Comparison of the Cardioprotective Effects of Cardos and Losartan in Rats with Experimental Chronic Cardiac Insufficiency

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Cardioprotective effect of cardos was revealed on rat model of experimental cardiac insufficiency induced by injection of isoproterenol. Cardos improved exercise tolerance, cardiac output, and stroke volume. Cardos administered for 28 days was no less effective than losartan.

Key Words: *chronic cardiac insufficiency; superlow doses; antibodies; angiotensin II receptor; losartan*

Chronic cardiac insufficiency (CCI) is a frequent, severe, and prognostically unfavorable complication of many cardiovascular diseases. By the present time at least 6 million patients suffer from CCI in Russia and about half-million new cases are registered annually. The armory of drugs for CCI includes angiotensin-converting enzyme inhibitors, β-adrenoblockers, antagonists of aldosterone and type 1 angiotensin II (AT_1) receptors, and their combinations [1]. The most perspective group of drugs for the therapy of CCI includes preparations targeted against AT_1 receptor [6,7].

We compared activities of losartan (reference AT_1 blocker) and a new drug cardos (antibodies to C-terminal fragment of AT_1 receptor; superlow doses for oral treatment) modulating the AT_1 receptor under conditions of experimental CCI in rats.

Hypotensive activity of cardos was demonstrated in previous experiments [2,4]. The effect of this drug is determined by modification of the functional activity of AT_1 receptor [5].

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MATERIALS AND METHODS

The study was carried out on 80 Wistar rats (40 females and 40 males) aging 4-5 months (220-250 g). Exercise tolerance was initially evaluated during forced swimming with a load (15% body weight), cardiac output (CO) and stroke volume (SV) were evaluated by rheography. The rheograms were recorded using a 4RG-2M rheograph and original software. Chronic cardiac insufficiency was induced by 2 subcutaneous injections of isoproterenol (isoprenaline hydrochloride; Sigma) in a dose of 80 mg/kg with a 24-h interval [3].

Seven days after repeated injection of isoproterenol, CO and SV were evaluated in survivors (n=71). Animals with the highest and lowest values in the exercise tolerance test were excluded from the experiment, and the remaining rats were divided into 3 groups (10 males and 10 females per group), the mean duration of forced swimming with a load differed by no more than 5% from the group mean. Rats of three experimental groups received distilled water (2.5 mg/kg), losartan (Cozaar, Merk Sharp & Dohme; 10 mg/kg), or cardos (Materia Medica Holding; 2.5 ml/kg) daily for 28 days (through a

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TABLE 1. Effects of Drugs on Duration (sec) of Forced Swimming with a Load in Wistar Rats (*M*±*m*)

Drug		Before CCI modeling	7 days after isoproterenol injection	After 14-day treatment	After 28-day treatment
Females	Control	150.2±13.1	93.3±2.6*	93.2±3.6	102.0±5.4
	Losartan	149.0±9.4	90.8±5.1*	106.8±4.3^{+o}	122.4±3.6^{+o}
	Cardos	157.9±5.4	94.8±3.9*	113.7±3.6^{+o}	121.2±3.6^{+o}
Males	Control	162.3±8.4	119.9±4.9*	114.0±4.7	126.5±7.9
	Losartan	156.9±4.4	117.5±4.1*	120.8±4.6	129.8±3.9
	Cardos	158.1±9.0	118.9±3.0*	122.1±3.8	128.2±3.8

Note. Here and in Table 2: $p<0.05$ compared to values *before CCI modeling, $^{+}$after isoproterenol injection, ^{o}control.

tube). Exercise tolerance and pumping function of the heart were repeatedly evaluated after 14 and 28 days of treatment.

Statistical processing of the data included estimation of the arithmetic means (*M*) and standard errors (*m*) for each group. The significance of differences between the groups was evaluated using parametric (Student's *t* test for dependent and independent variables) and nonparametric (Wilcoxon, Mann—Whitney) tests.

