A.V. Tarakanov, A.V. Ilyin,
N.V. Kartasheva, L.V. Klimova,
L.H. Musieva
Rostov-on-Don, Taganrog

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THE DEPENDENCE OF THE OXIDATIVE STRESS ON THE NUMBER OF STROKES IN EARLY POSTINFARCTION ANGINA PECTORIS.

Acute forms of coronary heart disease (CHD) arouse great clinicians' interest in spite of successful treatment of instable angina and myocardial infarction connected with new medications and methods of interventional surgical cardiology. Widely introducing new approaches into clinical practice, especially in thrombolytic therapy, changed the clinical picture of acute myocardial infarction, which was now characterized by increased frequency of the early postinfarction angina pectoris (EPAP) (V.A. Chernetsov, 1998; V.A. Shumakov and co-authors, 1998). The frequency of its development varies from 15-18% to 52%. The risk of recurrent myocardial infarction and fatal outcomes by PPIS patients during the first year reaches 40-57% in spite of drug therapy. Its adiaphoris to the accepted drug therapy is well known. Analyzing the effectiveness of treating EPAP showed positive results by the drug treatment only in 66.4% (S.F. Berkinbaev, 1993; J.V. Zimin, 1993; V.A. Shumakov and co-authors, 1998).

It is well known, that a considerable role in the pathogenesis of the ischemic reperfusion myocardial disruption, atherogenesis and atherosclerotic plaques' disruption is played by lipid peroxidation (LPO) against a background of decreasing antiradical protection of the body. Accumulating primary and secondary LPO products causes membranes' destruction, dissociates oxidative phosphorylation and provokes coronary vasospasm (V.Z. Lankin and co-authors,2000; N.A. Vaulin, N.A. Gratsiansky, 2001).

We showed before, that transdermal transcranial stimulation causes expressed analgesy by the patients with acute myocardial infarction, facilitates the formation of a postinfarction scar, improves the clinical course of a disease, decreases the factors of blood circulation deficiency and relapses of anginous diseases (A.P. Golikov and co-authors, 1989; V.R. Mkrtchyan, V.A. Estrin, 1982).

Studying possible ways of treating patients with PPIS with new generation electric stimulating devices seems to be crucial. The devices of SCENAR family (self-controlled electric neuroadaptive regulator) provide a minimal body adaptation to impulse current and non-damaging influence (J.Z. Grinberg, 1999; J.V. Gorfinkel, 1999; A.V. Tarakanov, 2003). SCENAR therapy applies the principles of reflex therapy (A.M. Vasilenko, 1998; D.M. Tabeeva, 2001) and can be referred to the informational ones (V.G. Zilov and co-authors, 2001).

The most important CHD risk factors include hyperlipoproteidemia (K.V. Sorokova, 1988), which lies in the basis of atherosclerosis pathogenesis, and progressive violations in the conversion of fatty acids of ω-6 иω -3 family (E.A. Endakova and co-authors, 2000). The changes in fatty-acidic structure of cell membranes towards their polyunsaturation causes the decrease in microviscosity, changes in the parameters of their physical state and functions, improving patient's status.

Starting from all mentioned above, the aim of our investigation is a comparative analysis of a new combined method's effectiveness. This method of treatment presupposes neuroadaptive influence upon a patient's skin with a SCENAR device and prescribing polyunsaturated fatty acids ω-3.

Work material and investigation methods.

To solve the set problem we examined 189 patients, who had undergone acute myocardial infarction (without thrombolysis) and those, who had been admitted from the hospital for further treatment and rehabilitation in 3-4 weeks to Rostov Regional Cardiological Sanatorium. All patients participating in the investigation had early postinfarction angina pectoris.

Average age of female patients was 52.7, male patients – 53.3, and there were 19 women in the examined group. 51.8% of patients had **non-Q myocardial infarction**, 49.2% - **Q-infarction**.

The required condition for being included in the investigation was significant antianginal and anti-ischemic dynamic effect receiving atenolol or egilok and monomak. Healing effect was achieved with the help of veloergometry and 6-minute test before and after the treatment (J.V. Zimin 1993; V.A. Shumakov and co-authors, 1997; V.A. Chernetsov, 1998; A.L. Rakov and co-authors, 1998; K.R.

