# Effect of Endothelin-1 on Cardiovascular Parameters of Lewis and Wistar Rats in Immobilization Stress

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Effect of low doses of endothelin-1 on the dynamics of blood pressure and heart rate is studied in Lewis and Wistar rats during 1-h immobilization stress. It is shown that endothelin-1 significantly lowers blood pressure in stress-sensitive Lewis rats during stress and has no effect on hemodynamic parameters in immobilized stress-resistant Wistar rats in comparison with the control.

**Key Words:** *endothelin; immobilization stress; Lewis rats*

Endothelin-1 (ET-1) is an endogenous vasoactive peptide. Being injected in picomolar doses *in vivo*, ET-1 increases mean blood pressure (MBP) and total peripheral resistance [7]. This suggests the involvement of this peptide into some cardiovascular pathologies. In particular, elevated blood ET-1 concentrations have been noted in pulmonary hypertension, myocardial infarction, ischemic heart disease, and stroke [3]. ET-1 probably plays a role in adaptive reaction. Blood content of ET-1 increases in exercise, hypoxia, and cold stress [4].

Emotional stress causes not only adaptive shifts, but also disturbances in the cardiovascular system. Immobilization stress is widely used as the model of emotional stress in experimental animals. It has been shown that in rats the resistance to stress-induced functional cardiovascular disturbances is genetically determined [2].

Taking into account the possible influence of ET-1 on adaptive reaction of the cardiovascular system, we explored the effect of a low dose of ET-1 on MBP and heart rate (HR) during immobilization stress in rats susceptible (Lewis) and resistant (Wistar) to stress.

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## MATERIALS AND METHODS

Experiments were carried out on Wistar ($n$=10) and Lewis ($n$=11) rats weighing 250-320 g. Behavioral parameters were preliminary recorded in an open field [1] during 2 min before and after stress (2-min combined influence of bell and 500 W lamp).

Changes in MBP and HR were recorded and test substances were infused using polyethylene catheters implanted under Nembutal narcosis (40 mg/kg) into the femoral artery and jugular vein. MBP and HR were recorded using a STATHAM pressure transducer connected to a computer (512 Hz digitalization frequency). The test substances were infused using a Veda-2 infusor.

The experiments were carried out on alert animals. Infusion of ET-1 was started ($2.2\times10^{-12}$ mol/kg/min infusion rate, $2\times10^{-10}$ mol/kg final dose) after stabilization of MBP and HR. Thirty minutes after the start of infusion (the estimated time of equilibration between infusion and elimination of ET-1, since half-life time for ET-1 is 40-68 sec [5]) the animals were subjected to 1-h immobilization stress (in the supine position with fixed head). Infusion was stopped simultaneously with the end of immobilization, and MBP and HR were recorded for one more hour. Control animals were subjected

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TABLE 1. Behavioral Parameters in Open Field Test

| State | | Behavioral parameters | | | |
|---|---|---|---|---|---|
| | | runs | enters to central zone | rearing | washing |
| Lewis | before stress | 71.3 | 2.9 | 7.6 | 3.5 |
| | after stress | 22.5** | 0.8** | 1.6** | 11.1* |
| Wistar | before stress | 81.8 | 2.6 | 11 | 2.8 |
| | after stress | 40.3* | 1.6 | 12.1 | 2.1 |

Note. *$p<0.01$, **$p<0.001$ compared with the same strain before and after stress.

to immobilization stress and received physiological saline.

Changes in MBP and HR are expressed in percent of the initial level (100%). The data were processed statistically using unpaired $t$ test or nonparametric Mann-Whitney test.

## RESULTS

Preliminary open field test revealed a difference in behavioral parameters of Wistar and Lewis rats: vertical activity in Lewis rats was lower than in Wistar rats ($p<0.05$). Stress considerably decreased the number of entries to the central zone and vertical activity ($p<0.001$) and increased the number of grooming acts ($p<0.01$) in Lewis rats, while in Wistar rats these parameters did not differ from the baseline values (Table 1).

These findings attest to increased anxiety of Lewis rats compared with Wistar rats [6]. Thus, in the open field test Lewis rats were more susceptible to stress than Wistar rats.

