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Problem Of Nitrato Resistance Occurrence And Ways Of It Overcoming

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The aim of our study was to improve the treatment of patients with stable Angina Pectoris functional class III with Hypertension and prevention of nitratoresistance development with usage of antioxidant (Mexicor) and NO-donor (L-arginine). The study involved 63 patients with stable angina pectoris FC III with concomitant Hypertension. All patients were divided into two groups. Patients of I group received basic therapy, patients of group II - except basic therapy received Mexicor and L-arginin. The effectiveness of antianginal therapy was assessed by dynamic of clinical indicators, tolerance to physical activity, endothelial function and the level of oxidative stress. Influenced by Mexicor and L-arginine patients better upgraded clinical, hemodynamic and biochemical predictors of nitratoresistance compare with the influence of only basic therapy.

Keyword: Stable Angina, Hypertension, Nitratoresistance.

INTRODUCTION: One of the components in the structure of the treatment of patients with coronary heart disease (CHD) is antianginal therapy, which is aimed primarily at preventing the development of myocardial ischemia and angina as its manifestation. This approach of treatment is aimed primarily at improving the quality of life in patients with angina [1, 2].

Organic nitrates are one of the groups of antianginal drugs, aimed to compensate the deficit of endogenous NO. Effects of nitrate are mainly associated with venous vasodilation, which provides reduced preload, reduction of myocardial wall tension and lowering blood pressure. At the same time, nitrates reduce afterload and improve blood flow in the coronary arteries, which is associated with their ability to dilate the arteries.

Due to the presence in some patients concomitant comorbid diseases (cancers, old age, etc.), social causes and the possibility of restenosis of stented region, nitrates together with revascularising methods remains an important weapon in the fight with stable angina [1, 3].

However, prolonged use of nitrates often leads to the development of resistance to them, resulting in a reduction or complete loss of anti-ischemic and hemodynamic actions of nitrates and requires increasing the dose and frequency of dosing.

Today, there are many theories of nitratoresistance. In fact, the process is complex and involves many links: endothelial dysfunction, oxidation of NO receptor deactivation of endogenous and exogenous nitric oxide, hyperactivation of renin-angiotensin-aldosteron system, neuro-humoral activation and higher levels of the circulating blood volume. However, the most significant element in this process is the oxide stress [1]. According to the existing theories of nitratoresistance conducted many studies to prevent its development. Among the most effective usage should be noted SH-groups donor (N-acetylcysteine, methionine, captopril), antioxidants (N-acetylcysteine, hydralazine, vitamins C, E), ACE inhibitors (captopril, enalapril), aldosterone antagonists (spironolactone), diuretics. However, despite numerous studies, the problem of nitratoresistance remains relevant till today [1, 3]. The most effective way to overcome nitratoresistance today is to consider compliance with the so-called "no-nitrate gaps" - 8-10 hour intervals between taking the drug. However, in patients with Stable Angina III-IV Functional Class observance of this period is very difficult. In addition, there is the risk of developing "symptom rebound".

One perspective drug for prolongation of antianginal effectiveness of nitrates and reducing the chance of nitratoresistance developing is antioxidant Mexicor and NO donor (L-arginine).

MATERIALS AND METHODS:

The study involved 63 patients with Stable Angina FC III and Hypertension who were treated in the Ivano-Frankivsk regional clinical cardiology clinic. The average age of patients was 53,4 (± 1,7) years. Among them were 39 male patients (61.9%), women - 24 (38.1%). The study also included 20 healthy persons for control the normal range of parameters. Patients were divided into two groups: Group I (BT, 32 patients) received combined therapy with antianginal drugs (prolonged nitrates, beta-blockers) antihypertensive drugs (ACE inhibitors or angiotensin II), antiplatelet agents (aspirin), lipid-lowering drugs (statins) . Patients of Group II (BT + M + T, 31 patients), except basic therapy received the drug Mexicor 5%-2.0 ml solution IV, dissolved in 150 ml of 0.9% sodium chloride 1 time per day during 10 days, with continuation with capsule Mexicor 0.1 g 3 times daily during 1 month and drug Tivortin 100.0 ml (4.2 g L-arginine) IV, 1 time per day during 10 days, with the continuation with oral form Tivortin Aspartat 15 ml 2 times daily during 1 month.

