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PROFILE OF NITRIC OXIDE METABOLISM INDICATORS IN PRETERM INFANTS WITH PERINATAL CENTRAL NERVOUS SYSTEM INJURIES
Poltava State Medical University

Introduction. Premature infants often experience a heightened risk of brain damage, potentially leading to various disorders affecting motor, cognitive, behavioral, social, and sensory functions. The underlying pathological processes of hypoxic-ischemic central nervous system (CNS) injury predominantly stem from compromised cerebral blood flow and oxygen transport. Timely diagnosis and treatment options for prematurely born children with perinatal CNS damage remain limited. Nitric oxide, a universal regulator of physiological functions, plays a crucial role. Endothelial dysfunction, marked by the loss of the neurovascular protective functions of nitric oxide, could significantly contribute to the development of cognitive impairment in hypoxic-ischemic CNS damage. Objectives. The study aims to evaluate the specificities of nitrate metabolism indicators in premature infants with hypoxic-ischemic CNS lesions in the early neonatal period. This involves examining and comparing clinical indicators characterizing hemodynamics, as well as the levels of nitrates, nitrites, and nitrosothiols in urine among patients in the studied groups. Subjects and Methods. The study comprised 14 premature infants with hypoxic-ischemic CNS injury (main group), with a separate selection of 4 infants who did not survive during the neonatal period. The comparison group included 20 relatively healthy prematurely born children. Stratification was based on the results of a genetic study, specifically the determination of the rs61722009 polymorphism of the eNOS gene. The patients underwent routine clinical examinations, including blood pressure measurements, and assessments of nitrates, nitrites, and nitrosothiols in urine. Subgroups were identified as follows: 1st subgroup - 4bb (n=10), and 2nd subgroup - 4aa/4ab (n=10). Results. It was observed that newborns who did not survive had significantly lower systolic and diastolic blood pressure readings on the first day of life, in comparison to relatively healthy children in the two control subgroups (day 1 - p=0.018; p=0.027; p=0.036; p=0.053). Additionally, they exhibited lower heart rate indicators on the first day (p=0.001; p=0.002). However, overall, hemodynamic indicators in newborns with hypoxic-ischemic central nervous system damage did not show statistically significant differences from the corresponding indicators in relatively healthy children. The results indicate a significantly lower level of diuresis in children who died as a result of severe with hypoxic-ischemic central nervous system damage, probably due to the development of multiple organ failure immediately after birth. As a result, it was found that the levels of nitrates (p<0.001; p=0.0001) and nitrates (p<0.01; p<0.0001) were reduced in children with with hypoxic-ischemic central nervous system damage, compared to children in the control groups, regardless of genotype variant. While the level of nitrosothiols did not differ significantly, it was even much higher in children who did not survive, 3.55±0.39 vs 2.23±0.22; p=0.008. The differences found may indicate a disruption of the regulatory effect of nitric oxide on vascular tone and the condition of neuroglia, particularly in children with hypoxic-ischemic central nervous system damage, as a result of its insufficient production, as well as insufficient mobilization from the depot due to nitrite and nitrate reductases. Conclusions. Hemodynamic patterns in children from the examined groups, except for those who did not survive, did not exhibit significant differences. The notably lower urine output in deceased children indicates the development of multiple organ failure due to severe hypoxia. In children with hypoxic-ischemic central nervous system damage, there is a reduction in the levels of nitrates and nitrites in urine compared to relatively healthy premature infants, while the level of nitrosothiols did not show significant differences and was even notably higher in children who did not survive. The outcome of studying the levels of nitrates, nitrites, and nitrosothiols in urine in a larger patient sample may lead to the development of an algorithm for early diagnosis and management, contingent on the severity of metabolic disorders resulting from hypoxia, considering the potential influence of nitric oxide on energy deficit and mitochondrial dysfunction.

Key words: premature children, hypoxic-ischemic CNS damage, nitric oxide, nitrates, nitrites, nitrosothiols of urine.

