Effect of Stress on Variability of Systemic Hemodynamics in Rats of Various Genetic Strains

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Power spectral density of heart rate fluctuations in the range of 0.02-5.00 Hz in August rats was lower than in Wistar rats. Changes in mean blood pressure and heart rate during stress (15-min immobilization) were similar in animals of both strains. As differentiated from Wistar rats, power spectral density of fluctuations in August rats considerably decreased after stress. August rats were characterized by low spectral power at rest and high resistance to the arrhythmogenic effect of 10-min acute myocardial ischemia.

Key Words: *hemodynamics; spectral analysis; stress; arrhythmias; Wistar and August rats*

Rats of various genetic strains are characterized by different resistance to stress. August rats more often die from catastrophic blood pressure (BP) drop during long-term immobilization stress than Wistar rats [9]. It should be emphasized that by several parameters August rats are less sensitive to stress than Wistar rats. For example, in August rats the incidence of stress-induced gastric ulceration [8] and mortality rate from acute myocardial infarction are lower than in Wistar rats [3]. Different resistance to stress is determined by the balance between regulatory systems realizing and limiting the stress response [6]. Indexes of BP and heart rhythm variability reflect the balance and functional activity of systems regulating blood flow. R. M. Baevskii *et al*. first revealed the relationship between heart rate (HR) variability at rest and severity of stress-induced damage [2]. Statistical treatment of the results showed that the incidence of stress-induced gastric ulceration in rats with intermediate HR variability is lower than in animals with low and high index. The relationship between variability of hemodynamic parameters and degree of the stress reaction is poorly understood. Variability of hemodynamic indexes in animals with different genetically determined resistance to stress is of particular interest. Here we studied variability of BP and heart rhythm in Wistar and August rats at rest and under stress conditions and correlated these parameters with the severity of ischemic arrhythmias and hypothalamic catecholamine content.

MATERIALS AND METHODS

Experiments were performed on male Wistar (n=7) and August rats (n=12) weighing 243±7 and 392±7 g, respectively. BP was recorded in awake freely moving animals. A catheter was introduced into the femoral artery under sodium thiopental anesthesia (40 mg/kg) 2 days before the experiment. We used a Statham 8200 P23AA tensiometric transducer, 16-bit precision analog-to-digital converter (L-Card), and IBP PC (250 Hz). The measurements were performed in a dark quiet room. Mean BP (BP_M) and pulse interval (PI) in each cardiac cycle were calculated using original software. Variability of BP_M and PI was estimated by standard deviation of cardiac cycles recorded over 1 h. Changes in BP_M and PI were studied by the spectral analysis. Values differing by 0.1 sec were estimated for each

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parameter by the method of linear interpolation. A 1-h interval was divided into non-overlapping 51.2-sec segments (512 points). Linear drift was corrected, and each segment was brought to a mean of zero. Power spectra were calculated using Fourier rapid transform and averaged. The power spectrum of BP_M was analyzed in low- (LF, 0.0195-0.2500 Hz), mid- (MF, 0.25-0.75 Hz), and high-frequency ranges (HF, 0.75-2.00 Hz).

Experiments were performed in 2 stages. At stage I indexes of functional hemodynamics and their variability were monitored for 1 h at rest, during immobilization on the back for 15 min, and 1 h after stress. In stage II arrhythmias were produced by short-term local myocardial ischemia 1-2 days after recording of BP. The development of cardiac arrhythmias was related to the influence of catecholamines during activation of the sympathetic nervous system (SNS). These arrhythmias could be prevented with β-adrenoceptor blockers [10]. The animals were narcotized with nembutal (50 mg/kg intraperitoneally). Experiments were performed after thoracotomy under conditions of artificial ventilation with atmospheric air on a VITA-1 device. Myocardial ischemia was produced by ligation of the left descending coronary artery for 10 min. The severity of arrhythmias was estimated by ECG recorded on a Mingograf-34 device (Siemens, lead I). The total duration of severe arrhythmias (ventricular tachycardia and ventricular fibrillation) was evaluated during occlusion. Hypothalamic catecholamine content was measured by high-performance liquid chromatography and electrochemical detection. The results were analyzed by Student's *t* test. The significance of differences in the severity of arrhythmias was estimated by Fischer's test.