In both Lewis and Wistar rats immobilization induced a rise of MBP and HR (Figs. 1 and 2). The maximum rise of MBP in Lewis rats was observed on the 20th min of immobilization: in animals received ET-1 and physiological saline it constituted 14.2±6.8% (14.7±7 mm Hg) and 25.7±5.6% (26.6±5.8 mm Hg), respectively, HR being increased by 17.3±5.3% (62±19 beats/min) and 20±1% (54±2.7 beats/min), respectively. After this transient phase, MBP and HR decreased but remained above the control level. In Lewis rats, maximum differences between the control and experimental groups were noted on the 50th min of immobilization (19.8%, 20.7 mm Hg). Thus, the rise of MBP in the experimental group was less pronounced than in the control ($p<0.05$). There were practically no differences in the dynamics of HR between Lewis rats receiving ET-1 and physiological saline (Fig. 1). After immobilization, MBP and HR decreased but remained above the initial values.

There were no significant differences in the dynamic of MBP and HR between Wistar rats receiving

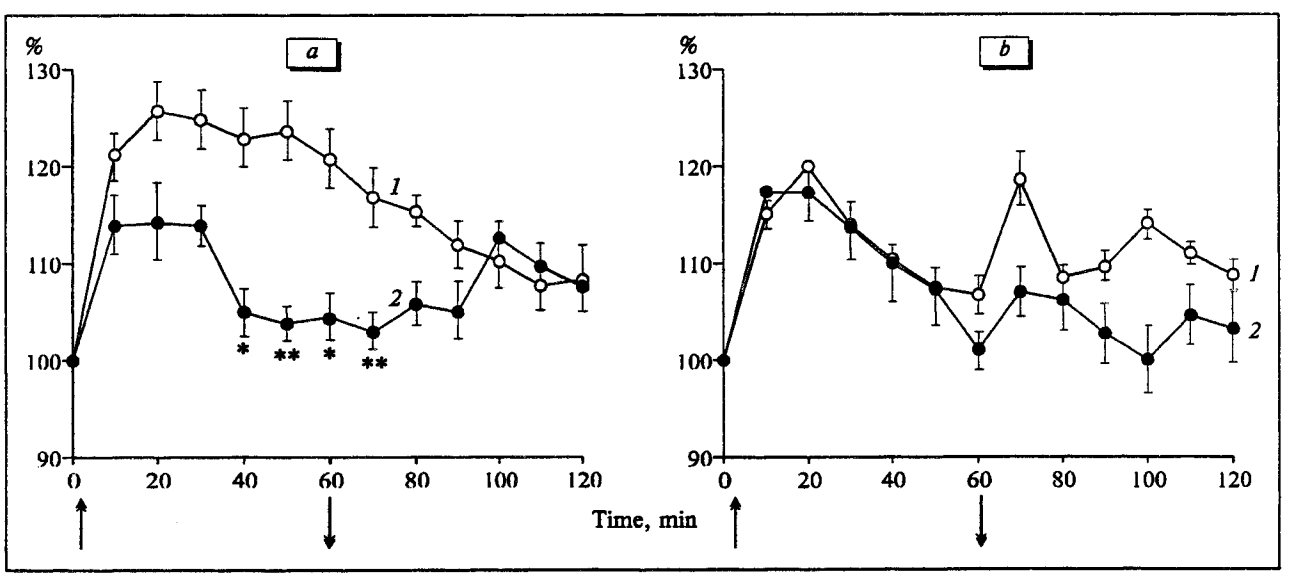


Fig. 1. Dynamics of mean blood pressure (*a*) and heart rate (*b*) in Lewis rats during immobilization. Here and in Fig. 2: *1*) control; *2*) infusion of endothelin-1; arrows indicate the start and end of immobilization. Here and in Fig. 3: *$p<0.05$, **$p<0.01$ compared with the control.

