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# FROM THE NOBEL PRIZE FOR PHYSIOLOGY TO THE NEW TRAINING AND COMPETITIVE PARADIGM OF COMPETITIVE SWIMMING

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**Abstract**
Nitric - monoxide is recognized as a molecule with a very simple structure, considered for a long time as an extremely toxic substance. Yet, due to the possibility of endogenous biosynthesis and the variety of biological actions it possesses, today it is considered as paracrine substance of exceptional pharmacological, physiological and pathophysiological interest. Bearing in mind the numerous negative ecological and health effects that it has on the human environment on a daily basis, extremely large initial efforts have been made for decades to suppress it to a certain extent.. However, the discoveries that, in the eighties of the last century, led to new scientific advances in the fields of chemistry, physiology and medicine, led to a stunning conclusion - that the survival of the most dominant species on Earth mostly depends on its (bio)synthesis. Depending on the concentration, it performs a dual role in the vasculature, since in lower concentrations it has the function of an extremely powerful vasodilator, while in the case of high concentrations it performs the role of cytotoxin and cytostatic, thereby contributing to the body's defense against parasitic infections and tumors. Maintaining its availability in the endothelium is crucial for the normal functioning of the cardiovascular system. The Nobel Prize, which was awarded in 1998. for the discovery of the signaling role of nitric oxide in the human body, opened up a series of specific questions, which primarily relate to the place and role of this molecule in various biochemical processes that constantly occur in the human body under different conditions. Accordingly, the theoretical and empirical issues of the role of nitric oxide in swimming, training, and the general health of swimmers (athletes) in water are the subject of this paper.

**Key words:** NITRIC OXIDE / TRAINING AND COMPETITION PREPARATION / THEORETICAL GENERALIZATION / DOCTRINE

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**THE EUREKA EFFECT: THE ROAD FROM ACCIDENTAL TO EPOCHAL SCIENTIFIC DISCOVERY**

In the foundations of man's understanding of the world, but also of living as a phenomenon, there is the basis of inductive reasoning - organic (biological) causality. In addition to adaptation, which at the same time represents a philosophical, physiological and biological phenomenon, but also one of the basic mechanisms responsible for the preservation of the species, for centuries man has been focused on the process of learning, which, according to an unwritten rule, is intertwined with the previous knowledge of humanity and the personal experiences of the individual. In other words, according to Hume, *"all kinds of thinking consist in nothing else, except in the discovery and comparison of cause-effect relationships of intentional or accidental events"* (Hume, 1983). Thanks to the aforementioned paradigm, nitric oxide (NO), which for centuries was viewed exclusively through the prism of toxicology, became a substance of crucial importance in the 20th century. Although it has been proven that one of the first interactions between man and nitrogen oxides occurred around 3000 years ago, the first scientific reflections on NO develop from the 13th century, during which *aqua fortis*, later "nitric acid", was first described (Karpenko, 2009). The modern method of its synthesis was developed by Johann Glauber, while Jan Baptist van Helmont noticed and described that, during its interaction with copper, iron and silver, a characteristic, then still unknown substance is formed, which he named "gas" after the Greek word "chaos". Soon after, Robert Boyle and Georg Ernst Stahl noticed that almost always, when it came into contact with other chemical elements from the atmosphere, that gas took on a brown hue (Butler, Nicholson, 2003). Although many famous chemists worked on the mentioned problem for many years, it was Joseph Prestley who defined it in 1772. as a "separate chemical entity" that he synthesized quite by accident, while working on one of the experiments with the help of which he discovered also oxygen (Gillman, 2019, Marsh&Marsh, 2000, Lancaster, 2020). During the next two centuries, NO was considered a highly toxic compound, since accidental or intentional inhalation of NO led to a fatal outcome for an extremely large number of chemists. Bearing in mind the above, it could not even be assumed that small amounts of this "deadly agent" in the organism of plants, animals, and especially humans, would play one of the crucial roles. The first turning point in the process of studying and understanding the action of NO was in the 19th century, when the Italian chemist Ascanio Sobrero, using NO, synthesized nitroglycerin, which was then used by Alfred Nobel, for industrial purposes in his dynamite factory. At the end of the sixties, two astonishing phenomena were observed in it; factory workers experienced severe headaches during the work week, which would disappear during the weekend. Also, workers suffering from angina pectoris (including Nobel himself) felt significantly better during the work week, while the chest pain reappeared on weekends, when they were not exposed to the mentioned substance (Marsh, 2000). Despite everything, for the answer to the question of what exactly leads to this mechanism of action, mankind had to wait almost 150 years, when biochemist and university professor Robert Furchgott proved that the presence of the mentioned substance is necessary for the above-mentioned effect endothelial cells, in whose receptors the oldest known neurotransmitter, acetylcholine, stimulates the release of a signal molecule, which then leads to relaxation of the smooth muscles of blood vessels (Furchgott, Zawadski, 1980). The new signaling molecule was initially named "endothelial-derived relaxing factor" (EDRF). Almost ten years after EDRF discovery, Palmer and Ignarro, independently of each other, managed to prove that it is, in fact, NO (Palmer, Ferrige, Moncada, 1987, Ignarro, Buga, Wood , et al., 1987). Relying on previously known hypotheses, Salvador Moncada showed that the basic substrate for its amino acid synthesis is L-arginine (Palmer, Ashton, Moncada, 1988). With this discovery, it is believed, the "new era" of many scientific disciplines begins.

All the mentioned, as well as numerous other researches that were initiated by them, contributed to the fact that in 1992, according to the magazine "Science", NO was declared "molecule of the year" (Koshland, 1992). Six years later, on October 12, 1998, thanks to the scientific contribution they made through joint work and discoveries, proving that it is an extremely important signaling molecule of the human cardiovascular system, Robert Furchgott, Louis Ignarro and Ferid Murad became laureates of the most prestigious recognition in the world of scientific research - the Nobel Prize, for discoveries in the field of physiology and medicine (Smith, 1998). The award-winning work proved, for the first time in history, that a molecule in a gaseous state can be an important biological messenger in the mammalian organism. By the beginning of the 21st century, NO managed to penetrate all the pores of medicine. Thanks to that, it was quickly recognized in the etiopathogenesis of different types of diseases. Today, almost 25 years after the aforementioned discoveries, it is extremely difficult to single out a disease or an organism's activity that is not, at least to a small extent, related to variations in the domain of the NO biosynthesis/bioactivity mechanism.