Karibaev and co-authors, 2000; V.N. Ardashev and co-authors, 2002; S.N. Filimonov and co-authors, 2002).

SCENAR-97.4 device was used in the complex therapy. The sessions were conducted in the morning after the breakfast. We used the following influence rate: comfortable (the patient feels slight pricking and vibration); intensive (the sensations are between comfortable and pain barrier). We used individually dosed regime according to the general zones: '3 paths, 6 points', with constant frequency 60 Hz.

In addition we influenced pain projection zones and special zones based on the methodology of SCENAR therapy (J.V. Gorfinkel, 1999).

3 groups of patients were formed by sampling for a further deeper investigation.

Group 1 included patients after **non-Q MI** and **Q-MI** (n=20), who were treated according to the modern approaches in the therapy of early postinfarction angina pectoris. If there were no contraindications, we prescribed several medications at once to all patients of the group.

1. Aspirin – 0.125 g/day.
2. Selective β_1– adrenoceptor antagonists without vasodilating characteristics: atenolol – average daily dosage 31.2 mg, metoprolol (egilok) - average daily dosage 34,9 mg.
3. Isosorbide mononitrate (mono mack) - average daily dosage 44,2 mg.
4. ACE inhibitor - enalapril maleate (renitec) - average daily dosage 5,6 mg

The choice of other medications depended on concomitant diseases, but there were no antioxidants.

The effectiveness of antianginal therapy was evaluated according to the quantity of angina pectoris episodes, their duration and severity, as well as sublingual nitroglycerine dose requirements.

Group 2 included 20 patients, who had undergone **non-Q MI** and **Q-MI**, which included both drug therapy and SCENAR therapy №10 (each session in 2-3 days).

Group 3 included 20 patients, who had undergone **non-Q MI** and **Q-MI**, and had been treated the same as those from Group 2, but the patients also received the medication OMEGA-3+ (SEDIKO) (1 capsule 2 times a day, 20 days).

Biochemical investigations were carried out in the SRC of Biology in Rostov State University. Data received from donors of a hemotransfusion station (n=17) was used as a control reflecting the status of intensity of free radical processes in the blood.

Generation of active oxygen forms was examined with chemiluminescence method (V.A. Shestakov and co-authors, 1972; J.I. Serkiz and co-authors, 1984). Superoxidegenerating plasma activity was investigated according to the method (Fried R., 1975). Netrosohemoglobin content in blood plasma was examined according to the method (I.I. Stepuro and co-authors, 1997). NOHb level in the plasma was determined according to the absorption maximum by two waves' lengths – 418 and 545 nm. The quantity of respiratory coefficient was determined by spectrophotometric analysis with a wavelength 232 nm (I.D. Stalnaya, T.D., J.A. Vladimirov, A.I. Archakov, 1972). LOP intensity was evaluated according to secondary molecular product's level - MDA (I.D. Stalnaya, T.D. Garishvili, 1977). Lipids from blood plasma and erythrocytes' membranes were extracted according to (E.G. Bligh, W.I. Dyer, 1959) method to determine the content of Shiff bases. LOP final products (Shiff bases) were determined by the maximum stimulation (360 nm) and maximum fluorescence (440 nm) (W.R. Bidlack, A.L. Tappel 1973). The degree of primary link activity of the cell's antioxidant protection was evaluated according to the SOD and catalase level in the erythrocytes (R. Fried, 1975; M. Luck, 1963). Oxydase ceruloplasmin (CP) activity in blood plasma was determined with substrate p-phenylendiamine according to Revin's method in modification (V.G. Kolba, V.S. Kamyshnikova, 1982). The amount of extraerythrocyte hemoglobin was determined by hemoglobin-cyanide method (A.V. Karakashov, E.P. Vichev, 1973) with a wavelength 540 nm. The content of medium-massed molecules was determined by a screening method described by (N.I. Gabrielyan and co-authors, 1983) in (V.V. Nikolajchik and co-authors, 1991). The samples were photometried on the spectrophotometer "Beckman DU-7" (USA) with a wavelength 210, 254 and 280 nm. The level of medium molecular-weight molecules was expressed in conventional units (c.u.) to 1 ml of plasma.

