Decrease of Constrictive and Increase of Dilatatory Reactions of the Isolated Resistive Artery in Experimental Myocardial Infarction. Effect of Adaptation to Hypoxia on this Phenomenon

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A drop of arterial pressure (AP) is known to occur in myocardial infarction as a result of both a decrease in the minute heart volume and pain stress [4]. Since AP is largely determined by the tonus of resistive arteries, a decrease of constrictive and an increase of dilatatory reactions of the resistive artery in response to transmitters and hormones may be assumed to play a role in the mechanism of this phenomenon. On the other hand, recent investigations have shown that preliminary adaptation to periodic hypoxia, in addition to its intrinsic hypotensive effect, prevents at the same time an AP drop in the first few hours following experimental myocardial infarction (EMI) [3,5]. These changes in AP after adaptation seem likely to depend to a greater or lesser extent on shifts in the reactivity of arteries to transmitters and hormones.

The aims of the present study were, first, to elucidate whether the constrictive and dilatatory reactions are changed in animals with EMI and, second, to evaluate the influence of preliminary adaptation to periodic hypoxia on the changes in the reactivity of the isolated resistive artery caused by myocardial infarction.

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MATERIALS AND METHODS

The experiments were carried out on male Wistar rats weighing 350-400 g. The animals were divided into 4 groups: the first group comprised intact rats (control); the second group consisted of animals which had survived EMI; the third group included animals adapted to periodic hypoxia, the fourth group comprised rats adapted to periodic hypoxia and survivors of EMI.

Adaptation to periodic hypoxia was performed in a pressure chamber for 4 hours a day at an "altitude" of 5000 m. For the first session the animals were "elevated" up to 1000 m, for the second up to 2000 m, and so on up to 5000 m. The course of adaptation consisted of 32-36 sessions of hypoxia.

EMI was modeled after Selye *et al.* [10] by ligation of the anterior descending branch of the left coronary artery. The animals were decapitated 3 hours after EMI, because this period has been shown to correspond to the maximal postinfarction drop of AP [2,3,5].

A segment of artery 8 mm long taken from the proximal part of the caudal artery was cannulated at both ends and placed in an incubation chamber. The segment was perfused with Krebs-Henseleit [1] solution by means of a Microstaltic roll pump under a constant flow rate (2 ml/min). The vessel was also

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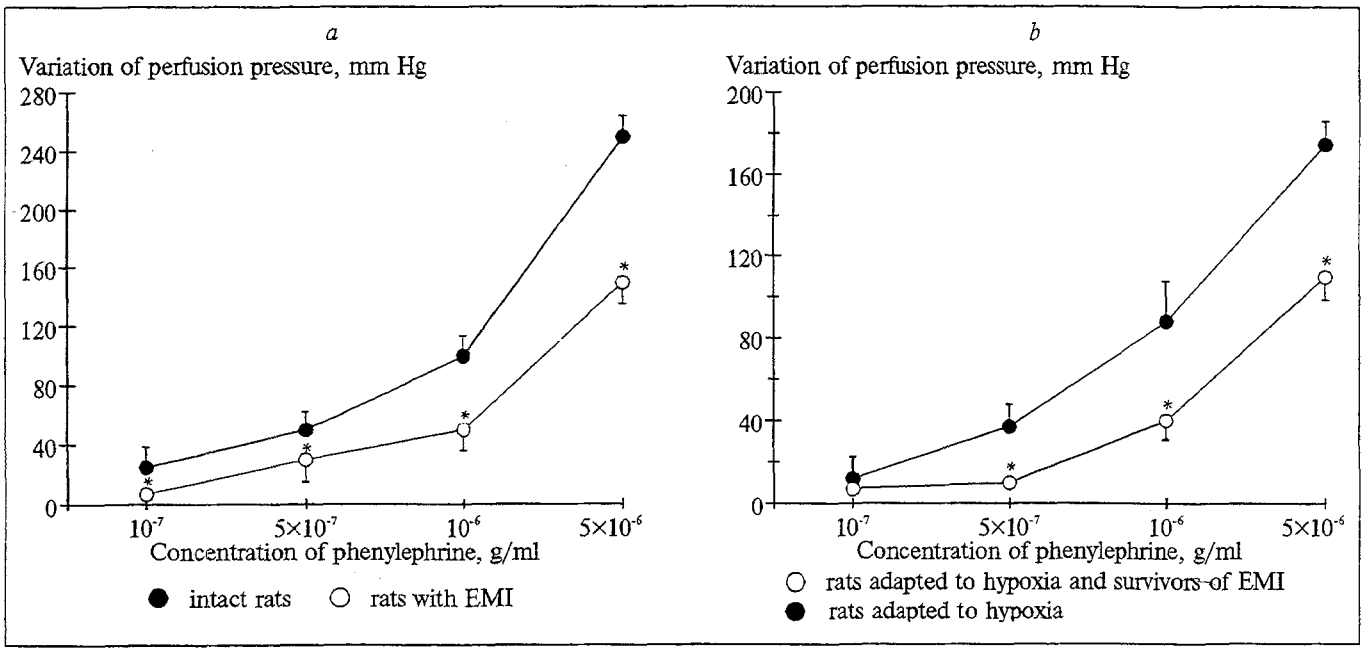

Fig. 1 Effect of preliminary hypoxia on reactivity of isolated caudal rat artery under the influence of phenylephrine in EMI: *a*) decrease of phenylephrine effects in EMI, *b*) increase of phenylephrine effect in EMI in animals adapted to periodic hypohia. Asterisk: $p<0.05$ vis – a – vis control.

washed on the outside with physiological saline, the temperature of which was maintained at 37°C. The reaction of the perfused vessel was estimated according to the changes in perfusion pressure detected with a Statham pressure transducer (USA) and recorded with a KSP-4 voltage meter.

