Adaptation of the Cardiovascular System to Postinfarction Cardiosclerosis in Rats with Congenital Adrenoreactivity of the Myocardium

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Three months after myocardial infarction the severity of heart failure and size of postinfarction scars in August rats with inherently reduced adrenoreactivity of the myocardium were similar to those in Wistar rats. The mortality rate in August rats was 2.5-fold lower than in Wistar rats. During the postinfarction period, myocardial adrenoreactivity in August rats remained lower, while the efficiency of cardiac function was 62% higher than in Wistar rats. The incidence of epinephrine-induced arrhythmias in August rats was much lower than in Wistar rats.

Key Words: *August and Wistar rats; postinfarction cardiosclerosis; heart failure; adrenoreactivity; arrhythmias*

Published data show that the mortality rate and incidence of arrhythmias and contractile dysfunction caused by acute myocardial infarction in August rats are much lower than in Wistar rats [1,3,9]. Stress-induced activation of the sympathoadrenal system (SAS) plays an important role in the pathogenesis of ischemic damage to the myocardium. Increased resistance of August rats to ischemia is associated with higher activity of the sympathetic nervous system and elevated concentration of catecholamines in the blood (as compared to Wistar rats) [7]. Activity of the parasympathetic nervous system and baroreflex sensitivity are reduced in August rats [4], which serves as a risk factor during myocardial infarction and heart failure [11]. It was demonstrated that high resistance of August rats to acute ischemia is determined by reduced adrenoreactivity of the myocardium (compared to Wistar rats) [3]. This phenomenon in August rats can be also associated with less significant activation of SAS under stress conditions [2]. Less pronounced activation of SAS in August rats probably contributes to increased activity of the NO system in these animals [6]. It remains unclear whether these advantages of August rats are preserved in the delayed period after myocardial infarction. The development of extensive cardiosclerosis during this period is followed by myocardial remodeling and heart failure. Catecholamines play an important role in this disorder, since they cause cardiac dysfunction and arrhythmias, stimulate apoptosis and hypertrophy of the myocardium, induce the release of proinflammatory cytokines, and activate the renin—angiotensin—aldosterone system [8]. Low adrenoreactivity of the myocardium in August rats probably contributes to inhibition of cardiac function, since desensitization of the β-1—adrenoceptor-G protein complex in cardiomyocytes during heart failure can decrease myocardial contractility [10].

Here we compared the state of the cardiovascular system, myocardial adrenoreactivity, and acti-

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vity of SAS in Wistar and August rats with prolonged postinfarction cardiosclerosis (PIC).

MATERIALS AND METHODS

Myocardial infarction in Wistar and August rats was modeled by the method of H. Selye. Sham-operated rats served as the control. After surgery the rats were maintained under standard conditions. Functions of the cardiovascular system in urethane-anesthetized rats (1.5 g/kg intraperitoneally) were studied 1 and 3 months after infarction modeling. Systolic and diastolic blood pressure was measured using a PE-10 polyethylene catheter inserted into the right carotid artery. This catheter was then introduced into the left ventricle. Parameters of cardiac function were monitored with an EMT-746 sensor using a Mingograf-34 device (Siemens-Elema). The following parameters were calculated from variations in left ventricular pressure: heart rate (HR), systolic pressure, end-diastolic pressure, developed pressure, and index of cardiac function (product of HR and developed pressure, double product). Studying of the efficiency of cardiac function was performed taking into account that August rats have lower body weight than Wistar rats of the same age. Hence, the relative weight of the heart in August rats is 30% lower than in Wistar rats. The structure/function relationship (SFR) was calculated as the ratio of an index of cardiac function to left ventricular mass. Cardiac function was estimated under conditions of relative physiological rest. Myocardial contractile reserve in rats with PIC of 3 months' duration was estimated by stimulation of the heart with epinephrine in high doses (5 and 10 μg/kg intravenously). Severe arrhythmias in Wistar rats were observed over the first seconds after injection of epinephrine in a dose of 10 μg/kg. Hence, it was impossible to evaluate cardiac function immediately after administration of the transmitter. Therefore, cardiac function in Wistar and August rats was evaluated only after injection of epinephrine in a dose of 5 μg/kg. Hypertrophy of heart chambers was determined from the ratio of the weight of the left and right ventricles to body weight. The size of postinfarction scars was measured by the method of planimetry and expressed in percent of the area of the left ventricular free wall. The size of scars in rats significantly varied 1 and 3 months after infarction. Since the number of rats with relatively small scars (20-25%) was low, we presented the data on animals with 30-90% scars.