The results were manipulated statistically using Student's t-criterion and non-parametrical Mann-Witney's rank test (G.F. Lankin, 1980) evaluating wild points according to Shovene's criterion (V.A. Kokunin, 1975). The data was processed on computer. The difference between two samples was considered reliable by $P<0,05$. By $0,05<P<0,1$ it was possible to talk about the tendency to the change. By $P>0,1$ the difference was considered unreliable.

Results.

As a rule, retained angina pectoris after the undergone acute myocardial infarction indicates fixed coronary arteries stenosis in other heart regions. The degree of its manifestation may be different.

As follows from Table 1, the accepted treatment of non-Q MI (Group 1) causes a 45.5% reduction of angina pectoris attacks (p<0,001) with 39.2% reduced amount of nitroglycerine pills taken (p<0,001). Additional SCENAR use and combining it with polyunsaturated fatty acids ω-3 improve these indices by more than two times. There was more than a 90% decrease in the amount of attacks and nitroglycerine pills taken in Groups 2 and 3.

The accepted treatment after the **Q MI** causes a 62,4% (P<0,001) and 66,5% (P<0,001) reduction of the amount of attacks and nitroglycerine pills correspondingly.

The additional SCENAR use and combining it with polyunsaturated fatty acids ω-3 (Groups 2 and 3) there was a 77,3% (P<0,001) and 76,2% (P<0,001) decrease in the attacks' frequency in these groups correspondingly.

There was also an 87,9% (P<0,001) and 88,8% (P<0,001) decrease in the amount of nitroglycerine pills correspondingly. There is a considerable number of patients discharged without pain attacks after **non-Q MI** as well as after PPIS.

Thus, using SCENAR therapy or its combination with polyunsaturated fatty acids ω-3 in complex treatment of patients with PPIS after **non-Q MI** or **Q MI** results in a high-grader treatment. It is apparent in the reliable and considerable decreased of pain episodes, the amount of nitroglycerine pills taken and greater amount of patients, who finish the treatment without angina pectoris attacks.

Table 1

*Comparative efficacy of different combined methods of treatment by EPAP after **non-Q IM***

Factor	**Group 1 (the accepted treatment)**		**Group 2 (the accepted treatment + SCENAR therapy)**		**Group 3 (the accepted treatment + SCENAR therapy +OMEGA-3+)**	
Number of patients	11		9		7	
Average age, years	51,7		50,6		56,4	
Period of investigation	before the treatment	after the treatment	before the treatment	after the treatment	before the treatment	after the treatment
Frequency of angina pectoris attacks (per day)	2,00 ± 0,16	1,09 ± 0,18 ***	1,56 ± 0,17	0,11 ± 0,10 ***	3,57 ± 0,19	0,29 ± 0,11 ***
Number of nitroglycerine pills taken (per day)	2,55 ± 0,24	1,55 ± 0,16 ***	3,33 ± 0,2	0,22 ± 0,12 ***	4,71 ± 0,21	0,29 ± 0,14 ***

Note: *the differences between the factors before and after the treatment are reliable by - * - p < 0,05; ** - p<0,01; *** - p<0,001.*

The dynamics of LPO intensity factors and the formation of active oxygen forms in blood plasma of patients with EPAP by different methods of treatment.

The accepted treatment (Group 1) causes further increase of active oxygen forms generation, which is registered by chemoluminescence method activated by luminol (Sm). It indicates generation of superoxide anion-radicals to a greater extent and of hydroxyl radicals, which is more dangerous.

Extreme generation of active oxygen forms in Group 1 causes intensification of LPO plasma lipoproteins and lipids of blood cells' membranes, which is manifested in a reliable increase of MDA level. MDA, as an intermediate product, causes considerable modification of protein amino acids, lipids, nucleic acids. Initial and tertiary products of blood plasma LPO were on the same initially high level.

Using SCENAR in complex therapy stops the generation of active oxygen forms, while including polyunsaturated fatty acids ω-3 in addition causes the regression of active oxygen forms products. It affects LPO products.