The Saved sensitivity to nitrates evaluated by the dynamics of clinical indicators (number of angina attacks and nitroglycerin tablets, taken extra per week), performance bicycle ergometry, level of CAVI (cardio-ankle vascular stiffness index), ultrasound method of D.Celermajer, K. Sorenson (1992) in the author's modification., the levels of malonic aldehyde (MA), endothelin-1 and total nitric oxide (total NO) [4].

Veloergometry was performed on bicycle "Cardio +" with registration of ECG in 12 conventional leads. The I test was performed on an empty stomach. The II test was performed after 2.5 h after taking of nitrate (20 mg mononitrate) [1]. Criterion of preserved sensitivity to nitrates was growth of performing time during II test compared with I test more than 120 s.

Definition CAVI and pulse wave velocity (PWV) was performed by a computer rheography and calculated with the formula:

CAVI-2ρh In (Ps / Pd) x PWV2/ΔR, where PWV- pulse wave velocity, Ps-systolic blood pressure, Pd-diastolic blood pressure, ΔP-pulse blood pressure, ρ-blood viscosity.

PWV = L / T, where L-distance in cm in interval shoulder-shin, and t -time, different between the blood and the brachial artery of tibia.

Endothelial function of the brachial artery was determined by duplex ultrasound scanning by conducting tests with reactive hyperemia using ultrasonic apparatus «Hitachi EUB-7000» (Tokyo, Japan) by the method described D. Celermajer, K.E.Sorensen (1992). Using high

resolution ultrasound, vessel diameter was measured at rest, during reactive hyperemia (with flow increase causing endothelium dependent dilatation).

The study of free-radical oxidation of lipids was investigated by the final product of lipid peroxidation - MA in serum. Determining the level of endothelin-1 in blood was performed by enzyme-linked immunosorbent assay (ELISA) using kits "DRG" (USA). The level of total nitrogen oxide was determined in serum by method, based on the transformation of nitrate to nitrite with the definition of the latter by reaction with the Griss reagent.

Table 1: **Dynamics of angina attack and additionaly taken nitroglycerin pills**

Index	Time of observation	BT (n=32)	BT+M+T (n=31)
Number of angina attack during 1 week; Δ, %; p	before treatment	18,8±0,33	18,9±0,34
	after 1 months	9,1±0,96 -51,6 <0,001	4,0±0,3 -78,8 <0,001
Number of additionaly taken nitroglycerin pills; Δ, %; p	before treatment	21,4±0,32	21,2±0,28
	after 1 months	11,1±0,65 -48,1 <0,001	5,0±0,31 -76,4 <0,001

Remarks: P - comparison between the indexes before and after treatment

RESULTS AND DISCUSSION:

Important to assess the effectiveness of treatment are such features as the number of angina attacks and nitroglycerin tablets (NG) taken additionaly (Table 1). So as a result of the treatment of patients in both groups experienced a significant decrease in the number of angina attacks and taken extra pills NG, but the best result was achieved in group BT + M + T, where the number of angina attacks decreased by 78.8% (p <0.001) and additional tablets taken - by 76.4% (p <0.001) versus 51.6% (p <0.001) and 48.1% (p <0.001) in group BT respectively.

One of the reliable methods for assessing the effectiveness of antianginal therapy and sensitivity to nitrates is a stress tests (Table 2).

Table 2: **Dynamics of pair Veloergometry indexes**

Index	Time of observation	BT (n=32)	BT+M+T (n=31)
I test, s; Δ, %; p_1	before treatment	232,5±7,0	241,9±6,52
	after 1 months	283,1 ±10,16 +21,8 <0,01	348,4 ±12,57 +44,0 <0,001
II test,s Δ, %; p_2	before treatment	386,3±6,6 +66,2 <0,001	404,5±6,52 +67,2 <0,001
	after 1 months	365,6±16,5 +29,1 <0,001	458,7±16,1 +31,7 <0,001

Remarks: p_1 - comparison of time duration – I test before and after treatment;

p_2 – II test with I.

Table 2 shows that the time of performance of physical activity until signs of ischemia occurrence during I test (performed on an empty stomach) after 1 month of treatment in group therapy base increase on 21.8% (p <0.001) and in group BT + M + T - on 44.0% (p <0.001).

Using Veloergometry it was found that in both groups of patients over time decreases the effectiveness of nitrates. Before treatment the duration of exercise during the II test of

Veloergometry increased in group BT on 66.2% (p <0.001), after 1 month – on 29.1% (p <0.001) compared with the I test. In group BT + M + T similar rates were: 67.2% (p <0.001) and 31.7% (p <0.001). Before beginning of the treatment in both groups were similar indexes of this indicator. After treatment the greatest loss of antianginal effects of nitrates was observed in the group of basic therapy.

