PULMONARY HEMODYNAMICS AND BLOOD PARAMETERS IN RATS EXPOSED TO LONG-TERM HIGH-ALTITUDE HYPOXIA

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Numerous investigations have shown that high-altitude-hypoxia leads to pulmonary hypertension and stimulates hematopoiesia [2, 8]. Under these circumstances the response to a comparatively short sojourn of lowland animals in the mountains has been studied most frequently. We know, however, that indigenous high-mountain animals and persons permanently dwelling in the mountains have significant differences in a number of important parameters of the blood and circulation (high erythrocyte count, high hemoglobin concentration in the erythrocytes, redistribution of blood flow in the lungs) [1, 11, 15]. On the basis of the facts described above and of experimental data indicating the development of altitude deterioration [6, 14], it can be concluded that even after a long sojourn in the mountains the adaptation process cannot be regarded as having stabilized at a particular level.

The aim of the present investigation was accordingly to study responses of the pulmonary circulation and the state of the red blood during a long-term (2, 5, and 10 months) sojourn of rats at an altitude of 3200 m above sea level (Tuya-Ashu Pass, Tyan'-Shan' Mountains).

EXPERIMENTAL METHOD

Experiments were carried out in summer on adult Wistar rats, transported beforehand (2, 5, and 10 months before the experiment began) to the mountain base and kept at room temperature on an ordinary diet with water and food ad lib. Some animals died during exposure, and 25 (2 months), 18 (5 months), and 10 (10 months) rats were used in the experiments. Acute experiments were conducted on rats lying supine, breathing naturally, and anesthetized with pentobarbital (30 mg/kg, intraperitoneally). The hematocrit index and hemoglobin concentration were determined by the usual methods and the erythrocyte counted with a "Picoscale P-4" instrument (Hungary). The pressure in the pulmonary artery and the blood flow in five conventionally chosen parts of the lungs (apical, ventromedial, ventrobasal, dorsomedial, and dorsobasal) were determined by catheterization of the pulmonary artery through the right jugular vein and by transbronchial regional electroplethysmography, by means of which the blood flow, the blood volume, and the air content could be determined per unit volume of the lungs [5]. The graph of recorded pressure, the electroplethysmogram, and the electrocardiogram were recorded on a Mingograf-34 automatic jet writer (Siemens-Elema). The position of the probe-transducer of the electroplethysmogram in the specified parts of the lungs was verified roentgenographically (Armal-1 apparatus) in two projections and after autopsy of the animals. The electrical resistance of the blood was measured during the investigation in a special cuvette (0.2 ml), by means of the same electroplethysmograph. The control consisted of 35 Wistar rats, studied in the plains.

The numerical results were subjected to statistical analysis by Student's test. Differences were considered to be significant at the $p < 0.05$ level.

EXPERIMENTAL RESULTS

The weight of the animals at the end of two months of exposure was 29% lower than in the control, and it continued to fall steadily (Table 1). The same picture also is observed

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TABLE 1. Pressure in Pulmonary Artery, Red Blood Parameters, and Body Weight of Rats after Different Periods of Sojourn in the Mountains (M ± m)

Parameter	Control	Length of sojourn in mountains, months		
		2	5	10
Pressure, mm Hg				
systolic	22,6±1,0	36,1±2,7**	35,9±3,7**	45,6±4,8**
diastolic	12,3±0,8	11,9±1,5	12,6±1,5	12,0±1,9
Specific electrical resistance of blood, Ω·cm	173±4	172±4	155±6*	174±14
Hemoglobin, g/liter	172±3	198±4**	215±7**	255±8**
Hematocrit, %	44,2±0,7	45,5±0,6	45,0±2,2	45,4±2,1
Erythrocyte count, $\times 10^{12}$/liter	7,42±0,36	6,79±0,31	6,08±0,40*	7,46±0,43
Body weight, g	355±12	254±6**	210±6**	189±16**

Legend. *p < 0.05, **p < 0.01, compared with control.

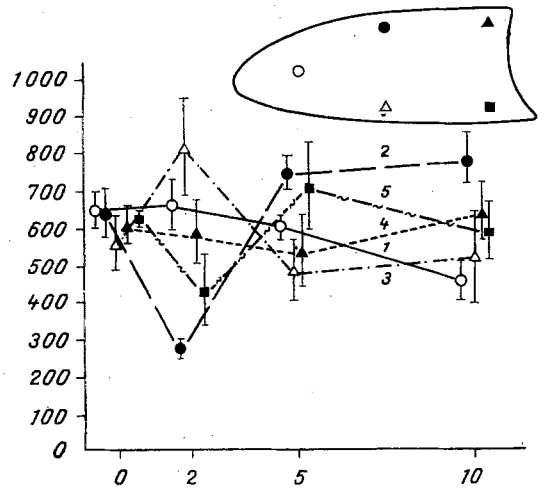

Fig. 1. Minute volume of blood flow in the lungs. Ordinate, ml/min/100 cm^3 volume of the lungs. Abscissa, months of adaptation. 1) Apical region of lung, 2) ventromedial, 3) dorsomedial, 4) ventrobasal, 5) dorsobasal part.

in man during a long stay in the mountains [6], and it is indirect evidence of the absence of stabilization of adaptation, even after what is for rats a long sojourn under high altitude conditions.

The erythrocyte count by this time, like the hematocrit index and electrical resistance of the blood, which depend mainly on the erythrocyte count, showed no significant change compared with the control, whereas the hemoglobin concentration (and also, correspondingly, the oxygen capacity of the blood) was significantly higher (Table 1).

