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**OPTIMIZATION OF MEDICAL REHABILITATION OF PATIENTS AFTER
ACUTE INFARCTION AND SURGICAL MYOCARDIAL
VASCULARIZATION USING NATURAL FLAVONOIDS**

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abstract

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GENERAL DESCRIPTION OF WORK

The relevance of the work

One of the most important tasks of restorative medicine is the improvement of rehabilitation programs for highly socially significant diseases using medical technologies aimed at for the correction of pathogenetic links, confirmed by modern research methods. Cardiovascular disease ranks first among the causes of death in the world population: coronary heart disease is the main cause of death in economically developed countries. Among those under dispensary observation, one in ten develops myocardial infarction within one year (Eur Heart J, 2007.28; Lyusov V.A., 2008; Chursina T.V., 2008; Rosstat, 2010).

Conducted by patients with coronary heart disease, including after acute myocardial infarction, drug therapy performs mainly optimization of the ratio between the needs of the heart muscle in oxygen and its delivery to the myocardium. Operative coronary revascularization: angioplasty, stenting, aortocoronary and mammary coronary bypass grafting are also designed to eliminate the dissonance between delivery and myocardial oxygen demand (Ferraris VA, 2005; Chazov E.I., 2007; Oganov R.G., 2009; Akchurin R. .S., 2007; Bokeria L.A., 2010). Accordingly, these medical and surgical agents

have only an indirect effect on the oxygen supply of the myocardium and are not able to improve oxygen utilization by cardiomyocytes, the violation of which is the pathogenetic essence of myocardial ischemia (Lee L. et al., 2004; Shilov A. M., 2007; Morozova T. E., 2008; Knyazeva T.A., 2008).

It has been proven that myocardial energy metabolism at the cellular level is disrupted during ischemia (Stanley WC et al., 1997, Horowitz J., 2004; Lankin V.Z. et al., 2006). Metabolic disturbances prevent oxygen utilization by ischemic cardiomyocytes. The most important role in the utilization of oxygen by myocardial cells is played by microcirculation processes, as well as the ratio of free radical lipid oxidation products and the activity of antioxidant defense enzymes. Currently, the correction of microcirculatory disorders and free radical lipid oxidation are considered as absolutely necessary treatment of all forms of myocardial ischemia (Kukharchuk V.I. et al., 2007; Knyazeva T.A., 2009; Belaya O.L. et al., 2009). The insufficiency of this correction largely explains the unsatisfactory practical medicine efficiency of the treatment of coronary heart disease, and especially its severe forms. The latter category includes patients with acute myocardial infarction and surgical revascularization of the myocardium.

Established on experimental biological models and in patients with other nosologies (Teselkin Yu.O., 2003; Nedosugova L.V., 2006; Britov A.N., 2006; Skedina M.A. et al., 2008; Koshkin V.M. , 2008, Nagornev S.N., 2010) a pronounced antioxidant effect of plant flavonoids (dihydroquercetin, dihydrokaempferol, etc.), their effect on microcirculation (stabilizing the barrier on the function of microvessels, reducing the permeability of capillary walls and, thereby, contributing to the reduction of congestion in the microcirculatory line) substantiated the rationality of a scientific study of increasing the effectiveness of early post-hospital rehabilitation of patients after acute myocardial infarction and aorto-coronary bypass grafting - by including natural flavonoids in rehabilitation treatment programs. The therapeutic potential of flavonoids is aimed at correcting the established above-mentioned causal links of insufficient therapeutic efficacy of therapeutic and rehabilitation effects in ischemic conditions of the myocardium (Plotnikov M.B. et al., 2005; Shakula A.V., 2007) .

In the available literature, there is no information on the use of bioflavonoids in the rehabilitation of patients with coronary artery disease who underwent coronary artery bypass grafting, there are single works on their use at the hospital stage of rehabilitation after acute myocardial infarction (Tyukavkina N.A. et al., 2006; Shchegolkov A.M. et al., 2007; Lupach N.M., 2011). At the same time, the clinical and pathogenetic features of the course of complicated forms of coronary artery disease: after an acute infarction, surgical myocardial revascularization (pronounced manifestations of microcirculation disturbances, blood rheological properties, oxidative stress,

signs of disseminated intravascular coagulation syndrome, the development of which also contributes to microcirculation disorders) and a pronounced antioxidant effect of dihydroquercetin, as well as its effect on microcirculation and rheology, the blood coagulation system (Balz Fray et al., 2003; Harold V. Panglossi et al., 2006; Kozlov V.I. et al., 2007) substantiate the study of the possibility of increasing the effectiveness of early post-hospital rehabilitation of patients after acute myocardial infarction and coronary artery bypass grafting when natural flavonoids are included in it.

Objective

Evidence-based optimization of medical early post-hospital rehabilitation of patients with coronary artery disease after acute myocardial infarction and coronary artery bypass grafting using natural flavonoid dihydroquercetin.

Research objectives:

1. To study in patients who have undergone acute myocardial infarction or early coronary bypass grafting, the post-hospital period of disturbances in microcirculation processes, rheological antioxidant protection, which aggravate the decrease in tissue oxygenation, cardiopulmonary hemodynamic disorders, ischemic, anginal effects, reduced tolerance to physical stress, psychological maladjustment - in order to establish pathogenetic links in the optimization of rehabilitation programs.

2. To study plant bioflavonoids (dihydroquercetin) for the regulation of microcirculation processes in patients after acute myocardial infarction and coronary artery bypass grafting

systems, external respiration function and blood oxygenation, correction of disorders of central and pulmonary hemodynamics.