For patients with nitratoresistance as a verification method was used pair Veloergometry. The criterion for the effectiveness of antianginal medication was increasing of the duration of exercise during the II test - pair Veloergometry (ΔT) for 120 s and more. Second test - pair Veloergometry is performed after 2.5 h after ingestion of the mononitrate dose, which was effective at the beginning of treatment. If the gain was less than 120 s, development of nitratoresistance was ascertained. So after 1 month of therapy revealed 14 (43.8%) patients with signs of nitratoresistance in I group and 4 (12.9%) patients in the II group.

For an objective evaluation of experimental regimens were studied dynamics of basic haemodynamic and biochemical predictors of nitratoresistance, determined by us in previous studies [4], (table 3).

CAVI after 1 month of treatment in the group of basic therapy didn't achieve significant changes. This index decreased in group BT by 5.2% (p> 0.05) and 17.2% (p <0.05) in the BT + M + T group.

FMD significantly increased in both groups, but the best changes were observed in the group, where patients used additionally Mexicor and L-arginine (Δ +83,0%, p <0.001).

Levels of malonic aldehyde significantly diminished in group of Mexicor and L-arginine by 14.2% (p <0.05). We did not achieve any significant changes in group BT.

Table 3: **Dynamics Of Nitratoresistance Predictors**

Index	BT (n=32)		BT+M+T (n=31)	
	before treatment	after 1 months	before treatment	after 1 months
CAVI Δ, %; p	9,69 ±0,4	9,19±0,5 -5,2 >0,05	9,47 ±0,57	7,84±0,46 -17,2 <0,05
FMD, %; Δ, %; p	3,67±0,21	5,2±0,37 +41,7 <0,01	3,83±0,22	7,01 ±0,58 +83,0 <0,001
Malohnic aldehide, nmol/ml; Δ, %; p	5,77±0,16	5,41 ±0,15 -6,2 >0,05	5,71±0,18	4,95 ±0,16 -14,2 <0,01
Total NO, mkmol/l; Δ, %; p	31,96±1,36	35,8±0,88 +13,5 <0,01	31,75±1,24	38,6±0,41 +20,8 <0,01
Ендотелін-1, pg/ml; Δ, %; p	8,63±0,15	7,6±0,21 -12,1 <0,001	8,7 ±0,21	7,06 ±0,19 -18,9 <0,001

Remarks: p— comparison between the indexes before and after treatment

In both groups was significantly decreased levels of endothelin-1 and increased of total nitric oxide. Most changes were seen in the group of Mexicor and L-arginine: reduction of endothelin-1 on 18.9% (p <0.001) and increased total NO on 20.8% (p <0.01).

Chance of nitratoresistance development in BT + M + T group compared with baseline therapy was (OR = 0,19; 95% CI 0,05-0,67; p = 0,015). In that group, patients of which additionally used L-arginine and Mexicor was significantly reduced the chance of nitratoresistance development.

It is known from experimental and clinical research data about antioxidant activity Mexicor. We can assume that the basis of the antianginal effects of the drug can be explained by the ability of Mexicor to prolong "life" of exogenous (coming from prolonged nitrates) and endogenous NO, and inhibit peroxidation modification of endothelial NO receptors. L-arginine, in turn, serves as a substrate for the synthesis of nitric oxide, thereby delivering NO and manifests itself as an antioxidant too.

Thus, the addition to basic therapy in patients with Stable Angina with concomitant Hypertension of antioxidant Mexicor and donator of NO - L-arginine can improve clinical complaints, hemodynamic parameters, tolerance to exercise, endothelial function, reduce the level of oxidative stress and compared reliably to baseline therapy is able to reduce the chance of nitratoresistance development.

CONCLUSIONS:

1. Inclusion in the treatment of patients with the Stable Angina FC III with concomitant Hypertension of Mexicor and L-arginine can improve the clinical course of the disease, reduce the number of angina attacks and nitroglycerin tablets taken further, increases physical activity, improves indices of subclinical damage to arteries, endothelial function and oxidative stress.

2. Drugs Mexicor and L-arginine in the basic treatment of Stable Angina FC III with concomitant Hypertension are able to enhance antianginal effect of long-acting nitrates, and significantly reduce the chance of nitratoresistance development in these patients (OR = 0,19; p = 0,015).

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