The systolic pressure in the pulmonary artery after a stay of 2 months was increased by 60% whereas the diastolic pressure remained unchanged (Table 1). As a result the pulse pressure was considered raised, indirect evidence of increased rigidity of the vessels in the territory of the pulmonary artery as the main cause of the rise of systolic pressure. This was confirmed by a rough calculation of the characteristic impedance [9], reflecting the measure of counteraction of the sufficiently large vessels of the pulmonary bed to the pulsatile blood flow. The impedance rose by about 30%, possibly indicating structural changes in these vessels, as an expression of the "autoregulation" described by Folkow [13] for

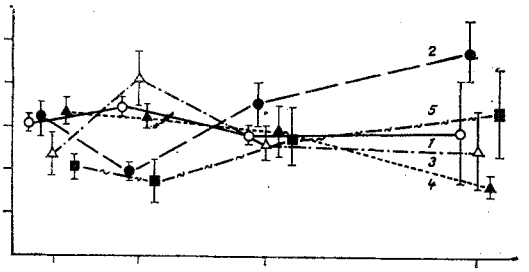

Fig. 2. Average blood volume of the lungs. Ordinate, ml/100 cm^3 lung volume for different parts of the lung in rats after different lengths of sojourn in the mountains. Remainder of legend as to Fig. 1.

vessels of the systemic circulation. Hypoxic stimulation of the carotid and aortic chemoreceptors, incidentally, also led to a decrease in compliance of the pulmonary arteries [12].

The role of a redistributive (for the blood flow), functionally advantageous active factor is ascribed to pulmonary hypertension [10, 11]. During analysis of the behavior of the blood flow and the blood volume in the lungs after adaptation of the rats for 2 months to high-altitude hypoxia, a significant decrease in the values of these parameters could be observed only in the ventromedial part (Figs. 1 and 2).

A stay in the mountains of 5 months led to return of the blood flow and blood volume in the above-mentioned part of the lung to the initial level, but the raised pressure in the pulmonary artery persisted (Table 1). The greatest changes in this series were observed in the blood: the specific electrical resistance, hematocrit, and erythrocyte counts all fell, but the hemoglobin concentration continued to rise. This led to an increase in the oxygen capacity of the blood to 29 ml/100 ml, and even with the small decrease in the erythrocyte count, this improves the oxygen supply to the body. Metabolic shifts leading to a change in the affinity of oxygen for hemoglobin and to an increase in its release by the tissues [4], may also probably contribute to this effect.

In the stage of 10 months of adaptation a further increase in systolic pressure was observed, but no increase in the diastolic pressure (Table 1). The blood flow in the ventromedial region was increased, whereas in the apical part of the lung it was significantly reduced (Fig. 1). The ventromedial region was most labile once again as regards the amplitude of response of the local blood volume (Fig. 2). The mechanisms of this redistribution are not yet clear and they do not agree with existing views of a more uniform regional blood flow under conditions of high-altitude hypoxia [11, 15]. Probably in this case more complex adaptive changes take place in the cardiovascular system [3].

It can be concluded from all the available facts that one of the constant and long-acting mechanisms of adaptation to high altitudes is an increase in the hemoglobin content in the erythrocytes and a corresponding increase in oxygen capacity of the blood. Together with a change in the dissociation constants of hemoglobin and adaptation to hypoxia at the tissue level [1, 7], this provides a basis for an energetically more advantageous adaptive mechanism. The role of erythrocytosis at high altitudes in the Tyan'-Shan' is evidently not so important, at least in the earlier stages of the sojourn in the mountains [6, 8].

As regards the role of pulmonary hypertension, which as the investigation showed is hypertension of systolic type, further investigations are needed to explain both the intimate mechanisms of its origin and its role in the regional distribution of the blood flow and blood volume in the lungs.

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EFFECT OF OPIATE RECEPTOR BLOCKADE BY NALOXONE ON DEVELOPMENT OF ISCHEMIC CARDIAC ARRHYTHMIAS

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Under certain conditions a change in activity of the higher levels of the brain, and, in particular, of the sensomotor cortex, complicates the course of acute myocardial ischemia. This effect is manifested as an increase in the frequency of onset of severe cardiac arrhythmias, including ventricular fibrillation [1, 2, 6, 9]. On the other hand, it has been shown [8] that CNS activity during the development of coronary insufficiency may be aimed at overcoming the consequences of myocardial ischemia, by giving rise to its own kind of adaptation to this pathological process and promoting survival. It has been suggested [5] that the prevention of disturbances of cardiac activity in acute myocardial ischemia by preliminary adaptation of animals to repeated stress may be associated with an increase in concentrations of opioid peptides (endorphins and enkephalins) in certain parts of the CNS and, in particular, in the cerebral cortex; the role of these substances in regulation of activity of the cardiovascular system is well known and has been widely studied [4, 7, 12-14].

Data on the role of opioid peptides in the pathogenesis of disturbances of cardiac activity during myocardial ischemia are conflicting. In this situation it is essential to use administration of naloxone, an antagonist of opiate receptors, as a way of evaluating the role of endogenous peptides in the mechanisms of disturbances of cardiac activity. The aim of the present part of the work was to study the pattern of development of cardiac arrhythmia in acute myocardial ischemia after preliminary administration of naloxone.

EXPERIMENTAL METHOD

Experiments were carried out on adult cats, male and female, weighing 2.5-4 kg, under pentobarbital anesthesia (30-40 mg, intraperitoneally). With artificial ventilation of the lungs with the "Vita-1" volume-frequency respirator thoracotomy was performed, the pericardium was opened, and a ligature was passed beneath the circumflex branch of the left coronary artery, close to its origin from the main trunk. Myocardial ischemia was induced by compressing the circumflex branch of the left coronary artery for 15 min. Naloxone hydrochloride

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