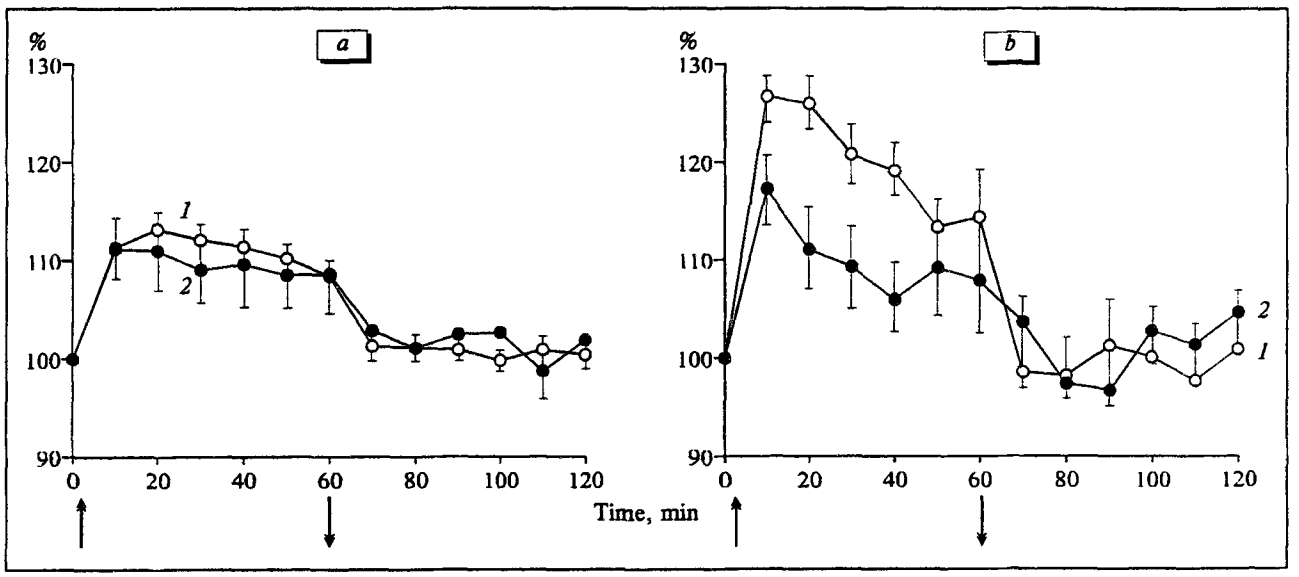


Fig. 2. Dynamics of mean blood pressure (*a*) and heart rate (*b*) in Wistar rats during immobilization.

ET-1 and physiological saline; however, the mean HR in control Wistar rats was higher than in other groups. The maximum rise of MBP in experimental ($n$=5) and control ($n$=5) groups constituted 11.3±4.4% (14.5±5.6 mm Hg) and 13.2±2% (16.9±2.5 mm Hg), respectively, while the rise of HR was 17.3±8.7% (72±36 beats/min) and 26±4.8% (108±20 beats/min), respectively. Forty minutes after immobilization these parameters returned or were close to initial values.

We found no differences in the dynamics of MBP between Lewis and Wistar rats subjected to immobilization stress against the background of ET-1 infusion, while in control Wistar and Lewis rats the dynamics of MBP differed significantly ($p$<0.05, Fig. 3). The maximum rise of MBP in response to immobilization stress was observed in Lewis rats against the background of physiological saline, while other groups differed little from each other in this parameter. The dynamics of HR was similar in all groups.

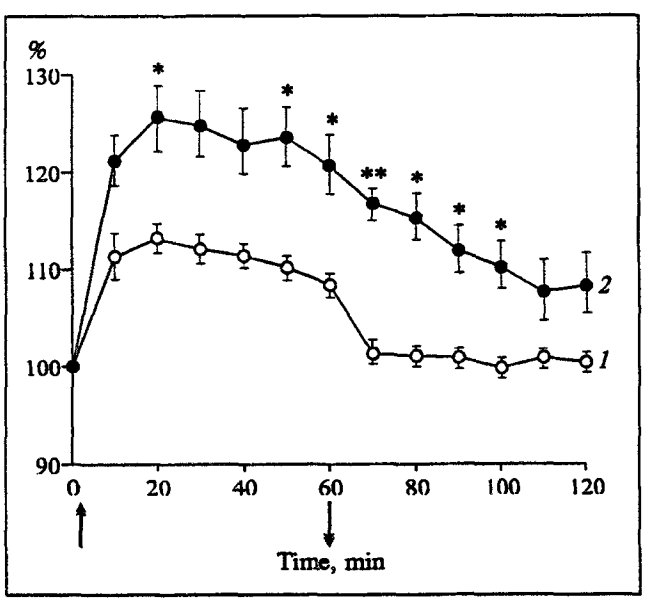


Fig. 3. Dynamics of mean blood pressure during immobilization against the background of infusion of physiological saline in different rat strains. *1*) Wistar; *2*) Lewis.

The differences in the dynamics of MBP during immobilization stress in Lewis rats suggest that ET-1 modulates reactivity of hemodynamic parameters and induces a hypotensive reaction in these animals. This effect is presumably due to a decrease in peripheral resistance, since no differences in HR were noted. Similar dynamics of MBP and HR in Lewis and Wistar rats suggests that long-term infusion of low doses of ET-1 restricts the rise of MBP in stress-susceptible Lewis rats to a level typical of stress-resistant rats. In this case ET-1 probably acts as an adaptogen and improves the resistance of the cardiovascular system to stress.

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