## BIOSYNTHESIS OF NITRIC OXIDE IN THE HUMAN ORGANISM

Nitric oxide is the first gaseous signaling molecule that is involved in the entire spectrum of (patho)physiological processes in the mammalian organism. It is extremely unstable and rapidly degrades to stable products. It is noticeable that in current publications it is often attributed different, often intimate roles, since it causes a whole variety of reactions, depending on the environment in which it is located, the concentration of the gas itself, but also the models on which the tests are performed. At the core of its biosynthesis process are enzymes, complex highly selective proteins that, under clearly determined conditions (neutral pH value and optimal body temperature), convert natural substances - substrates (in this case, nitrogen and oxygen) into NO. The group of enzymes crucial for synthesizing this molecule is called nitric-oxide-synthase (NOS) and more will be said about it in the rest of the paper. In each of the approximately 200 different types of cells in the human body, the presence of NO, endogenous or exogenous, can be observed. Endogenous NO is an extremely important mediator of endogenous processes, especially those related to intestinal motility and mucosal permeability (Izzo, Mascolo, Maiolino, Capasso, 1996). It can be formed primarily in non-enzymatic and enzymatic reactions. Non-enzymatic NO is produced in acidic environments from nitrite, while the enzymatic pathway of synthesis involves the action of the NOS group of enzymes (Eiserich, Patel, O'Donnell, 1998). So far, four different isoform groups of NOS have been isolated, consisting of large and complex polypeptide homodimers: neural / constitutive (nNOS / type I), inducible (iNOS / type II), endothelial constitutive (eNOS / type III) and bacterial (bNOS). Neuronal NOS and endothelial NOS are expressed constitutively, while inducible NOS is induced by interleukins - inflammatory cytokines, that is, it is expressed exclusively during cell activation and is not present in a resting cell. All the mentioned isoforms as an endogenous substrate for the synthesis of NO sine qua non use an isomer of one of the conditionally essential amino acids, L-arginine (Billiar, Cirino, Fulton, Motterlini, Papapetropoulos, Szabo, 2019), which is present in high concentrations in blood, extracellular fluid , but also within the cell itself. In other words, in the mammalian organism, NO is produced by the catalytic activity of the enzyme NOS, which catalyzes oxidation, i.e. converts L-arginine to NO and L-citrulline (Alderton, 2001), with the help of O2 and NADPH. Since the monomeric form of NOS cannot bind the substrate and tetrahydrobiopterin (BH4, THB) as a cofactor, NO generates superoxide anion (O2-) (Förstermann, Sessa 2012, Zhao et al. 2015). The mentioned process is called *"NOS uncoupling"* and is a basic feature of the entire spectrum of obstructions and diseases that attack the human cardiovascular and respiratory system (Daiber et al, 2019). Also, the effects of the described vaporization, as well as increased iNOS activity, were also observed in patients suffering from the COVID-19 virus (Guimarães, Rossini, Lameu, 2021). NOS activity is controlled by a negative feedback loop with NO (Alderton, Cooper, 2001). Oxidation of NO into inorganic nitrate (NO3) and nitrite (NO2-) is the main way of rapid inactivation of the mentioned, extremely potent, biological messenger (Qin et al, 2012). For a very long time, the mentioned anions were considered molecules of great biological interest, due to the fact that they represent by-products of the NO oxidation process. However, in the mid-1990s, research showed that it is a two-way process, that is, that nitrates and nitrites can be reduced again to NO (Zweier, 1995). The initial step in the bioactivation of NO3 depends on the bacteria of the oral cavity, as well as the intestinal microbiota; circulating nitrate is taken up by salivary glands (Qin et al, 2012), while commensal bacteria of the oral cavity reduce it and thus form more reactive nitrites. They then go through the process of ingestion, and participate in the creation of NO and other reactive nitrogen oxides in the blood and tissues. Enzymatic and non-enzymatic mechanisms, thanks to which the mentioned process is realized, are numerous (Lundberg, Weitzberg, Gladwin, 2008), and it is interesting to point out that all of them are accelerated in an acidic environment and conditions of hypoxia. In other words, the "nitrate - nitrite - NO" pathway can be considered a "reserve system" for the synthesis of NO, in conditions when the NOS production process is, for any reason, dysfunctional. In view of the above, and bearing in mind that nitrates and nitrites are an integral part of the daily human diet, the question arises as to how much influence nutrition and dietetics have on the mentioned axis and the described pathways, especially in the body of an athlete - a swimmer, bearing in mind the specifics of the sports branch.

## SYSTEMATIC SYNTHESIS OF THE ROLE OF NITROGEN MONOXIDE IN THE THEORETICAL AND PRACTICAL PROGRESS OF SWIMMING PHYSIOLOGY

Having in mind the health benefits of this molecule, it is of great importance to additionally highlight its most significant (patho)physiological functions, both for the human population in general, and for the athlete - swimmer in the narrower sense.

