Energostim in Therapy of Chronic Ischemia of the Lower Limbs

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Positive changes were more pronounced in patients with chronic ischemia of the lower limbs treated with energostim alone and in combination with trental in comparison with patients receiving trental monotherapy. The best effect was attained in patients treated with energostim in combination with trental.

Key Words: *microcirculation; energostim; chronic ischemia of the limbs*

The majority (85%) of patients with chronic ischemia of the lower limbs (CILL) belong to older age groups [3,9]. Standard conservative trental-based therapy of CILL is often impossible because of coronary disease (trental provokes episodes of angina pectoris in patients with coronary disease, thus augmenting cardiac insufficiency in decompensated patients) [2,6]. Therefore the search for new drugs with antihypoxic and cardiotropic effects for the treatment of CILL is an important task [5,8].

Energostim used in clinical cardiology is a complex preparation consisting of nicotinamide dinucleotide (0.5 mg), cytochrome C (10 mg), and inosine (80 mg). The main effects of energostim are antihypoxic and antioxidant. This drug also reduces histotoxic hypoxia and restores the erythrocyte elasticity (deformability). This improves oxygen supply to cells, prevents disorders in glycolysis and oxidative phosphorylation in the Krebs cycle, and reduces oxygen demand of the myocardium [1,4,5,7].

We studied the possibility of using energostim for the treatment of CILL of atherosclerotic origin in patients with concomitant coronary disease.

MATERIALS AND METHODS

This study is based on the results of examinations and treatment of 90 patients with CILL stage IIB (according to A. V. Pokrovskii classification) caused by atherosclerotic involvement of the femoro-popliteo-tibial arterial segment hospitalized in "one day" Center of Surgery and in Department of Vascular Surgery, Municipal Clinical Hospital No. 3, in Krasnodar in 2001-2002. The age of patients varied from 43 to 82 years (mean age 64.7 years). The overwhelming majority (93.3%) were men.

The patients were divided into 3 groups. Group 1 patients (n=34, 37.7%) were treated with trental, group 2 (n=29, 32.3%) received energostim, and group 3 (n=27, 30%) received energostim and trental. Trental and energostim were injected intravenously by drip infusion in doses of 5 ml and 200 mg, respectively, in 200 ml 0.9% NaCl. The course of treatment lasted for 15 days. Since trental is considered as the "gold standard" of CILL treatment, we regarded group 1 as the control.

In 68 (75.5%) patients concomitant involvement of coronary arteries clinically manifested by coronary heart disease (Table 1).

Echocardiography was carried out in all patients in order to evaluate the function of the myocardium. The study revealed decreased stroke volume, cardiac output, and left-ventricular ejection fraction in group 2 patients *vs.* groups 1 and 3 and in group 3 *vs.* group 1 (Table 2). These data confirm satisfactory pumping function of the myocardium in group 1 patients, reduced function in group 3, and low function in group 2.

Left-ventricular hypertrophy was detected in 33.6% of group 1 patients, 74.6% group 2 patients, and in 42.3% group 3 patients; of these, hypo- and akinetic zones were detected in 28.3% group 1 patients, in

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70.1% group 2 ones, and in 38.5% of group 3 ones. Diffuse contractility disorders were detected in 57.7% group 2 patients compared to only 25.4% in group 1 and 43.2% in group 3.

These data indicate that group 2 consisted of more grave patients, with greater probability of cardiac complications in comparison with other groups. That is why in order to rule out provocation of angina pectoris episodes against the background of trental treatment and prevent the progress of cardiac insufficiency, these patients were treated with energostim. Patients of two other groups were prescribed trental as the basic drug. Due to this approach no cardiac side effects of conservative therapy occurred.

For topical diagnosis and evaluation of the severity of microcirculatory disorders in the limbs we used ultrasonic dopplerography of the lower limbs with spectral analysis of Doppler signal and segmentary measurements of regional systolic pressure, duplex scanning with color mapping, X-ray contrast angiography of the lower limb vessels, rheovasography (RVG), and laser Doppler-flowmetry (LDF).

LDF findings were the most significant for the evaluation of the severity of microcirculation disorders in the limbs and efficiency of conservative therapy. The study was carried out in an isolated room at 20°C, with the patient lying, on a Transonic Systems MLF-21 device using type N pickup for studies of skin microcirculation. The pickup was fixed on the planar surface of the thumb and on the back of the sole in the first interdigital space. Basal bloodflow was recorded for 3 min. LDF was carried out in all patients before and on day 15 of the treatment.