RESULTS

At rest BP_M in Wistar and August rats was 121.0±1.5 and 115.0±3.3 mm Hg, respectively ($p>0.05$). BP_M variability did not differ in animals of these strains (5.90±0.44 and 6.80±0.48 mm Hg, respectively). HR in August rats was higher than in Wistar rats (408±12 and 357±6 bpm, respectively, $p<0.001$), which was probably related to their smaller size. It cannot be excluded that the increased HR in August rats is associated with higher vascular tone. This assumption is confirmed by high blood level of catecholamines in August rats [5]. PI variability in August rats was lower than in Wistar rats (9.20±1.37 and 11.10±0.72, respectively, $p>0.05$).

Immobilization increased BP in August and Wistar rats to a similar extent (25.0±1.8 and 22.0±1.6%, respectively, $p>0.05$). However, the stress-induced increase in HR in August rats was less pronounced than in Wistar rats (25.0±3.2 and 37.0±2.7%, $p<0.05$). Probably, the less pronounced increase in HR in August rats after immobilization was due to high HR at rest. A negative correlation was revealed between HR under resting and stress conditions in Wistar and August rats (R=-0.82, $p<0.001$, Spearman test). Hemodynamic indexes in these animals were similar at the peak of stress reaction. Over the first hour after stress BP_M in August rats decreased more rapidly than in Wistar rats. It was probably related to intensive production of nitric oxide (NO) in the vascular endothelium of August rats [7]. It should be emphasized that during the post-stress period HR in August rats surpassed that in Wistar rats (Fig. 1). These differences were associated with lower activity of the parasympathetic nervous system (PNS) in August rats. The dynamics of

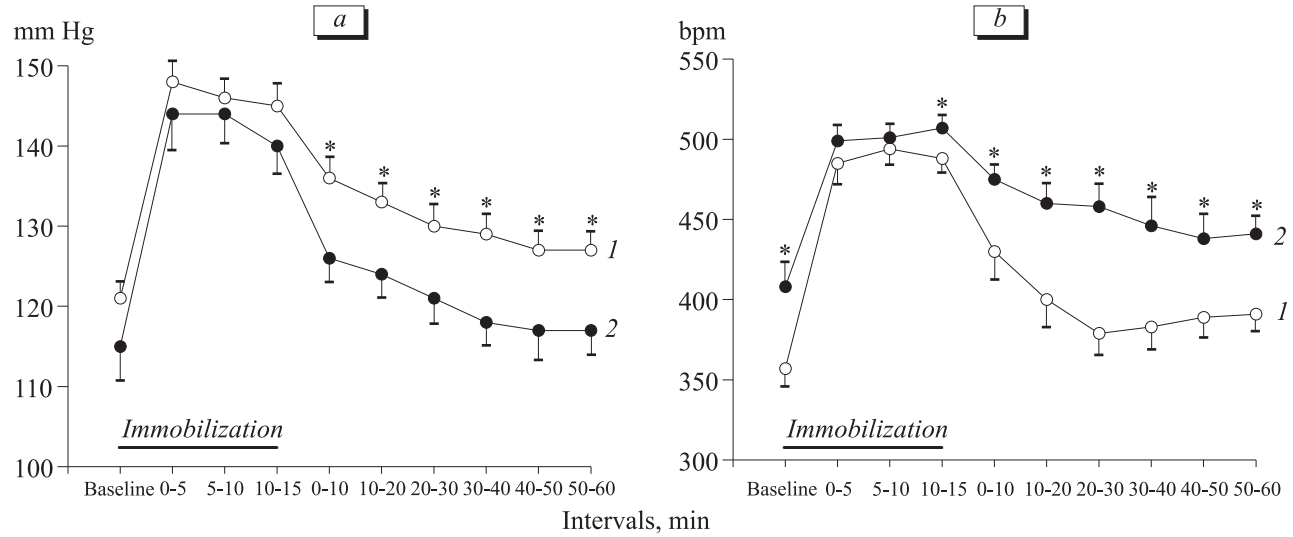

Fig. 1. Changes in mean blood pressure (*a*) and heart rate (*b*) in Wistar (*1*) and August rats (*2*) during 15-min immobilization and 1 h after stress. *$p<0.05$ compared to *1*.

poststress recovery in HR and BP_M was similar in August and Wistar rats. BP_M returned to normal more rapidly that HR (Fig. 1).

BP_M underwent different changes in August and Wistar rats. Power density of BP_M fluctuations in the LF range in August rats was 142% higher than in Wistar rats (Table 1). As a result of these differences, the total power of fluctuations increased by 2 times. Published data show that the power of BP_M fluctuations in the LF range depends on changes in the content of angiotensin II or kinins in the blood [13] and rhythmic activity of blood vessels [11]. Moreover, the power of BP fluctuations in the LF range depends on locomotor activity of animals [15]. It is difficult to understand which mechanism increases the power of BP fluctuations in the LF range in August rats.

