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ENDOTHELIAL DYSFUNCTION DUE TO SODIUM NITRITE

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Abstract

In the report of the World Health Organization from 1990 to 2016 to this day, Ukraine continues to occupy first place in the European region in morbidity and mortality from diseases of the cardiovascular system. One of the predictors and key links in the development of CVD is endothelial dysfunction. In this work, it was shown that chronic loading with sodium nitrite provokes the development of oxidative stress (an increase in 2,3-bisphosphoglyceric acid), inflammation (an increase in the level of interleukin-1-beta, which, in turn, causes a sharp increase in iNOS activity), the development of endothelial dysfunction (increase in von Willebrand factor). L-arginine alone, and in conjunction with the drug “Vin-Vita” cause a decrease in the negative effect of sodium nitrite.

Key words: endothelial dysfunction; sodium nitrite; Vin-vit; bioflavonoids; L-arginine

РОЗВИТОК ЕНДОТЕЛІАЛЬНОЇ ДИСФУНКЦІЇ ПІД ВПЛИВОМ РОЗЧИНУ НІТРИТУ НАТРІЮ

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Резюме

У звіті Всесвітньої організації охорони здоров'я з 1990 по 2016 рік і донині Україна продовжує посідати перше місце в європейському регіоні за захворюваності і смертності від хвороб серцево-судинної системи. Одним із предикторів та провідною ланкою у розвитку патології серцево-судинної системи є ендотеліальна дисфункція. У даній роботі показано, що хронічне навантаження нітритом натрію провокує розвиток окисного стресу (збільшення 2,3-бісфосфогліцерінової кислоти), запалення (підвищення рівня інтерлейкіну-1-бета, яке, в свою чергу, викликає різке збільшення активності iNOS), розвиток ендотеліальної дисфункції (збільшення фактора Віллебранда). L-аргінін окремо, і в сукупності з препаратом "Він-Віта" обумовлюють зниження негативного ефекту нітриту натрію.

Ключові слова: ендотеліальна дисфункція; нітрит натрію; Він-Віта; біофлавоноїди; L-аргінін

РАЗВИТИЕ ЭНДОТЕЛИАЛЬНОЙ ДИСФУНКЦИИ ПОД ВОЗДЕЙСТВИЕМ РАСТВОРА НИТРИТА НАТРИЯ

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Резюме

В отчете Всемирной организации здравоохранения с 1990 по 2016 год и по сей день Украина продолжает занимать первое место в европейском регионе по заболеваемости и смертности от болезней сердечно-сосудистой системы. Одним из предикторов и ключевых звеньев в развитии патологии ССС является эндотелиальная дисфункция. В данной работе показано, что хроническая нагрузка нитритом натрия провоцирует развитие окислительного стресса (увеличение 2,3-бисфосфоглицериновой кислоты), воспаление (повышение уровня интерлейкина-1-бета, которое, в свою очередь, вызывает резкое увеличение активности iNOS), развитие эндотелиальной дисфункции (увеличение фактора Виллебранда). L-аргинин отдельно, и в совокупности с препаратом “Вин-вита” обуславливают снижение негативного эффекта нитрита натрия.

Ключевые слова: эндотелиальная дисфункция; нитрит натрия; Вин-вита; биофлавоноиды; L-аргинин

Relevance

In the report of the World Health Organization from 1990 to 2016 and to this day, Ukraine continues to occupy first place in the European region in morbidity and mortality from diseases of the cardiovascular system. These disappointing statistics dictate to us the need for a thorough study of the factors affecting CVS. [1].

Including the vascular endothelium. Endothelial cells are a highly selective barrier and metabolic organ, and play an important role in the regulation of local homeostasis, immune function, maintaining a delicate balance between vasoconstrictor and vasodilator function. Chronic exposure to risk factors for cardiovascular disease and oxidative stress suppresses the protective mechanisms of vascular endothelium, followed by endothelial dysfunction.

According to many authors, endothelial dysfunction is one of the main pathogenetic links in the development of vascular disorders in the process of chronic diseases. Currently, the role of endothelial dysfunction in the development of diseases such as diabetes mellitus, chronic obstructive pulmonary disease, chronic kidney disease, inflammatory bowel disease, etc. has been proven. In addition, ED is observed at an early stage of most cardiovascular diseases such as atherosclerosis, arterial hypertension, chronic heart failure. Therefore, early clinical detection of ED can be a critical point in the prevention of cardiovascular disease, because early detection of ED can be the initial reversible step in the development of these diseases. [2]

Therefore, it is so necessary to study risk factors for the development of endothelial dysfunction and methods for their correction.