The present study is a contribution to the research project conducted by the Department of Pediatrics No. 1 with Neonatology, Poltava State Medical University «Elaboration of clinical and laboratory criteria and methods for prediction and prevention of metabolic disorders in young children». State registration number: № 0120U102856
abnormalities [3]. The majority of pathological phenomena associated with hypoxic-ischemic damage to the central nervous system (CNS) stem from compromised cerebral blood flow and impaired oxygen transport to the brain. The pathophysiological effects of hypoxic-ischemic "stroke" (as commonly termed in foreign sources) are intricate, unfolding gradually over a specific period, posing challenges for medical professionals in determining timely and appropriate treatment options [4]. Recent publications increasingly discuss energy deficits at the neuronal level in infants with asphyxia and hypoxic-ischemic encephalopathy [5]. Currently, options for the timely diagnosis and treatment of prematurely born children with perinatal CNS damage are limited. Numerous studies point to mitochondrial dysfunction and the activation of autophagy [6].

When searching for methods of early diagnosis of hypoxic-ischemic CNS injury in prematurity born children, we paid attention to indicators of nitrate metabolism. Nitric oxide is one of the universal regulators of physiological functions of the body with a wide range of action. The vasodilating effect of nitric oxide (NO), attributed to the impact of cyclic guanosine monophosphate (cGMP) in reducing the cytosolic Ca\(^{2+}\) concentration in muscle cells while increasing Na\(^{+}\), has been extensively studied. Additionally, NO influences the calcium transport systems of mitochondria, and an imbalance in this regulation quickly leads to energy deficits and activates free radical oxidation processes. Conversely, an excess of NO, potentially produced by inducible nitric oxide synthase (iNOS), plays a pivotal role in neuronal damage by impairing mitochondrial function and contributing to the accumulation of mitochondrial substrates [7].

NO is the final product of l-arginine conversion by both NOS constitutive and non-constitutive isoforms. To date, three NOS isoforms are known: neuronal or neural (nNOS), endothelial (eNOS), and inducible (iNOS). The nNOS and eNOS are constitutional types of enzyme and ensure the synthesis of nitric oxide under normal conditions; iNOS is activated in response to pathogenic stimuli and produces significantly higher NO levels, playing an important role in tissue inflammation and body defense [8]. Changes in the expression of different NOS isoforms, lack or hyperproduction of NO lead to an imbalance of active forms of nitrogen and oxygen. The main links of NO conversion are nitrosylation of proteins with the formation of S-nitrosothiols, oxidation of NO to NO\(_2^{}\) and NO\(_3^{}\). Nitrosothiols are one of the forms of NO deposition and an important source of it under physiological conditions. Therefore, the cellular NO content depends on the activity of NO synthases, the activity of nitrite and nitrate reductases, and the presence of a sufficient pool of deposited NO. There are studies that indicate that nitric oxide is produced in larger intravascular amounts in newborns than in adults [9]. A decrease in the level of nitrates and nitrites due to NO deficiency potentially indicates vascular ischemia and vasospasm and the severity of oxidative stress [10]. Endothelial dysfunction, manifested by the loss of neurovascular protective functions of NO, can significantly contribute to the development of cognitive disorders [11].

The purpose of the study is to evaluate the peculiarities of nitrate metabolism indicators in premature children with hypoxic-ischemic CNS injuries in the early neonatal period, by studying and comparing clinical indicators that characterize hemodynamics, as well as the levels of nitrates, nitrites and nitrosothiols in urine in patients of the studied groups.

**Subjects and methods**

A study was undertaken involving 14 premature infants with hypoxic-ischemic lesions of the central nervous system (the main group), and a separate selection was made for 4 infants who died during the neonatal period. The comparison group comprised 20 relatively healthy prematurely born children. Exclusion criteria encompassed the presence of congenital malformations, genetic pathology, and parental refusal to participate in the study.