3. To evaluate the clinical effectiveness of post-hospital rehabilitation programs with the inclusion of dihydroquercetin in patients after acute myocardial infarction and after aortocoronary angioplasty, anti-ischemic effects, shunting: myocardial contractility, exercise tolerance - in the immediate and long-term after rehabilitation.

4. Establish the effectiveness of the rehabilitation program using dihydroquercetin to eliminate postinfarction and postoperative psychological maladjustment of patients.

Scientific novelty

The results of this study, for the first time in patients who underwent acute myocardial infarction or surgical myocardial revascularization, found at an early post-hospital stage of rehabilitation aggravation (compared to chronic coronary artery disease) of pathological microcirculation disorders, hypercoagulation syndrome, a decrease in antioxidant protection during activation of lipid peroxidation processes that play a crucial role in utilization by ischemic cardiomyocytes of increased oxygen delivery.

For the first time, studies were carried out that proved the optimization of early post-hospital rehabilitation of the above severe categories of patients by the inclusion of plant bioflavonoids (dihydroquercetin) in it. An improvement in properties of microcirculation, blood, blood coagulation and anticoagulation systems, an improvement in external respiration function indicators, which leads to an antianginal and anti-ischemic effect, hemodynamics and, as a result, to a reduction in exercise intolerance and psychological postoperative maladjustment of patients.

It is shown that the restoration of the above pathogenetic mechanisms is a consequence of an increase in oxygenation of tissues, including the myocardium, due to an improvement in the utilization of oxygen by them, which significantly increases the efficiency of rehabilitation of patients with coronary artery disease in

early terms after acute myocardial infarction and surgical myocardial vascularization by coronary artery bypass grafting.

Practical significance and recommendations for implementation.

The paper scientifically substantiated and developed comprehensive programs for the medical rehabilitation of patients with coronary heart disease using bioflavonoids at an early post-hospital stage after acute myocardial infarction or surgical myocardial revascularization by coronary artery bypass grafting.

The expediency of including natural bioflavonoids (dihydroquercetin) in the rehabilitation program of this category of patients at an early post-hospital stage in order to improve the utilization of oxygen delivered to the myocardium by ischemic cardiomyocytes is shown.

This achieves an improvement in microcirculation, hemostatic properties of blood, an increase in the activity of the antioxidant system, violations of which do not allow sufficient use of the increase in oxygen delivery to the myocardium, achieved by modern medical and surgical treatments.

The developed optimized programs make it possible to increase the efficiency of rehabilitation of patients with coronary heart disease at an early post-hospital stage due to a significant effect on antioxidant protection, microcirculation, the state of cardio hemodynamics and exercise tolerance, which ultimately leads to an improvement in the quality of life of patients.

The developed rehabilitation programs with the use of dihydroquercetin can be recommended for the rehabilitation of patients at an early post-hospital stage after myocardial infarction and after coronary artery bypass grafting - in polyclinic rehabilitation centers, stationary

cardiological departments of hospitals and sanatoriums.

Basic provisions for defense

1. At the early post-hospital stage of rehabilitation of patients with coronary artery disease who underwent acute myocardial infarction or surgical revascularization of the myocardium, along with severe disorders of tissue oxygenation, the functional state of the cardiorespiratory system, cardiac and pulmonary hemodynamics, and the psycho-emotional state, an aggravation was revealed (compared to chronic ischemic heart disease)

pathological disorders of microcirculation, hypercoagulation syndrome, activation of lipid peroxidation processes with a decrease in antioxidant protection, which justifies the development of optimization of rehabilitation programs.

2. In the course of early post-hospital rehabilitation with the inclusion of plant bioflavonoids (dihydroquercetin) in patients who underwent acute myocardial infarction or coronary artery bypass grafting, an improvement in microcirculation, blood rheological properties, the state of blood coagulation and anticoagulation systems, blood oxygenation, and improvement in external respiration function were found, which led to an increase in: antianginal and anti-ischemic effects, correction of post-infarction and postoperative disorders of central and peripheral hemodynamics, and as a result, to an increase in exercise tolerance.

3. The clinical efficacy of the drug was manifested by an antianginal and anti-ischemic effect, correction of post-infarction and postoperative disorders of central and pulmonary hemodynamics. The integral indicators of the effectiveness of the rehabilitation program with the inclusion of bioflavonoids were: a significant increase in exercise tolerance, improvement in the psycho-emotional state of patients, manifested in the correction of psychological post-infarction and postoperative maladjustment of patients.

Implementation of the results of the work into practice

The developed rehabilitation programs have been introduced into the practical work of the Branch No. A.A. Vishnevsky of the Ministry of Defense of the Russian Federation", and in the educational process at the Department of Medical Rehabilitation and Physical Methods of Treatment of the Medical Institute for Advanced Training of Doctors of the State Educational Institution of Higher Professional Education MGUPP.

Approbation of work and publication

The materials of the work were reported at the X International Conference "Modern technologies of restorative medicine", 2008; All-Russian scientific forum "ReaSpoMed 2008"; International Symposium: "Occupational health and quality of life" Cuba, 2009 (reports). Approbation of the work was carried out at a meeting of the Scientific and Methodological Council of the Federal State Budgetary Institution "Russian Scientific Center for Medical Rehabilitation and Balneology of the Ministry of Health and Social Development of the Russian Federation" on March 16, 2012. The dissertation was recommended for defense. On the topic of the dissertation

12 printed works were published, 5 of them - in publications recommended by the Higher Attestation Commission of the Ministry of Education and Science of Russia.

The structure and scope of the dissertation.

The dissertation is presented on 145 pages of typewritten text, illustrated with 33 tables and 9 figures. It consists of an introduction, 5 chapters, including: a review of the literature, a description of the methods of research and treatment, the results of own research and long-term results; discussion, conclusions, practical recommendations and literature index. The list of literature includes 169 sources, of which: 107 domestic and 52 foreign.