The results were statistically processed using Student's t test.

RESULTS

The findings of instrumental methods of examination suggest that the three groups were homogenous by the localization of lesions and by the severity of limb ischemia, except the incidence of concomitant diseases which was higher in group 2 (Fig. 1). However, there was no statistical difference between the parameters in the three groups.

Duplex scanning with color mapping showed occlusion of the surface femoral artery combined with occlusive stenotic involvement of the popliteal and tibial arteries. In cases with dubious data of duplex scanning, X-ray contrast arteriography was carried out for the evaluation of the possibility of reconstructive surgery (in 11 patients), which confirmed failure of the distal vessels of the lower limb.

During the treatment all patients noted cessation of dumbness, paresthesia and cooling of the soles; the distance of walking without pain increased after the course of treatment (Table 3).

Self-evaluation of the health status showed best results in groups 2 and 3 receiving energostim.

Ultrasonic dopplerography showed that collateral bloodflow in the lower limbs was retained in all patients after a course of conservative therapy. The parameters of the malleolar pressure index remained unchanged as well (Fig. 1, *a*).

Analysis of RVG data showed that conservative therapy did not lead to appreciable increase in the rheographic index (Fig. 1, *b*).

A significant ($p<0.05$) increase of the basal bloodflow was observed in patients of all groups after a course of conservative therapy: by 15.35% of the initial level in group 1, by 54.53% in group 2, and by 81.38 in group 3. It is noteworthy that the basal bloodflow in group 2 increased significantly greater ($p<0.05$) than in group 1, but significantly less ($p<0.05$) than in group 3. LDF findings indicated that energostim more effectively than trental stimulated the bloodflow in the capillaries of the ischemic limb. On the other hand, combined therapy with these drugs led to a more significant increase in the basal microcirculatory bloodflow than monotherapy with energostim.

No side effects, including allergic reactions, progress of chronic cardiac insufficiency, or provoked attacks of angina pectoris, were observed in any of the patients during therapy.

TABLE 1. Concomitant Diseases in Patients with CILL

Disease	Group						Total	
	1st		2nd		3rd			
	n	%	*n*	%	*n*	%	*n*	%
Coronary disease	23	68	24	80	21	78	68	75.5
Arterial hypertension	16	53.3	20	66.7	23	76	59	65.5
Chronic nonspecific pulmonary diseases	9	30	12	40	7	23.3	28	31.1
Gastroduodenal ulcer	4	13.3	5	16.6	3	10	12	13.3

