Efficiency of Refracterin in Patients with Chronic Cardiac Insufficiency Caused by Coronary Heart Disease

S. G. Kanorskii, P. A. Galenko-Yaroshevskii, and K. B. Zingilevskii

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Composite preparation refracterin administered in a dose of 300 mg/day for 3 days in addition to routine therapy significantly improved the results of treatment of severe cardiac insufficiency of ischemic genesis compared to placebo. Improvement of clinical status of patients is determined by positive dynamics of systolic and diastolic functions of the left ventricle.

Key Words: *refracterin; ischemic heart disease; chronic cardiac insufficiency*

Chronic cardiac insufficiency (CCI), a syndrome occurring in 1-2% Europeans, most frequently aggravates coronary heart disease (CHD), primarily after myocardial infarction [14]. Despite wide introduction of modern clinical methods based on the use of angiotensin-converting enzyme (ACE) inhibitors and β-adrenoblockers antagonists into CCI treatment, the prognosis of the disease is unfavorable [12,13,14]: 50% patients die within 4 years after diagnosis [11].

Recent attention returned to the treatment of CCI patients with cardiac glycosides and even inotropic stimulators [5]. However, the role of ischemia and energy deficiency in cardiomyocytes during CCI received little attention [1,2]. This imbalance can be remedied by the use of drugs improving myocardial function via stimulation of energy metabolism at the cellular level and normalizing redox processes, *e.g.* refracterin, a composite of nicotinamide adenine dinucleotide (NAD, 0.5 mg/ampoule), β-acetyldigoxin (0.075 mg/ampoule), oxyphedrine (0.3 mg/ampoule), cytochrome C (10 mg/ampoule), and inosine (80 mg/ampoule) [7].

Previously, the effect of refracterin was studied in patients and experimental animals predominantly during noncoronary myocardial diseases [3,6-8] or in the late period after the coronary artery bypass surgery [4]. The efficiency of this preparation in patients with CCI caused by CHD and postinfarction cardiosclerosis or in cases of short-term therapy is still unknown.

Our aim was to assess the efficiency of short-term refracterin therapy in patients with severe CCI accompanied by CHD.

MATERIALS AND METHODS

The study was carried out on 58 patients (31 men and 27 women) aging 53-74 years (mean age 66.5±2.9 years) hospitalized because of inefficiency of outpatient treatment of CCI. In all cases, the basic pathology was CHD accompanied by angina pectoris functional class I-III. Fifty-two patients (89.7%) had old Q-wave myocardial infarction. The patients with valvular disease, cardiomyopathy, chronic pulmonary diseases, and oncological pathology were excluded from the study. Before admission to the hospital the patients received ACE-inhibitors (n=47, 81%), diuretics (n=45, 77.6%), cardiac glycosides (n=16, 27.6%), and β-adrenoblockers (n=13, 22.4%) in adequate doses, respectively. Despite this therapy, in all cases the symptoms of pronounced CCI of III and IV functional degrees (NYHA classification) against the background sinus rhythm remained in 43 (82.8%) and 10 (17.2%) patients, respectively.

The patients were randomized into two groups of 29 persons each. In all cases, the treatment started

Krasnodar Research Center, Russian Academy of Medical Sciences, Administration of Krasnodar Krai; Krasnodar City Emergency Hospital

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with ACE-inhibitor perindopril (Prestarium, Servier, 4 mg/day *per os*), diuretic furosemide (Akrikhin, 40-80 mg/day, intravenously), cardiac glycoside digoxin (Gedeon Richter, 0.25 mg/day *per os*), and aldosterone antagonist spironolactone (Verospiron, Gedeon Richter, 25 mg/day *per os*). In addition, the group 1 patients daily received refracterin (300 mg in 3 ampoules for 3 days) dissolved in 100 ml of 0.9% NaCl, which was intravenously drip-fed in an hour by single blind method. The group 2 patients received placebo (100 ml of 0.9% NaCl) administered in the same regimen.

In addition to routine clinical examination at admission and after 3-day treatment, standard echocardiography was performed with a Combison-420 apparatus in 2D-scanning and pulse-wave Doppler modes [10]. The systolic function of the left ventricle (LV) was assessed: ventricular ejection fraction has calculated by the method of Simpson. The diastolic function of LV was evaluated with Doppler transmitral spectrum by determining the maximum blood flow velocity values and their ratio in phases of early and late (atrial) fillings.

The data were processed statistically using Student's t test at $p<0.05$.

TABLE 1. Initial Indices in Randomized Groups of Patients ($M\pm m$)

Index	Group 1 (n=29)	Group 2 (n=29)
Sex, man/women	15/14	16/13
Age, years	68.1±3.3	64.9±3.0
Anamnestic myocardium infarction	25 (86.2%)	27 (93.1%)
Functional class of stable angina		
I	4 (13.8%)	3 (10.4%)
II	17 (58.6%)	19 (65.5%)
III	8 (27.6%)	7 (24.1%)
Functional class of CCI		
III	23 (79.3%)	25 (86.2%)
IV	6 (20.7%)	4 (13.8%)
Treatment before enrolling into study		
ACE inhibitors	23 (79.3%)	24 (82.8%)
diuretics	24 (82.8%)	21 (72.4%)
cardiac glycosides	8 (27.6%)	8 (27.6%)
β-adrenoblockers	7 (24.1%)	6 (20.7%)

RESULTS

The examined groups were matched for sex, age, incidence of infarction (anamnestic data), severity of angina pectoris and CCI, and strategy of therapy before the study (Table 1).

