EFFECT OF NITROGLYCERIN ON FUNCTIONAL STATE OF THE MYOCARDIUM DURING TRANSIENT ISCHEMIA

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KEY WORDS: transient ischemia; nitroglycerin; partial pressure of oxygen; local contractility.

Transient ischemia of the myocardium, serving as an experimental model of an anginal attack, can give rise to considerable disturbances of myocardial function [2, 6, 8]. The most effective means of relieving the attack of angina is still by the use of nitroglycerin and its derivatives. However, despite more than a century of clinical use, much still remains unexplained about the mechanism of the therapeutic action of nitroglycerin.

In the investigation described below changes in local contractility and in the partial pressure of oxygen (pO_2) in the center of the ischermic zone, in the boundary zone, and in intact areas of the superficial and deep layers of the myocardium were studied during transient ischemia treated with nitroglycerin.

EXPERIMENTAL METHODS

Experiments were carried out on 19 mongrel dogs of both sexes weighing 15-20 kg. The animals were anesthetized with hexobarbital (1% solution, intravenously) after premedication with 1% morphine solution (1 ml/kg, intramuscularly). After thoracotomy the descending branch of the left coronary artery was occuluded for 60 sec in its lower third by means of a tourniquet. The pressure in the left ventricle, its rate of change with time, and the ECG were recorded. The partial pressure of oxygen (pO_2) in the myocardium was recorded polarographically by means of electrodes 15-20 μ in diameter, with closely matched characteristics [1], fitted with a cuff by means of which the depth of insertion of the electrode into the myocardium could be controlled. To record the local contractility of the myocardium, modified miniature arched strain gauge transducers were used. The force of contraction of segments of the superficial and deep layers of the myocardium was recorded separately by orienting the transducers parallel or perpendicular to the long axis of the heart and piercing the myocardium to different depths [2]. Nitroglycerin, in a dose of 5 μg/kg, was injected intravenously 1 min before the beginning of ischemia. Changes in pO_2 and the force of contraction of the segment of myocardium, expressed as percentages of the initial, pre-occlusion level, at the peak of the effect of ischemia (at the 60th second) were compared in experiments without preliminary injection (control) and after injection of nitroglycerin.

EXPERIMENTAL RESULTS

The doses of nitroglycerin used had only a weak effect on the cardiodynamics and hemodynamics, and in some experiments they caused a slight and transient fall of intraventricular pressure (5.7 mm Hg). Changes in pO_2 and the force of contraction of the ischemized and distant segments of myocardium at the peak of the effect of occlustion of the coronary artery, under the influence of nitroglycerin, differed but not statistically significant from changes in these parameters in the control experiments (Fig. 1). Greater changes in the functional state of the myocardium under the influence of nitroglycerin were observed in an area in direct contact with the zone of ischemia. In the upserficial layers of the myocardium of the boundary zone contractility during ischemia and under the influence of nitroglycerin was inhibited less (89.6 ± 2.5% of the initial level compared with 87.6 ± 3.2% in the control, $P > 0.05$), whereas pO_2 was increased more, than in the control experiments (108 ± 2.95 and

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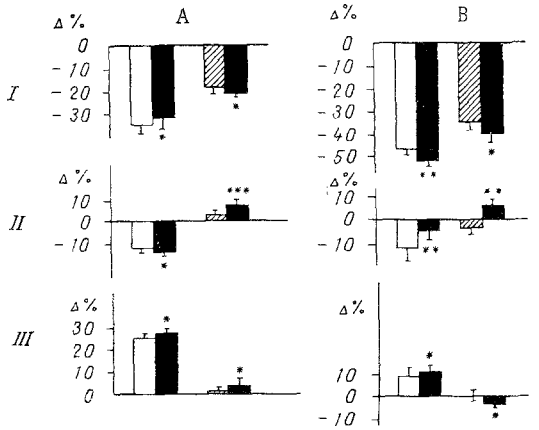

Fig. 1. Effect of nitroglycerin on pO_2 and force of contraction of segment of superficial and deep layers of myocardium at peak of effect of ischemia lasting 60 sec (in % of initial level). Unshaded columns denote contractility in control occlusions; obliquely shaded columns show pO_2 in control occlusions; black columns show same parameters after administration of nitroglycerin. *P > 0.05; **P < 0.05; ***P < 0.01. A) Surface layers; B) deep layers. Ordinate: I) zone of ischemia, II) boundary zone, III) normal zone.