MATERIAL AND RESEARCH METHODS

Research material. 121 patients with coronary artery disease (men) who were admitted for staged medical rehabilitation to the cardiology departments of the rehabilitation center were under observation. Of these, 41 patients had (AMI) 16-28 days before admission to the rehabilitation department, 54 patients were transferred on days 12-17 after aorto-coronary bypass surgery (CABG). To evaluate the effectiveness of the proposed rehabilitation program, patients from each of these groups were randomly assigned into 2 subgroups: the main (26 patients after acute myocardial infarction, 35 patients after coronary artery bypass grafting) and control (respectively - 15 and 19 patients).

For the purpose of comparative characteristics, 26 patients with chronic coronary artery disease who received only drug therapy (comparison group) were also examined. By age, FC of angina pectoris and concomitant pathology of the groups of patients did not differ significantly. The groups were comparable in terms of the main clinical, functional and psychological characteristics. Long-term results after 6 months were evaluated in 87 patients at the outpatient-polyclinic stage of rehabilitation.

Most patients suffered from angina pectoris III FC (52.1%), 51.9% of patients had a history of myocardial infarction. The presented data indicate an extremely serious clinical contingent of patients.

Among the examined patients, the largest proportion (81.8%) were persons aged 40-60 years, for whom recovery

employability is the most important task. The most numerous was the group with a duration of IHD from 1 to 5 years, it included 58.5% of patients with acute myocardial infarction, 46.3% after coronary artery bypass grafting, and 46.2% of patients with CIHD. Of the comorbidities in the examined patients, hypertension was most often diagnosed - in 65.9%, 53.7% and 53.8%, respectively.

Methods of rehabilitation. The control groups included patients, rehabilitation of the standard rehabilitation program was carried out, including drug therapy, doses 1-2 mg, physical therapy, cervicothoracic spine using a sparing technique - against the background of the necessary drug therapy (beta-blockers, ACE inhibitors, statins, nitrates - according to indications). Patients of the main groups underwent

an optimized program that additionally includes taking the drug Diquertin (manufactured by Flavir LLC, Russia, registration number: P No. 000056/02 dated 05/19/06): 2 tablets in the morning and 1 tablet in the afternoon and evening. The composition of 1 Diquertin tablet includes: 20 mg of dihydroquercetin and auxiliary components: sorbitol, calcium stearate. Thus, patients received 80 mg of dihydroquercetin per day per os, divided into 3 doses.

Research methods. At all stages of medical rehabilitation, the patient examination program included: general clinical, laboratory, functional and psychological methods

research and was carried out in the first three days of admission and before discharge.

Laboratory studies, in addition to a clinical blood test and standard biochemical parameters, included determining the state of the blood coagulation and anticoagulation systems, including: APTT, activated recalcification time, patient prothrombin time, INR, thrombin time, Quick prothrombin index, plasminogen, fibrinogen. A study was made of the rheological properties of blood with the determination of the indices of aggregation and deformability of erythrocytes and platelets, RFMK-test with O-phenanthroline -

paracoagulation phenanthroline test - for the quantitative determination of soluble fibrin monomer complexes (SFMK) in blood plasma, which are markers of thrombinemia during intravascular blood coagulation. lipid peroxidation

included the determination of final (MDA) and primary (diene conjugates), lipid peroxidation products, as well as the enzyme of the antioxidant system - catalase. Lipid and carbohydrate metabolism were also assessed - according to generally accepted methods, the acid-base state of the blood: the value of the active reaction of the solution (pH), buffer bases, the partial tension of carbon dioxide and oxygen, total carbon dioxide and blood oxygen saturation (using the ABC-2 apparatus of the company "Radiometr ", Denmark).

The state of microcirculation processes was assessed by laser Doppler fluometry (using the LAKK-02 apparatus, NPP Lazma, Moscow) and conjunctival biomicroscopy.

To assess the state of the cardiorespiratory system, an electrocardiographic study was performed in 12 standard and additional leads (according to Nab, orthogonal), bicycle ergometry was performed using a continuous, stepwise-increasing method, echocardiography was performed according to the method of the Committee for Standardization and Nomenclature of Two-Dimensional Echocardiography of the American Society of Cardiology (1981) with an assessment morphofunctional and hemodynamic parameters; the function of external respiration and bronchial patency was studied on a spiroanalyzer from the Fucuda company (Japan) with the results processed on a microprocessor of the same company.

The methods of psychological examination of patients included: an abbreviated multifactorial questionnaire for the study of personality - SMOL and the Spielberger Khanin test - to assess personal response to the disease, current psychopathological manifestations, features of the motivational sphere and personality orientation, WAN test (well-being - activity - mood).

The examination was carried out upon admission of the patient to the rehabilitation center and after the end of the rehabilitation course. Statistical processing of the data was carried out by the methods of variational statistics using the Student's criterion of reliability and by the methods of nonparametric statistics. The obtained data were processed on a computer using the STATISTICA 6.0 program and using standard programs included in Microsoft Excel.

RESULTS OF OWN RESEARCH

Microcirculation disorders were detected in all patients after acute myocardial infarction and coronary artery bypass grafting, and the degree of disorders in these patients was more significant than in patients with chronic coronary artery disease who were on conservative treatment.

