Sex-Related Differences in Cardiovascular Stress Reactivity in Healthy and Hypertensive Rats

T. G. Anishchenko, O. V. Glushkovskaya-Semyachkina, V. A. Berdnikova, and T. A. Sindyakova

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In healthy females the chronotropic effects of stress are more pronounced, while the hypertensive effects are weakened compared to males. Hemodynamic parameters in females returned to normal more rapidly than in males. Renovascular hypertension in males is more pronounced than in females and is associated with increased cardiovascular stress reactivity (in females it is associated with decreased cardiovascular stress reactivity), which increase the risk of cardiovascular complications in males.

Key Words: *cardiovascular system; stress; hypertension; sex differences*

The incidence and severity of hypertension as a nosological entity and serious risk factor of various cardiovascular disorders in men are higher than in premenopausal women [14]. Essential hypertension in women is characterized by a lower risk of lethal outcome [12]. Studies on animals with modeled hypertension showed that blood pressure (BP) in males is higher than in females [14], while the resistance to stress-induced cardiovascular disorders is higher in females [1]. Increased predisposition of men to hypertension is associated with a more significant vascular response to stress (compared to women) [13]. Sex-related differences in cardiovascular stress reactivity in experimental animals and the role of the gender factor in the effects of stress on the cardiovascular system in hypertensive humans are little studied.

Here we studied the dynamics of cardiovascular responses of normotensive and hypertensive (HT) female and male albino rats to acute stress.

Department of Human and Animal Physiology, N. G. Chernyshevskii Saratov State University. ***Address for correspondence:*** glushkovskaya@mail.ru. O. V. Glushkovskaya-Semyachkina

MATERIALS AND METHODS

Experiments were performed on 20 healthy and 16 HT female and male albino rats. Hypertension was induced by the method of H. Goldblatt *et al*. [10]. To this end, a silver clamp was applied to the left renal artery under nembutal anesthesia (35-40 mg/kg). The control group included intact, but not sham-operated animals, since blood corticosterone level returns to normal 1 day after laparotomy [2]. Persistent hypertension in rats developed 7 weeks after clamping. Normotensive and HT animals were subjected to 60-min immobilization stress (IS). BP was measured using a catheter. The study was performed on a PowerLab/400 ML401 multichannel complex using Chart 4 software (ADInstruments Ltd.). Mean BP (MBP) and heart rate (HR) were recorded during IS and over 60 min after the end of stress.

Statistical treatment of data involved Statistica 5.0 software. The influence of factors (sex and stress) on hemodynamic parameters was estimated by the analysis of variance (ANOVA). Duncan rank test was used for multiple comparison. The differences were significant at $p<0.05$.

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RESULTS

Basal MBP practically did not differ in normotensive females and males (96±3 and 99±2 mm Hg, respectively). HR in females was lower than in males (394±4 and 371±4 bpm, respectively, $p<0.05$). The hemodynamic effects of stress were different in females and males. HR was elevated from the 1st minute to the end of IS. HR in females increased more significantly and recovered more rapidly than in males. HR in females did not differ from the initial values 40 min after the end of IS, while in males tachycardia persisted over 60 min after IS (Fig. 1, *a*). In both females and males, the vascular effects of stress were less pronounced than the chronotropic effects. It should be emphasized that in females demonstrating more severe tachycardia the amplitude and duration of the HT response were lower than in males. In particular, significantly increased MBP values were recorded for 1 min in females and for 15 min in males (Fig. 1, *b*). After IS, the HT responses in females were weak, which probably reflects the compensatory response to stress-induced hypertension. MBP in females returned to normal by the end of the recovery period, while males demonstrated a tendency to elevated MBP.

Despite more severe tachycardia under stress conditions in females, the amplitude and duration of MBP elevation were lower than in males, which attested to predominance of cardiac components of the cardiovascular stress response in females and vascular components in males. In humans, the cardiovascular stress response is also characterized by more pronounced chronotropic effects in women and more potent HT reaction in men [4,6,13]. HR and MBP in stressed females returned to normal more rapidly than in males, which is consistent with published data on animals [15] and humans [4,6,13].

Renal ischemia was followed by the development of hypertension. The severity of hypertension in males was higher than in females, which is consistent with the results of previous experiments on various models of hypertension [14]. MBP in females and males increased to 118±4 and 140±3 mm Hg, respectively (123 and 141% of the basal level, respectively, $p<0.05$). The weight of the left kidney in males and females decreased by 15.8 and 8.3 times, respectively ($p<0.05$, Fig. 2).