By contrast, the power of PI fluctuations in LF, MF, and HF ranges in August rats was lower than in Wistar rats by 47, 59, and 35%, respectively (Table 1). Therefore, the total power of fluctuations decreased by 2 times. Previous studies showed that heart rhythm fluctuations in the studied range are associated with activity of the autonomic nervous system in rats. The influence of PNS predominate at rest [12]. Low power of PI fluctuations in August rats (compared to Wistar rats) reflects less pronounced effect of PNS on the heart and high activity of SNS [1]. Decreased HR variability in August rats can be related to low adrenoreactivity of heart structures [3].

During recovery after immobilization stress the power of BP_M fluctuations remained unchanged in Wistar rats, but decreased (LF range) or decreased in August rats (MF and HF ranges). After stress the total density of fluctuations insignificantly differed from the initial level. The power of PI fluctuations in Wistar rats decreased by 37% only in the HF range. In August rats this parameter decreased in LF, MD, and HF ranges by 59, 59, and 40%, respectively, compared to the control (Table 1). Therefore, stress decreased the total density of PI fluctuations in August rats by 2 times. Sharp changes in variability of hemodynamic parameters in August rats indicate that stress produces more potent effects in these animals compared to Wistar rats. The increase in the power of BP fluctuations in the MF range and the decrease in the power of PI fluctuations reflect more pronounced activation of the sympathoadrenal system, which persists over 1 h after stress. These results are consistent with previously reported increase in blood catecholamine level in August rats during immobilization stress [5].

The total duration of severe ischemic arrhythmias in August rats was much lower than in Wistar rats (59.0±18.9 and 125.0±31.2 sec, respectively, $p<0.05$). The development of arrhythmias during acute ischemia results from activation of SNS. The data suggest that August rats with reduced adrenoreactivity of the myocardium are characterized by lower sensitivity of the heart to sympathetic influences compared to Wistar rats [3]. Moreover, high resistance of August rats to arrhythmias can be associated with higher activity of the NO system (compared to Wistar rats) [7]. Published data show that this system inhibits SNS [14] and reduces sensitivity of the myocardium to ischemia.

We measured the content of catecholamines in the hypothalamus. Dopamine content did not differ in August and Wistar rats (0.58±0.07 and 0.55±0.03 ng/mg tissue, respectively). However, norepinephrine concentration in August rats was lower than in Wistar rats (2.06±0.10 and 2.44±0.12 ng/mg tissue, respectively, $p<0.05$). It was hypothesized that the reduced metabolism of norepinephrine in hypothalamic nuclei

TABLE 1. Power Spectral Density of Fluctuations in BP_M and PI in Wistar and August Rats (1-h Intervals, $M\pm m$)

Parameter	At rest		After stress	
	Wistar	August	Wistar	August
Power spectral density of BP_M fluctuations, mm Hg^2				
LF	7.14±0.87	17.26±3.20*	7.36±0.78	13.39±1.94*+
MF	5.75±1.20	6.64±1.11	6.85±0.79	10.28±1.91+
HF	1.46±0.28	4.76±2.64	2.36±0.65	6.57±2.43+
Total density of fluctuations	14.36±2.09	28.65±5.46*	16.57±1.25	30.24±5.60*
Power spectral density of PI fluctuations, $msec^2$				
LF	12.01±2.45	6.33±1.26	13.32±1.44	2.80±0.41*+
MF	2.6±0.7	1.08±0.19	2.54±0.45	0.44±0.06*+
HF	5.17±0.72	3.36±0.27*	3.23±0.22+	2.00±0.09*+
Total power density of fluctuations	19.78±3.38	10.76±1.65*	19.10±1.96	5.23±0.52*+

Note. $p<0.05$: *compared to other group; +compared to rest period.

of August rats plays a role in the development of hemodynamic disturbances under stress conditions [4].

Our results indicate that August and Wistar rats differ in variability of hemodynamic indexes. In August rats the power of BP fluctuations is higher, while the power of HR fluctuations is lower than in Wistar rats. The narrower range of HR fluctuations in August rats compared to that in Wistar rats is associated with high resistance to the arrhythmogenic effect of myocardial ischemia and low content of norepinephrine in the hypothalamus. As differentiated from Wistar rats, short-term stress considerably reduces spectral power of HR fluctuations in August rats. These changes persist for a long time, which reflects less labile regulation of the cardiovascular system in August rats.

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