- It prevents the adhesion of platelets and leukocytes to the endothelium of blood vessels, inhibits the aggregation of platelets and initiates the dissociation of blood cells that have nevertheless aggregated (Radomski, Zakar, Salas, 1996).
- NO deficiency causes accelerated atherogenesis in animal organisms (Cayatte, Palacino, et al., 1994; Huang Z, Huang PL, Ma, et al., 1994) while high concentrations inhibit the proliferation of smooth muscle cells and can induce apoptosis (Chung, Pae , et al, 2001, Guyton, 2000).
- NO exhibits its toxic properties by initiating various chronic inflammatory diseases, autoimmune diseases, etc. (Moncada et al., 1991, Loscalzo, Welch, 1995, Hierholzer et al., 1998).
- The results of studies conducted on laboratory animals indicate that NO also plays a role in certain types and phases of the learning process, such as spatial learning (Hölscher, McGlinchey, et al., 1996), an important aspect of training, learning and improvement in sports swimming.
- In addition to prophylaxis, NO has a significant place and role in treatment; Treatment with organic nitrates, including nitroglycerin, has been used in clinical practice for more than 150 years, much longer than its role as a signaling molecule in mammals. Inhalation of gaseous NO is approved for clinical use in infants with respiratory distress syndrome and pulmonary hypertension (Peliowski, 2012). Thus applied, NO achieves its "dual selectivity", which means that, since it is administered by

inhalation, it dilates only the vessels that supply well-ventilated parts of the lung, further contributing to the balance of the pulmonary ventilation-perfusion ratio. Also, due to the rapid removal of NO from the blood, systemic vasodilation is minimized.

Swimming, as a coordinated rhythmic movement of the human body on the surface of the water, but also a kind of cultural phenomenon, it represents one of the most popular, planetary-wide, physical activities. In it, on a global level, both the healthy and the population exposed to various health risk factors, diseases and comorbidities participate en masse (Conti, 2015). In other words, the public health importance of swimming has been recognized for long time, especially thanks to the multifactorial genesis of the entire spectrum of diseases, according to which physical inactivity is one of the key risk factors for disease, since the modern way of life largely suppresses regular physical exercise, one of the fundamental stimuli human general health.

A number of mechanisms have been identified through which swimming, as well as being in water in general, reduce the risk of contracting chronic non-communicable diseases (including effects on lipid metabolism and lipid profile, endothelial functions, vasodilatation, coagulation, insulin sensitivity and the like) unknown. However, in terms of their prevention, the biosynthesis of nitric oxide (NO) (Koshland, 1992), a molecule that is synthesized in almost all cells of the human body and has attracted a great deal of attention in the world of science in the last thirty years, is extremely important. Current publications increasingly confirm the theory that it is an important hemodynamic and metabolic regulator important for performing almost all forms of physical activity, including swimming. Due to the effects it exerts on the body as a whole, it has a special effectiveness in restoring the dysfunctions of the endothelial cells of the vascular system, which is a process that today is considered a prophylaxis of atherosclerotic, but also of numerous other pathophysiological processes in the modern human body. The reason for this is partly the fact that NO has important roles in transmitting information in both physiological and pathophysiological processes, i.e. the knowledge that it can have both toxic and beneficial effects in the same organism (Calabrese, 2023).

In the human body, NO, thanks to its physical properties, moves freely until it "collides", that is, enters into a chemical reaction with one of the target molecules (Chen, Keshive, Deen, 1998). In other words, almost all cell components can be "targets" of NO. Its two most important physical properties are solubility/volatility and diffusibility, which also depends on its concentration in the observed localities. Understanding these properties is extremely important for understanding the biological action of NO. The molecular mechanisms of its action are very complex and, since they are not the subject of this paper, it is sufficient to point out that their effects can be divided into direct and indirect (Wink, Mitchell, 1998). Direct refers to reactions in which NO directly reacts with target molecules and involves physiological aspects of cell metabolism. Indirect action, on the other hand, refers to redox transformation and the formation of reactive nitrogen species (RNS), thus nitrosative stress, and implies pathophysiological activities of cellular metabolism.

**Respiratory system**

As is the case at the level of the entire human organism, NO has significant and numerous roles in his respiratory system. First of all, it makes a significant contribution to the regulation of bronchial smooth muscle tone, lung vasculature and pulmonary blood flow, the function of surfactants, but also processes such as antioxidant homeostasis, local host defense, lung development, etc. (Antosova et al, 2017). Each type of cell, of at least 40 different types that participate in the construction of the human respiratory system, has the ability to produce NO by synthesizing one or more types of NOS.

A large number of studies conducted on a sample of children, but also of the adult population, indicated statistically significantly higher values of respiratory muscle strength in children and adults who engaged in swimming, compared to other forms of physical activity. The same trend was observed in a sample of athletes who do sports outside the water, after the implementation of swimming in the training program - the strength of the inspiratory muscles increased by 35.9%, and the strength of the expiratory muscles by 30.1% (Karaula, Homolak, Perzel, 2022). Research also shows that the benefits of swimming increase with increasing "swimming experience", as a form of regular physical activity (Cumming, 2017). Due to all of the above, it is often recommended to sufferers of the aforementioned chronic respiratory diseases, as well as other degenerative conditions in which maintaining or building the strength of the respiratory muscles is extremely important.

The role of NO in the control mechanism of pulmonary circulation has been studied by various methods, from inhibition of NOS by pharmacological means, to the implementation of knockout experiments on an animal model, in order to study each of the recognized isoforms of NOS (Moncada, Higgs, 2006). Current studies particularly emphasize the importance of NO in hypoxia (Dias-Junior et al., 2008), a frequent condition in the training and competitive system of sport swimming. There are several theories about the mechanisms of hypoxic vasodilatation during swimming, which is mediated by NO (Dweik, 2001). In studies conducted on laboratory animals, in cases where they were introduced to a state of hypoxia, to which the pulmonary vasculature responds by vasoconstriction, pulmonary hypertension was higher than in control groups. The release of eNOS, the main NO, is greatly reduced in chronic hypoxia (Adnot et al, 1991). On the other hand, excessive synthesis of NO had a positive effect on the remodeling of the vasculature of the pulmonary parenchyma and hypertrophy of the right ventricle, caused by chronic hypoxia (Ozaki et al., 2001).