The development of microcirculatory disorders in IHD is mainly due to changes in the rheological properties of blood due to impaired deformability of erythrocytes, increased aggregation of them and platelets, as well as changes in the dynamics of microvessels, which lead to an increase in the volume of the microcirculatory bed, centralization of blood flow and microcirculation inefficiency. A spastic type of microcirculation was noted. Thus, the indicator of average perfusion in the considered periods in patients after acute myocardial infarction bypass grafting was reduced to 2.92 ± 0.3 and 2.86 ± 0.33 c.u. compared not only with healthy individuals, but also with patients with chronic coronary artery disease, in whom it was 4.92 ± 0.38 and 4.31 ± 0.28 c.u. respectively (Table 1), myogenic tone was increased to 3.12 ± 0.32 and 3.2 ± 0.33 at $p < 0.05$ compared with healthy and chronic coronary artery disease patients.

Hypercoagulation syndrome in patients after acute myocardial infarction and after coronary artery bypass grafting is more pronounced than in patients with chronic coronary heart disease, is realized by increasing the blood coagulation potential: increasing the level of fibrinogen (up to 5.6 ± 0.3 g / l in patients after CABG and up to 5.2 ± 0.59 g / l after acute myocardial infarction at 2.8 ± 0.35 g/l in healthy people), the content of soluble fibrinogen and fibrinogen-fibrin degradation products, and a decrease in plasminogen.

A sharp violation of microcirculation processes, hemostatic and fibrinolytic potential of the blood leads to a decrease in the supply of oxygen to tissues and an increase in the partial pressure of carbon dioxide, which is manifested by aggravation of hypoxemia and hypoxia of organs and tissues, more pronounced in patients after myocardial infarction and CABG surgery than in patients with coronary heart disease .

There are manifestations of oxidative stress, which is confirmed by an increase in the level of malondialdehyde to 7.12 ± 0.3 nmol/l after AMI and up to 7.56 ± 0.41 nmol/l after CABG (in healthy people - 5.08 ± 0.15 nmol/ml, $p < 0.001$) against the background of a decrease in the activity of the antioxidant defense enzyme catalase: up to 9.23 ± 0.34 after AMI and up to 9.53 ± 1.02 mmol H₂O₂ / (min·g Hb) after CABG (in healthy people - 14.9 ± 1.02 mmol H₂O₂ / (min·g Hb), $p < 0.001$).

Table 1.

Indicators of the state of microcirculation, hemorheology and blood oxygenation

in patients upon admission to a rehabilitation center

Patient groups	Healthy s	sick s	Sick after AMI (n=41)	Sick after US (n=41)
Indicators(M+m)		HIBS (n=26)		
M - medium perfusion, c.u.	38 4.92±0,	.28 4.31±0	°°° 2.92±0.3**	3****°°° 2.86±0.3
kv - coefficient variations, c.u.	37 9.93±0,	.45 9.34±0	° 8.64±0.51	8.7±0.46°
NT - neurogenic tone, c.u.	eighteen 1.61±0,	,12 1.68±0	1.76±0.17	1.8±0.24
MT - myogenic tone, c.u.	25 2.14±0,	.28 2.63±0	° 3.12±0.32	3.2±0.33°
PS - indicator shunted ia, c.u.	08 1.33±0,	.06 1.57±0	*°°° 1.77±0.07	6*°°° 1.78±0.0
APTT, sec.	82 32.8±2,	30.9±4.23	28.7±2.82	26.9± 3.83

plasminogen, n, %	137.2± 5.22	135.5± 4.64	108.6±5.5 6****oo	105.7± 5.13****oo
fibrinogen, g/l	2.8±0.3 five	2.9±0.42	5.2±0.59** oo	5.6±0.3** *oo
RFMK test with phenanthroline, mg/ dl	3.38±0, 22	3.52±0.35	5.78± 0.65****oo	6.74± 0.7****oo
ΔP, mm Hg	36.8±1.92	39.6±1 .44	42.7±1.74 o	44.4±1.4* oo
pO ₂ , mm Hg	82.6±2.7	78.9±1.69	69.7±1.92 ****oo	65.4±2.5* ****oo

* - significance of differences in comparison with the CHD group p<0.05; ** - p<0.01; *** - p<0.001;

o - reliability of differences in comparison with healthy people p<0.05; p<0.01; oo - p<0.001.

In 39.3% of patients after AMI and 62.9% of patients after CABG operations at the early post-hospital stage of rehabilitation, there are violations of the function of external respiration, mainly of the obstructive type - after AMI and restrictive type - after CABG, indicating a decrease in respiratory reserves. Violations of the function of external respiration lead to respiratory failure and, in combination with heart failure, aggravate the condition of patients and complicate the course of the recovery period. It was found that the reduced ejection fraction in patients with coronary artery disease at the early post-hospital stage of rehabilitation is in direct correlation with the indicator of lung capacity (r=0.54) and maximum lung ventilation (r=0.46) (p<0.05). An inverse correlation was found between the average pressure in the pulmonary artery and the vital capacity of the lungs (r=-

0.47), forced expiratory volume (r=-0.48), ratio of forced expiratory volume to vital capacity (r=-0.48), (p<0.05).

The dependence of exercise tolerance on the function of external respiration is confirmed by a direct correlation with maximum ventilation of the lungs ($r=0.48$, $p<0.05$). Indicators of respiratory function after acute myocardial infarction and especially after CABG, with

which, as a result of intraoperative dissection of the pleura, reactive pleurisy develops, were statistically significantly lower in comparison not only with healthy, but also with patients with chronic coronary artery disease

A significant decrease in exercise tolerance was noted: up to 74.2 ± 4.5 W in patients after AMI and 71.9 ± 4.1 W after CABG (in healthy people -124.2 ± 11.5 W, $p<0.01$), a decrease in myocardial contractility: a decrease in the ejection fraction to $49.7 \pm 1.3\%$ and $51.1 \pm 1.4\%$, respectively, was registered, with an indicator in healthy -

$64.3\pm 1.5\%$, $p<0.01$. There was a significant increase in mean pressure in the pulmonary artery up to 23.8 ± 2.1 in patients with AMI and up to 24.0 ± 3.0 mm Hg. in patients after CABG - compared with healthy ones: 17.0 ± 2.4 mm Hg, $p<0.05$.