Subsequently, relatively healthy children were stratified according to the results of a genetic study based on determining the rs61722009 polymorphism of the eNOS gene in order to take into account possible physiological variations in the NO concentration when compared with the indicators of sick children. eNOS is the constitutive form of the enzyme and is the main NO producer under physiological conditions, while iNOS is activated under pathological conditions. Two alleles have been identified in the 27 bp repeat of intron 4 of the eNOS gene, the larger of which, eNOS-4b, has 5 of 27 bp tandem repeats (GAAGTCTAGACCTGCTG(A/C)GGGTTGAG), and the smaller one, eNOS-4a, has four repeats. 27 bp-VNTR reduces the concentration of nitric oxide in plasma [12]. The study involved the division into two subgroups: control subgroup 1 with the 4bb genotype variant (n=10) and control subgroup 2 with the 4aa/4ab genotype variant (n=10). Peripheral blood from newborns served as the material for this study, collected in a volume of 0.25 ml. The samples were stored at a temperature of -20°C until the study was conducted. The isolation of DNA samples from the collected material was performed using a commercial kit of reagents, specifically the "Quick-DNA Universal Kit."

Subsequently, molecular genetic research was carried out using the polymerase chain reaction (PCR).

Urine was the object of biochemical research. Determination of the concentration of low molecular weight nitrosothiols was carried out by calculating...
the difference in the concentration of nitrites (NO$_2^-$) before and after the oxidation of nitrosothiol complexes (S-NO) to nitrites with a solution of mercuric chloride (HgCl$_2$). An aliquot of urine with a volume of 0.2 ml was taken for the study [13]. The concentration of nitrites was determined by determining the content of diazo compounds formed in the reaction with sulfanilic acid, and then the reaction was carried out with α-naphthylamine (Griss-Ilosvay Reagent), resulting in the formation of red derivatives (azo dyes) [14]. The concentration of nitrates is determined by the increase in the concentration of nitrites after the reduction of nitrates to nitrites with sulfuric hydrazine. Aliquots of 0.2 ml of urine were used to determine the concentration of nitrates and nitrites.

By decision of the Bioethics Commission No. 217 dated 12.06.2023, the materials of the scientific work comply with the Rules of Humane Treatment of Patients in accordance with the requirements of the Tokyo Declaration of the World Medical Association, the International Recommendations of the Helsinki Declaration on Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, the Laws of Ukraine, the orders of the Ministry of Health of Ukraine and the requirements of the Code of Doctor’s Ethics in Ukraine.

Statistical analysis was performed using Microsoft Excel Pro Plus 2016 and SPSS v.27 software packages. When analyzing the basic clinical characteristics, the mean value ± standard deviation was calculated. Spearman’s correlation analysis was conducted between the studied indicators. The studied indicators were checked for normality of distribution using the Kolmogorov-Smirnov test. In the case of a normal distribution, the probability of differences in quantitative results was determined using the Student’s t-test, in the case of a distribution that differed from the normal, the Mann-Whitney U-test was used. Differences were considered probable for all types of analysis at a significance level (p) of less than 0.05.

**Results and discussion**

Considering that one of the important functions of nitric oxide is its regulatory impact on vascular tone, the initial stage of the study involved assessing clinical indicators of hemodynamics in the prematurely born children of the studied groups (see Table 1).

