Acute Hypoxia during Organogenesis Affects Cardiac Autonomic Balance in Pregnant Rats

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Changes in ECG parameters were studied in pregnant rats exposed to acute hypobaric hypoxia during the period of organogenesis (gestation days 9 to 10). Rats with low, medium, and high tolerance to hypoxia exhibited pronounced autonomic nervous system imbalance, which become apparent as a loss of correlation between various parameters of ECG signals recorded at rest and during exposure to some stress factors existing under normal conditions.

Key Words: *hypoxia; pregnant rats; ECG; autonomic balance*

Acute hypoxia during gestation is a potent factor leading to dysfunction of many vitally important systems of the organism. The most critical period corresponds to organogenesis [3].

Destructive influences of acute hypoxia on the cardiovascular system are of special interest as a major factor of long-term functional dysadaptation of maternal organism or fetal organism in both antenatal and postnatal period [4]. ECG monitoring combined with statistical analysis of ECG parameters provides a mean for assessment of alterations in the autonomic balance [1].

In the present work we analyzed long-term changes in ECG parameters observed in pregnant rats after their exposure to acute hypobaric hypoxia during organogenesis (9-10 gestation days).

MATERIALS AND METHODS

The study was performed on random-bred albino rats exposed to acute high-altitude hypoxia on gestation day 9 or 10. The day when spermatozoa were first detected in vaginal smear was considered as the first day of pregnancy [3]. Hypoxia was simulated in a high-altitude chamber at atmospheric pressure of 145 mm Hg, which corresponded to an altitude of 11,500 m above sea level (ascent took 1 min). Then we measured a period between the end of the ascent to apnea, named as "life time at high altitude" [2]. Depending of this parameter, the rats were divided into three groups with a different level of hypoxia tolerance: low tolerance (LT, life time at high altitude 0-300 sec); medium tolerance (MT, 301-600 sec); high tolerance (HT, >600 sec).

Subcutaneous ECG electrodes were implanted under Nembutal anesthesia (30 mg/kg, intraperitoneally) one day before exposure to hypoxia in order to monitor ECG in one of standard leads. On the next day after hypoxic exposure the rats were placed into "open field" and ECG signals were recorded in freely moving animals for 4 min. Total "open-field" period (240 sec) was not uniform and included five main periods: stress reaction to placing into the field (0-30 sec); period of relative rest or adaptation to novel environment (30-120 sec); stress reaction to switching on white light (120-150 sec); adaptation to light (150-180 sec); and poststimulus period after switching off the light (180-240 sec).

Continuous analog ECG signals were digitized at discretization rate of 500 Hz and recorded using ISCOUP software. The recorded data were processed using SPIKE-C3 and INTERVALS 1.02 software. The

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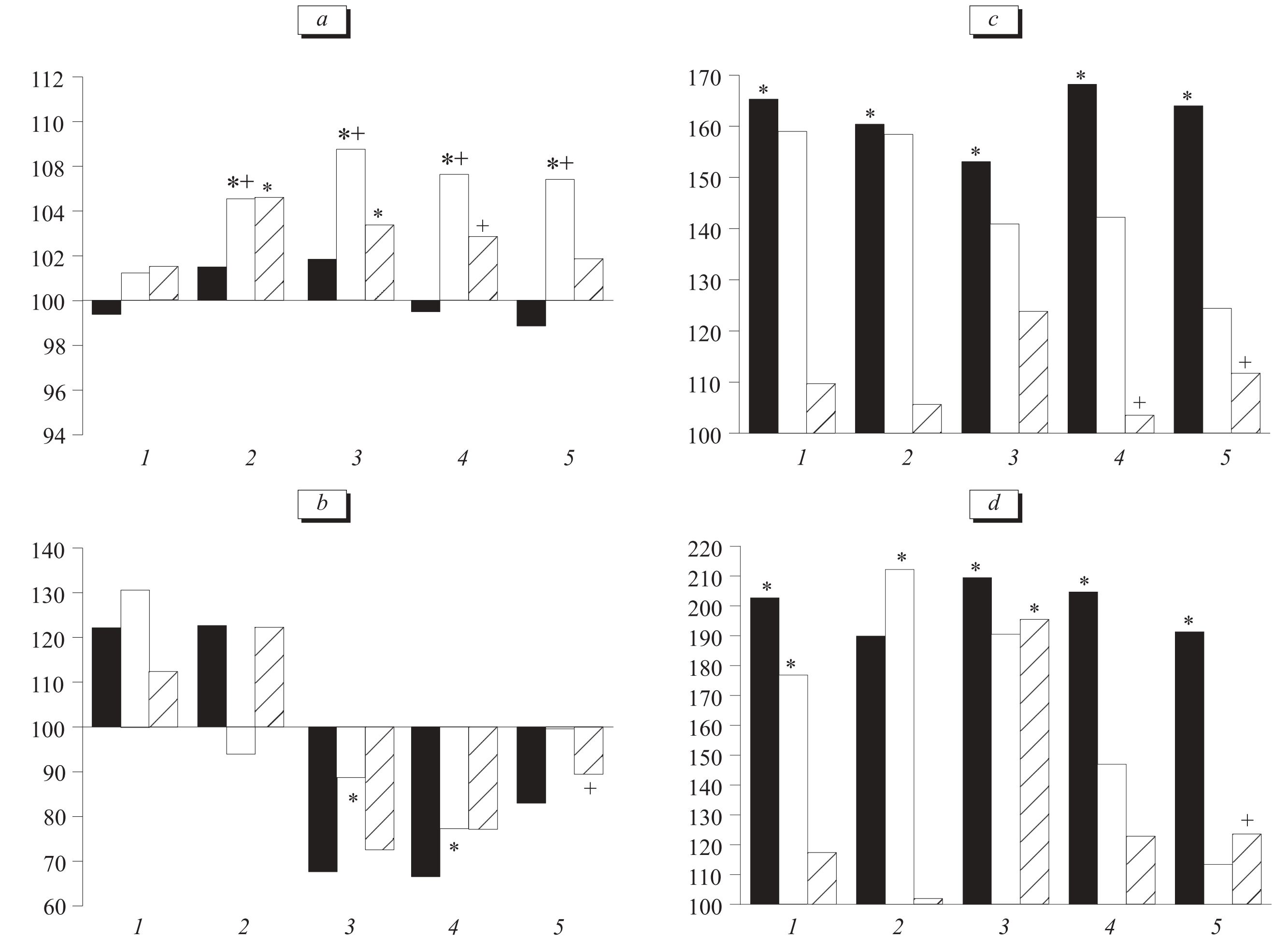

