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The Mechanism of Pulmonary Hypertension in Rats with High-Altitude Hypoxia

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 121, № 3, pp. 324-327, March, 1996
Original article submitted March 16, 1995

Morphofunctional examinations of the lungs of rats exposed to high-altitude conditions for 3 to 300 days revealed that systolic pulmonary hypertension observed during the entire period of study is caused by a total increase of the elastic resistance of pulmonary arteries. Adequate bloodflow in such a case is provided by intensive work of the right-ventricular myocardium against this resistance.

Key Words: *high–altitude; pulmonary vessels; pulmonary hypertension; vascular resistance*

High-altitude hypoxia is regularly associated with rise of pressure in the pulmonary artery [4]. Usually hypertension in the pulmonary circulation is diagnosed from a rise of the mean pressure, and the actual process of pressure change is modeled on the basis of Poiseuille's model of the circulation, according to which a pressure rise in this vascular bed with the bloodflow decreased or intact means an increase of the pulmonary peripheral resistance (PPR). However, structural changes in the pulmonary network of vessels are diverse and cannot be interpreted unequivocally solely as an increase of PPR.

Therefore, the purpose of our study was to analyze the pulmonary hemodynamics under high-altitude conditions on the basis of natural pressure values in the pulmonary artery together with other hemodynamic parameters and data on the structural changes developing in the lungs during the exposure of animals to a mountain environment.

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MATERIALS AND METHODS

Experiments were carried out in summer with male Wistar rats brought to an altitude of 3200 m above sea level beforehand and kept at room temperature on the standard diet. Animals kept under the same conditions on the plain were controls.

The pressure was measured and pulmonary bloodflow, blood filling, and air content in the lungs per unit volume of the organ were assessed by catheterization of a lung artery through the jugular vein and transbronchial electroplethysmography. The parameters were recorded using a Siemens-Elema Mingograf-34 ink-jet recorder. The methods of investigation were described in detail previously [3]. The animals were exposed to the mountain altitude for 3, 10, 20, 30, 60, 150, and 300 days. After the experiments the lungs