NOS inhibitors are known to prevent plasma leakage in the microvasculature, induced by substance P and leukotriene, but not after histamine. The above clearly indicates the importance of NO in extravascular plasma leakage caused by some of the inflammatory agents (Kageyama et al., 1997). At the same time, the authors point out that the plasma leakage induced by these substances increases in response to endogenous NO, especially in the extrapulmonary, but not in the intrapulmonary airways (Ricciardolo, 2003). Considering the explained mechanism, the potential role of swimming in controlling bronchial and allergic asthma should not be overlooked, since it, compared to other forms of physical activities, causes little or no broncho-obstruction (Geinger, Henschke, 2015). If we take into account the fact that the environment in which swimming takes place includes humidity, low exposure to respiratory allergens and hydrostatic pressure on the chest walls, it is clear that swimming has an extremely favorable effect on the development of cardiorespiratory fitness and increasing lung volume, but also on the quality of technique breathing en general (Cumming, 2017).

The benefits of swimming, and even immersion itself, are partially conditioned by the translocation of blood into the thoracic region, as well as the compression of the chest walls by hydrostatic pressure, in the regulation of which NO participates. As a consequence of the aforementioned joint action, a decrease in vital capacity by 6-9% is observed (Cumming, 2017), but also an increase in breathing frequency during immersion, which implies that staying in an adequate water environment is extremely suitable for the process of respiratory training and rehabilitation.

**Cardiovascular system**

The cardiovascular system can be seen as a "biotope of NO", since its very discovery came from experiments performed on the endothelium of the vasculature. The heart of mammals, as is known, consists of two atria, which collect blood, and two ventricles, which pump it out. The electrical impulse initiated in the right atrium propagates through the conduction system of the heart to coordinate myocardial contraction. Two isoforms of NOS, (nNOS and eNOS) are randomly distributed in the heart (Strijdom, 2009) and participate in this process. In tissues such as the heart, there is a whole series of NO synthesis pathways from nitrite, the potentiation of which is particularly pronounced in hypoxia, including xanthine oxidoreductase (XOR), deoxygenated myoglobin (deoxy-Mb), enzymes of the mitochondrial chain and the like. The described pathways, as well as the synthesis of NO from S-nitrosothiol, participate in the modulation of inflammation, inhibit mitochondrial respiration and the formation of reactive oxygen species, while also triggering cGMP-dependent signaling during anoxia (Lundberg, Weitzberg, Gladwin, 2008). Therefore, it is clear that a disturbance in the biosynthesis of this substance can play a central role in the creation and progression of cardiovascular diseases.

The cardiovascular system maintains a constant level of NO for optimal blood flow. When flow increases, the endothelium releases more NO to maintain its concentration. In the case of the presence of various pathological processes, such as the deposition of cholesterol plaques on the walls of arteries, NO is not produced to the extent necessary, which leads to vasoconstriction, which reduces blood flow, increases blood pressure and leads to a hypertensive state.

In the cardiovascular system, NO can also be synthesized from platelets. Synthesized in this way, it plays a role in the prevention of coagulation, thrombus formation and blockage of arteries. The emergence of pathological mechanisms within this system leads to the genesis of coronary thrombosis and is the main cause of cerebrovascular insult.

By itself, the human heart releases a significant amount of NO during systole and diastole. In physiological conditions - in the beating heart, it is produced by endothelial cells, which are usually always located in the immediate vicinity of myocytes. Without mechanotransduction/production of NO, cardiac output would change rapidly with sudden changes in workload. The aforementioned gradual response of the heart to sudden changes in load mediated by NO is also called "cardiac memory". The human heart is more sensitive to low levels of NO than to low levels of oxygen; the interruption of the supply of NO to the organism will lead to a lethal outcome in 10-15 seconds, which is significantly faster than the interruption of the supply of oxygen, which leads to death in 5-7 minutes (Murphy, 1999).

Swimming, as a form of physical exercise, improves circulation and increases blood flow, and studies conducted on dogs have shown an increase in the diameter of the coronary vasculature after exercise (Bowe, Dewey, 1985). These conclusions are considered the basis of new studies, which have shown that an adequate and properly dosed program of exercise in water can reduce peripheral vascular resistance, both in hypertensive patients (Nelson et al., 1986) and in healthy individuals (Jennings et al., 1986). Given the fact that blood flow is increased, swimming induces shear stress on the surface of the endothelium, which is also one of the physiological stimuli for the formation of NO (Cooke, Rossitch, Andon, et al, 1991, Miller, Burnett, 1992). Therefore, one of the essential physiological mechanisms that lie at the core of the benefits that swimming brings to the human cardiovascular system is precisely the increase in NO production. In addition, research shows that in the population of swimmers, the risk of mortality from all causes is lower, especially due to cardiovascular diseases, compared to those who sit, walk or run (Chase et al., 2008). Studies on laboratory rats have shown that swimming training has positive effects on the contractile function of the heart, as well as the response to insulin. This process is primarily facilitated by the facilitation of glucose uptake into the heart muscle, stimulated by insulin. The molecular basis of this process relies on increased translocation of glucose transporter type 4 (GLUT4). Also, a significantly increased concentration of protein kinase and eNOS was observed in the group that was exposed to swimming training.

All the mentioned mechanisms, which swimming training promotes, increase the total biosynthesis of NO in heart muscle (Zhang et al., 2007). Newer experimental studies, carried out on an animal model, showed that swimming training can play an important role in the prevention of atherosclerotic conditions and diseases by suppressing eNOS phosphorylation, i.e. ensuring plaque stability (Pellegrin et al., 2009). A study from 2002 showed that the human species has a gene that encourages physical activity, while the modern, sedentary lifestyle is a factor that suppresses it (Booth, Chakravarthy, Spangenburg, 2002). Accordingly, the authors conclude that physical exercise is a factor that restores homeostatic mechanisms to the physiological range. The results of recent studies show that swimming, in addition to other forms of physical exercise, led to an improvement in the function of blood vessels in a group of people with cardiovascular diseases, while the changes in healthy subjects were less consistent. In other words, endothelial functions are more susceptible to improvement due to physical exercise-swimming in the population of people suffering from cardiovascular diseases, than it is the case in the young or healthy population (Maiorana, et al 2003), which will need significantly greater continuity, intensity or volume of training for such an effect.