In HT females, the chronotropic effects of stress were weakened: HR during IS increased by only 10-16% ($p<0.05$, Fig. 3, *a*), while in healthy animals this parameter increased by 25-30% ($p<0.05$). In HT females, HR returned to normal 5 min after IS, while in healthy females it returned to normal 40 min after the end of IS. Vascular reactions in HT and healthy females developed over the 1st minute of IS and did not differ by the amplitude. However, in HT females we observed hypotensive reactions, which developed by the 10th minute of IS and persisted over 60-min poststress period (Fig. 3, *b*). Variations in cardiac and vascular components of the stress response in HT females reflect activation of protective mechanisms preventing long-term increase in BP during stress.

In males hypertension was accompanied by an increase in cardiac and vascular components of cardiovascular stress reactivity. The chronotropic effect of stress in HT males was more pronounced than in normotensive animals. HR in HT and nor-

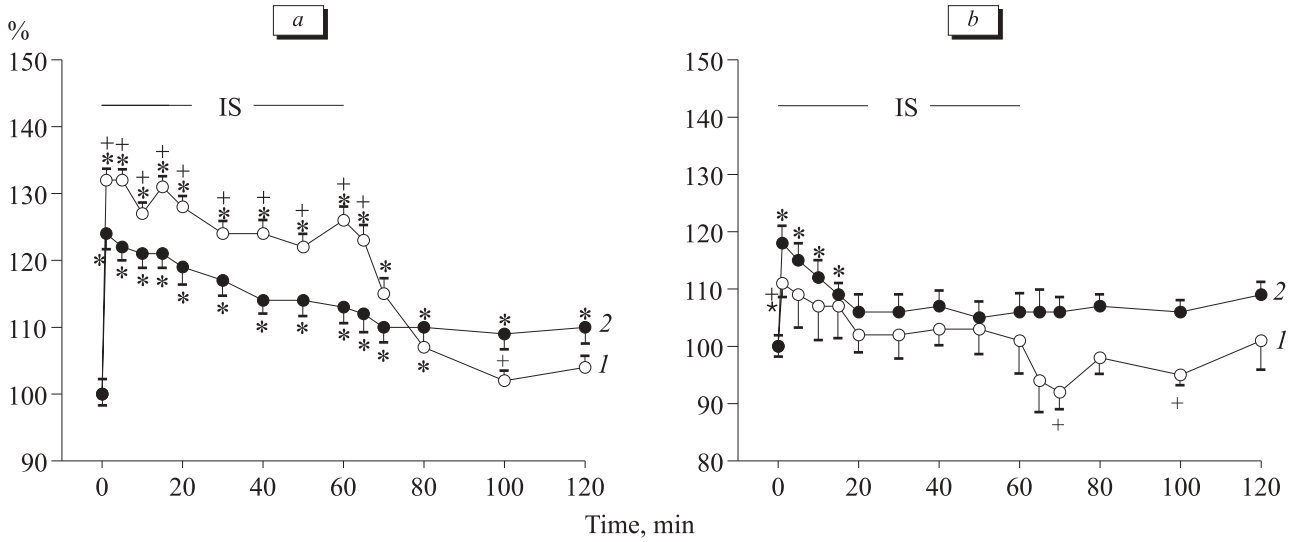

Fig. 1. HR (*a*) and MBP (*b*) in normotensive female and male rats during IS. Here and in Fig. 3: females (*1*) and males (*2*). $p<0.05$: *compared to the basal level; +compared to males.

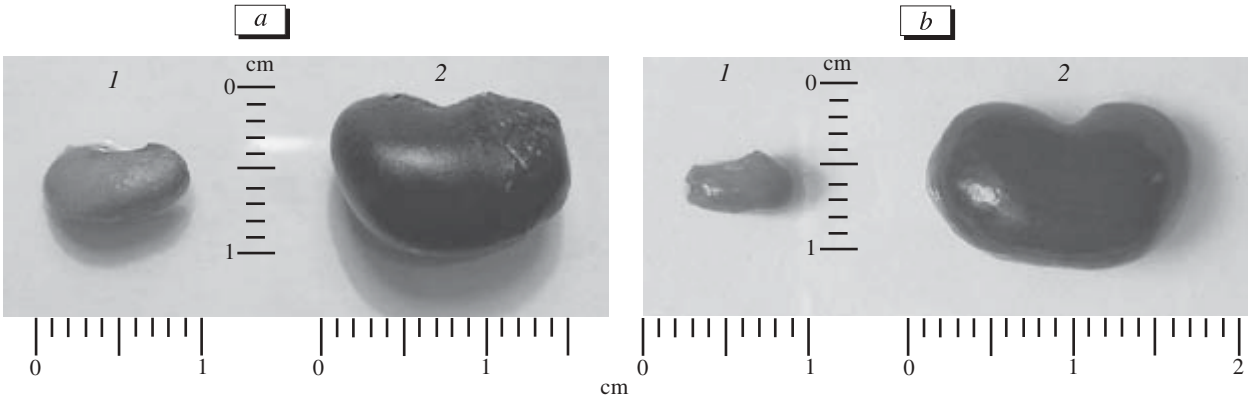

Fig. 2. Ischemic (*1*) and normal kidneys (*2*) in HT female (*a*) and HT male (*b*).