The concentration of catecholamines in the left adrenal gland and blood of rats was measured 1 month after myocardial infarction by the method of high-performance liquid chromatography with electrochemical detection [5].

The results were analyzed by Student's *t* test and Mann—Whitney *U* test.

RESULTS

One month after myocardial infarction, body weight of August and Wistar rats (4-month-old animals) was 241±8 and 402±16 g, respectively. The size of scars in August and Wistar rats practically did not differ during this period (42±2 and 50±4.8%, respectively). The weight of the left ventricle in rats

TABLE 1. Effect of PIC on Blood Pressure and Cardiac Contractile Function in Wistar and August Rats

Group	HR, bpm	Blood pressure, mm Hg		Developed pressure, mm Hg	Index of cardiac function, bpm×mm Hg	SFR, mm Hg/mg/min
		systolic	diastolic			
1 month after infarction						
Sham-operated Wistar rats (n=9)	366±11	113.0±4.8	84.0±3.2	124.0±6.8	45,320±2882	57.0±5.4
Wistar rats with PIC (n=11)	327±13*	105.0±3.5	79.0±3.9	109.0±4.5*	36,280±2144*	53.0±3.3
Sham-operated August rats (n=10)	349±9	111.0±3.4	63.0±3.2^{++}	131.0±6.4	45,751±2908	77.0±4.8^{++}
August rats with PIC (n=12)	352±10	99.0±2.3**	66.0±4.4^{o}	119.0±4.2	41,482±2978	79.0±4.2^{oo}
3 months after infarction						
Sham-operated Wistar rats (n=8)	380±12	118.0±3.6	72.0±4.3	130.0±3.5	49,636±2205	73.0±4.2
Wistar rats with PIC (n=11)	390±13	111.0±3.8	73.0±3.8	122.0±4.5	46,477±2853	55.0±3.7**
Sham-operated August rats (n=7)	404±16	128.0±4.7	75.0±3.8	156.0±9.3^{+}	63,662±3020	114±11^{+++}
August rats with PIC (n=10)	412±9^{o}	100.0±5.5*	60.0±4.9*^{o}	121.0±6.2***	50,075±3187***	89.0±6.4***^{o}

Note. Here and in Table 2: $^{+}p<0.05$, $^{++}p<0.01$, and $^{+++}p<0.001$, differences between sham-operated animals; $^{*}p<0.05$, $^{**}p<0.01$, and $^{***}p<0.001$, differences between postinfarction and sham-operated animals; $^{o}p<0.05$, $^{oo}p<0.01$, and $^{ooo}p<0.001$, differences between animals with PIC.

of both groups decreased by 18-21%. However, severe hypertrophy of the right ventricle was observed in Wistar (82%, $p<0.001$) and August rats (62%, $p<0.001$). Over the 1st month of the study, the mortality rate in August rats was much lower than in Wistar rats (11 and 26%, respectively). It should be emphasized that August rats differed from Wistar rats by increased SFR (Table 1), which is consistent with published data [3]. This parameter in sham-operated August and Wistar rats differed by 35% ($p<0.001$). Cardiac function in rats of these groups was not significantly suppressed 1 month after infarction. However, Wistar rats with PIC differed from August rats with PIC by slightly lower values of HR and developed pressure and significantly higher value of end-diastolic pressure (9.8±0.8 and 5.7±0.7 mm Hg, respectively, $p<0.05$). The index of cardiac function in Wistar rats with PIC was 20% lower than in sham-operated animals. This parameter in August rats did not differ from the control. However, intergroup differences in SFR were preserved.