**The role of nitric oxide in the central nervous system**

One of the main roles of NO in the brain is the control of presynaptic function, which affects neuroplasticity and long-term potentiation (Hardingham, Dachtler, Fox, 2013). As is known, neuronal activity, and with it all the functions attributed to the central and peripheral nervous system, are based on the synthesis and release of neurotransmitters. It is precisely on these processes that the increase and decrease in the production of electrical signals in the brain depends, which are caused by the flow of positively and negatively charged ions through the neuron, which affects the change in the electrical potential of the neuromembrane. The end result of this process is the excitation or inhibition of neurons (Malinski, 2000).

In the central nervous system, NO acts precisely as a neurotransmitter, primarily in the cerebellum. Since it is a labile free radical, it is important to note that it is not stored in synaptic vesicles, like other neurotransmitters. On the contrary, if necessary, it must be synthesized from its precursor, L-arginine, with the help of the action of one of the most biologically regulated enzymes, NOS, capable of rapid modulation. The NO synthesized in this way cannot be released by the process of exocytosis, but diffuses from the nerve endings, and instead of binding to protein receptors on neighboring cells, it also diffuses into them. Neurons that synthesize it are primarily observed in the cortex, striatum, but it is also contained in the pedunculopontine tegmental nucleus and substantia nigra compacta (Vincent, Kimura, 1992) - brain regions that play a significant role in the motor control of human movement. More precisely, the activities that take place during swimming technique training and motor learning, i.e. the simultaneous potentiation of the nerve pathway, from its beginning in the brain, to the muscles and other parts of the effector system, takes place to a large extent thanks to the synthesis of NO within the nervous system itself. This molecule is also involved in the control of hippocampal activity (Hu, Zhu, 2014), and therefore in the control of learning and memory processes (Paul, Ekambaram, 2011, Susswein, Katzoff, Miller, Hurwitz, 2004). In other words, it is considered a crucial factor for the development of long-term memory. Its high concentrations are cytotoxic for most nerve cells, due to iron loss, inhibition of DNA synthesis, mitochondrial respiration, and aconitase activity within the cell itself (Hibbs, Taintor, Vavrin, Rachlin, 1988, Calabrese et al, 2007).

Research conducted on laboratory animals, which involved performing a spatial task (including swimming), found a significant increase in nitrite concentration in the hippocampus, even up to 45% (Harooni, Naghdi, Sepehri, Rohani, 2009). Performing tasks that required a special engagement of spatial memory was accompanied by an increase in the concentration of NOS, in the same locality (Zhang, Chen, Wang, 1998).

In the last ten years, there has been a noticeable increase in the number of scientific publications that observe the role of NO in the genesis of neurodegenerative diseases, including Alzheimer's, Huntington's and Parkinson's diseases, amyotrophic lateral sclerosis, but also acute brain ischemia (Stankowski, Gupta, 2011, Sultana et al, 2006, Wang, Hong, Yang, 2022). Recent research suggests that NO modulation of glutamatergic calcium signaling is neuroprotective in non-pathogenic conditions, with increased concentrations of nNOS and NO contributing to spontaneous calcium signaling in neurons affected by Alzheimer's disease (Balez, Stevens, Lenk, Sidhu, Sutherland, Ooi, 2024).

## NITROGEN MONOXIDE: A NEW UNDERSTANDING OF SWIMMERS TRAINING AND COMPETITION PREPARATION

Numerous discoveries about different (patho)physiological roles justify the observation of NO through the prism of one of the "most unexpected discoveries" in biological and coordination chemistry, i.e. the fact that it still represents a challenging research field on which multidisciplinary research groups work worldwide. However, it was only the discovery of extremely important regulatory mechanisms that it possesses in mammalian organisms, for which the Nobel Prize for Medicine and Physiology was awarded in 1998, that placed it in an important place in research in the field of medicine, but also in other related scientific disciplines, and all more often sports and physical exercise. Intentions to precisely define its place and role within the system of physical activity regulators, but also in the rehabilitation process after various injuries (Filippin, 2009, Bokhari., 2012, Murrell, 2007) are increasingly noticeable. The following statements should be viewed precisely in that direction, that is, in the direction of the New Doctrine of training and competitive preparation of swimmers.

### Nitrogen monoxide in the process of learning swimming skills

The stimuli of the environment in which swimming takes place - water, greatly influence spatial learning and over time can contribute to the modification of the structure and function of the brain (Gómez-Pinilla, So, Kesslak, 1998). One of the theories used to explain these mechanisms advocates the view that the aforementioned effect is realized thanks to the proper activity of nNOS in glial cells, which further influence the initiation of various factors with a great influence on the expression of certain genes. On the other hand, various disorders in the biosynthesis of NOS within the hippocampus, which affect the hyperproduction of NOS and NO, thereby causing an increase in the concentration of metabolites, can be considered one of the causes of disturbances in spatial, but also in almost all other forms of learning (Hosseini et al., 2010 ). Long-term potentiation in the hippocampus represents an outstanding field for strengthening synaptic neuroplasticity, while at the same time it is believed to correlate to some extent with the learning and memory process (Teyler, DiScenna, 1987). It is initiated by the activation of postsynaptic NMDA receptors, and its maintenance requires both presynaptic and postsynaptic alternations (Kullman, Nicoll, 1992). Since it has been proven that NOS inhibitors block the induction of long-term potentiation of the hippocampus, and therefore, like large amounts, interfere with certain types of learning, it is considered that the regular synthesis of NO plays an extremely large role in the regulation of the aforementioned mechanisms (Mizutani, Sato, Abe, 1993, Ohno, Yamamoto, Watanabe, 1993). In other words, as Toyoda, Saito and Matsuki concluded in their 1996 study, NO is one of the necessary agents, without which spatial learning would be impossible (Toyoda, Saito, Matzuki, 1996) In this regard, it is about one of the important segments of the competitive skills of swimmers.