In Group 2 there is a certain decrease of initial formation of LPO-CD products and an uncertain decrease of secondary products' formation (MDA) and final products – shiff bases (SB).

Adding polyunsaturated fatty acids ω-3 (Group 3) somehow increases the MDA level. The data is listed in Table 2.

The accepted treatment doesn't cause the decrease of oxidative stress by PPIS after **Q MI**, though there is a certain clinical effect and stabilization of hemodynamic indices. There is a greater production of active oxygen foms than by non-Q MI. Induced chemoluminescence (Sm) accumulates on 84.3% (P<0,001). Using SCENAR (Group 2) and its combination with polyunsaturated fatty acids ω-3 decreases the production of active oxygen forms, but not so considerably as after non-Q MI.

We consider body autoimmunization index very important. The accepted treatment doesn't stop the process by the patients with non-Q MI, proved by significant increase of circulating immune complex by 35.1% (P<0,05). Using transdermal neurostimulation and its combination with polyunsaturated fatty acids ω-3 causes a considerable (50.4% and 35.1% correspondingly) decrease of circulating immune complex production in Groups 2 and 3 (P<0,05).

Autoimmunization processes after Q MI go on and increase by the accepted treatment. There is a greater increase of circulating immune complex than that of other patients after non-Q MI. It makes 55.7% (P<0,001) if compared to the beginning of treatment. There is significant decrease in formation of circulating immune complex in Groups 2 and 3 (24.3%, P<0,05, and 38.6%, P<0,05, correspondingly).

By **non-Q MI** there are uncertain changes in extraerythrocyte hemoglobin (EEH) level, which indicates, that the treatment almost didn't influence erythrocyte membranes' permeability, which was slightly decreased in the beginning of the treatment. It is worth mentioning, that EEH level in Group 1 was initially considerably higher than in Groups 2 and 3, which is connected with individual patients' data in the group.

Table 2

*The intensity of lipid peroxidation (LP) and luminol - H_2O_2 – induced chemoluminescence (CL) in blood plasma of patients with EPAP after **non-Q MI** by different methods of combined treatment*

Factor	**Group 1 (the accepted treatment)**		**Group 2 (the accepted treatment + SCENAR therapy)**		**Group 3 (the accepted treatment + SCENAR therapy +OMEGA-3+)**	
Number of patients	11		9		7	
Period of investigation	before the treatment	after the treatment	before the treatment	after the treatment	before the treatment	after the treatment
CD nmole/ml	27,64 ± 1,84	27,16 ± 1,64	18,84 ± 1,05	14,99 ± 1,65 *	12,48 ± 0,98	11,45 ± 1,07
MDA nmole/ml	34,35 ± 2,08	45,96 ± 2,65 ***	34,05 ± 1,38	31,03 ± 1,21	48,98 ± 2,76	54,77 ± 3,13
SB un.fl./ml	1,74 ± 0,19	1,62 ± 0,14	2,27 ± 0,18	1,96 ± 0,21	1,39 ± 0,16	1,36 ± 0,17
H mm	4,91 ± 3,04	70,73 ± 3,56 **	75,88 ± 4,23	70,25 ± 3,54	51,29 ± 3,24	40,40 ± 2,27*
Sm • 10^4 **rel.un.**	70,73 ± 4,48	114,46± 5,87 ***	101,75± 5,65	102,63± 4,98	93,00 ± 4,21	70,60 ± 4,54 **

Note: *the differences between the factors before and after the treatment are reliable by - * - $p < 0,05$; ** - $p<0,01$; *** - $p<0,001$.*

Catalase activity in blood plasma did not change in Group 1 during the treatment. But in combined treatment with SCENAR and polyunsaturated fatty acids ω-3 there is an 11.6% (P<0,05) and 12.1% ferment activity decrease. This decrease of activity also correlates with the decrease of active oxygen forms generation in the groups. The lower the 'substrate', the lower the activity.