The electrical stimulation of nerve terminals in the vessel wall was performed with a pair of electrodes. A metal cannula inserted into the vessel served as one of these, and the second electrode was attached to the vessel specimen from the outside. Square alternating pulses (0.1 msec, 50 V, 15 Hz) were used for the electrical stimulation.

Vasoactive agents (5×10^{-7} g/ml norepinephrine, 10^{-7}, 5×10^{-7}, 10^{-6}, 5×10^{-6} g/ml phenylephrine, 10^{-7}g/ml isoproterenol, and 10^{-7} g/ml acetylcholine) were added to the physiological solution which was used for perfusion of the vessel segment. The dilatatory reactions were studied using a norepinephrine-precontracted vessel preparation. The norepinephrine concentration was so chosen as to induce a contraction of the isolated vessel approximately to 100 mm Hg.

The results were processed statistically using Student's *t* test.

RESULTS

The "dose-effect" curves on Fig.1 characterize the constrictive responses of the isolated artery to phenylephrine and show that these responses are lower in EMI and after adaptation to hypoxia than those in the control. The same relationship was observed for the responses to norepinephrine.

The quantitative results of the experiment are presented in Table 1, which shows that the only reliable shift for electrical stimulation was observed in the group adapted to hypoxia, in conformity to our previous data [3], the shifts in the other series being insignificant. On the other hand, norepinephrine and phenylephrine caused pronounced shifts in all experi-

TABLE 1. Effect of Preliminary Adaptation to Hypoxia on Constrictive Reactions of Isolated Resistive Artery in Experimental Myocardial Infarction ($M\pm m$)

Experimental conditions	Changes in perfusion pressure, mm Hg		
	electrical stimulation, 15 Hz	norepinephrine, 5×10^{-7} g/ml	phenylephrine, 5×10^{-7} g/ml
Control	116±16	210±24	107±13
Myocardial infarction	99±10	126±19*	72±6*
Hypoxia	77±10*	61±11*	42±6*
Hypoxia + infarction	119±15***	124±27*,***	89±19***

Note. Here and in Table 2 asterisks denote reliable differences ($p<0.05$): one asterisk – in comparison with the control; two – in comparison with EMI; three – in comparison with adaptation to hypoxia.

TABLE 2. Effect of Preliminary Adaptation to Hypoxia on Dilatatory Responses of Isolated Resistive Artery in EMI ($M \pm m$)

Experimental conditions	Acetylcholine		Isoproterenol (β_2-agonist)	
	initial pressure, mm Hg	dilatatory response, %	initial pressure, mm Hg	dilatatory response, %
Control	100±13	6±1	110±11	7±2
Infarction	95±8	17±3*	102±11	11±1*
Hypoxia	85±7	12±3*	101±13	13±3*
Hypoxia + infarction	104±10	7±1**,***	118±13	5±2**,***

mental series which were codirected for EMI and for adaptation to hypoxia. EMI caused a reliable decrease of the constrictive responses of the isolated artery evoked by both the nonselective agonist of adrenoreceptors norepinephrine and the selective α_1-agonist phenylephrine. The adaptation to periodichypoxia by itself also weakened these constrictive responses but to a far greater extent (40% for EMI and 71 % for adaptation to hypoxia).

In the animals adapted to hypoxia, the EMI-induced decrease in the constrictive responses was similar to that in nonadapted animals, i.e., adaptation did not abolish the postinfarction hyposensitivity to norepinephrine and phenylephrine. At the same time, the decrease of constrictive reactions in EMI and after adaptation was not cumulative. On the contrary, EMI against the background of preliminary adaptation caused an enhancement of constrictive reactions in comparison with adaptation to hypoxia alone ($p<0.05$). In other words, EMI decreased the constrictive responses of the isolated artery in the control animals and increased them in the animals adapted to hypoxia.

The severe stress inevitably accompanying myocardial infarction leads to marked activation of the sympathetic nervous system, which, in turn, results in reduced sensitivity of the resistive artery to vasoconstrictive agents [7-9]. There is some evidence that the vasoconstrictive effect of catecholamines lasts only 30-40 min after myocardial infarction [6]. The enhanced reactivity of the isolated artery to norepinephrine and phenylephrine in EMI in the animals adapted to hypoxia evidently indicates the increased resistivity of the vascular system to acute stress.

Table 2 shows the changes in the dilatatory reactions of the isolated caudal artery to acetylcholine and the β-agonist isoproterenol in EMI.

Myocardial infarction resulted in a significant increase of the dilatatory responses to acetylcholine and isoproterenol in comparison with the control, the initial vascular tonus being equal. Adaptation to hypoxia acted in the same manner. However, EMI did not enhance the dilatatory responses of the isolated artery in the adapted animals; on the contrary, they completely normalized and did not differ reliably from the control. Thus, in animals preliminarily adapted to hypoxia EMI does not increase the dilatatory reactions to acetylcholine and isoproterenol, while the reactivity to the vasoconstrictive agents norepinephrine and phenylephrine is enhanced. These data may explain the previously described [3] prevention of a postinfarction drop of AP in animals adapted to hypoxia.

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