Comparative Therapeutic Efficacy of Adenocin and Non-Glycoside Cardiotonic Drugs in Chronic Heart Failure at Rest and under Conditions of Heart Overload

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Experiments were performed on the model of chronic heart failure. Functional capacity of myocardial structures under conditions of maximum pressure overload was within the upper limit of normal after treatment with Adenocin. The myocardial functional reserve and potential capacity index were shown to increase to normal under these conditions. Dobutamine, levosimendan, and milrinone increased functional capacity under conditions of maximum pressure overload. Treatment with adenocin restored diastolic function of the heart under conditions of maximum pressure overload. The end-diastolic pressure increased, but remained 1.7 times below the level observed in heart failure. After treatment with dobutamine and milrinone, the end-diastolic pressure (8th episode of ligation) did not differ from the level observed in heart failure, while after administration of levosimendan this parameter decreased by 31%. Contraction-relaxation coupling was completely restored under the influence of Adenocin in all episodes of ligation both before and after removal of the ligature. Nearly all animals with heart failure were resistant to 8 episodes of ligation after treatment with Adenocin (89 *vs.* 96% under normal conditions). Under these conditions, the survival rate of animals after administration of levosimendan, milrinone, and dobutamine was 65, 60, and 61%, respectively, (the mortality rate of animals with heart failure was 75%). Adenocin, a cardiotonic drug with cardioprotective properties, in contrast to other cardiotonic drugs, has a modulatory effect on the system of cell energy supply, restores myocardial reserves, and improves myocardial function under conditions of overload.

Key Words: *heart failure; Adenocin; pressure overload; myocardial functional reserve*

Despite much progress in the therapy of heart failure (HF) leading to improvement of quality of life and increase in survival rate of patients, the frequency of complications and mortality rate from HF remain very high [8-10]. Angiotensin-converting enzyme inhibitors, β-adrenoceptor antagonists, and aldosterone antagonists are the drugs of choice in chronic HF. Much attention is paid to the possibility of optimization of therapy with inotropic drugs. It is interesting to compare the effects of various drugs. The mechanism for action of β-adrenoceptor agonists (dobutamine) suggests an increase in intracellular cAMP and calcium. Phosphodiesterase III and IV inhibitors (milrinone) have the inotropic and vasodilating effects. Highly selective inhibitor of phosphodiesterase III (levosimendan) does not modify activity of phosphodiesterase IV. Levosimendan is the only drug of a non-glycoside nature (calcium sensitizer) that can be used to re-

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lieve the symptoms of decompensation of chronic HF [6,7]. The original cardiotonic drug Adenocin contains β-acetyldigoxin (cardiac glycoside) with cardioprotective properties [4].

Here we studied the effects of cardiotonic drugs with various mechanisms of action on myocardial adaptability to overload.

MATERIALS AND METHODS

Experiments were performed on 43 male and female Chinchilla rabbits weighing 2.8-3.6 kg. The animals were quarantined in a special vivarium under similar conditions and fed a standard diet. The surgery for graduated stenosis of the posterior descending coronary artery (2 months) was performed in 28 rabbits. The animals were randomized into 4 groups. Group 1 consisted of 8 conventionally healthy rabbits (thoracotomy of the same duration under similar conditions). Seven rabbits of group 2 (control) were subjected to graduated stenosis (60 days) followed by ligation of the artery (20 min) and subsequent administration of 50 ml 5% glucose (for 15 min and then for 4 days). Group 3-6 rabbits with stenosis (7 animals per group) received an intravenous injection of the following drugs (immediately after stenosis and for the next 4 days): Adenocin (181.7 mg/kg) in 50 ml 5% glucose (group 3); levosimendan (24 μg/kg, group 4); milrinone lactate (37.5 μg/kg, group 5); and dobutamine (100 μg/kg, group 6). Therapy was started immediately after the first episode of 20-min artery ligation and was continued for 18 days. The drugs were dissolved in 20 ml physiological saline and infused intravenously for 20-30 min (in a dropwise manner). Intracardiac hemodynamics was studied [1,2,5]. The functional reserve (FR) under normal and pathological conditions was calculated by the formula of V. I. Kandror. Actual FR (AFR) was calculated as the ratio of FR under pathological conditions to FR under normal conditions (the same episode of ligation; method of S. V. Paukov and V. A. Frolov). The potential capacity index was estimated as described previously [1]. Control animals and treated rabbits were killed 4 days after the end of therapy.

The significance of differences was evaluated by Student's *t* test.

RESULTS

Under normal conditions, HR decreased by 17% in the 8th episode of artery ligation (as compared to HR in rest). P_{syst} increased by 51% during the 8th episode of ligation. dP/dt_{max} and functional activity of structures (FAS) did not differ under experimental and resting conditions (Table 1). Despite a tendency to the increase in dP/dt_{min}, end-diastolic pressure (EDP) was shown to increase by 43% in the 8th episode of ligation. The coupling of diastolic and systolic functions did not change after 8 episodes of ligation (r=0.78, p<0.01).

Under conditions of HF, HR in the 8th episode of ligation did not differ from normal. However, HR in these rabbits was lower than in HF animals under resting conditions. P_{syst} increased by 176% during the 8th episode of ligation. P_{syst} in HF rabbits was 49% higher compared to that observed during the 8th episode of ligation under normal conditions. dP/dt_{max} and FAS increased by 57 and 116%, respectively, in the 8th episode of ligation. Therefore, HF is not accompanied by adaptation of cardiac systolic function to overload. The myocardial mass unit is characterized by a greater functional load to perform the same work (as compared to normal; Tables 1 and 2). This process requires a greater energy supply. Cardiac diastolic function under these conditions was significantly impaired (as compared to normal). EDP in animals of the treatment group increased more significantly and exceeded the normal level by 2.6 times. dP/dt_{min} was 2.6-fold lower compared to normal. Studying the hemodynamics showed that cardiac systolic function and diastolic function in HF animals are uncoupled during ligation, inter-ligation periods, and rest (r=0.13-0.31).