motensive males subjected to IS increased by 28-21 and 24-15%, respectively ($p<0.05$, Fig. 3, *a*). The decrease in the chronotropic component of stress in females, and its increase in males during hypertension led to inversion of the sex-related differences in the degree of stress-induced tachycardia. In HT animals (in contrast to normotensive animals), the stress-induced increase in HR was most pronounced males (Figs. 1, *a*, 3, *a*).

The IS-induced vascular reactions in HT males persisted for a longer time compared to healthy animals. MBP in healthy males increased over 15 min of IS. Stress-induced hypertension in HT males persisted for 40 min of IS. MBP in HT males remained high in the following 20 min of IS (Fig. 3, *b*).

The increase in cardiovascular stress reactivity in HT males is consistent with published data on male rats with borderline hypertension [11] and men with moderate hypertension [7]. These changes are probably related to activation of the sympathoadrenal system [11] and increase in cardiovascular sensitivity to sympathoadrenal influences during hypertension [5]. This process in females is probably limited by high functional reserves of the cholinergic system [3] and more potent cholinergic influences on the cardiovascular system [8,9].

In healthy and particularly in HT animals, the dynamics of cardiovascular reactions during stress is more favorable in females than in males from the viewpoint of resistance to cardiovascular disorders. Normotensive females are characterized by more severe tachycardia, lower HT response to stress, and more rapid recovery of HR and MBP compared to males. The impairment of renal blood flow results in the development of hypertension, which is more pronounced in males than in females. Weakening of the chronotropic effect of stress and lengthening of the phase for compensatory hypotension after stress-induced BP elevation reduce the risk of progressive hypertension and cardiovascular disorders in females. Potentiation of cardiac and vascular reactions in HT males during stress is a nega-

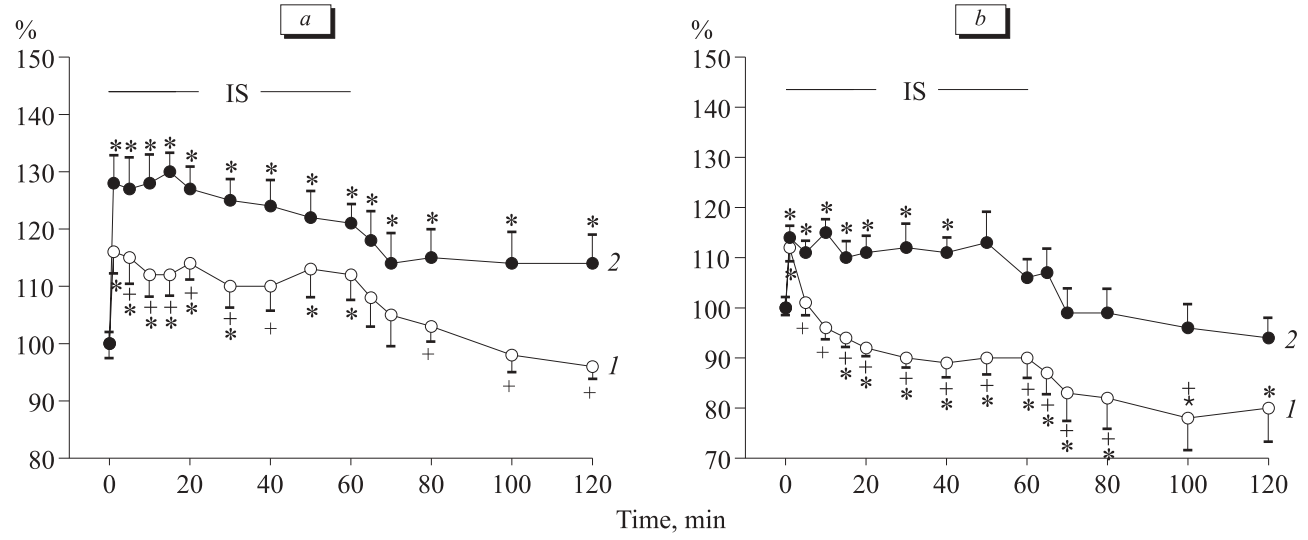

Fig. 3. HR (*a*) and MBP (*b*) in HT female rats and HT male rats during IS.

tive factor promoting hypertension development and increasing the risk of cardiovascular complications.

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