The situation is different in the patients after **Q MI**. The treatment in Groups 1 and 2 causes the decrease of erythrocyte membranes' permeability and hemoglobin emission. Thus, there was a certain decrease of ectoglobular hemoglobin by 40.5% in Group 1(P<0,001), and a 27% decrease in Group 2 (P<0,001). The level of ectoglobular hemoglobin was initially low in Group 3, where SCENAR and polyunsaturated fatty acids ω-3 were used. There was a 94,2% (P<0,001) decrease of the total peroxidase activity (TPA) in Group 1. Complementing SCENAR-therapy with polyunsaturated fatty acids ω-3 also causes a certain, but not so reliable increase of TPA activity up to 43% (P<0,001) and 24.1% (P<0,01). This increase is specific in all cases, as TPA activity in all groups didn't differ from the control initially before the treatment.

There are unreliable shift in catalase activity in all three groups of patients. As for ceruloplasmin activity of the patients with PPIS after Q MI, there is the same regularity as by the patients with **non-Q MI**. There is a certain increase in the activity level only in Group 1 (53,5% – P<0,01), where there is a reliable increase in generation of active oxygen forms in the blood.

The status of free radical oxidation and antioxidant erythrocyte system of the patients with PPIS after infarctions in different methods of treatment.

Intensifying the processes of active oxygen forms formation of the patients with PPIS after infarctions activates LP processes in blood cells. We analyzed LP state and structural state of erythrocyte membranes depending on the treatment. The data is listed in Tables 3 and 4.

The accepted treatment after the undergone Q MI does not limit erythrocyte membranes' LP. There is a decrease of initial, secondary and final LP products' level in Groups 2 and 3. The effect is realized at the expense of reliable increase of SOD and catalase activity. This phenomenon of SOD activity increase becomes more apparent in the situations, when PPIS is registered after 'completed' **Q MI**, but not by 'infarct in full swing' – **non-Q MI**.

Thus, the accepted treatment doesn't cause the decrease in generation of active oxygen forms by the patients with PPIS after myocardial infarction of different intensity. Positive effect of the suggested combined method of treatment – transdermal SCENAR stimulation and including polyunsaturated fatty acids ω-3 into the patients' dietary intake as a structural material of the body membranes – lies in intensifying antiradical protection, reducing generation of active oxygen forms and, consequently, considerable decrease of lipid peroxidation products' damaging action.

Redundant generation of active oxygen forms registered in patients with EPAP as a result of constant ishemic attacks, causes LP in plasma lipoproteins and cells' membranes, especially erythrocyte membranes, as we have already mentioned above. The accumulation of LP products causes membranes' and their bilayer's structural changes, which facilitates changes in membrane proteins' submerging, membrane canals' functions and membranes' stiffness. These changes cause the violations of membrane's function and naturally have an effect on the patients' general status.

Table 3

The factors of free radical oxidation and antioxidant erythrocyte system intensity in different methods of combined treatment by EPAP, non-Q MI

Factor	**Group 1 (the accepted treatment)**		**Group 2 (the accepted treatment + SCENAR therapy)**		**Group 3 (the accepted treatment + SCENAR therapy +OMEGA-3+)**	
Number of patients	11		9		7	
Period of investigation	before the treatment	after the treatment	before the treatment	after the treatment	before the treatment	after the treatment

CD nmole/ml Hb	10,52 ± 0,57	8,92 ± 0,48 *	11,74 ± 0,54	9,82 ± 0,44 **	9,82 ± 0,44 **	6,41 ± 0,36 *
MDA nmole/ml Hb	3,78 ± 0,22	3,71 ± 0,26	6,53 ± 0,28	5,82 ± 0,25	5,14 ± 0,21	4,67 ± 0,19
SB rel. un.fl./ml Hb	0,81 ± 0,11	0,94 ± 0,13	0,66 ± 0,07	0,58 ± 0,09	0,81 ± 1,12	0,77 ± 0,08
SOD un./mg Hb	2,58 ± 0,27	2,69 ± 0,22	2,85 ± 0,25	3,06 ± 0,19	2,85 ± 0,17	3,09 ± 0,24
Catalase nmole/mg Hb	12,68 ± 1,25	14,45 ± 1,11	18,12 ± 1,07	21,27 ± 1,11 *	18,35 ± 1,34	19,35 ± 0,99

Note: *the differences between the factors before and after the treatment are reliable by - * - p < 0,05; ** - p<0,01; *** - p<0,001.*

The parameter Fo – F/Fo characterizing the effectiveness of radiationless transmission of energy of electronic stimulation from tryptophan membrane proteins' heels to the pyren and indicating the degree of proteins' submerging into lipid matrix and the expressiveness of membrane proteins' aggregation by the patients with PPIS after the undergone infarction of different intensity and square is not measured identically.