RESULTS

Two injections of isoproterenol caused a significant reduction of the duration of forced swimming with loading for males and females (by 24.7 and 37.9%, respectively; Table 1). According to rheography data, cardiac insufficiency developed 7 days after isoproterenol injection: pumping function of the heart decreased, which led to decrease in SV and CO by ~50% (Table 2). It is noteworthy that in this model CCI was more severe in females than in males.

In controls, a slight natural recovery of exercise tolerance (by 9.6%) and hemodynamic parameters (SV: by 31.8%; CO: by 24.6%) was observed after 28-day treatment.

Losartan treatment for 28 days restored exercise tolerance in the females: the duration of swimming after 14 and 28 days increased by 17.6 and 34.8%, respectively (Table 1). Cardiac function also improved: SV increased by 30.3 and 68.4% on days 14 and 28 of treatment, CO by 28.5 and 59.4%, respectively (Table 2).

Cardos was not inferior to losartan by its effect on exercise tolerance. In females treated with cardos, the duration of forced swimming after 14 and 28 days increased by 19.9 and 27.9%, respectively (Table 1).

The pumping function of the heart also improved, though the effect developed slower: the

TABLE 2. Effects of Drugs on Hemodynamic Parameters of Wistar Rats with CCI (*M*±*m*)

Parameters			Before CCI modeling	7 days after isoproterenol injection	After 14-day treatment	After 28-day treatment
Females	SV, ml	Control	0.165±0.018	0.066±0.010*	0.075±0.011	0.087±0.010
		Cardos	0.165±0.017	0.069±0.005*	0.078±0.005	0.111±0.011^{o+}
		Losartan	0.165±0.018	0.076±0.008*	0.099±0.008^{o}	0.128±0.013^{o+}
	CO, ml/min	Control	61.7±6.3	27.95±4.20*	29.9±4.7	34.4±3.6
		Cardos	58.8±7.5	28.6±2.3*	30.6±2.7	41.98±3.70^{o}
		Losartan	57.6±5.9	29.8±3.3*	38.3±4.0	47.5±4.5^{+o}
Males	SV, ml	Control	0.143±0.009	0.075±0.006*	0.075±0.009	0.081±0.007
		Cardos	0.145±0.008	0.089±0.007*	0.088±0.008	0.107±0.008^{+o}
		Losartan	0.133±0.007	0.058±0.004*^{o}	0.076±0.006^{+}	0.103±0.008^{+o}
	CO, ml/min	Control	58.5±3.8	32.5±2.1*	32.1±4.0	34.3±3.1
		Cardos	56.1±2.45	38.4±2.6*	37.4±3.2	42.1±2.5^{+o}
		Losartan	52.4±3.2	25.5±2.2*^{o}	31.5±2.7	40.7±2.8^{+}

effect of cardos on day 14 of treatment was less pronounced in comparison with that of losartan, but on day 28 of therapy there were no appreciable differences between the groups. In females receiving cardos, SV increased by 13.0 and 60.8% and CO increased by 7.0 and 46.8%, on days 14 and 28, respectively, compared to initial values in CCI (Table 2).

In male rats the cardioprotective effect of the drugs was less pronounced, presumably because of lesser initial severity of CCI. Treatment with losartan and cardos did not lead to an appreciable increase in exercise tolerance in males: on day 28 of drug treatment it virtually did not differ from the control.

On the other hand, both drugs had a positive impact on cardiac function in male rats: on day 28 SV increased by 27.2 and 32.1% ($p<0.05$), CO by 18.7 and 22.9%, respectively, compared to the control.

These results suggest that by its the cardioprotective effect cardos is not inferior to losartan (reference drug used in the treatment of CCI). The effect of cardos developed slower, but the differences between the groups leveled after long-term treatment.

The detected cardioprotective activity of cardos under conditions of experimental CCI induced in rats by isoproterenol injections indicates good prospects of its use in pathogenetic therapy of CCI.

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