Assessment of the state of hemodynamics, myocardial contractility and the ability to endure physical activity in patients with coronary artery disease after CABG and after acute myocardial infarction play an important role in identifying the adaptive-compensatory capabilities of the body and rehabilitation. The data obtained indicate a more severe clinical condition of postoperative post-infarction patients compared with patients with chronic coronary heart disease. And

An increase in the scores on the scales of the neurotic triad was revealed, which indicates psychological maladaptation in patients after acute myocardial infarction and surgical myocardial revascularization (Fig. 1). Anxiety disorders were common.

Thus, along with the existing severe disorders of the cardiorespiratory system, psycho-emotional state, the patients showed an aggravation of pathological disorders of microcirculation processes, hypercoagulation syndrome, and changes in the antioxidant system.

Rice. 1. Averaged profiles of SMOT in patients after acute infarction myocardial, CABG and chronic ischemic heart disease.

It is relevant to study the use of flavonoids (dihydroquercetin) in the rehabilitation programs of these patients, taking into account the stimulant found in patients with other pathologies.

the effect of flavonoids on tissue blood flow, the stabilization of the barrier function of microvessels and the permeability of capillary walls, as well as their primary antioxidant effect.

Rehabilitation of patients after acute myocardial infarction.

results dynamic processes of microcirculation during the rehabilitation of patients after acute myocardial infarction indicate a positive trend after the course of treatment, as evidenced by the improvement in microcirculation (Table 2).

Frequency-amplitude analysis of LDF-grams showed a change in the spectral characteristics due to the weakening of the role of high-frequency oscillations, which are associated with an increase in the activity of the vasomotor mechanism of microcirculation regulation. The data obtained reflect the weakening of passive regulatory mechanisms associated with the state of outflow tracts and indicate a decrease in congestion in the microcirculation system. According to laser Doppler flowmetry, during the rehabilitation of patients with acute myocardial infarction with the inclusion of dihydroquercetin, there was an increase in basal blood flow by 26.6%.

As a result of the treatment, a positive coagulogram was noted in patients taking plasminogen and fibrinolytic activity. The dynamics of the decrease in the RFMK test (soluble fibrinomer complexes), indicating thrombinemia, in

group of patients with dihydroquercetin was more pronounced than in the control group.

Table 2.

Dynamics of microcirculation and hemorheology indicators during rehabilitation

patients after acute myocardial infarction #

Indicators, units measurements (M±m)	Control group (n=15)		Main (n=26) Group	
	Before treatment I	After treatment	Before treatment	After treatment
M - average perfusion, at. e.	28 2.91±0,	29* 3.96±0,	31 2.93±0,	8** 4.33±0.3
NT neurogenic tone, c.u.	23 1.80±0,	22 1.69±0,	fourteen 1.74±0,	8 1.64±0.1
MT myogenic tone, c.u.	33 3.21±0,	24 2.59±0,	32 3.07±0,	2 2.43±0.2
PS indicator shunting, c.u.	08 1.78±0,	06* 1.53±0,	06 1.76±0,	nine** 1.48±0.0
oh activated recalcification time, s	eleven 62.3±3,	53 66.4±3,	22 63.4±3,	3* 72.8±2.8

Plasminogen, %	109.2±7 .22	118.4±5 .24	108.3±4 .73	124.4±5, 12*
fibrinogen, g/l	5.1±0.5 2	3.8±0.3 6*	5.2±0.6 2	3.6±0.42 *
RFMK test with <small>ABOUT</small> phenanthralin, mg/ dl	5.74±0.71	4.24±0, <small>five</small>	5.81±0, 62	3.82±0.5 <small>one*</small>
fibrinolytic Yes activity (min)	227.2±2 .29	230.3±1 .87	225.4±1 .85	231.4±2, 26*

* - reliability of differences between indicators before and after treatment $p < 0.05$; ** - $p < 0.01$;

*** - $p < 0.001$;

- the table shows the data of indicators, which showed a more significant dynamics in the process of rehabilitation with the use of dihydroquercetin compared with the control group.

Dihydroquercetin contributes to the normalization of lipid peroxidation processes in the early stages after acute myocardial infarction: the concentration of malondialdehyde decreased from 7.12 ± 0.28 nmol/l to 6.01 ± 0.26 nmol/l, $p < 0.01$. To a greater extent than in the control group, there was a restoration of the antioxidant system catalase activity to the level of healthy individuals: from 9.23 ± 0.34 to 16.2 ± 0.41 mmol H₂O₂/(min·g Hb), $\dot{y} < 0.01$, and in the control group - up to 13.9 ± 0.39 mmol H₂O₂/(min·g Hv).

An increase in lung capacity from $82.4 \pm 5.9\%$ to $101.6 \pm 4.3\%$ ($p < 0.01$) was combined with an improvement in bronchial patency (increase in forced expiratory volume in 1 second from $83.9 \pm 4.8\%$ to $96.4 \pm 3.9\%$, and forced vital capacity from $78.5 \pm 4.1\%$ to $89.1 \pm 4.3\%$, $p < 0.05$). Improving microcirculation and external respiration function contributed to an increase in blood oxygenation: pO₂ increased

s 69.9 ± 1.57 mm Hg to 78.2 ± 1.62 mm Hg, $p < 0.01$, with a decrease in pCO_2 in the blood from 43.0 ± 1.81 to 38.1 ± 1.1 mm Hg, $p < 0.05$.