Three months after myocardial infarction, body weight of August and Wistar rats (6-month-old animals) was 270±10 and 480±11 g, respectively. The size of postinfarction scars in August (n=17) and Wistar rats (n=22) practically did not differ during this period (62±3.5 and 56±3.9%, respectively). Left ventricular hypertrophy was not revealed in August rats, but reached 10% in Wistar rats ($p<0.01$). Right ventricular hypertrophy in August and Wistar rats was 78 ($p<0.001$) and 47% ($p<0.001$), respectively. More severe hypertrophy of the right ventricle in August rats can be explained by higher vascular resistance in the pulmonary artery (as compared to Wistar rats). Over 3 months after infarction, the mortality rate of August and Wistar rats with PIC was 7 and 22%, respectively. It should be emphasized that dilation of the heart was observed in many animals with scars of 50-90%. These changes reflect the development of heart failure. However, end-diastolic pressure in rats of these groups was 5.6 mm Hg (*vs.* 0.0 and 3.1±1.3 mm Hg in sham-operated August and Wistar rats, respectively). The index of cardiac function in August rats with PIC was reduced by 22% ($p<0.05$) due to a 23% decrease in developed pressure ($p<0.05$). This parameter decreased only slightly in Wistar rats (Table 1). However, SFR decreased similarly in animals of both groups (by 22-25%, $p<0.001$). This parameter in August rats with PIC remained 62% higher than in Wistar rats ($p<0.001$). Hence, the observed differences were similar to those between sham-operated animals. As differentiated from Wistar rats with PIC, changes in cardiac function in August rats with PIC were accompanied by a compensatory decrease in systolic and diastolic blood pressure. The rates of myocardial contraction and relaxation in sham-operated August rats were 11,094±836 and 6719±517 mm Hg/sec, respectively. These parameters in Wistar rats were 8203±481 ($p<0.002$) and 4492±347 mm Hg/sec ($p<0.01$), respectively. The rates of myocardial contraction and relaxation in August rats with infarction decreased by 36 ($p<0.001$) and 12% ($p<0.05$), respectively. In Wistar rats the rate of myocardial contraction decreased by 16% ($p<0.05$), while the rate of myocardial relaxation remained unchanged. However, the test parameters in August rats with PIC were comparable with those in Wistar rats. Hence, impairment of cardiac function in animals with prolonged PIC is manifested in a decrease in SFR. The efficiency of cardiac function in August rats exceeded that in Wistar rats, which was related to baseline differences in this parameter.

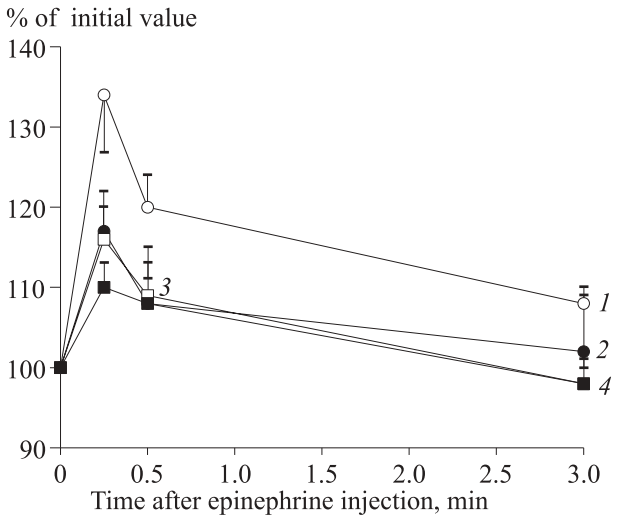

Fig. 1. Effect of epinephrine (5 mg/kg) on SFR in Wistar and August rats with PIC of 3 months' duration. Here and in Fig. 2: sham-operated Wistar rats (*1*); Wistar rats with PIC (*2*); sham-operated August rats (*3*); and August rats with PIC (*4*).

The cardiac response to epinephrine in sham-operated August rats was lower than in Wistar rats. Developed pressure in sham-operated Wistar and August rats increased by 34 and 16%, respectively ($p<0.01$ compared to the basal level), over the first seconds after injection of epinephrine in a dose of 5 μg/kg (maximum response). Similar differences were revealed in SFR (Fig. 1). Published data show that myocardial adrenoreactivity decreases during the postinfarction period [10]. This effect was also revealed in Wistar rats with PIC. However, adrenoreactivity in August rats remained low (developed pressure and SFR) or decreased to a greater extent (myocardial contractility). Developed pressure and

TABLE 2. Catecholamine Concentration in Adrenal Glands and Blood of Wistar and August Rats 1 Month after Myocardial Infarction

Catecholamines	Sham-operated		Rats with PIC	
	Wistar (*n*=12)	August (*n*=9)	Wistar (*n*=9)	August (*n*=9)
Adrenal glands				
Norepinephrine, ng/mg tissue	108.0±4.9	243.0±15.7^{+++}	85.0±6.5**	254.0±20.2^{ooo}
Epinephrine, ng/mg tissue	458.0±25.8	734.0±37.2^{+++}	369.0±45.9*	735.0±43.8^{ooo}
Dopamine, ng/mg tissue	11.6±0.9	19.1±2.2^{+++}	7.8±1.2*	17.1±1.7^{ooo}
Dopamine/norepinephrine	0.112±0.001	0.078±0.010^{++}	0.088±0.010*	0.070±0.010
Blood				
Norepinephrine, ng/ml plasma	0.82±0.10	1.68±0.36^{+}	1.18±0.12*	1.70±0.28
Epinephrine, ng/ml plasma	1.20±0.09	2.22±0.33^{++}	1.38±0.11	2.67±0.23^{ooo}