After treatment with cardiotonic drugs, HR in HF animals tended to decrease during the 8th episode of ligation (Tables 1 and 2). The increase in P_{syst} during the 8th episode of ligation was not accompanied by significant changes in the maximum rate of ventricular filling (compared to the rest value). By the 8th episode of ligation, FAS in Adenocin-receiving animals was within the upper limit of normal. FAS of the myocardium to overcome the load did not differ from normal. FAS after treatment with dobutamine, levosimendan, and milrinone increased by 22, 16, and 21%, respectively, under conditions of maximum pressure overload.

Cardiac diastolic function under conditions of maximum pressure overload was completely restored after treatment with Adenocin. dP/dt_{min} increased during the 8th episode of ligation, but returned to normal after removal of the ligature. EDP increased by 1.5 times, but was 1.7-fold lower compared to that in HF animals. After treatment with dobutamine and milrinone, EDP in the 8th episode of ligation did not differ from that in HF. Levosimendan caused a 31% decrease in EDP. Contraction-relaxation coupling was completely restored under the influence of Adenocin. It was found in all episodes of ligation (before and after removal of the ligature; maximum values for Adenocin, r=0.81, p<0.001). The corresponding pa-

TABLE 1. Effect of Cardiotonic Drugs on Intracardiac Hemodynamics in HF at Rest (*M*±*m*)

Parameter	Normal	HF				
		control	adenocin	dobutamine	levosi-mendan	milrinone
HR, bpm	212±14	286±12*	214±8^{+}	262±13^{*o}	270±12^{*o}	254±8^{*o}
P_{syst}, mm Hg	73±6	75±4*	69±6	75±7	72±4	80±5
dP/dt_{max}, mm Hg/sec	1740±103	1017±94*	1680±86^{+}	1547±95^{+}	1347±104^{*+}	1480±96^{*+}
FAS, mm Hg/sec	540±93	409±58	687±65^{+}	695±46^{*+}	909 ±58^{*+}	737±36^{*+}
dP/dt_{min}, mm Hg/sec	1813±111	766±105*	1739±89^{+}	1067±121^{*+o}	1325±95^{*+o}	1339±79^{*+o}
EDP, mm Hg	7±2	22±6*	10±2^{*+}	16±2^{*o}	18±4^{*o}	20±2^{*o}

Note. Here and in Table 2: $p<0.01$: *compared to normal; $^{+}$compared to the control; ^{o}compared to Adenocin; ^{x}compared to dobutamine.

TABLE 2. Effect of Cardiotonic Drugs on Intracardiac Hemodynamics in HF during Pressure Overload (*M*±*m*)

Parameter	Normal	HF				
		control	adenocin	dobutamine	levosi-mendan	milrinone
HR, bpm	186±12	223±17	183±13	228±15	218±12	230±20
P_{syst}, mm Hg	110±17	163±15*	109±15^{+}	112±12^{+}	141±13^{ox}	139±14^{ox}
dP/dt_{max}, mm Hg/sec	1584±122	1595±134	1352±109	1664±126	1567±89	1492±98
FAS, mm Hg/sec	562±80	886±67*	604±58^{+}	788±75^{*o}	1058±55^{*o}	894±48^{+}
dP/dt_{min}, mm Hg/sec	1312±94	737±44*	1084±77^{+}	953±90^{*+}	780±44^{*+o}	804±63^{*+o}
EDP, mm Hg	10±2	26±5*	15±4^{+}	22±2^{*o}	18±4^{*+}	21±4*

rameters were calculated for levosimendan (r=0.59, $p<0.05$), milrinone (r=0.53, $p<0.05$), and dobutamine (r=0.59, $p<0.05$).

Studying the functional reserves (dP/dt_{max} and FAS) showed that myocardial contractility significantly decreases during HF (as differentiated from normal). These changes are observed up to the 5th episode of ligation. It results in death of animals after the 1st (14% rabbits) and 5th episode of ligation (45% rabbits). The decrease in contractile function and mortality rate of animals remain unchanged in the follow-up period (70% mortality rate by the 8th episode of ligation). FR of the heart in HF animals decreased from 2.2 to 1.4 (by 42.7%; method of V. I. Kandror). The method of S. V. Paukov and V. A. Frolov allowed us to evaluate AFR. AFR reflects not only exhaustion of the reserves with an increase in the load, but also the degree of these changes in normal myocardium. We found that AFR decreases from 1.4 to 0.73 (by 45.2%). The potential capacity index decreases from 0.65 to 0.54 (by 20%).

dP/dt_{max} and FAS curves in HF animals with cardiac pressure overload were shown to return to normal after treatment with Adenocin. FR and FAS in Adenocin-receiving rabbits increased to 2.4 and 1.08, respectively. The potential capacity index in these animals increased to 0.68. The estimated indexes in rabbits receiving phosphodiesterase inhibitors and dobutamine practically did not differ from those in HF animals. Among all these drugs, only Adenocin contributes to the recovery of systolic and diastolic functions of the myocardium. Systolic-diastolic coupling in Adenocin-receiving animals was observed not only under resting conditions, but also under conditions of maximum pressure overload. Nearly all rabbits with HF survived 8 episodes of ligation after treatment with Adenocin (89 *vs*. 96% under normal conditions).

Thus, Adenocin, a cardiotonic drug with cardioprotective properties in contrast to other cardiotonic drugs, produces a modulatory effect on the system of cell energy supply, restores the myocardial reserves, and improves myocardial function under conditions of overload.

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