There was an improvement in central hemodynamics and pulmonary circulation, which is confirmed by an increase in the ejection fraction from $49.3 \pm 0.6\%$ to $53.5 \pm 0.8\%$, $p < 0.05$; a decrease in mean pressure in the pulmonary artery from 24.2 ± 2.0 mmHg up to 16.2 ± 3.2 mm Hg, $p < 0.05$ - with unreliable dynamics of this indicator in patients of the control group (23.1 ± 2.2 mm Hg— 18.8 ± 3.0 mm Hg, $p > 0.05$).

The clinical result of the presented changes was antianginal and anti-ischemic effects: there was a decrease in the number of people with functional class III angina pectoris due to an increase in the number of patients with FC II angina pectoris, i.e. the class of myocardial ischemia decreased (Fig. 2).

Rice. 2. Redistribution of patients with acute myocardial infarction by functional classes of angina during rehabilitation using dihydroquercetin.

By reducing the manifestations of pulmonary (which can be judged by a decrease in mean pressure in the pulmonary artery) and heart failure (increased ejection fraction), increased oxygenation of blood and tissues in patients of the main group, exercise tolerance increased: from 73.6 ± 4.4 W to 92.3 ± 4.2 W, $p < 0.01$, in patients of the control group - from 75.5 ± 4.6 W to 89.3 ± 4.4 W, $p < 0.05$.

In the group of patients taking dihydroquercetin, a decrease in total cholesterol and triglycerides was registered, while an increase in high-density lipoprotein cholesterol was registered. The lack of dynamics of indicators of biochemical studies: AST, ALT, bilirubin, urea, creatinine, glucose indicates the safety of using dihydroquercetin in patients with acute myocardial infarction (Table 3).

Table 3

Dynamics of biochemical parameters of blood during the rehabilitation of patients

after acute myocardial infarction #

Indicators,	Control group (n=14)	Main group (n=26)

units measurements (M±m)	Before treatment 	After treatment	Before treatment 	After treatment
AST, ME	3 21.5±2,	20.2±2.1	3 21.3±2,	20.4±2.4
ALT, ME	4 26.6±2,	23.3±3.1	five 26.6±2,	22.4±2.2
Bilirubin, µmol/l	five 11.2±1,	10.2±1.2	4 11.8±1,	10.3±1.5
Urea, µmol/ l	7.8±1.2	7.6±1.4	7.8±1.4	7.6±1.2
Creatinine, µmol/l	78.7±2,	77.9±2.2	five 77.7±2,	75.6±2.4
Glucose, mmol/l	2 4.7±0.5	4.6±0.36	4.5±0.6	4.5±0.41
total cholesterol, mmol/l	2 7.7±0.3	* 6.6±0.42	7.6±0.3	6.3±0.54*
LDL cholesterol, mmol/l	2 3.7±0.4	3.6±0.34	4 3.8±0.4	3.4±0.61
HDL cholesterol, mmol/l	04 1.12±0,	4* 1.24±0.0	03 1.10±0,	five** 1.28±0.0

Triglycerides dy, mmol/l	1.82±0, 05	1.68±0.0 4*	1.86±0, 04	1.64±0.0 6**
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* Reliability of differences between indicators before and after treatment at $p < 0.05$; ** at $p < 0.01$.

- the table shows the data of indicators, which showed a more significant dynamics in the process of rehabilitation with the use of dihydroquercetin compared with the control group.

Rehabilitation treatment with the inclusion of dihydroquercetin contributed to the improvement of the psycho-emotional state of patients. The index of reactive anxiety decreased significantly in the main group (from 48.2 ± 4.11 to 34.4 ± 3.0 , $p < 0.01$), in the control group - from 46.4 ± 5.16 to 39.5 ± 4.42 , $p > 0.05$). Among the patients of the main group, the number of patients without violations of psychological adaptation and with mild violations of psychological adaptation increased significantly. In the control group, the positive dynamics was unreliable. After the treatment, there was no significant decrease in the scores on the scales of the neurotic triad, which indicates the persisting psychological maladjustment in some patients requiring additional correction (Fig. 3).

Fig.3. Averaged profiles of SMOT of patients of the main group during treatment.

Rehabilitation of patients after coronary artery bypass grafting

As a result of the implementation of rehabilitation programs in the early post-hospital period in patients who underwent coronary artery bypass grafting, in both groups, positive dynamics of a number of indicators of the clinical and functional state was noted: shortness of breath decreased during exercise, general weakness, pain along the way postoperative sternum, normalized peripheral blood, recovered dream, improved exercise tolerance. At the same time, the dynamics of most indicators in patients of the main group was more significant than in patients of the control group (Table 4). All patients

indicated good tolerability of the dihydroquercetin preparation, an improvement in overall well-being.

The positive therapeutic effect of the course use of dihydroquercetin, which determines the normalization of microcirculation parameters, is similar in its mechanism of action to that in patients after acute myocardial infarction and is associated with the removal of congestion in the venular link, a decrease in intravascular

aggregation of erythrocytes, which is confirmed by an increase in the microcirculation index (M). Frequency-amplitude analysis of LDF-grams indicates a change in the spectral characteristics due to the weakening of the role of high-frequency (HT) oscillations. The data obtained indicate a decrease in congestion and microvascular permeability, especially at the level of capillaries. Revealed positive dynamics (according to conjunctival biomicroscopy) general conjunctival (K10), vascular (K11), extravascular (K111) and intravascular (K1111) indices (Table 4). In rehab

As a result of the use of dihydroquercetin, an increase in the number of functioning capillaries, a decrease in the severity of arteriole spasm, and the normalization of arteriolo-venular ratios and the diameter of microvessels were noted.