SFR in Wistar rats with PIC increased by 25 and 17%, respectively. The increase in these parameters was less pronounced in August rats (by 19 and 10%, respectively; statistically insignificant). It should be emphasized that August rats with PIC and reduced response to epinephrine had greater absolute value of SFR compared to Wistar rats. The rates of myocardial contraction and relaxation in Wistar rats with PIC increased by 40 and 29%, respectively ($p<0.05$, Mann—Whitney U test). These parameters in August rats increased by 15 and 11%, respectively ($p<0.05$, Student's t test). Hence, the rates of myocardial contraction and relaxation in August rats were less sensitive to epinephrine (Fig. 2). The exception was end-diastolic pressure. This parameter in rats of both groups increased similarly over the first 30 sec after injection of epinephrine in doses of 5 and 10 mg/kg (from 14 to 20 mm Hg), which reflects the development of heart failure. It should be noted that the test parameters in August rats more rapidly returned to normal than in Wistar rats (Figs. 1 and 2).

Epinephrine in both doses induced arrhythmias (primarily extrasystoles). The arrhythmogenic effect of epinephrine in August rats with PIC was less pronounced than in Wistar rats with PIC. Multiple extrasystoles were noted in 13 of 16 Wistar rats (81%) over the first 15 sec after injection of epinephrine in a dose of 10 μg/kg. Bradycardia was rarely observed in these animals. Only several extrasystoles were found in 6 of 14 August rats (43%) over the first seconds after epinephrine injection. High resistance of August rats to arrhythmias is probably associated with reduced adrenoreactivity of the myocardium. We conclude that August and Wistar rats have the same size of scars and similar

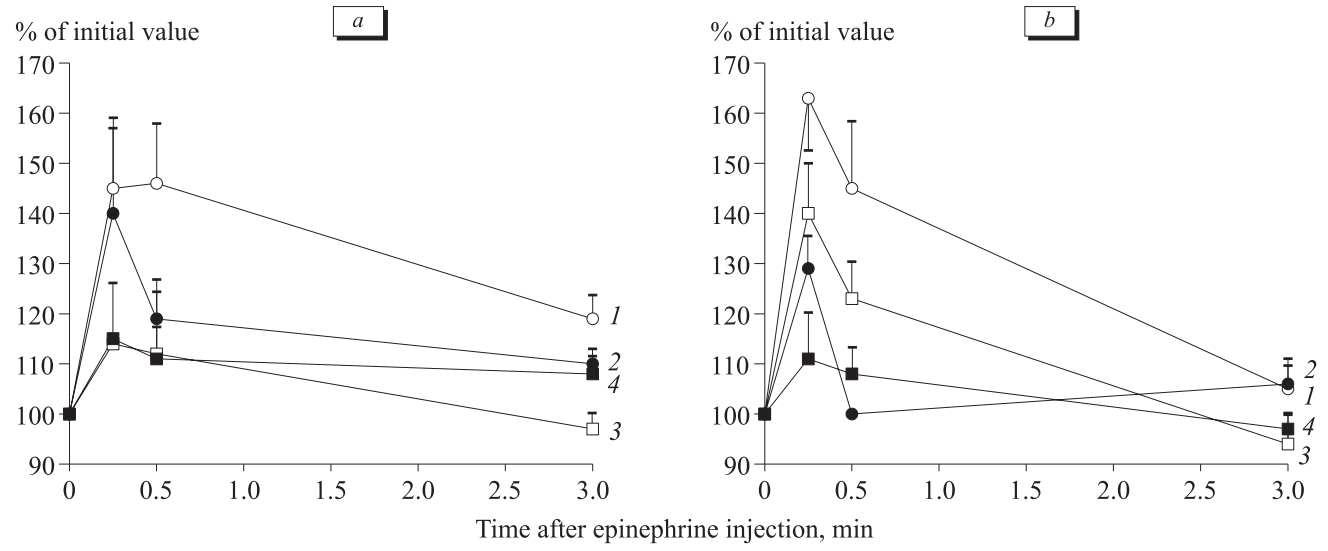

Fig. 2. Effect of epinephrine (5 mg/kg) on rates of myocardial contraction (*a*) and relaxation (*b*) in Wistar and August rats with PIC of 3 months' duration.

signs of heart failure in the delayed period after myocardial infarction. In August rats, the mortality rate is lower, while the efficiency of cardiac function and resistance to the arrhythmogenic effect of epinephrine is higher than in Wistar rats.