**Table 1**

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Control subgroup 1, n=10</th>
<th>Control subgroup 2, n=10</th>
<th>Patients with CNS damage, n=14</th>
<th>Died patients, n =4</th>
<th>P$_{1-3}$</th>
<th>P$_{1-4}$</th>
<th>P$_{2-3}$</th>
<th>P$_{2-4}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats per min)</td>
<td>154,3±2,32</td>
<td>152,7±1,55</td>
<td>154,8±2,97</td>
<td>142,25±16,21</td>
<td>0,569</td>
<td>0,368</td>
<td>0,001</td>
<td>0,002</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>54,8±1,34</td>
<td>53,8±1,03</td>
<td>55,3±2,87</td>
<td>49,5±4,04</td>
<td>0,557</td>
<td>0,674</td>
<td>0,018</td>
<td>0,027</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>27,1±1,11</td>
<td>26,0±0,89</td>
<td>25,8±2,07</td>
<td>22,0±8,6</td>
<td>0,434</td>
<td>0,562</td>
<td>0,036</td>
<td>0,053</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>33,7±1,21</td>
<td>32,5±0,82</td>
<td>32,8±1,85</td>
<td>29,25±4,57</td>
<td>0,412</td>
<td>0,867</td>
<td>0,078</td>
<td>0,069</td>
</tr>
<tr>
<td>3rd day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats per min)</td>
<td>155,0±1,69</td>
<td>152,0±2,01</td>
<td>153,3±2,15</td>
<td>154,6±1,43</td>
<td>0,712</td>
<td>0,814</td>
<td>0,453</td>
<td>0,518</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>54,7±0,86</td>
<td>56,4±0,97</td>
<td>63,2±0,77</td>
<td>61,1±0,87</td>
<td>0,067</td>
<td>0,057</td>
<td>0,154</td>
<td>0,209</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>26,4±0,77</td>
<td>29,6±0,96</td>
<td>33,1±0,98</td>
<td>30,8±0,80</td>
<td>0,066</td>
<td>0,133</td>
<td>0,059</td>
<td>0,272</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>33,7±0,70</td>
<td>35,8±0,95</td>
<td>39,3±0,93</td>
<td>37,3±0,75</td>
<td>0,088</td>
<td>0,015</td>
<td>0,067</td>
<td>0,104</td>
</tr>
</tbody>
</table>
The study revealed that newborns who did not survive had notably lower systolic and diastolic pressure readings on the first day of life compared to relatively healthy children in the two control subgroups (day 1 – p=0.018; p=0.027; p=0.036; p=0.053). Additionally, they exhibited lower heart rate (HR) indicators on the first day (p=0.001; p=0.002). However, overall, hemodynamic indicators in newborns with hypoxic-ischemic central nervous system (CNS) damage did not show statistically significant differences from the corresponding indicators in relatively healthy children.

Disruptions in hemodynamics with internal organ hypoperfusion can swiftly lead to acute kidney damage and, consequently, a reduction in urine output [15]. Therefore, we assessed the hourly urine output in children from the studied groups on the 1st to 3rd day of life (see Table 2).

<table>
<thead>
<tr>
<th>Day after birth</th>
<th>Control subgroup 1, n=10</th>
<th>Control subgroup 2, n=10</th>
<th>Patients with CNS damage, n=14</th>
<th>Died patients, n=4</th>
<th>p1-3</th>
<th>p2-3</th>
<th>p1-4</th>
<th>p2-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>2.00±0.15</td>
<td>2.30±0.20</td>
<td>3.00±0.16</td>
<td>0.50±0.16</td>
<td>0.078</td>
<td>0.064</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2nd</td>
<td>3.20±0.19</td>
<td>3.30±0.18</td>
<td>3.10±0.19</td>
<td>1.10±0.17</td>
<td>0.781</td>
<td>0.654</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3rd</td>
<td>3.50±0.20</td>
<td>3.80±0.17</td>
<td>3.40±0.20</td>
<td>1.40±0.20</td>
<td>0.572</td>
<td>0.345</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 3: Indicators of nitrate metabolism in prematurely born children

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Control subgroup 1, n=10</th>
<th>Control subgroup 2, n=10</th>
<th>Patients with CNS damage, n=14</th>
<th>Died patients, n=4</th>
<th>p1-3</th>
<th>p2-3</th>
<th>p1-4</th>
<th>p2-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>The level of nitrites in urine, nmol/l</td>
<td>3.13±0.28</td>
<td>3.40±0.17</td>
<td>1.82±0.17</td>
<td>1.44±0.14</td>
<td>&lt;0.001</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Level of nitrates in urine, nmol/l</td>
<td>6.84±0.59</td>
<td>7.44±0.37</td>
<td>4.56±0.39</td>
<td>3.87±0.36</td>
<td>&lt;0.01</td>
<td>&lt;0.0001</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Level of nitrosothiols in urine, μmol/l</td>
<td>2.23±0.22</td>
<td>3.52±0.35</td>
<td>2.59±0.34</td>
<td>3.55±0.39</td>
<td>0.3931</td>
<td>0.0524</td>
<td>0.0080</td>
<td>0.3736</td>
</tr>
</tbody>
</table>

The results indicate a significantly lower level of urine output in children, who died, as a result of severe CNS injury, probably due to the development of multiple organ failure immediately after birth.

