Efficiency and Mechanisms of the Antioxidant Effect of Standard Therapy and Refracterin in the Treatment of Chronic Heart Failure in Elderly Patients with Postinfarction Cardiosclerosis

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Refracterin therapy of patients with chronic heart failure caused by coronary heart disease and postinfarction cardiosclerosis markedly promoted improvement in the pulmonary and systemic circulation in comparison with patients receiving traditional therapy. The mean functional class of chronic cardiac failure decreased by 43% under the effect of refracterin *vs.* 27% decrease in the group receiving traditional therapy. After 1-month refracterin course the end-systolic and end-diastolic sizes of the left ventricle decreased by 12 and 7%, respectively, ejection fraction increased by 7.2% in comparison with the initial level, total oxidant activity and MDA content in the plasma decreased significantly, while total antioxidant activity, catalase and SOD activities, cytochrome *C*, NADH, and NADPH levels increased. The prooxidant-antioxidant system was shifted towards antioxidants, which attests to activation of the defense and adaptive mechanisms after administration of refracterin, which is especially important in elderly patients with initially decreased reserve potentialities of the antioxidant defense system.

Key Words: *chronic cardiac failure; elderly age; antioxidant system; refracterin*

Severe course of coronary heart disease and postinfarction cardiosclerosis combined with progressive chronic cardiac failure (CCF) can lead to the development of oxidative stress [1,4,5] in myocardial structures and circulating lipid-protein complexes. This metabolic state promotes activation of apoptosis and hibernation of cardiomyocytes and the formation of pathological intravascular phenomena [3,8]. All these phenomena are significant for the progress of coronary heart disease and its complications in elderly patients with decreased reserve potentialities of the antioxidant system and increased rate of apoptotic reactions [4,5].

We studied the effect of refracterin, a preparation containing 0.075 mg β-acetyldigoxin, NAD, cytochrome *C*, oxyfedrine, and inosine on the antioxidant-prooxidant system during treatment of elderly patients with CCF.

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MATERIALS AND METHODS

Forty-seven patients aging 67-87 years (mean age 72.5±5.6 years) with coronary heart disease, postinfarction cardiosclerosis, CCF of NYHA functional classes II-IV (mean functional class 3.25±0.25) were examined. After general clinical examinations all patients were randomly divided into 2 groups. Controls (n=24) received cardiac glycoside (1 ml 0.025% digoxin parenterally for 10 days and then orally in a daily dose of 0.25 mg), angiotensin-converting enzyme inhibitor (captopril, 12.5-50 mg/day), diuretic (lasix in a daily dose of 40-120 mg parenterally for the first 10

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days, then furosemide or hydrochlorothiazide orally). Patients of the main group (n=23) instead of digoxin received refracterin (2 flasks, 230 mg) twice a day by intravenous drip infusion in 70 ml 5% glucose or saline (in case of concomitant diabetes mellitus) for 45-60 min for 10 days, after which they received 2 flasks once a day in the same volume for 10 more days, and then 1 flask in 5 ml water for injections intramuscularly for 10 more days.

The severity of CCF was scored, cardiac function was evaluated by two-dimensional and Doppler-echocardiography on a Hewlett Packard Sonos-100 device. In order to evaluate the plasma prooxidant-antioxidant status, plasma total antioxidant activity (TAA), total oxidant activity (TOA) [2], SOD and catalase activities, content of MDA, cytochrome *C* (as the mitochondrial necrotic marker), NAD, NADH, NADP, and NADPH pyridine nucleotides were measured by biochemical methods. Based on the findings, the TAA/TOA, NAD/NADH, NADP/NADPH, and SOD/MDA ratios were calculated.

RESULTS

The severity of CCF symptoms decreased by 57% in the control group and by 75% in the main group. This was paralleled by positive changes in ECG in both groups. In the control group heart rate decreased by 17% in patients with sinus rhythms, and pulse deficit decreased by 67% in patients with atrial flutter. In the main group heart rate decreased by 27% and the tachisystolic flutter transformed into normosystolic form without pulse deficiency. The mean arterial pressure in the control group decreased by 15% in the subgroup with moderate arterial hypertension, while in the group receiving refracterin by 22%. Due to refracterin therapy, the double product (Opie index) decreased by 31% *vs.* 19% in the control group.

