to weaken and reverse inflammatory reactions by neutralizing and then accelerating the elimination of proinflammatory cells from inflamed tissues. However, the role of NO in inflammation is complex, as model studies involving viral infection suggest that this gaseous mediator may also contribute to inflammation.

In response, many bacterial pathogens have developed mechanisms of resistance to nitric oxide. Since nitric oxide can serve as an inflammometer (inflammation meter) for conditions such as asthma, there has been increased interest in using exhaled nitric oxide as a breath test for diseases with inflammation of the respiratory tract. Reduced levels of exhaled NO have been associated with exposure to air pollution in cyclists and smokers, but, in general, levels of exhaled nitric oxide are associated with exposure to air pollution.

In cells, two broad classes of nitric oxide reactions include S-nitrosation of thiols and nitrosylation of certain metalloenzymes.

S-nitrosation involves the (reversible) conversion of thiol groups, including cysteine residues in proteins, to form S-nitrosothiols (RSNOs). S-nitrosation is a mechanism of dynamic posttranslational regulation of most or all major classes of proteins.

Nitric oxide is converted into a transition metal ion such as iron or copper, forming nitrosyl metal complexes. Typical cases include nitrosylation of heme proteins such as cytochromes, thereby disabling the normal enzymatic activity of the enzyme. Nitrosylated divalent iron is particularly stable. Hemoglobin is a prime example of a heme protein that can be modified by NO both by direct attack of NO and, independently, by attack by S-nitrosothiols, including the transfer of NO from S to Fe.

Iron-containing proteins ribonucleotide reductase and aconitase are deactivated. It has been demonstrated that NO activates NF-kB in peripheral blood mononuclear cells transcription factor in iNOS gene expression in response to inflammation. Although NO affects many metalloproteins, it does so by deactivating them.

Guanylate cyclase is a key component of the well-known NO properties that relax smooth muscles. It is a heme-containing enzyme that is affected by NO, which binds to heme. Cyclic-GMP activates protein kinase G, which causes the reuptake of Ca2+ and the opening of calcium-activated potassium channels. A drop in Ca2+ concentration ensures that the myosin light chain kinase (MLCK) will no longer be able to phosphorylate the myosin molecule, thereby stopping the cross-bridging cycle and leading to relaxation of smooth muscle cells.

Nitric oxide dilates blood vessels, increasing blood supply and lowering blood pressure. Conversely, it helps protect tissues from damage due to low blood supply. Also being a neurotransmitter, nitric oxide acts in

nitrergic neurons, is active in smooth muscles, and is abundant in the gastrointestinal tract and erectile tissue. Sildenafil (Viagra) inhibits the enzyme phosphodiesterase PDE5, which increases the concentration of cGMP by inhibiting conversion to GMP.

Nitric oxide (NO) promotes vascular homeostasis by inhibiting vascular smooth muscle contraction and growth, platelet aggregation, and leukocyte adhesion to the endothelium. People with atherosclerosis, diabetes, or hypertension often have disorders of the NO pathways.

Nitric oxide (NO) is a mediator of vasodilation in blood vessels. It is induced by several factors, and after the synthesis of eNOS, it leads to the phosphorylation of several proteins that cause smooth muscle relaxation. The vasodilating effect of nitric oxide plays a key role in the renal control of extracellular fluid homeostasis and is important for the regulation of blood flow and blood pressure. NO also plays a role in penis and clitoral erection.

Nitric oxide also acts on the heart muscle, reducing contractility and heart rate. NO contributes to the regulation of heart contractility. Emerging evidence suggests that coronary heart disease (CHD) is associated with defects in the generation or action of NO.

In plants, nitric oxide can be produced by any of four pathways: (i) L-arginine-dependent nitric oxide synthase, (although the existence of animal NOS homologues in plants is debated), (ii) plasma membrane-bound nitrate reductase, (iii) mitochondrial electron transfer chain, or (iv) non-enzymatic reactions. It is a signaling molecule that acts mainly against oxidative stress, and also plays a role in interacting with plant pathogens. It has been shown that treatment of cut flowers and other plants with nitric oxide increases the time to wilt.

In plants, NO also regulates some interaction of the plant with the pathogen, stimulation of plant hypersensitivity reactions, symbiosis (for example, with organisms in nitrogen-fixing root nodules), the development of lateral and accessory roots and root hairs, as well as control of the opening of stomata. Nitric oxide is known to be produced by cellular organelles, including mitochondria, peroxisomes, and chloroplasts. It plays a role in the reaction of antioxidants and reactive oxygen species.

The perception of nitric oxide by plants is mediated by the N-end rule of proteolysis and controls reactions to abiotic stress such as hypoxia caused by flooding, salt stress and drought.

Nitric oxide interactions have been found in the signaling pathways of plant hormones such as auxin, ethylene, abscisic acid, and cytokinin.

