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PREVENTION OF POSTISCHEMIC REOXYGENATION DISTURBANCES OF CARDIAC FUNCTION BY ADAPTATION BY HIGH-ALTITUDE HYPOXIA

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Preliminary adaptation to periodic and high-altitude hypoxia increases the resistance of the heart to ischemic injury and, in particular, reduces the size of the focus of ischemic necrosis [2, 8]. It has recently been shown that serious injuries to cardiomyocytes may arise not only in ischemia, but also during reperfusion of the myocardium, under the influence of the restored inflow of oxygen — reoxygenation [9, 10]. The importance of reoxygenation injuries is very great, for they may arise immediately after the transient ischemia associated with any coronary episode, as the result of reperfusion caused by the development of collaterals [1]. Meanwhile the effect of preliminary adaptation to high-altitude hypoxia on the resistance of the myocardium to reoxygenation injury has not hitherto been investigated.

The aim of the present investigation was to study the effect of preliminary adaptation of animals to high-altitude hypoxia at medium altitudes in the mountains on reoxygenation disturbances of cardiac contractile function, which regularly arise after transient ischemia caused by temporary occlusion of the coronary artery.

EXPERIMENTAL METHOD

Two series of experiments (eight or nine animals in each series) were carried out on male Wistar rats weighing 270-290 g: Series I was the control, series II consisted of animals adapted for 32-35 days in the mountains at an altitude of 2100 m at the Priél'brus'e Medical-

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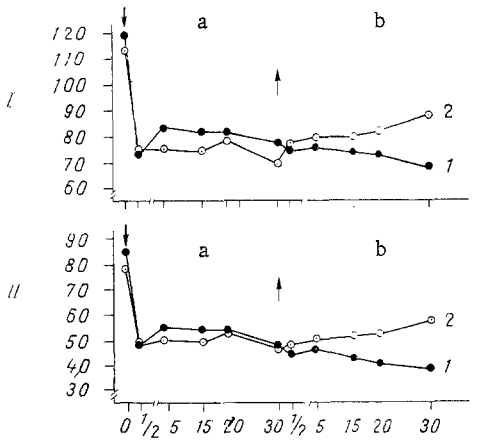

Fig. 1. Effect of transient ischemia (a) and subsequent reperfusion (b) on contractile function of the heart in control rats (1) and rats adapted to high-altitude hypoxia (2). Arrow pointing downward — beginning of ischemia, arrow pointing upward — end of ischemia. Abscissa, time (in min); ordinate: I) developed pressure (in mm Hg), II) IFS (in mm Hg·n/mg).

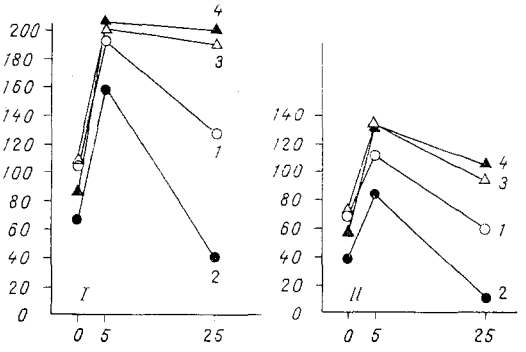

Fig. 2. Effect of maximal isometric loading caused by compression of aorta on contractile function of heart after ischemia and reperfusion in control rats and rats adapted to high-altitude hypoxia. 1) Control, 2) control after ischemia and reperfusion, 3) adaptation, 4) adapted rats exposed to ischemia and reperfusion. Abscissa, time (in sec); ordinate: I) developed pressure (in mm Hg), II) IFS (in mm Hg·n/mg).

Biological Station, Academy of Sciences of the Ukrainian SSR. Acute experiments were carried out under urethane anesthesia (150 mg/kg) after thoracotomy, with artificial ventilation. The intraventricular pressure was recorded through a catheter introduced into the left ventricle by means of a Mingograph-34 electromanometer (Siemens, Elema Schönander, Sweden). The systolic, diastolic, and developed pressure, heart rate, and intensity of functioning of structures (IFS), i.e., the product of the developed pressure (in mm Hg) and the heart rate (n), expressed per unit mass of the left ventricle (per milligram), were calculated. The experiments were carried out in three stages. First the response of the heart was studied to ischemia caused by ligation of the descending branch of the left coronary artery for 30 min, after which the ligature was released on the artery and for the next 30 min the response of the heart to reperfusion was observed. In the third stage, to assess the functional state of the heart after transient ischemia and reperfusion, the heart was subjected to maximal isometric loading by compression of the ascending aorta for 30 sec.

EXPERIMENTAL RESULTS

It will be clear from Fig. 1 that adaptation to hypoxia did not affect the developed pressure or IFS of the heart in a state of relative physiological rest; the heart rate also

was similar in the control and experimental groups (381 and 391 beats/min, respectively). Ischemia caused considerable depression of the contractile function of the heart, which was expressed equally in the control and the adapted animals. For instance, after 30 min of ischemia the heart rate was reduced a little and the developed pressure in the control group and after adaptation fell by 35 and 39%, respectively, and IFS fell by 44 and 40% compared with its initial level. However, in the reperfusion stage the time course of these parameters differed in the two series: By the 30th minute of reperfusion the developed pressure in the control animals was already 44% lower, and IFS was 55% lower than initially. Meanwhile in animals adapted to hypoxia, partial restoration of cardiac function was observed, as a result of which the developed pressure after 30 min of reperfusion was siginficantly higher (by 30%) than in the control rats ($P < 0.05$), the heart rate was 8% higher, and ultimately IFS was increased by 49% ($P < 0.05$) compared with the control.