The aim of the work was to study the development of endothelial dysfunction under the influence of sodium nitrite solution, as well as correction methods using l-arginine and antioxidant terrapia.

Materials and methods

In our researches we used 40 auto breeding periadolescent Wistar male rats, body weight approximately 120 -150 grams , of which were formed four groups (ten heads each) by principle of analogy:

- The first group - intact - on standard vivarium food and drink.
- The second group received a 6,28 mg/kg (1/50 lethal dose) 0.2-1% solution of sodium nitrite intragastric.
- The third group receiving the above nitrite loading on the background of L-arginine (200 mg/kg), to study the effect of its compensatory properties in these conditions.
- The fourth group receiving complex sodium nitrite, L-AR and Vin-Vitus (it contains bioflavonoids that will show us the effectiveness of antioxidant therapy).

The duration of the diet is 1 month.

At the beginning of the experiment, as well as at the end of the second and fourth weeks, the weight of laboratory rats was measured to determine the effect of sodium nitrite and the nitric oxide cycle on the development of the body weight of rats in puberty.

All data obtained were processed by conventional biomedical research methods using statistical analysis by standard software packages. Mathematical processing included

calculations of arithmetic mean values (M), their errors ($\pm m$). The establishment of the probability of intergroup differences in the values of the change during the experiment was performed using the Student's parametric t-test. Differences were considered statistically significant at $p \leq 0.05$.

Measurements blood changes

Von Willebrand factor

The von Willebrand factor is synthesized and secreted by the vascular endothelium to become part of the perivascular matrix. vWf promotes platelet adhesion in hemostasis by binding to a receptor on the platelet surface membrane (glycoprotein Ib / IX), thereby attaching platelets to the vessel wall. vWf is also required to maintain normal levels of plasma factor VIII. vWf levels can temporarily increase with stress, exercise, pregnancy, inflammation, or infections. [3]

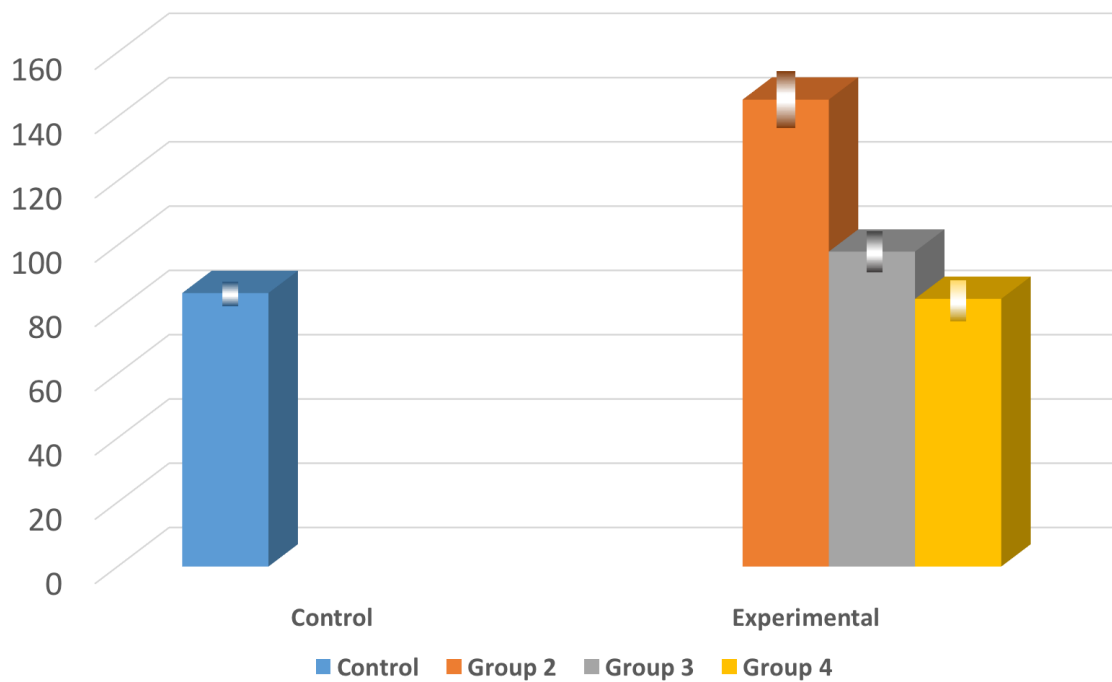
As we can see in *annex 1*, in the **second group**, which received a load of sodium nitrite solution, was a sharp increase in the relative concentration of sodium nitrite, above the permissible values. ($p < 0.001$).