**Nitrogen - monoxide in the process of recovery and rehabilitation of swimmers**

Training in a broader sense, and accordingly swimming training, represents a set of acute challenges to which the body of an athlete (or a physically active individual) is exposed, with the aim of achieving chronic adaptation of its physiological characteristics, i.e. the final improvement of its competitive efficiency (Bishop, Jones, Wood, 2008). The phenomenon of sports training has been receiving increasing attention for decades, and the largest number of publications has long been focused on the study of training components, despite the decades-known claim that the adaptation of the organism caused by physical exercise takes place to the greatest extent during the recovery process after training (Barnett, 2006). In (elite) sports, and more often in the field of recreation, an extremely large number of methods and techniques are used today, the aim of which is to speed up the recovery process. Precisely for the stated reason, knowledge of the effectiveness of these techniques and methods, in order for an adequate method to be recognized and applied in the recovery process, has never been more necessary. A number of publications that have dealt with this topic place in the center of the theory they advocate, among others, NO; Almost all NOS isoforms are synthesized in human skeletal muscles.

In this regard, it has been proven that NO affects the process of regulating muscle force generation, but also the activation of muscle stem cells (myosatellite cells) - small multipotent cells, which are located in the basal lamina of skeletal muscles and play a vital role in the regulation of the recovery of damaged muscle tissue (Galler, Hilber, Göbesberger, 1997). One of the first studies dealing with the role of NO in skeletal muscle damage was conducted in 2000 by Anderson (Radak, Naito, Taylor, Goto, 2011). An extremely important conclusion emerged from it - NO facilitates the activation of myosatellite cells, which is also one of the first steps in the process of regeneration of damaged muscle tissue. Also, during the recovery process of tendons, whose injuries occurred as a result of continuous overexertion, i.e. due to the constant repetition of repetitive movement patterns, which is one of the most frequent ways of injury in swimming, a significant increase in NO production was observed. The mentioned additionally points to its role in the recovery process of swimmers, especially when it comes to shoulder and knee joint injuries (Szomor, Appleyard, Murell, 2006).

Exogenous administration of NO, produced in a specialized device, has also recently been investigated; In one of the most recent publications by Zaborova and colleagues, it was shown that exogenous application of NO has a positive effect on microvasculature disorders, accelerates the transition from the inflammatory to the proliferative phase, enhances angiogenesis, fibroblast proliferation, and collagen fibrogenesis (Zaborova, Butenko, Shekhter, et al., 2023). Also, it was observed that the feeling of pain, edema and hematoma decreases earlier, as well as their complete absence and a shortening of the total duration of the rehabilitation process was observed, compared to the control group of subjects who used exclusively anti-inflammatory pharmacological agents (Zaborova et al., 2023). In a study conducted in 2021 with the aim of examining for the first time the causality between NOS and the application of cryotherapy, a method that is very often used in the recovery process of swimmers after great efforts, it was shown that continuous exposure to cryogenic temperatures leads to an increase in the concentration of iNOS ( Weicek, Szygula, Gradek, Kusmierczyk, Szymura, 2021), due to which the recovery process is accelerated.

When it comes to immanent immersion swimming, the mere immersion in water exposes the individual to environmental pressure, which (even at relatively shallow depths) exceeds the venous pressure, as a result of which the blood moves upwards (Arborelius, Ballidin, Lilja, Lundgren, 1972), through the venous and the lymphatic system, first into the thighs, then into the vessels of the abdominal cavity, and finally into the great vessels of the chest and into the heart. As a result of the mentioned cascade, there is an increase in pulse pressure, increased heart filling and a decrease in heart rate during thermoneutral or immersion in cold water (Gabrielsen, Warberg, Christensen, 2000).

One of the significant agents that have noticeable effects on the length and quality of swimmers' recovery, and which can be linked to the production of NO, is the nutrition and supplementation of athletes. Recently conducted research has shown that NO supplementation improves the performance and recovery of athletes - swimmers (Mor, Atan, Agaoglu, Ayyildiz, 2018). Additionally, a review of the literature found that there are a number of different methods of supplementing with arginine, citrulline, and ornithine (Copp, Hirai, et al, 2010, Nyberg, Jensen, et al, 2012), known as NO precursors, which in terms of recovery, they gave more or less consistent results. An almost identical trend was observed with nutrients, such as caffeine and cocoa, which promote the biosynthesis of NO (Watson, Preedy, Zibadi, 2013, Ludovici et al, 2017) in the athlete's organism.

The role of various foods and supplements rich in NO in the training and recovery process of swimmers has been confirmed in a large number of studies, which will be discussed in more detail in the next chapter. *Summa summarum*, its roles in the very mechanisms of the athletes' recovery process after training and competition, but also after injuries, are multiple and increasingly noticeable. However, this field of study, which undeniably holds great potential, is still underexplored.