0007-4888/96/0003-0296$15.00

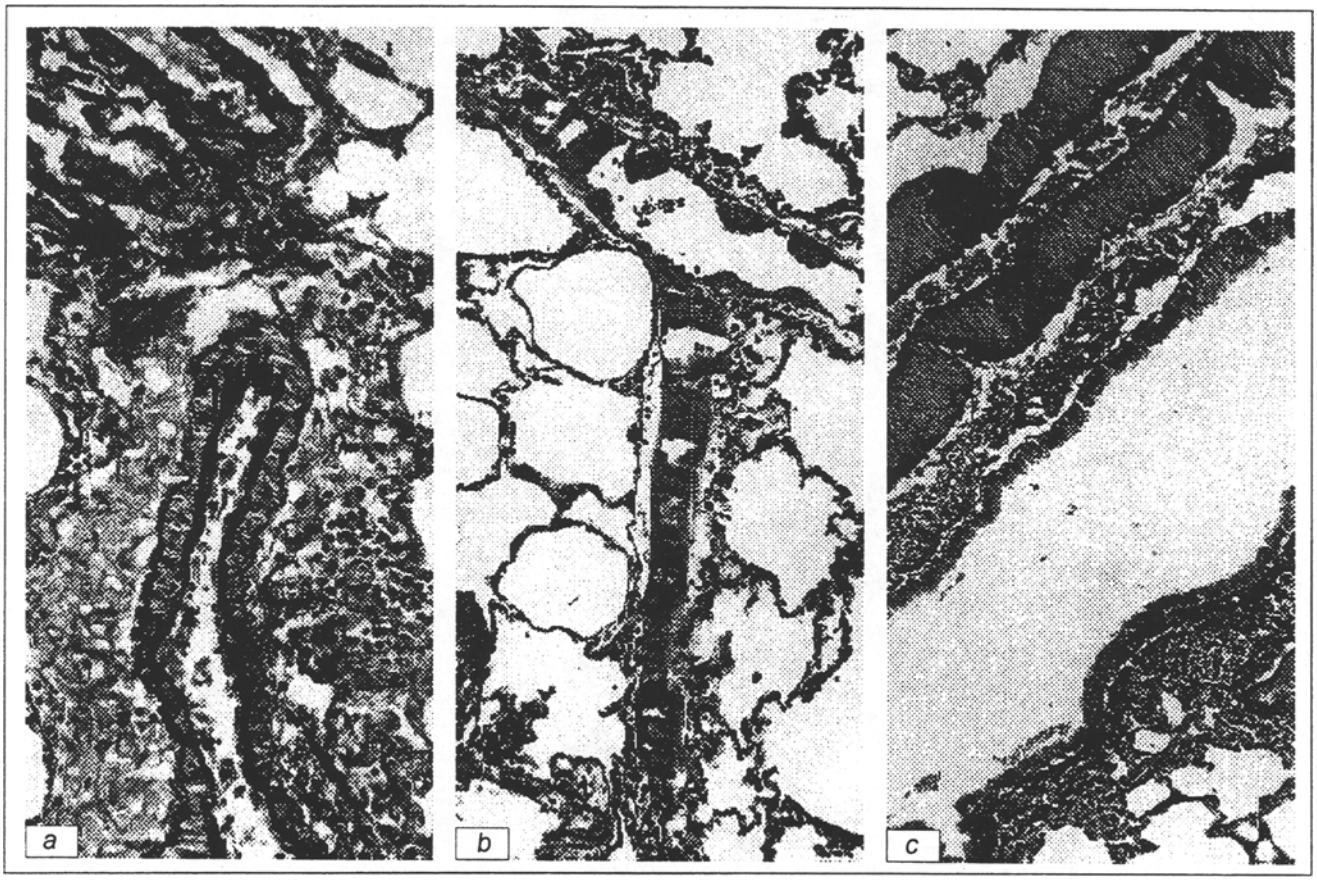

Fig. 1. Morphological changes in rat lungs exposed to high-altitude conditions for a long time. *a*) moderate hypertrophy of smooth-muscle cells, hyperelastosis, and fibrosis of artery walls after 2 months in the mountains. ×200; *b*) cushionlike thickenings in the muscle layer of interlobular veins after 5 months. ×125; *c*) manifest thickening of the muscle layer of arteries as a result of hyperplasia and hypertrophy of smooth-muscle cells after 10 months. ×250. *a*, *c*) Van Gieson staining; *b*) hematoxylin-eosin staining.

were fixed in 10% neutral Formalin. Paraffin slices were stained with hematoxylin-eosin and after Van Gieson, and the PAS reaction was carried out.

RESULTS

Systolic pressure (SP) was reliably increased in comparison with the control as early as on day 3 in the mountains, while by day 10 it was almost twice as high as the pressure in the controls and remained high over the entire period of observation (Table 1). Diastolic pressure (DP) did not reliably change during almost the entire experiment, reliably increasing only on day 30. Pulse pressure was high in accordance with the elevated SP. If we calculate or measure the mean pressure, however, its value will demonstrate an increase, which is an inevitable result of the sharp rise of SP for a virtually unchanged DP.

The minute volume of the pulmonary bloodflow was reduced in comparison with the control at all times of the experiment (Table 1), deviations from the norm being unreliable. However on day 30, at the time when there was a reliable increase of DP, the reduction of the bloodflow was close to reliable. As was previously demonstrated [3], in some areas of the lungs the bloodflow was reliably increased, and in others reliably decreased, but on the whole it changed negligibly.

Blood filling of the lungs and the content of air did not appreciably change over the entire period of observation; only on day 30 was a reliable increase of both parameters observed.

In terms of Poiseuille's model, when PPR is calculated from the value of the mean pressure (increased in our case) and bloodflow (virtually unchanged), it will always be increased, which is usually attributed to a blocking of the bloodflow at the lung periphery. But if we ignore Poiseuille's model and just proceed from the naturally existing time course of changes in SP and DP and their difference - pulse pressure, then the question as to the level at which the main obstacle for the actually existing pulse regimen of the pulmonary bloodflow arises may be interpreted quite differently.

The mere fact of a sharp increase of SP and pulse pressure in the presence of a little-changed DP indicates pulmonary hypertension of a systolic type and, just like systolic hypertension in the greater circulation, may be attributed to an increased rigidity of the majority of pulmonary vessels.

TABLE 1. Hemodynamic Parameters of the Lungs during Various Periods of Rat Exposure to High-Altitude Conditions (*M±m*)

Parameter	Control group (plain)	Mountain stay, days						
		3	10	20	30	60	150	300
Number of animals	66	8	6	10	17	12	7	5
Heart rate, beats/min	388±3.86	390±7.22	387±11.60	352±14.70	360±8.29	360±11.50	365±10.40	369±6.97
Pressure in pulmonary artery, mm Hg:								
SP	23.9±0.76	30.0±2.40*	45.0±2.35*	38.3±4.08*	54.1±8.16*	36.1±9.68*	38.9±3.70*	45.6±4.80*
DP	10.5±0.36	12.5±2.65	12.0±1.72	11.3±1.70	16.5±3.08*	11.9±1.46	12.6±1.49	12.0±1.90
Pulse	13.5±0.74	17.1±2.55	32.5±1.53*	27.4±2.05*	36.1±6.60*	24.2±2.84*	23.2±2.84*	33.6±5.16*
Bloodflow in the lungs per 100 cm^3 of organ volume, ml/min	652±47.2	566±48.9	562±48.4	590±42.2	536±40.4	536±46.2	618±46.6	608±49.7
Blood content per 100 cm^3 of organ volume, ml	19.5±0.58	20.7±1.35	20.7±1.23	19.7±1.03	23.3±1.66*	19.4±1.18	20.1±1.49	20.5±1.68
Air content, %	60.9±1.16	58.5±2.69	58.4±2.66	60.6±1.99	53.4±3.70*	60.8±2.39	59.8±2.99	58.6±3.97

Note. *$p<0.05$ in comparison with the control.