We extended our investigation to explore a potential link with the disruption of the regulatory influence of nitric oxide, both at the level of vascular tone and the cellular (mitochondrial) level. This could potentially serve as a risk factor for the development of hypoxic encephalopathy in premature infants. The measurement of nitrites and nitrates in urine reflects the intravascular concentration of nitric oxide during the day preceding sampling, whereas the concentration of S-nitrosothiols is associated with the storage of nitric oxide in the body and the potential for its release under physiological conditions (see Table 3).

It was found that the levels of nitrites (p<0.001; p<0.0001) and nitrates (p<0.01; p<0.0001) were reduced in children with CNS injury, compared to children in the control groups, regardless of genotype variant. While the level of nitrosothiols did not differ significantly, it was even significantly higher in children who died – 3.55±0.39 vs 2.23±0.22; p=0.008. The differences found may indicate a disruption of the regulatory effect of NO on vascular tone and the condition of neuroglia, particularly in children with hypoxic-ischemic CNS injury, as a result of its insufficient production, as well as insufficient mobilization from the depot due to nitrite and nitrate reductases. The substrate for NOS activity and NO generation is L-arginine, and therefore NOS function is reciprocally regulated by arginase through depletion of the substrate...
(arginine) [8,16]. Another reason for low concentrations of nitrates and nitrates in the urine can be arginine deficiency. Critical determinants of neuronal survival after hypoxia are the degree of vascular dysfunction, inflammation and oxidative stress and the possibility of reparative processes. It is known that after the initial period of hypoxic damage, when resuscitation measures are carried out, there is a delayed, long-term decrease in cerebral perfusion associated with inhibition of metabolism, followed by hyperperfusion and an increase in cerebral oxygenation, associated with a violation of neurovascular communication and a disruption of cerebral autoregulation [17]. There are conflicting reports on the effect of NO on neuronal activity after prolonged hypoxia. Some studies indicate a protective effect, while others indicate a toxic effect [18]. A more detailed study of the pathophysiological processes in the immature brain is necessary for effective diagnosis and treatment of prematurely born children with hypoxic-ischemic CNS injury.

**Conclusion**

Hemodynamic patterns in children from the examined groups, excluding those who did not survive, showed no significant differences. The notably lower diuresis in deceased children suggests the development of multiple organ failure due to severe hypoxia.

In children with hypoxic-ischemic central nervous system (CNS) injury, there is a reduction in the levels of nitrates and nitrites in urine compared to relatively healthy premature infants. However, the level of nitrosothiols did not differ significantly and was even notably higher in children who did not survive. This may indicate a disturbance in the regulatory influence of nitric oxide on the condition of vessels and parenchyma in the immature brain.

The exploration of nitrates, nitrites, and nitrosothiol levels in urine on a broader patient sample can contribute to the development of an algorithm for early diagnosis and management, tailored to the severity of metabolic disorders resulting from hypoxia. This takes into account the potential impact of nitric oxide on energy deficit and mitochondrial dysfunction.

**Prospects for Further Research**

To ensure reliable outcomes, further studies with an expanded spectrum of genetic investigations and consideration of potential iatrogenic influences are essential on a larger patient sample.

**Особистий внесок авторів:**

Чернявська Ю.І.: а) концепція та дизайн; г) збір та узагальнення даних; д) аналіз та інтерпретація результатів; е) написання рукопису; Похилько В.І.: б) адміністративна підтримка; д) аналіз та інтерпретація результатів; ж) редагування рукопису; з) остаточне затвердження рукопису.