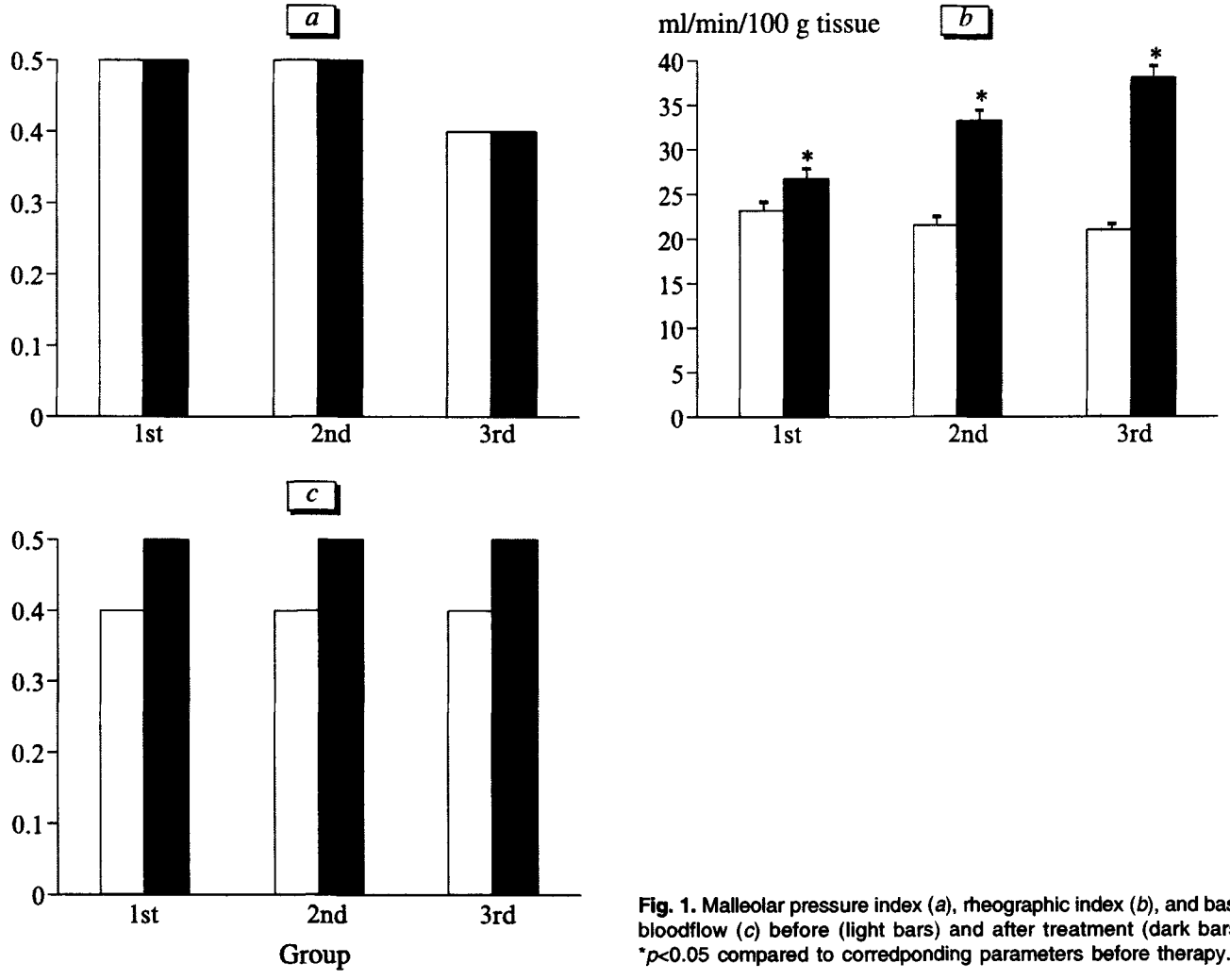

Fig. 1. Malleolar pressure index (*a*), rheographic index (*b*), and basal bloodflow (*c*) before (light bars) and after treatment (dark bars). *$p<0.05$ compared to corredponding parameters before therapy.

Hence, the study carried out in 3 groups of patients before and after therapy showed that the treatment led to an appreciable improvement of the ischemic limb. Paresthesia and chilliness disappeared, the distance of walking without pain increased. Positive changes were more pronounced in group 2 patients *vs.* group 1 treated with trental. The maximum effect was attained in group 3 patients treated with energostim in combination with trental.

The absence of positive shifts after conservative therapy in all groups according to RVG and ultrasonic dopplerography in the presence of pronounced subjective improvement indicate that the therapeutic effects of trental and energostim are realized mainly at the expense of improvement of microcirculation in the lower limbs. Vasodilating effect of energostim, described for experimental rats, was virtually not observed in the patients.

TABLE 2. Central Hemodynamic Parameters (*M±m*)

Group	Stroke volume, ml	Cardiac output, liter/min	Ejection fraction, %
1st	83.23±8.13	6.15±0.42	61.46±3.45
2nd	70.25±10.26*	5.18±0.34	51.26±3.42*
3rd	77.55±7.75*	5.75±0.53	55.84±2.63*

Note. *$p<0.05$ compared to group 1.

The studies showed that energostim was effective in the treatment of CILL as a monotherapy in coronary patients with class III chronic cardiac insufficiency and in combination with trental in class II chronic cardiac insufficiency. In this group we observed a combination of disaggregant, fibrinolytic, and weak vasodilating effects of trental with antihypoxic and antioxidant effects of energostim [4,7]. This combination leads to better blood perfusion, reduces the damaging effects of free radicals on tissues, removes energy deficit in tissues by restoration of aerobic glycolysis and oxidative phosphorylation in the Krebs cycle. The unique capacity of energostim to restore the erythrocyte elasticity and their capacity to pass through 2.5-μ capillaries [1,5] played an important role in improvement of microcirculation in the limb.

TABLE 3. Dynamics of Clinical Symptoms

Group	Disappearance of dumbness, paresthesia, chilliness of soles		Increase of distance of walking without pain by the end of treatment	
	day of treatment	number of patients	meters	number of patients
1st	9-10	27 (100%)	30	23 (85,2%)
2nd	6-7	34 (100%)	45	34 (100%)
3rd	5-6	29 (100%)	50	29 (100%)

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