After 3 days of treatment, the mean heart rate (HR) decreased by 20.9 and 15.7% in groups 1 and 2, respectively (Table 2). More pronounced bradycardia in patients treated with refracterin can be related to general improvement of hemodynamic status, rather than to negative chronotropic action of digoxin. Somewhat more pronounced and significant deceleration of HR was observed during long-term courses of refracterin [6].

The decrease in end-diastolic size of LF was insignificant in all groups. Significant increase in LV ejection fraction by 10.1% was observed only in group 1 ($p<0.05$), while in group 2 it was insignificant (2.8%). It is known that 20-30-day course of refracterin can decrease the end-diastolic size of initially dilated LV by 15-25% and increase its ejection fraction by 20-30% [6,8].

In patients receiving refracterin, the maximum early diastolic blood flow velocity decreased by 11.1% ($p<0.05$), while the maximum diastolic blood flow velocity during atrial systole increased by 13.8% ($p<0.05$). The ratio of these values decreased by 21.9% ($p<0.01$), which indicates transformation of most dangerous restrictive type of LV diastolic dysfunction into less severe pseudonormal type. The positive shifts in transmitral diastolic flow were observed also in group 2 patients, although they were less pronounced. The more pronounced improvement of LV diastolic function in our study in comparison with [6] can be explained by the use of ACE inhibitor.

The treatment with refracterin was not accompanied by significant changes in blood pressure. No side effects of refracterin were observed, including glycoside intoxication. Other researches also reported good tolerance to refracterin [4,6-8].

The mean functional class of CCI (an integral clinical index) decreased from 3.21±0.14 to 2.05±0.09 (by 36.1%, $p<0.01$) and from 3.14±0.12 to 2.56±0.10 (by 18.5%, $p<0.01$) in groups 1 and 2, respectively. As early as after three days of refracterin treatment, 93.1% patients demonstrated improvement of their clinical status. The corresponding value in placebo group was 58.6% ($p<0.01$). Two patients of the second group died from pulmonary edema.

Rapid stabilization of the status of patients hospitalized with progressive CCI is the most urgent problem of treatment, because the answer to this challenge prevents fatal outcome. Our data explain more pronounced improvement of clinical status of refracterin-treated patients by significantly better positive changes of systolic and diastolic function of LV. To a certain degree, the increase of LV ejection fraction can be explained by positive inotropic effect of oxyphedrine

TABLE 2. Changes of Basic Echocardiographic Indices during Treatment of Group 1 and 2 Patients ($M \pm m$)

Index	Group 1		Group 2	
	initial	after 3 days	initial	after 3 days
n	29	29	29	27
HR, min^{-1}	104.6±7.8	82.7±5.3*	102.5±7.7	86.4±5.6*
End-diastolic size of LV, cm	6.58±0.24	6.43±0.22	6.49±0.21	6.37±0.18
LV ejection fraction, %	42.5±2.1	46.8±2.3*	43.0±2.5	44.2±2.6
V_e (cm/sec)	79.3±4.6	70.5±3.9*	76.8±4.7	72.5±4.1
V_a (cm/sec)	40.5±2.8	46.1±2.7*	39.2±2.4	43.6±2.5
V_e/V_a	1.96±0.10	1.53±0.08*	1.96±0.09	1.66±0.08*

Note. V_e is maximum early diastolic blood flow velocity; V_a is maximum diastolic flow velocity during atrial systole. *$p<0.05$ compared to the initial value.

and to a lesser degree, by a low dosage of digoxin, which is capable to moderate the hyperactivity of neurohumoral systems in patients with CCI.

An important feature of refracterin treatment is complex approach to metabolic therapy. Experiments showed that combination of NAD, cytochrome C, and inosine improves myocardial tolerance to ischemia, restores ATP level, and prevents disturbances in glycolysis and oxidative phosphorylation in Krebs cycle [2]. The effect of refracterin on production of macroergic compounds is not underlain by supply of the substrates to Krebs cycle as is characteristic of routine metabolic therapy, but by restoration of damaged compartments of energy machinery in the cytosol and mitochondria, which stimulates synthesis of ATP and creatine phosphate in the cardiomyocytes [7]. Elimination of energy deficiency in ischemic heart with refracterin seems to be the key factor in the improvement of contractile function of LV in patients with CCI accompanied by CHD. The use of refracterin makes it possible to restore normal content and the ratio between pyrimidine nucleotides, cytochrome C, pyruvate, and lactate. In addition, this drug enhances glycolytic activity of the blood. As a result, refracterin improves functional activity of cardiomyocytes and myocardium [6].

In most cases, diastolic dysfunction of LV combines in CCI patients with systolic dysfunction or even prevails over it, although the diastolic dysfunction defies correction by positive inotropic agents [9]. In this respect, the potency of refracterin to augment the positive effect of routine therapy of CCI on LV diastolic function seems to be very important, and it can be related to elimination of ischemic contracture of the myocardium [1]. Refracterin actively participates in the intracellular metabolic processes in the myocardium, and restores homeostasis of the systems responsible for contraction and relaxation thereby eliminating dysfunction of LV [3].

Thus, compared to placebo treatment, a 3-day-long refracterin therapy greatly improved the results of routine therapy of severe ischemia-induced CCI. This improvement resulted from the positive changes in systolic and diastolic functions of LV.

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