Atmospheric nitric oxide can penetrate into the stomata of most vascular species and can have various effects, from the appearance of spots on leaves to growth retardation and necrosis.

Blood-sucking insects use vasodilation caused by NO to provide their blood food. These insects include Cimex lectularius (bed bug) and Rhodnius proxlixus (kissing bug). These insects secrete NO from their carrier nitrophorin, which is contained in their saliva.

Although nitric oxide is commonly known to stop bacterial growth as part of the immune response, in one case NO protects the bacterium. The bacterium Deinococcus radiodurans can withstand extreme levels of radioactivity and other stresses. In 2009, it was reported that nitric oxide plays an important role in the recovery of these bacteria after radiation exposure: the gas is necessary for division and reproduction after DNA damage is repaired. A gene was described that increases the production of nitric oxide after ultraviolet radiation, and in the absence of this gene, the bacteria were still able to repair DNA damage, but did not grow.

In the European Union, nitric oxide in combination with ventilation support and other relevant active substances is indicated:

- for the treatment of newborns at gestation ≥34 weeks with hypoxic respiratory failure associated with clinical or echocardiographic signs of pulmonary hypertension, in order to improve oxygenation and reduce the need for extracorporeal membrane oxygenation (ECMO);
- as part of the treatment of peri- and postoperative pulmonary hypertension in adults and newborns, infants and toddlers, children and adolescents aged 0-17 years in combination with heart surgery, in order to selectively reduce pulmonary artery pressure and improve right ventricular function and oxygen saturation.

In the United States, improved oxygenation and reduced need for extracorporeal membrane oxygenation have been shown in full-term and immediate (> 34 weeks of pregnancy) newborns with hypoxic respiratory failure associated with clinical or echocardiographic signs of pulmonary hypertension, in combination with ventilation support and other appropriate means.

The most common side effects include thrombocytopenia (low platelet count in the blood), hypokalemia (low potassium levels in the blood), hypotension (low blood pressure), atelectasis (destruction of the entire lung or part of it) and hyperbilirubinemia (high bilirubin levels in the blood).

Nitric oxide/oxygen mixtures are used in intensive care to stimulate capillary and lung dilation in the treatment of primary pulmonary hypertension in newborns[86][87] and aspiration after meconium associated with birth defects. It is often a gas mixture of the last resort before using extracorporeal membrane oxygenation (ECMO). Nitric oxide therapy has the potential to significantly improve the quality of life and, in some cases, save the lives of infants at risk of pulmonary vascular disease.

People with diabetes typically have lower nitric oxide levels than patients without diabetes. A decrease in nitric oxide intake can lead to vascular damage such as endothelial dysfunction and vascular inflammation. Vascular damage can lead to a decrease in blood flow to the extremities, as a result of which diabetic patients are more likely to develop neuropathy and non-healing ulcers, as well as an increased risk of amputation of the lower extremities.

The main application is in the form of nitroglycerin in the form of tablets or liquid aerosols, which, as a prodrug, is denitrated and releases the active metabolite nitric oxide (NO). As is the case with all nitric oxide additives, the reaction is short-lived, because, as is usually the mechanism of internal physiological control, increased concentrations lead to an increase in the rate of excretion, which is the reason that the effectiveness of prolonged use of nitroglycerin for vasodilation is nullified after several hours or days. In the United States, permanent direct application of nitric oxide is allowed only for newborns.

In an adult intensive care unit, inhaled NO can improve hypoxemia in acute lung injury, acute respiratory distress syndrome, and severe pulmonary hypertension, although the effects are short-lived and there are no studies demonstrating improved clinical outcomes. It is used on a case-by-case basis in intensive care units as an adjunct to other definitive treatments for reversible causes of hypoxemic respiratory distress.

Nitric oxide is absorbed systemically after inhalation. Most of it passes through the pulmonary capillary bed, where it connects with hemoglobin, which is 60-100% saturated with oxygen.

Nitrate has been identified as the predominant metabolite of nitric oxide excreted in urine, accounting for >70% of the inhaled dose of nitric oxide. Nitrate is excreted by the kidneys from plasma at a rate approaching the glomerular filtration rate.

Nitric oxide is considered an antianginotic drug: it causes vasodilation, which can help with ischemic pain, known as angina pectoris, by reducing the load on the heart. By dilating the arteries, nitric oxide preparations reduce blood pressure and left ventricular filling pressure. Nitric oxide can contribute to reperfusion injury when an excess amount formed during reperfusion (after a period of ischemia) reacts with

superoxide to form the damaging oxidant peroxynitrite. On the contrary, inhaled nitric oxide has been shown to promote survival and recovery after poisoning with paraquat, which produces superoxide that damages lung tissue and interferes with NOS metabolism.

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