**Конфлікт інтересів**

**Відсутній.**

**References**

ОСОБЛИВОСТІ ПОКАЗНИКІВ ОБМІNU ОКSIDУ АЗОТУ У ПЕРЕДЧАСНО НАРОДЖЕНИХ ДІТЕЙ З ПЕРИНАТАЛЬНИМИ УРАЖЕННЯМИ ЦНС

Чернявська Ю.І., Похилько В.І., Акімов О.Є., Цвіренко С.М., Яковенко О.В.

Ключові слова: недоношені діти, гіпоксично-ішемічне ураження ЦНС, оксид азоту, нітрати, нітрозотіоли сечі.

Вступ. Передчасно народженні діти мають високу частоту ушкоджень мозку, що може призвести до моторних, когнітивних, поведінкових, соціальних, сенсорних розладів. Більшість патологічних явищ, що лежать в основі гіпоксично-ішемічного ураження центральної нервової системи, є наслідком порушення мозкового кровотоку та транспорту кисню до мозку. Можливості своєчасної діагностики та лікування передчасно народжених дітей з перинатальним ураженням центральної нервової системи обмежені. Оксид азоту є одним з універсальних регуляторів фізіологічних функцій організму широкого спектру дії. Ендотеліальна дисфункція, що проявляється втратою нервово-судинних протективних функцій оксиду азоту, може істотно сприяти розвитку когнітивних порушень при гіпоксично-ішемічному ураженні центральної нервової системи.

Мета і завдання дослідження. Мета дослідження – оцінити особливості показників нітратного обміну у недоношених дітей з гіпоксично-ішемічним ураженням центральної нервової системи в ранньому неонатальному періоді шляхом вивчення та порівняння клінічних показників, що характеризують гемодинаміку, а також рівні нітратів, нітрозотіолів у сечі у пацієнтів досліджуваних груп.

Матеріалі та методи. Проведено дослідження, до якого увійшло 14 недоношених дітей з гіпоксично-ішемічним ураженням центральної нервової системи (основна група), окремо виділено 4 новонароджених, які померли в неонатальному періоді. Групу порівняння склали 20 передчасно народжених дітей, які були відносно здоровими. Їх стратифікували за результатами генетичного дослідження – визначення поліморфізму rs61722009 гену eNOS (1 підгрупа – 4bb (n=10), 2 підгрупа 4aa/4ab (n=10). Пацієнти проходили планове клінічне обстеження з вимірювання артеріального тиску та нітратів, нітратів і нітрозотіолів у сечі.

Результати. У результаті встановлено, що у новонароджених, які померли, очікувано у першу добу життя були нижчі показники систолічного та діастолічного тиску, порівняно з умовно здоровими дітьми 2-х контрольних підгруп (1 доба – p=0,018; p=0,027; p=0,036). ; p=0,053), зниження показників частоти серцевих скорочень у першу добу (p=0,001; p=0,002). Тоді як в цілому гемодинамічні показники у новонароджених з гіпоксично-ішемічним ураженням центральної нервової системи статистично не відрізнялися від відповідних показників у відносно здорових дітей. Результати свідчать про достовірно нижчий рівень діурезу у дітей, які померли внаслідок тяжкого з гіпоксично-ішемічним ураженням центральної нервової системи, внаслідок його недостатньої продукції, а також недостатньої мобілізації з боку депо нітратів, нітрозотіолів сечі.

Висновки. Показники гемодинаміки дітей досліджуваних груп, за винятком померлих, достовірних відмінностей не мали. Значно менший рівень діурезу у померлих дітей свідчить про розвиток поліорганної недостатності відразу після народження. У результаті встановлено, що у дітей з гіпоксично-ішемічним ураженням центральної нервової системи рівні нітратів (p<0,001; p<0,0001) та нітрозотіолів знижено порівняно з дітьми контрольних груп незалежно від варіантів генотипу. Хоча рівень нітрозотіолів достовірно не відрізнявся у померлих дітей від здорових, вони були значно вищими – 3,55±0,39 проти 2,23±0,22; р=0,008. Виявлені відмінності можуть свідчити про порушення регуляторної дії оксиду азоту на енергетичний дефіцит і мітохондріальну дисфункцію.