**The place of nitrogen monoxide in the understanding of the nutrition process of swimmers**

Proper nutrition is one of the important factors that can have a major impact on the overall health, body composition and efficiency of an athlete. Since it has a direct impact on his organism, it can relatively easily lead to improvement (or deterioration) in the training and competition efficiency of the swimmer. In other words, both the quantity and quality of food consumed can significantly affect the quality of performance, and it is important to point out that the adoption of adequate eating habits should be given special attention in training practice when working with young swimmers, since quality nutrition is one of several important prerequisites for performance of quality training and competition (Maglischo, 1993). The nutritional requirements of swimmers are highly variable. However, the ultimate goal is almost always aimed at ensuring the appropriate amount of energy, as well as its availability, for the needs of training and competition (Shaw, Boyd, Burke, Koivisto, 2014), while maintaining the athlete's long-term health. Taking into account the energy expenditure of swimmers, sometimes the intake of the optimal amount of nutrients, fluids, electrolytes, and also providing the appropriate amount of energy to perform work, is a big challenge. For the above reasons, as well as numerous other reasons, swimmers often resort to using different types of dietary supplements (Knapik, Steelman et al, 2016). Due to the extremely large number of studies conducted with the aim of examining the effects of supplementation on the organism and overall health of the athlete, his recovery, as well as on his effectiveness in the training and competition system, the process of supplementing swimmers has become much more complex than it was in the past. In the last two decades, a lot of attention in the field of swimmers' nutrition has been attracted by those dietary manipulations that can influence the production of NO, but also other nitrogen oxides in the body, from which NO could potentially arise. Before its role in endogenous signaling was observed, research was mainly related to examining the potentially harmful role of dietary nitrate and nitrite, as precursors of carcinogenic nitrosamines (Tannenbaum, Sinskey, Weisman, Bishop, 1974). However, the association between high nitrate intake and cancer has not yet been observed (EFSA, 2008, Lundberg, Weitzberg, 2022). On the contrary, the discovery of the nitrate-nitrite-NO synthesis pathway in the mammalian organism has awakened great interest in the use of nitrates in the diet, in order to increase the systemic bioactivity of NO, since this molecule is extremely abundant in beets and green vegetables. It is beet juice that has been used in a huge number of studies, considering that natural juice contains very large amounts of NO, while nitrate-depleted beet juice is suitable for use in trials as a placebo (Gilchrist, Winyard, Fulford, Anning, Shore, Benjamin, 2014).

In addition to the above, research into the ergogenic effects of inorganic nitrates is also significant, which showed that both acute and chronic intake in athletes reduces oxygen consumption (Larsen, Weitzberg, Lundberg, Ekblom, 2007), but also improves overall efficiency (Jones, Thompson , Wylie, Vanhatalo, 2018). In the population of swimmers, the aforementioned effects are achieved at the expense of increased mitochondrial efficiency (Larsen, Schiffer, Borniquel, et al, 2011), improved blood flow to working muscles (Lee, Stebbins, Jung, Nho, Kim, Chang, Choi, 2015 ), as well as increasing efficiency in the domain of muscle contractility (Bailey, Fulford, Vanhatalo, et al, 2009).

Long-term supplementation with the mentioned compounds does not *per se* cause better efficiency, but contributes to its maintenance, while it also does not lead to the formation of tolerance to the supplement. It is important to point out that similar effects can be achieved with regular and adequate nutrition (Hord, Tang, Bryan, 2009).

The effects of nitrate supplementation to a certain extent depend on the procedure of the supplementation process itself, and especially on the dose of NO3- and the duration of the mentioned process. Accordingly, the effects of improving the economy of exercise observed after acute consumption of nitrates remain observed for up to 15 days, in cases where subjects consumed 5.2 mmol (322 mg) of nitrates per day (Vanhatalo et al, 2010), i.e. up to 28 days, in cases when they consumed 6 mmol (372 mg) of nitrate during the day (Wylie, de Zevallos, Isidore, Nyman, Vanhatalo, Bailey, Jones, 2016). On the other hand, in the population of elite swimmers, better capillarization of skeletal muscles (Jensen, Bangsbo, Hellsten, 2004), increased concentration of $Ca2^{+}$ - handling proteins (Kinnunen, Mänttäri, 2012) and/or a lower proportion of type II muscle fibers (Tesch, Karlsson, 1985). All of the above may affect the slightly lower effectiveness of nitrate supplementation in the population of top swimmers, compared to less trained ones. Since the enzymatic way of synthesizing NO, as mentioned, requires the presence of oxygen and other essential agents, it was observed that the NO3-NO2-NO reduction pathway can compensate for the NO deficit by increasing NOS activity, in conditions of reduced oxygen availability, i.e. in conditions of hypoxia, characteristic for sports swimming (Lundberg, Carlström, Larsen, Weitzberg, 2011). Consequently, the mentioned pathway can be seen as a potential ergogenic aid during training at high altitude. In addition, it can also be used therapeutically, in conditions where the flow of oxygen to individual cells is acutely or chronically reduced, as is the case with lung and cardiovascular system disorders, but also with sleep disorders, and even as a consequence of aging (Jones et al, 2018). Exercise in hypoxia is associated with reduced muscle oxidative function and decreased exercise tolerance. Dietary nitrates have the potential to ameliorate these effects to some extent; studies suggest that the exercise capacity of physically active individuals in hypoxia is improved when nitrate supplementation is administered for six days, over 24 hours (Horiuchi, Endo, Dobashi, 2017, Kelly, Vanhatalo, Bailey, 2014, Masschelein, Van Thienen, Wang, 2012 ), which is not the case even after acute consumption (Gassier, Reinhold, Loiselle, Soutiere, Fothergill, 2017).

An important entity that represents one of the key determinants of an athlete's success is their cognitive efficiency (McMorris, Graydon, 1996), whether they are athletes who compete in individual sports or those who compete in collective sports, who must bring important decisions quickly, while simultaneously performing motor tasks of varying degrees of complexity. Given this, there is great interest in procedures that could potentially improve decision-making accuracy and/or reaction time in a competitive environment. Some studies have shown that NO and nitrate supplementation can improve cerebral perfusion (Wightman, Haskell, Thompson, 2015, Presley, Morgan, Bechtold, 2011), especially in regions responsible for executive functions (Presley et al, 2011), which is closely related to the mentioned problem. However, studies that, at least up to this point, have investigated the impact of nitrate supplementation on the cognitive performance of swimmers during swimming have not been conducted so far. From all of the above, it can be concluded that the observation of NO3 through the prism of a dietary supplement represents one of the significant innovations in sports nutrition during the last three decades.