Adaptation of hypoxia thus had no effect on the character of depression of cardiac function during ischemia but led to partial recovery of function on resumption of the blood supply.

The resistance of the heart to a reperfusion, i.e., essentially a reoxygenation disturbance of function, when increased by adaptation to hypoxia, could be detected even more definitely when the heart was subjected to maximal isometric loading. Previous investigations showed that in animals adapted to high-altitude hypoxia, fatigue during compression of the ascending aorta developed much more slowly than in unadapted animals, and the hearts of these animals could develop a much greater pressure and IFS than the control animals. This fact is explained on the grounds that during adaptation to hypoxia the power of the ATP resynthesis system is increased [3]. In the present experiments, when the aorta was compressed before ischemia the parameters of contractile function at the 25th second also were significantly higher in adapted animals than in the control.

After ischemia followed by reperfusion the difference in the character of the response of the control and adapted animals to isometric loading increased even more (Fig. 2). In the control rats fatigue during compression of the aorta developed much faster than in the preischemic period: For instance, at the 25th second of compression the developed pressure was 60% less than before ischemia, whereas the heart rate and IFS were reduced by 50 and 84%, respectively. Meanwhile in the adapted animals, also exposed to ischemia followed by reperfusion, the response of the heart to compression of the aorta was the same as before ischemia. Ultimately in the adapted animals at the 25th second of compression of the aorta the developed pressure was significantly (5 times) higher than in the controls ($P < 0.001$), whereas the heart rate and IFS were respectively 2.5 and 10 times greater than in the control ($P < 0.001$).

Experiments with compression of the aorta thus showed that ability to tolerate maximal loads is preserved in adapted animals after exposure to ischemia and reperfusion of the heart at the level attained during adaptation to hypoxia, whereas in control animals substantial disturbances of cardiac function arise as a result of the previous ischemia and reperfusion. It must be noted that this resistance is achieved only through prolonged adaptation to high-altitude hypoxia, as shown by the fact that in the period of acute adaptation, i.e., during the first few days of the rats' stay at a high altitude, the resistance of the heart to ischemia and reperfusion was sharply reduced. The results are evidence that adaptation to hypoxia increases the resistance of the heart to disturbance of its contractile function by reoxygenation.

When this result is assessed it must be recalled that destruction of the membranes of the cardiomyocytes and excessive inflow of calcium into them plays an important role in the mechanism of disturbances of cardiac function due to reperfusion and, consequently, to reoxygenation [7]. In turn, activation of lipid peroxidation (LPO), which has been demonstrated in the myocardium during reoxygenation of the heart after prolonged anoxia [6], may play an essential role in the development of the membrane injuries. Since preliminary adaptation to hypoxia is known to largely prevent activation of LPO during stress and in experimental infarction [4], it can be tentatively suggested that in the present experiments prevention of activation of LPO by reoxygenation played an important role in the protective effect of adaptation to hypoxia against reoxygenation.

Another no less important factor which may play a role in the mechanism of this effect is the increase in resistance of the myocardium of adapted animals to the harmful action of ischemia itself [2] and of the stress which accompanies it [5], which was demonstrated previously. The lower degree of ischemic injury under these circumstances evidently predetermines the lower degree of reoxygenation disturbances of the contractile function of the heart.

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RESPIRATORY MOVEMENTS OF THE FACIAL MUSCLES AND RESISTANCE TO BREATHING

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Resistance to breathing intensifies not only activity of the respiratory muscles of the chest, but also the respiratory movements of the facial muscles. The study described below showed that the latter are of great importance in compensating the respiratory disturbances caused by an increase in the resistance to breathing.

EXPERIMENTAL METHOD

Experiments were carried out on 10 tracheotomized rabbits, breathing spontaneously and anesthetized by intravenous injection of pentobarbital (30 mg/kg). Electrical activity was recorded from the muscles of the nostrils and from the diaphragm. The resistance to breathing was raised by occlusion of the tracheotomy tube.

EXPERIMENTAL RESULTS

According to data in the literature occlusion of the trachea causes an immediate increase in the amplitude and duration of the inspiratory volleys of the diaphragm [2, 4]. The corresponding changes in electrical activity recorded from muscles of the alae nasi were absolutely synchronous, but there was one important difference. The increase in the discharges in muscles of the alae nasi soon after occlusion of the trachea was significantly greater than the increase in discharges in the diaphragm (Fig. 1). In some experiments mouth-breathing also began or became more marked. In the tracheotomized animal air can enter the lungs without having to pass through the upper respiratory passages. The fact that respiratory movements of the facial muscles still take place under these circumstances provides an exceptional opportunity of investigating their role in the mechanism of compensation of breathing disturbances caused by an increase in the resistance to breathing.

As already mentioned, an increase in resistance to breathing causes an increase in the amplitude and duration of inspiratory volleys of the diaphragm. If, against this background, the respiratory movements of the facial muscles are obstructed by squeezing by the hand, further intensification of the respiratory volleys of the diaphragm immediately occurs (Fig. 2). Preventing respiratory movements of the facial muscles evidently causes even greater breathing disturbances.

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