This indicates a violation of the local regulation of hemostasis, and about damage to the endothelium and the active development of the inflammatory reaction in the vessel wall.

In **third** the group, indicators are within the normal range, however, there is a statistically significant difference with the control group ($p < 0.05$). That shows the compensatory properties of l-arginine on a chronic load of sodium nitrite.

In the **fourth** group using the Vin-Vita, the indicators did not make a statistically significant difference with the control group, and amounted to 89.3% ($\pm 10.2\%$). Rats intake of l-arginine with antioxidant therapy reduces the negative effects of sodium nitrite.

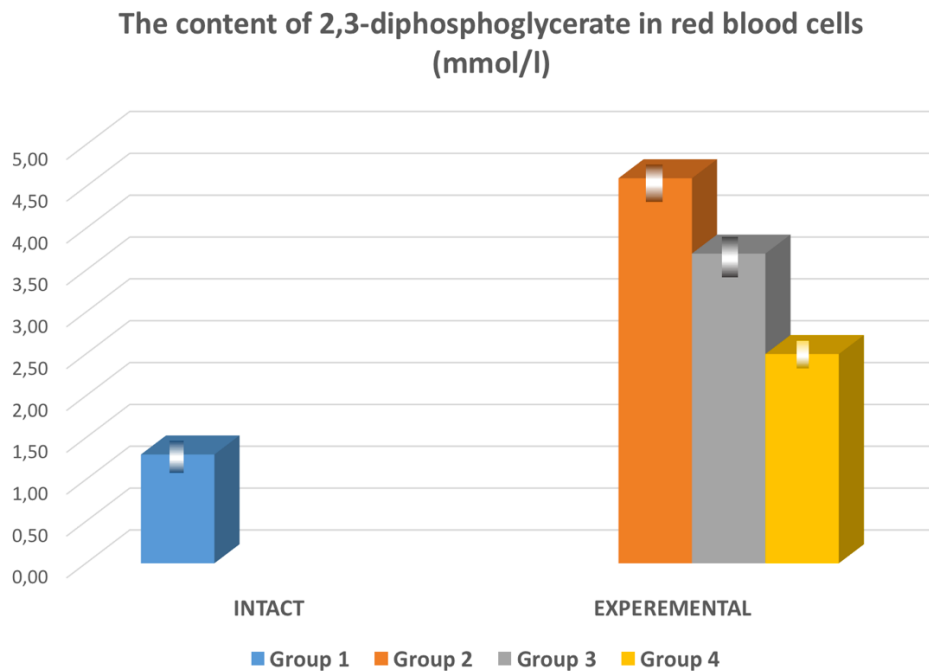
The content of von Willebrand factor in rat's blood (%)



2,3-Bisphosphoglyceric acid

2,3-BPG interacts with deoxygenated hemoglobin beta subunits and so it decreases the affinity for oxygen and allosterically promotes the release of the remaining oxygen molecules bound to the hemoglobin; [4] therefore, it enhances the ability of RBCs to release oxygen near tissues that need it most.