Dyspnea was the most stable and informative symptom for evaluating treatment efficiency and predicting the disease course in severe CCF. Its intensity decreased by 35 and 47% in the control and main groups, respectively. This parameter directly correlated with the functional class of CCF (r=0.74, p<0.01). Refracterin therapy reduced congestion in the lungs and liver and markedly improved pulmonary and systemic circulation, these processes being much more rapid than in the control group. As a result of refracterin therapy, the functional class of CCF decreased by 43% *vs.* 27% after traditional therapy.

After refracterin treatment the end-systolic and end-diastolic sizes of the left ventricle decreased by 12 and 7%, respectively, while the ejection fraction increased by 7.2% compared to the initial level.

The studies revealed a significant decrease in plasma TOA and MDA content, and an increase in TAA, catalase and SOD activities and contents of cytochrome *C*, NADH, NADPH (Table 1) in patients treated with

TABLE 1. Content of Pyridine Nucleotides, Cytochrome *C*, SOD, Catalase, and MDA and Changes in TAA and TOA in Elderly Patients with CCF ($M\pm m$)

Parameter	Control group		Main group	
	before therapy	after therapy	before therapy	after therapy
Cytochrome *C*, nmol/ml	0.32±0.03	0.38±0.03	0.31±0.04	0.56±0.04^{**++oo}
NAD, nmol/ml	8.4±0.9	9.2±0.8	7.6±1.0	15.3±1.1^{**++oo}
NADH, nmol/ml	13.9±0.4	14.8±0.3	11.8±0.9	18.3±1.0^{**++oo}
NADP, nmol/ml	7.4±0.5	8.8±0.4	7.6±0.8	13.9±0.9^{**++oo}
NADPH, nmol/ml	11.1±1.6	14.1±1.2*	12.8±0.8	17.3±1.1^{**++oo}
NAD/NADH	0.60±0.05	0.62±0.05	0.64±0.07**	0.84±0.07^{**++oo}
NADP/NADPH	0.67±0.06	0.62±0.07	0.59±0.04	0.80±0.06^{**++}
TOA, %	43.4±2.6	41.4±2.0	47.0±3.6	23.6±3.8^{***+oo}
TAA, %	16.7±2.1	18.7±2.3	14.5±5.6	31.8±3.6^{**+oo}
TAA/TOA	0.38±0.06	0.45±0.06	0.30±0.10	1.35±0.06$^{***+++ooo}$
SOD, arb. units	1.1±0.5	1.3±0.5	1.0±0.6	5.7±2.6$^{***+++ooo}$
Catalase, arb. units	1.1±0.4	2.1±0.4*	0.6±0.2^{*+}	5.0±2.7$^{**+++ooo}$
MDA, μmol/ml	1.82±0.12	1.52±0.14	2.4±0.3^{+}	0.98±0.06$^{***+++ooo}$
SOD/MDA, arb. units/μmol	0.61±0.04	0.61±0.05	0.41±0.04^{*+}	5.81±0.13$^{***+++ooo}$

Note. One symbol: p<0.05; two symbols: p<0.01; three symbols: p<0.001 compared to *control group before therapy; $^{+}$control group after therapy; ^{o}main group before therapy.

refracterin. The redox potential of the energy supply system (NAD/NADH) virtually did not change in the control group after treatment, but increased after refracterin therapy (Table 1). A stable decrease in the NAD/NADH ratio can indicate activation of both anabolic and catabolic processes (in favor of the latter ones), and the decrease in the NADP/NADPH ratio can be regarded as a prerequisite for the disadaptation status [6].

Mitochondrial dysfunction is caused by disorders in the chain of reducing equivalent transfer to oxygen because of cytochrome *C* release. Blood content of cytochrome *C* increased in the main group and remained below the normal in the control group. As a result of recovery of oxidative phosphorylation in the mitochondria and glycolysis under the effect of refracterin, degenerative processes in the myocardium were largely arrested. In the control group redox potentials of the energy supply system remained low.

Analysis of these data indicates a shift in the prooxidant-antioxidant system towards antioxidants, which attests to activation of the defense and adaptation mechanisms in response to refracterin.

Oxidative stress is associated with intensification of LPO and drastic increase of the plasma MDA content. The fact that SOD/MDA ratio (parameter characterizing the ratio of the main enzyme antioxidant factor to the marker of the pathogenic effect of free radicals on membrane lipids) decreases under the effect of refracterin confirms the hypothesis about LPO intensification and relative insufficiency of the antioxidant component.

The detected disorders in oxidative metabolism in elderly patients with coronary disease, postinfarction cardiosclerosis, and complicated CCF necessitate monitoring of free radical processes and adequate drug correction of oxidative stress within the framework of traditional therapy.

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