Early on during the animals' stay in the mountains, no marked morphological changes are found in the lungs: small veins and capillaries are moderately plethoric and there is moderate spasm of small arteries. The large pulmonary arteries at this time are morphologically little changed and most frequently are in a state of moderate spasm. A rather diverse, but on the whole similar picture is described by other scientists [8]. It is, however, worth noting that the pulmonary vessels of animals native to the mountains look like vessels with low PPR.

The most marked structural changes in pulmonary vessels develop at later periods. After 60 days in the mountains, a moderate thickening of the middle layer is seen in the pulmonary arteries, mainly on account of hypertrophied smooth-muscle cells, hyperelastosis, and moderate fibrosis of artery walls (Fig. 1, *a*). Spasm develops in smaller arteries, manifest spiralization of the inner elastic membrane, and a marked thickening of the muscle layer. Capillaries are mainly plethoric, and many of them are twisted. The PAS reaction reveals an increased level of glycoproteins in the basal layer of capillaries. Interlobular veins are plethoric and characterized by uneven thickening of the walls due to the formation of subintimal longitudinal muscle layers. The airiness of lung tissue is notably decreased at some sites as a result of pronounced mononuclear infiltration of alveolar septa; signs of hemorrhages are seen.

By day 150 a thick longitudinal muscle layer forms in the interlobular veins, presenting as a cushionlike outgrowth narrowing the vessel lumen (Fig. 1, *b*). The elastic membrane of the veins is thickened and fibrosis of the longitudinal muscle layer has progressed. During this period hemorrhages are still observed, as well as plasmorrhages, indicative, together with other morphological signs (fibrosis of the muscle layer, hyperelastosis, thickening of the basal layer of capillaries), of developing decompensation of the vascular bed (mainly the microcirculatory and venous compartments). At the same time manifest structural changes develop in the myocardium: disorders of circulation, pronounced hypertrophy of cardiomyocytes, and myoelastofibrosis of intramural arteries [1,2].

Later (after 300 days) manifest circulatory disorders, such as plethoric vessels, plasmorrhages, and hemosiderosis, persist in the lungs. Artery walls are thickened even more than previously as a result of hypertrophy and hyperplasia of smooth-muscle cells (Fig. 1, *c*). A longitudinal muscle layer is formed in the large branches of the pulmonary artery under the inner elastic membrane. This period of stay in the mountains is characterized by expressed myoelastofibrosis

of the vessels, particularly of the veins. On the whole, the lung tissue regains its airiness in the majority of animals, although in many cases manifest infiltration of alveolar septa is observed. Sclerosis of alveolar septa develops in all animals, with an increased number of thickened elastic fibers in them.

Hence, the morphological changes in the lung vessels observed in the course of the whole experiment, but mainly during the later periods, give us reasons to think that high-altitude hypoxia is associated with a total increase of vascular rigidity in the lungs. A tentative quantitative estimation of the characteristic impedance of the lungs [3], representing a measure of the resistance of the large arteries to the pulsed regimen of the bloodflow, demonstrates that a 1.5-fold increase of these vessels' rigidity leads to an approximately 2-fold increase of the pulse pressure in the pulmonary artery (Table 1). An increase of the rigidity of pulmonary vessels has been observed in chronic venous hypertension in the lungs [6] and during stimulation of the sympathetic nerves [7]. Experiments with postural reactions in rats under high-altitude conditions yielded similar results [5].

It is possible that whereas after a lengthy stay in the mountains the increase of the elastic vascular resistance of the lungs (rigidity) is mediated by structural changes, in the early periods the material substrate of the increased elastic resistance of lung vessels is evidently strain (increased tone) of smooth-muscle cells of the entire arterial network of the lungs, possibly of a sympathetic nature. The morphofunctional correlations suggest that the pulmonary hypertension observed in rats under high-altitude conditions is a result of intensive work of the right-ventricular myocardium aimed at combating the increased elastic resistance (rigidity) of all lung vessels, so as to maintain such a vital parameter as the minute circulation volume at a virtually normal level.

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