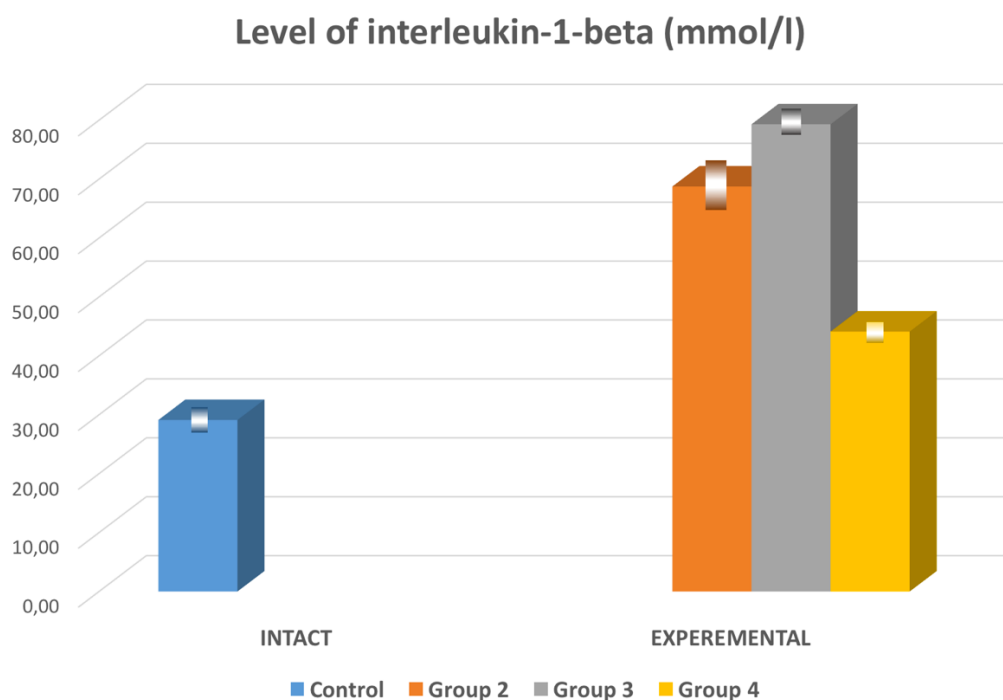
A statistically significant increase in 2,3-BPG in all groups indicates tissue hypoxia.



Interleukin 1-beta

Interleukin-1 β (IL-1 β) is a potent pro-inflammatory cytokine that is crucial for host-defence responses to infection and injury [1]. It is produced and secreted within cells of the innate immune system, such as monocytes and macrophages. It is produced in response to molecular motifs carried by pathogens called 'pathogen associated molecular patterns' (PAMPs).

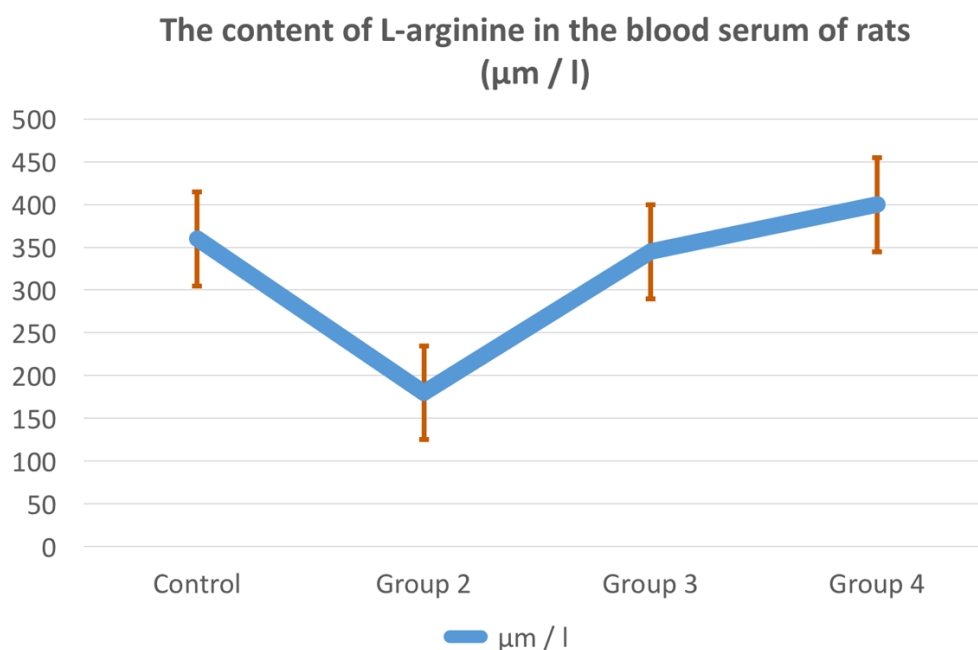
An increase in interleukin in the second and third group indicates an inflammatory reaction. ($p < 0.01$).