103 ± 2.79%, respectively, P < 0.01). In the inner layers of the myocardium, bordering on the ischemized zone, pO_2 during occlusion was increased by the action of nitroglycerin, up to 106 < 4.1% of the initial level at the peak of the effect, whereas in the control experiments pO_2 during ischemia was 96.4 ± 6% of the initial level (P < 0.05). The contractility of segments of the deep layers of the myocardium in the boundary zone at thepeak of the ischemic effect was 96.1 ± 6.1% of the initial level after administration of nitroglycerin, compared with 88 ± 7.1% as a result of control occlusions (P < 0.05).

The combination of methods used to record pO_2 and myocardial contractility enabled the functional state of the heart muscle to be estimated over a period of time and the action of different factors on the myocardium during ischemia to be studied.

There is as yet no general agreement on the mechanism of action of nitroglycerin in coronary insufficienty. Schaper [10], for instance, cites more than 30 different views on the effect of nitroglycerin. Most workers attribute the antianginal action of the drug to its effect on the peripheral hemodynamics, reducing the load on the heart through a decrease in pressure and volume of the left ventricle [4, 9]. Data of the effect of nitroglycerin on myocardial contractility in ischemia are contradictory. Both improvement [12] and weakening [6] of myocardial contractility during ischemia have been observed experimentally under the influence of nitroglycerin. Strengthening of the contractile response of the ischemized myocardium is linked with a reduction in the after-load under the influence of nitroglycerin. Lowering of pO_2 in the myocardium by nitroglycerin is explained by a fall in arterial pressure following intravenous injection of the drug [1].

The small doses of nitroglycerin which we used had only a slight effect on the hemodynamics and, accordingly, its direct action on the myocardium during ischemia could be examined. Improvement of the state of myocardial function in the boundary zone under the influence of nitroglycerin, revealed by these experiments, is a positive factor in the action of this drug.

The question of the existence of a boundary zone in ischemia, especially if its of short duration, has been debated. Many biochemical studies have shown the absence of any well-defined boundary zones, intermediate between ischemia and normal [5, 13]. The results of the present experiments point to the existence of an area which can be regarded as a boundary zone in the early stages of development of ischemia. The functional state of this zone is very important in the prognosis of ischemia. The beneficial action of nitroglycerin on the

boundary zone with the ischemized myocardium can be explained by an improvement in the blood supply of this zone through vasodilatation and augmentation of the collateral blood flow [3], on account of a rise in the pressure gradient between the perfused and unperfused areas of myocardium in the boundary zone. The fact that nitroglycerin exerts its strongest action on the inner layers of the myocardium was probably the results of selective action of the drug on vessels of the subendocardium [11].

The results of this investigation thus provide additional evidence on the mechanism of the therapeutic action of nitroglycerin in short-term ischemia. Even in transient disturbances of the coronary circulation (of the spasm type, for example, when treatment is aimed mainly at abolishing the spasm) the effect of the drug on the functional state of the myocardium bordering on the ischemized zone must be borne in mind.

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EFFECT OF GLUTAMIC AND ASPARTIC ACIDS ON METABOLISM AND FUNCTION OF THE HYPOPERFUSED HEART

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An urgent problem at the present time is the search for substances capable of preventing the fall in the level of adenine nucleotides and creatine phosphate caused by ischemia. The use of exogenous amino acids, which can improve the contractile function of the heart in ischemia [2, 3], seems a promising way of achieving this goal. The mechanism of the protective effect of amino acids is not yet clear.

The object of the present investigation was to study whether improvement in the contractile function of the heart is connected with a rise in the ATP and creatine phosphate levels and also with intensification of detoxication reactions of the ammonia which accumulates during ischemia [6, 7].

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