In the group of patients treated with dihydroquercetin, there was an improvement in the rheological properties of blood, a decrease in the level of fibrinogen and platelet aggregation, an increase in the filterability (deformability) of erythrocytes, and an improvement in the functional activity of capillaries.

Table 4

Dynamics of the studied parameters based on the results of rehabilitation of patients with coronary heart disease who underwent coronary artery bypass grafting#

Indicators, units measurements (M±m)	Control group (n=19)		Main (n=35) Group	
	Before treatment	After treatment	Before treatment	After treatment
M – average perfusion, c. e.	2.89±0, 31	4.06±0.3 4*	2.85±0, 34	4.36±0.4 2**

kv coefficient variations, u. e.	57 8.72±0,	3 9.11±0.6	61 8.69±0,	-- 9.32±0.4
NT– neurogenic tone, y. e.	25 1.81±0,	-- 1.73±0.2	24 1.79±0,	8 1.58±0.1
MT– myogenic tone, c.u. units	34 3.23±0,	6 2.75±0.2	32 3.19±0,	2* 2.39±0.2
PS– indicator shunting, c.u.	07 1.78±0,	8* 1.59±0.0	06 1.78±0,	8** 1.51±0.0
CI0 (points)	-- 8.1±0.3	7.6±0.21	7 8.3±0.3	6.9±0.39*
KII (points)	twenty 0.89±0,	3 0.88±0.2	35 0.89±0,	6 0.80±0.3
KIII (points)	42 5.80±0,	five 5.64±0.4	40 5.78±0,	five 4.85±0.3
KIII (points)	17 0.99±0,	-- 0.92±0.2	twenty 0.98±0,	five 0.95±0.3
ÿÿÿ2, mm Hg	24 43.6±1,	4* 39.4±1.4	48 44.8±1,	3** 38.3±1.3

RO2, mm Hg	24	65.0±2,	3*	71.8±2.4	62	65.6±2,	6**	76.8±2.4
fibrinogen, g/l	2	5.4±0.2	*	4.7±0.26	4	5.6±0.3	*	4.5±0.22*
VC, %	2	86.0±4,	*	97.2±3.1	4	86.8±3,	five**	101.9±3,
FVC, %	2	81.4±5,		83.8±5.4	4	81.8±4,		96.9±4.5*
FEV1, %	3	87.4±4,		91.7±4.4	five	86.8±3,		97.9±3.4*
MOS50,%	3	89.8±5,	6*	105.9±5,	...	90.1±5,	4**	112.2±5,
MOS75, %	2	82.4±4,	*	96.2±4.8	8	81.4±5,		98.3±5.2*
MVL, %	nine	64.2±4,		78.1±5.2	0	66.1±5,		82.7±5.7*
FI, %	3	51.8±1,	*	55.4±1.2	4	50.8±1,	*	56.2±1.5*
Avg, mm Hg	2	23.9±3,		18.7±3.4	nine	24.0±3,		16.1±2.4
TFN, W	8	74.4±3,	*	88.5±3.4	3	70.7±4,	*	94.3±4.2*

*Reliability of differences between indicators before and after treatment at $p < 0.05$; - at $p < 0.01$.

- the table shows the data of indicators for which a more significant dynamics was noted in the process of rehabilitation with the use of dihydroquercetin - compared with the control group.

In the main group, during rehabilitation, restoration of antioxidant protection was established: an increase in the level of catalase from 9.52 ± 1.01 to 14.4 ± 1.04 mmol H₂O₂/(min·g Hb), $p < 0.001$, in the control group - from 9.55 ± 1.03 to 13.6 ± 1.06 mmol H₂O₂/(min·g Hb), $p < 0.01$) with a decrease in DC from 0.362 ± 0.010 to 0.306 ± 0.015 OD/mg lipids, $p < 0.01$, malonic dialdehyde - from 7.56 ± 0.41 nmol/l to 6.25 ± 0.21 nmol/l, $p < 0.01$ (no statistically significant dynamics was found in the control group).

The rehabilitation program with the inclusion of dihydroquercetin ensured the normalization of the gas composition of the blood. A significant increase in blood oxygen saturation was noted: from 65.6 ± 2.62 mm Hg. to 76.8 ± 2.46 mm Hg, $p < 0.01$, with a decrease in the partial tension of carbon dioxide in the blood from 44.8 ± 1.48 mm Hg. up to 38.3 ± 1.33 , $p < 0.01$. A decrease in the manifestations of respiratory and heart failure was established: an increase in indicators of the function of external respiration (an increase in the vital capacity of the lungs, forced vital capacity of the lungs), an improvement in bronchial patency (an increase in forced expiratory volume in 1 sec., an average maximum expiratory volume velocity), an increase in the ejection fraction from $50.8 \pm 1.4\%$ to $56.2 \pm 1.5\%$, $p < 0.01$ (see Table 4).

An increase in exercise tolerance was established: from 70.7 ± 4.3 W to 94.3 ± 4.2 W. None of the patients had an increase in angina attacks and episodes of painless ischemia.

The transfer of patients to a more "favorable" FC occurred in patients of the main group: the number of patients with angina of the 3rd FC decreased from 16 people to 9, and with the 2nd FC increased from 12 to 19, most patients in the control group remained in the same FC.

The implementation of an optimized rehabilitation program contributed to the improvement of the psycho-emotional state of patients. Significantly improved: well-being, activity, mood; in the main group, the indicator of reactive anxiety decreased from 49.1 ± 2.83 to 38.1 ± 3.42 ($p < 0.05$) (in the control group, from 49.3 ± 2.74 to 43.7 ± 4.12 , $p > 0.05$). However, it should be noted that the dynamics of indicators for 1–3

th scale of the neurotic triad (according to the 1st - from 65.1 ± 1.34 to 61.6 ± 1.37 T-points; according to the 2nd - from 64.7 ± 1.22 to 61.5 ± 1.27 T-points; according to the 3rd - from 66.0 ± 1.32 to 62.4 ± 1.35 T-points ($p > 0.05$)) indicates the persisting psychological maladjustment of the operated patients, which requires appropriate correction.