L-arginine level

Arginine is a necessary precursor for the synthesis of proteins and many biologically important molecules, such as ornithine, proline, polyamines, creatine and agmatine. However, the main role of arginine in the human body is to be a substrate for the synthesis of nitric oxide (NO). [6]

A statistically significant ($p < 0.01$) decrease in the amount of arginine in the blood of rats indicates the presence of negative feedback with exogenous intake of sodium nitrite. In the second and third groups, no statistical difference is observed, which is associated with the simultaneous exogenous intake of l-arginine as well.

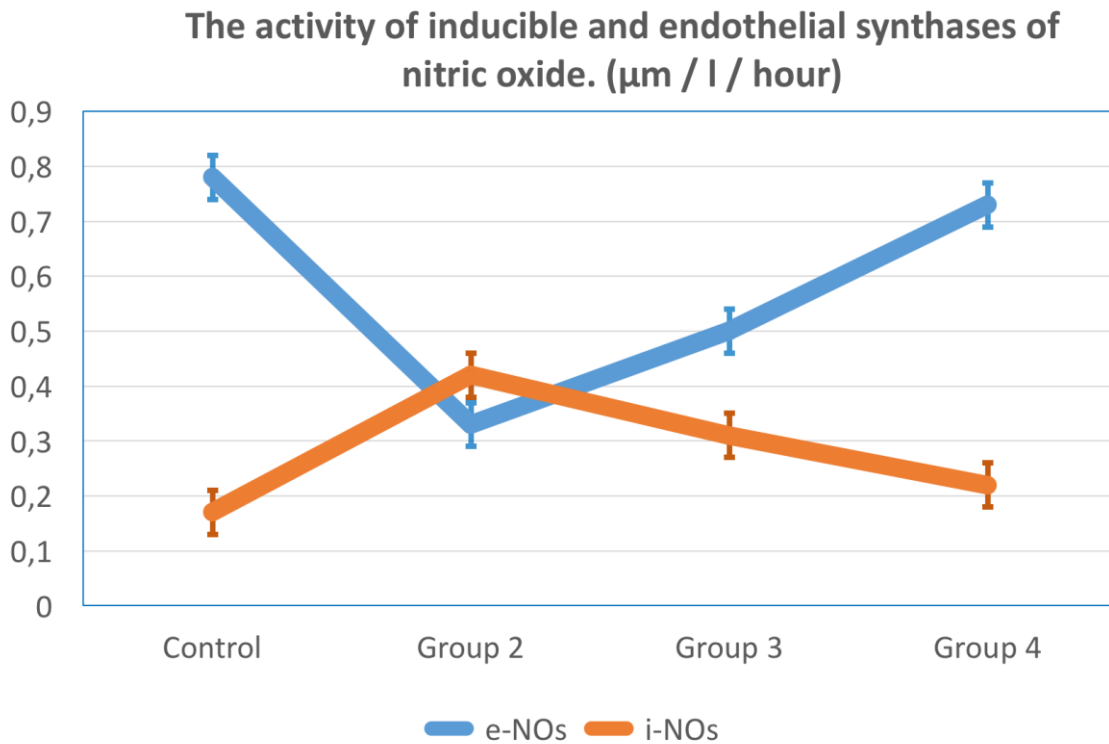


Expression of inducible and endothelial nitric oxide synthase

In the second group, the activity of **eNOS** has statistically significant difference ($p < 0.01$). This indicates the progression of endothelial dysfunction.

A statistically significant increase ($p < 0.01$) of **iNOS** activity indicates the presence of inflammation in the vessel wall.

In groups with a compensatory effect, the situation with activity of enzymes improves, however, there is still a statistically significant difference.



Conclusions

- 1) A constant load of sodium nitrite occurs:
 - oxidative stress (an increase in 2,3-bisphosphoglyceric acid),
 - inflammation (an increase in interleukin-1 beta, which in turn causes a sharp increase in iNOS activity),
 - the development of endothelial dysfunction (an increase in von Willebrand factor).

- 2) A decrease in the level of l-arginine in the group that received sodium nitrite indicates a negative feedback between the level of sodium nitrite and l-arginine.

- 3) A sharp decrease in eNOS activity indicates the progression of endothelial dysfunction.-

- 4) The use of l-AR led to a relative or complete compensation for the action of

sodium nitrite.

5) The use of a bioflavonoid almost completely compensated for the effect of sodium nitrite.

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