**Nitrogen - monoxide in the process of adaptation of the swimmer's organism to the demands of training and competition**

The human organism is constantly forced to make numerous adaptations due to the continuous action of various stressogenic factors. One of the biggest is certainly training, that is, physical activity, especially one that involves many different muscles or large muscle groups, which is performed at a moderate intensity for an extended period of time. To a large extent, sports swimming, that is, exercising in water, corresponds to the mentioned description. In this regard, adaptations of the swimmer's organism, resulting from the application of continuous training, have been the subject of study for quite a long time. On the other hand, the idea that NO also plays a part in a large part of the studied adaptation mechanisms is relatively new. Some of the latest studies related to determining the connection between NO and physical exercise-swimming, often emphasize the importance of NO in the framework of cardiorespiratory fitness (CRF), which represents one of the total five components of physical fitness (related to health - health related) and is considered "general by the measure of human health". It has a crucial role in instructing the cardiovascular and respiratory systems to supply oxygen and energy to working muscles, which, especially during exercise in water, desperately need it (Song et al, 2022, Wu, 2022). A 2022 study that looked specifically at CRF was one of the first to show that swimming training can cause its overall improvement, thanks to functional adaptations of NO in the oxygen transport system (Wu, 2022). NO plays a significant role in the adaptation of the organism to training under hypoxia conditions, while hypoxia, on the other hand, modulates NOS activity, affects the availability of NO in tissues, the expression of genes that affect NOS synthesis, etc. (Manukhina, Downey, Mallet, 2006).

Looking at vascular structures, animal studies have shown that short-term exercise, lasting two to four weeks, increases endothelial NO synthesis in skeletal muscle arterioles (Sun, Huang, Koller, Kaley, 1994). On the other hand, after extensive training, at least in the peripheral circulation, an increased production of NO and other mediators that potentially cause structural changes in blood vessels was observed (Prior, Lloyd, Yang, Terjung, 2003). Recently, the number of studies dealing with finding the optimal modality and intensity of exercise for the sake of improving the structure and function of the vascular system of athletes, but also the relationship between these factors, and improving the function of the endothelium and the system of antioxidant protection in the body of swimmers, is increasingly evident.

## CONCLUSION

Parallel to the period of the emergence of the first civilizations, the opinion that water, and later swimming, possessed certain healing properties also developed. Through centuries of observation, trial and error, the mentioned idea, and the very technique of treatment using the properties of water based on tradition, has noticeably advanced. Water is, therefore, a medium in which therapeutic as well as recreational exercise takes place, in which people of all ages participate. Swimming itself, as a striking example of an exercise activity in the water environment, is a favorite activity of a large number of exercisers, which encourages both his recovery and the development of various personality traits. As it was established a long time ago, it brings a bunch of benefits to people with different types of diseases, while also having a positive effect on associated conditions and comorbidities.

A precise theoretical analysis and assessment of the influence of as many different factors as possible on the system of training and competition of swimmers is an extremely important component of the work, both for researchers dealing with sports sciences, as well as for coaches and athletes themselves. This approach allows sports experts to notice new potential variables, on the basis of which correction and improvement of the training process can be carried out, and therefore a step forward in terms of results and overall progress of swimmers. This cognitive path leads to the development of the theory of this sports branch, that is, to the spread of the training-competition doctrine. In this regard, the purpose of this work is to synthesize a number of scientific contributions, derived from different scientific disciplines, into a coherent body of knowledge about the biochemistry of swimming, i.e. to acquire available data and analyze with reference to the availability and utilization of NO in the system of sports swimming (but also water exercise in the broadest sense) determines the degree of connection between the mentioned entities.

Accordingly, it is important to conclude that NO in the system of sports swimming in a broader sense could have significant and numerous roles, as is the case with the organism of the swimmer himself, in a narrower context. During the swimming and water safety training phase, but also in later phases within the system, which involve constant work on swimming technique, NO could play a significant role, since it exerts a certain influence on the cortical structures responsible for spatial learning, which was confirmed in numerous animal studies, but also studies that were done on samples that participated in other sports.

In the area of recovery of swimmers after training and competition, but also in the field of rehabilitation after sports injuries, a potential place of NO is also looming. First of all, thanks to the fact that almost all isoforms of NOS are synthesized in human muscles, which affects the activation of myosatellite cells, which play a role in regulating the recovery of damaged muscle tissue. Furthermore, the exogenous application of NO in the rehabilitation of swimmers has a positive effect on microvasculature disorders, accelerates the transition from the inflammatory to the proliferative phase, enhances angiogenesis, the proliferation of fibroblasts, as well as the fibrogenesis of collagen, and therefore earlier decreases the feeling of pain, edema and hematoma, as well as their complete absence, but also a shortening of the total duration of the rehabilitation process.

One of the most promising fields suitable for research is certainly the nutrition and supplementation of swimmers with NO, i.e. with nitrites and nitrates, but also with certain precursors of NO. Supplementation with the mentioned compounds does not per se cause a better swimmer's efficiency, but contributes to its maintenance, and it is important to indicate once again that the effects of supplementation depend to a certain extent on the procedure of the supplementation process itself, the dose (quantity) of $NO3^-$ and the duration of the mentioned process, but also on the degree training of swimmers.

Recently, the connection between NO and cardiorespiratory fitness has been emphasized more and more often, i.e. the fact that swimming training can cause its overall improvement, primarily thanks to the functional adaptations of NO achieved in the oxygen transport system. Nevertheless, it is certain that most of the research processed for the purposes of writing this paper would probably not exist at this moment, if the discovery of the general roles of NO in the mammalian organism had not been awarded the Nobel Prize at the end of 1998, due to which prestige and reputation this molecule received an extremely large publicity. Accordingly, it is clear that this is a topic of exceptional importance for understanding the functioning of the human organism, as well as human physical activity.

In the end, it is important to point out that the aforementioned Nobel Prize greatly helped the long process of transformation of humanity, in addition to the fact that it influenced the generation of a whole series of new, more sophisticated and specific questions, it encouraged general progress and allowed man to develop in many different directions. Most importantly, to an extremely large extent, it helped man to penetrate to the essence of the various processes that surround him, build him up, as well as those in which he voluntarily participates. In this way, for the umpteenth time, man managed to get to know himself better, but also to become aware of his environment, as well as the place and role he occupies in the Universe.

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