Thus, during the early post-hospital rehabilitation of patients with the inclusion of a plant bioflavonoid - Dihydroquercetin corrects significant pathogenetic syndromes of coronary artery disease, aggravated after complications of acute myocardial infarction bypass surgery: syndrome of or after aorto-coronary microcirculatory disorders, hemocoagulation and lipid peroxidation. This increased antianginal and antiischemic effects, correction of postinfarction and postoperative disorders of central and peripheral hemodynamics. The consequence of these effects was a more significant increase in activity, which has

of paramount importance for all subsequent stages of rehabilitation of this severe category of patients.

conclusions

1. At the hospital stage of rehabilitation in patients with coronary artery disease after acute myocardial infarction and coronary artery bypass surgery, microcirculation disorders, hypercoagulation are aggravated syndrome, activation of lipid peroxidation processes with a decrease in the activity of antioxidant protection, which correlates with a decrease in blood oxygenation, disorders of the central and pulmonary

hemodynamics, prolongs the decrease in exercise tolerance and psychological maladjustment of patients. These data substantiate the need to optimize the rehabilitation program aimed at the utilization of oxygen by ischemic cardiomyocytes and the neutralization of oxidative

stress.

2. The inclusion of plant bioflavonoids (dihydroquercetin) in the early post-hospital rehabilitation of patients after acute myocardial infarction or coronary artery bypass grafting contributes to improvement of microcirculation processes, which is manifested by an increase in the microcirculation index from 2.85 ± 0.34 c.u. up to 4.36 ± 0.42 c.u. ($p < 0.01$), increased active vasomotor mechanisms of microcirculation regulation, reduced permeability of the capillary bed and congestion in it.

3. Medical rehabilitation programs using dihydroquercetin have a corrective effect on the state of the blood coagulation and anticoagulation systems, are accompanied by a decrease in the products of free radical oxidation of lipids in the blood plasma and an increase in the activity of antioxidant enzymes, which improves blood oxygenation, respiratory function and leads to the correction of postinfarction disorders of the central and pulmonary hemodynamics.

4. The inclusion of dihydroquercetin in the rehabilitation programs of patients with myocardial infarction or after myocardial revascularization contributes to an increase in the clinical effect of rehabilitation: anti-ischemic and antianginal, exercise tolerance (from $70.7 \pm 4.3W$ to $94.3 \pm 4.2W$, $p < 0.01$), a decrease in psychological postinfarction and postoperative disorders with a decrease in the level of reactive anxiety by 13.8 points ($p < 0.01$), in the control group - by 7 points ($p > 0.05$), however, while maintaining the psychological maladjustment of patients, requiring additional correction.

5. In terms of up to 3-6 months, there is stability of the results achieved after the end of the course of treatment, the integral indicator of which is a higher percentage of patients who returned to work: those who had myocardial infarction - 69.2% (in the control group - 53.8%), coronary artery bypass surgery - 70% (50%).

PRACTICAL RECOMMENDATIONS

1. In order to comprehensively assess the condition of patients with coronary artery disease after myocardial infarction and myocardial revascularization operations, a differentiated approach to the choice of rehabilitation programs, it is recommended, along with the study of central and peripheral hemodynamics, structural and functional parameters of the cardiovascular system, lipid spectrum, to conduct a study of microcirculation, peroxide lipid oxidation and antioxidant system. The same studies, carried out in dynamics, will allow us to evaluate the effectiveness of medical rehabilitation.
2. To increase the effectiveness of rehabilitation measures and prevent complications of the course of coronary artery disease in patients in the early stages after acute myocardial infarction or aorto-coronary bypass operations, it is advisable to comprehensive rehabilitation programs for patients with natural bioflavonoids, in particular, the antioxidant dihydroquercetin.
3. The severity of the clinical action and good tolerability of dihydroquercetin justify the use of the drug as a necessary means of correcting pathogenetic disorders of microcirculation processes and antioxidant protection (courses up to 3 months at a daily dose of 80 mg).

Absolutely indicated for the appointment of dihydroquercetin are patients with preserved post-infarction postoperative angina pectoris and painless myocardial ischemia, tk.

It is the insufficient correction of microcirculation processes in the myocardium that causes the absence of an antianginal and anti-ischemic effect.

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List of abbreviations

ALT, AST	alanine aminotransferase, aspartate aminotransferase
US	coronary artery bypass grafting
DC	diene conjugates
units	units
VC	lung capacity
<small>ischemic heart disease</small>	coronary artery disease
kv	the coefficient of variation
CI	conjunctival index

LDF	laser doppler flowmetry
MVL	maximum ventilation of the lungs
ISO (50.75)	maximum volumetric velocities at 50%, 75% forced vital capacity
M	average perfusion
MT	myogenic tone
NT	neurogenic tone
AMI	acute myocardial infarction
FEV1	forced expiratory volume in 1 second
HCO	total serum cholesterol
PS	shunt rate
RFMC	soluble fibrin monomer complexes
SMOL	Abbreviated Multivariate Questionnaire for Personality research

avdla mean pulmonary artery pressure

TFN exercise tolerance

c.u. conventional units

FZhEL forced vital capacity

FI exile faction

FC functional class

LDL cholesterol low density lipoprotein cholesterol

HDL cholesterol high density lipoprotein cholesterol

pCO₂ partial pressure of carbon dioxide

pO₂ partial pressure of oxygen

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