# Involvement of the Renin-Angiotensin System in the Regulation of Lung Norepinephrine Inactivation during Immobilization Stress in Rats

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The effect of immobilization stress on inactivation of norepinephrine in the lungs is studied in intact rats and against the background of blockade of the renin-angiotensin system with captopril (0.4 mg/kg intravenously). Captopril is shown to prevent the drop of lung inactivation of norepinephrine during immobilization stress.

**Key Words:** *norepinephrine; lungs; immobilization stress; angiotensin II*

The lungs represent one of the main sites of utilization of circulating norepinephrine (NE). About 45% of the total clearance of NE occurs in the lungs [7]. Despite the fact that such well-known factors as arterial and pulmonary hypertension, age, hemorrhage, mental stress, and others [4,8,9,11,14] affect lung inactivation of NE (LIN), the physiological regulation of this process is still poorly understood.

Immobilization stress was previously shown by us to reduce LIN in rats [3]. Stress is known to be accompanied by activation of the renin-angiotensin system (RAS) [6], which results in an increased content of angiotensin II (AT) in the circulation. At the same time, infusion of AT to rats has been previously shown [2] to reduce LIN in a dose-dependent manner. We hypothesized that the stress-induced reduction of LIN may be partially caused by activation of RAS.

To check this assumption we studied the effect of immobilization on LIN in rats against the background of inhibition of RAS with captopril.

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## MATERIALS AND METHODS

The experiments were carried out on laboratory rats weighing 200-300 g, maintained under standard conditions. One or two days before the experiment the animals were narcotized with nembutal (40 mg/kg, i.p.), and the right ventricle and the aorta were catheterized through the right jugular vein and the left carotid artery, respectively. On the day of the experiment the rats were immobilized in the supine position. Ten minutes prior to immobilization the rats of the first group ($n$=7) were infused with physiological saline and those of the second group ($n$=8) with captopril (0.4 mg/kg).

Arterial and mixed venous blood was sampled after 60 min of immobilization, 0.6 ml each. In some rats ($n$=7) blood for catecholamine determination was drawn 30 min prior to the experiment. The plasma content of catecholamines was determined by high-performance liquid chromatography with electrochemical detection [1]. The value of LIN was calculated by the formula presented in our previous publication [3]. Arterial pressure (AP) and the pressure in the right ventricle was tensometrically recorded during the experiment.

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TABLE 1. Values of Recorded Parameters during Immobilization of Intact Rats and against the Background of Inhibition of RAS ($M \pm m$)

| Parameter | Control | Immobilization + physiological saline | Immobilization + captopril |
|---|---|---|---|
| AP, mm Hg | | | |
| before immobilization | | 103±5 | 89±4 |
| after 60 min of immobilization | | 116±6 | 83±7* |
| Pressure in right ventricle, mm Hg | | | |
| before immobilization | | 9±1 | 10±1 |
| after 60 min of immobilization | | 16±2** | 13±1 |
| Content of NE in arterial blood, pg/ml | 364±67 | 2671±508** | 2836±570** |
| Content of epinephrine in arterial blood, pg/ml | 296±55 | 4483±1345** | 3868±773** |
| Lung inactivation of NE, % | 21.3±3.6 | 6.4±3.7** | 15.8±2.3* |

The data were processed using the method of variational statistics. The reliability of the differences was evaluated using the Student $t$ test.

## RESULTS

The experimental data are presented in Table 1. Immobilization caused a sharp increase in the amplitude of AP fluctuation. The mean AP was increased during the first few minutes of immobilization in both groups and then dropped, the drop being more pronounced in the captopril-treated group than in intact controls. The pressure in the right ventricle to the end of the immobilization period in rats of the first group reliably surpassed the initial level, while in the second group it remained virtually unchanged.

Stress increased the concentration of circulating catecholamines in both groups, but in animals with the blockade of RAS the level of NE was higher and that of epinephrine lower than in intact animals. After 60-min immobilization LIN dropped 3-fold in intact rats. In captopril-treated animals LIN was somewhat decreased but it reliably surpassed that in control rats after stress. Thus, immobilization against the background of captopril blockade of RAS did not cause as pronounced a drop of LIN as in the control group, i.e., inhibition of RAS prevented the drop of LIN characteristic for intact animals.

LIN is determined by three main factors: 1) the intensity of NE uptake by endothelial cells; 2) the area of active endothelium; 3) the rate of pulmonary circulation. Immobilization in rats was previously shown [5] to reduce the minute volume of the heart, which, in turn, leads to an enhancement of LIN due to prolonged contact of the blood with active endothelium. However, in our experiment we observed an inhibition of LIN during stress, and consequently the decrease of LIN in stress is not related to changes in the rate of pulmonary circulation. The mechanism of action of AT on LIN probably consists in inhibition of the uptake and transport of NE across the membrane of the endothelial cell and/or in changes in pulmonary circulation leading to a reduction of the area of active endothelium.

The first mechanism is confirmed by the presence of AT receptors on endotheliocytes of pulmonary vessels [13] and AT-mediated inhibition of NE neuronal uptake [12], which is similar to its lung uptake in a number of parameters [10].

Another possible mechanism of AT action is a redistribution of the pulmonary microcirculation. AT is known to be a potent constrictor of pulmonary vessels. At the same time, immobilization stress is reported to be accompanied by enhanced arteriovenous bypass in the lungs [5], which reduces the area of active endothelium. A certain role in this is probably played by AT. The results of this study allow for indirect monitoring of the changes in pulmonary circulation by the pressure in the right ventricle. Immobilization stress induced an almost 2-fold rise of the pressure in the right ventricle in intact animals, while in captopril-treated rats the pressure remained at the initial level.

Thus, our results suggest that RAS plays a part in regulating LIN, which implies one more level (metabolic) of the activating effect of AT on the sympathetic-adrenal system: the inhibition of LIN by AT, which in turn increases the concentration of NE in the blood [2]. It is significant that this mechanism manifests itself during the substantial activation of the sympathetic-adrenal system which takes place in immobilization stress, when the blood concentration of NE is high enough to exert its metabolic and vascular effects [15], whereupon it acts as a hormone.

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# Respiratory and Circulatory Disorders in Experimental Poisoning with an Organophosphorus Pesticide

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Acute poisoning with Anthio is associated with a gradual drop of blood pressure in the greater circulation and the development of intensive metabolic acidosis, despite normoxia still observed in the arterial blood and a somewhat increased oxygen capacity of the blood, this indicating mitochondrial injury and disordered tissue respiration.

**Key Words:** *acute poisoning; organophosphorus compounds; respiration; circulation; cat*

The wide use of chemicals in agriculture, household use of toxic chemicals, and the emergence of toxicomania present a whole array of practical medical problems such as rapid diagnosis, effective treatment, and prevention of possible complications in subjects suffering from acute and chronic poisoning. Pesticides of the group of organophosphorus compounds (OPC) are priority objects to be studied because of their high toxicity and chemical stability. Accumulating in the soil, water, and foodstuffs, they may lead to imperceptible chronic poisoning of the population and, in the case of large-scale uncontrolled consumption, to acute poisoning, this frequently resulting in unpredictable complications and grave consequences. Reports have been published on a relationship between the intensity of pesticide use in agricultural regions and the incidence of respiratory diseases in the local population [1,2,5,7].

The aim of this research was a comprehensive examination of the activities of the respiratory, cardiovascular, and circulatory systems in anesthetized cats exposed under conditions of an acute experiment to the agent Anthio (formothion, Sandoz), an OPC systemic insecticide and acaricide widely used in agriculture to protect plants from pests.

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