Fig. 1. *RR* interval (*a*) and parameters of its variability, such as SD*RR* (*b*), mode amplitude (*c*), and factor of monotony (*d*), derived from ECG of pregnant rats with different hypoxia tolerance. Relative rest (*1*); placing into open field (*2*); switching on the light (*3*); adaptation to the light (*4*); and switching off the light (*5*). Rats with low (dark bars), medium (light bars), and high (shaded bars) tolerance to hypoxia. $p<0.05$: *compared to the control; +compared to relative rest.

following parameters of ECG were determined: mean *RR* interval; *RR* variability (standard deviation, SD*RR* in msec); mode amplitude (percentage of the most frequent *RR* interval, in %); and the monotony index (mode amplitude divided by SD*RR*). The last three indices allow us to assess the sympatho-vagal balance in the cardiac autonomic control [1].

RESULTS

Analysis of changes in the mean values of *RR* interval and *RR* variability, which depend on relative activity of the sympathetic and parasympathetic systems, showed the following. In the control group, placing into open field induced a substantial increase in RR vari-

TABLE 1. ECG Indices Calculated for Various Test Periods in Control Rats (n=19)

Parameter	Relative resting	Placing into open field	Light switched on	Adaptation to the light	Light switched off
RR interval, msec	119.2	119.5	118.1	122.5	123.1
SD*RR*, msec	39.7	59.3*	55.7	53.7	56.5
Mode amplitude, %	8.4	8.2	7.5	6.7*	6.7*
Monotony index	0.2	0.2	0.2	0.2	0.2

Note: *$p<0.05$ compared to relative rest.

ability, while adaptation to stress and subsequent post-stimulus period was characterized by a significant decrease in mode amplitude. No more statistically significant changes were observed in the control group (Table 1).

In LT rats, ECG parameters did not change significantly throughout the test periods (Fig. 1). Remarkable lengthening of *RR* intervals was typical of all stress reactions in MT rats. Moreover, prolonged RR intervals persisted during adaptation to stress and even after its removal. Moreover, the monotony index decreased in MT rats in the poststimulus period. In HT rats, mean *RR* intervals increased during adaptation, while *RR* variations increased just after placing into the field (*i. e.*, in the first stress period). Mode amplitude significantly decreased during adaptation and in the poststimulus periods (Fig. 1).

Thus, our experiments revealed remarkable distinctions in the autonomic responses to stress between different rat groups.

Comparative analysis between the groups of rats with different tolerance to hypoxia showed that LT rats were characterized by the greatest incidence of significant changes in the test parameters compared to their control values. Posthypoxic values of the mode amplitude and monotony index were decreased in these rats throughout all open field tests (Fig. 1). *RR* variability in this group decreased considerably during the stress reaction to switching on the light and the following period of adaptation. In MT rats, hypoxia lengthened the mean *RR* interval throughout all period of ECG recording and increased the monotony index during the period of relative rest. In HT rats, the incidence of significant changes in the test parameters against the control was the lowest. These rats manifested increased *RR* intervals during all stress periods and a concomitant rise in the monotony index during switching on the light (Fig. 1).

Thus, exposure of pregnant rats to acute hypoxia during organogenesis period leads to a loss of normally existing cross-correlation between various ECG parameters. These results suggest that acute hypoxia induces long-lasting posthypoxic disturbances in the autonomic balance in pregnant rats. The degree of these disagreements in ECG parameters differed in rats with different hypoxia tolerance. In HT rats the effect of hypoxia on the autonomic regulation of the heart in the posthypoxic period was less pronounced, despite longer hypoxic exposure.

It is concluded that long-term impairment of the autonomic balance in pregnant rats exposed to hypoxia during organogenesis period can produce harmful effects on fetal circulation and development of the fetus.

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