Table 4

The factors of free radical oxidation and antioxidant erythrocyte system intensity in different methods of combined treatment by EPAP, Q MI

Factor	**Group 1 (the accepted treatment)**		**Group 2 (the accepted treatment + SCENAR therapy)**		**Group 3 (the accepted treatment + SCENAR therapy +OMEGA-3+)**	
Number of patients	11		9		7	
Period of investigation	before the treatment	after the treatment	before the treatment	after the treatment	before the treatment	after the treatment
CD nmole/ml Hb	9,41 ± 0,44	9,71 ± 0,47	10,40 ± 041	9,31 ± 0,25 *	10,04 ± 0,38	8,39 ± 0,41 **
MDA nmole/ml Hb	4,01 ± 0,19	4,19 ± 0,21	6,49 ± 0,23	5,23 ± 0,25 **	5,66 ± 0,24	4,56 ± 0,18 **
SB rel. un.fl./ml Hb	2,00 ± 0,15	1,62 ± 0,17	0,52 ± 0,12	0,46 ± 0,13	0,84 ± 0,14	0,66 ± 0,15
SOD un./mg Hb	2,33 ± 0,31	2,51 ± 0,27	2,66 ± 0,23	3,05 ± 0,16	2,77 ± 0,21	3,35 ± 0,17 *
Catalase nmole H_2O_2/mg Hb	14,61 ± 1,43	14,95 ± 1,27	17,04 ± 1,08	19,21 ± 0,97	17,84 ± 1,13	21,14 ± 1,21 *

Note: *the differences between the factors before and after the treatment are reliable by - * - p < 0,05; ** - p<0,01; *** - p<0,001.*

Thus, after non-Q MI there is a tendency to an uncertain increase in a greater degree, than after the accepted treatment (Group 1). After Q MI there is a considerable (72,6% (P<0,001)) increase of this parameter by the patients from Group 3 while using SCENAR and polyunsaturated fatty acids ω-3. Such tendency to the certain increase of the factor coincides with the improvement of membrane's functional characteristics.

The decrease of this parameter may indicate the following negative phenomena: decreasing proteins' submerging into lipid matrix, oligomerization of membrane proteins by interacting with free radical and molecular products LPO like MDA, plasma proteins' association with erythrocyte membranes.

CONCLUSION.

1. Using transdermal SCENAR neurostimulation combined with the accepted therapy activates the sanogenesis mechanisms in the body of patients with PPIS, which are realized in the line of eliminating the extreme oxidative stress.
2. Using SCENAR therapy or its combination with polyunsaturated fatty acids ω-3 in complex therapy of the patients with PPIS activates the certain decrease of pain episodes, the amount of nitroglycerine pills taken and certain increase in the number of patients, who finishes the treatment without angina pectoris attacks.
3. Including SCENAR therapy or its combination with polyunsaturated fatty acids ω-3 in complex therapy causes the regress in formation of active oxygen forms, if compared to the initial state by EPAP after **non-Q MI,** and causes the decrease of active oxygen forms after **Q MI**. Using SCENAR therapy or its combination with polyunsaturated fatty acids ω-3 results in a certain decrease of circulating immune complexes' level.
4. Using SCENAR therapy or its combination with polyunsaturated fatty acids ω-3 in complex therapy of the patients with PPIS decreases all LP products' level in erythrocyte membranes. The effect is realized at the expense of certain increase of SOD and catalase activity, especially after **Q MI**. There is increasing membrane fluidity and improving their structural characteristics.
5. Using SCENAR therapy facilitating active oxygen forms' generation, activating the ferments of antiradical protection and prescribing polyunsaturated fatty acids ω-3, which is necessary for building cells' membranes may be a perspective method of treating early postinfarction angina pectoris.