The mechanisms of this phenomenon were evaluated by comparing activity of SAS in rats with PIC of 1 month duration. Table 2 shows that the initial concentrations of norepinephrine and epinephrine in August rats were higher than in Wistar rats (by 125 and 60%, respectively, in the adrenal glands; and by 105 and 85%, respectively, in the blood). Our results are consistent with published data [7]. The concentrations of norepinephrine and epinephrine in the adrenal glands of Wistar rats significantly decreased during the postinfarction period. However, catecholamine content remained unchanged in August rats. The dopamine/norepinephrine ratio significantly decreased in Wistar rats, but remained unchanged in August rats. As differentiated from August rats, catecholamine metabolism in the adrenal glands of Wistar rats significantly increased 1 month after infarction. Blood catecholamine level increased in rats of both groups. However, intergroup differences in this parameter were preserved. Blood catecholamine level in August rats was higher than in Wistar rats. Hence, activity of SAS in August rats with PIC was lower than in Wistar rats. It can be hypothesized that SAS activity in August rats remains low 3 months after infarction.

During the postinfarction period August rats are characterized by higher efficiency of cardiac function than Wistar rats. These differences can result from several reasons. Our results indicate that inherently reduced adrenoreactivity of the myocardium and less pronounced activation of SAS play a protective role in August rats. Hence, adrenergic damage in August rats is less severe during the acute and delayed period after myocardial infarction. The decrease in inotropic stimulation contributes to preservation of myocardial contractile reserve and maintenance of myocardial viability. At the systemic level, high-efficiency cardiac function in August rats with PIC is probably provided by hemodynamic unloading due to lower level of blood pressure (as compared to Wistar rats with PIC). This effect in August rats can be associated with induction of NO synthesis, which serves as a potent vasodilating agent. High efficiency of cardiac function in August rats with PIC during the postinfarction period can be also associated with a decrease in activity of the renin—angiotensin—aldosterone system due to lower activation of SAS.

REFERENCES

1. L. M. Belkina, T. N. Kirillina, M. G. Pshennikova, and Yu. V. Arkhipenko, *Byull. Eksp. Biol. Med*., **133**, No. 6, 625-628 (2002).
2. L. M. Belkina, E. V. Popkova, V. L. Lakomkin, *et al*., *Ros. Fiziol. Zh*., **92**, No. 2, 221-231 (2006).
3. L. M. Belkina, V. A. Saltykova, and M. G. Pshennikova, *Byull. Eksp. Biol. Med*., **131**, No. 6, 624-628 (2001).
4. T. N. Kirillina, M. A. Usacheva, and L. M. Belkina, *Ibid*., **142**, No. 10, 376-381 (2006).
5. E. G. Larskii, V. P. Barkhatova, and E. G. Demina, *Lab. Delo*, No. 9, 519-522 (1985).
6. V. D. Mikoyan, L. N. Kubrina, E. B. Manukhina, *et al*., *Byull. Eksp. Biol. Med.*, **121**, No. 6, 634-637 (1996).
7. S. S. Pertsov, E. V. Koplik, W. Krauzer, *et al*., *Ibid*., **123**, No. 6, 645-648 (1997).
8. A. S. Poskrebysheva, V. V. Grinevich, Yu. V. Smurova, *et al*., *Uspekhi Fiziol. Nauk*, **3**, No. 3, 3-20 (2003).
9. M. G. Pshennikova, L. M. Belkina, L. Yu. Bakhtina, *et al*., *Byull. Eksp. Biol. Med*., **132**, No. 8, 153-155 (2001).
10. M. Packer, *J. Am. Coll. Cardiol*., **20**, 248-254 (1992).
11. E. Vanoli and P. J. Schwartz, *Basic Res. Cardiol*., **85**, Suppl. 1, 305-321 (1990).
12. P. Schwartz, R. Diem, N. J. Dun, and U. Forstermann, *Circ. Res*., **77**, No. 4, 841-848 (1995).