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COMBINED USE OF HYPERBARIC OXYGENATION AND ANTIOXIDANTS IN THE TREATMENT OF EXPERIMENTAL MYOCARDIAL INFARCTION

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Oxygen deficiency is the leading factor triggering injury to cardiomyocytes and disturbance of intercellular metabolic relations in a focus of myocardial ischemia and in the periischemic zone. Naturally increased oxygenation or a reduced oxygen demand of the ischemized heart are the main methods used in pathogenetic treatment of myocardial infarction (MI). Hyperbaric oxygenation (HBO), as various experimental and clinical investigations have shown, occupies an important place among antihypoxic measures directed toward the ischemized myocardium [1, 11, 12].

Meanwhile evidence is constantly accumulating to show that in ischemia the oxygen-dependent process of lipid peroxidation is considerably activated in the heart [3, 7, 9], because, it is suggested, of disturbance of the mechanisms of antioxidant cell protection [5, 10, 13]. The use of synthetic or natural antioxidants has been shown to limit the size of the focus of ischemic necrosis and to accelerate repair processes should MI develop [8, 9, 10].

The investigation described below showed that a combination of increased oxygenation with an antioxidant gives an additive therapeutic effect on the state of the cardiac function during experimental MI.

EXPERIMENTAL METHOD

In 28 chinchilla rabbits weighing 2.3-3.3 kg the left descending coronary artery was ligated in its middle third. Of the 28 animals used, 14 were placed in a BKI-191 pressure chamber in an atmosphere of pure oxygen under a pressure of 2026 GPa (2 atm) for 1 h, 30-40 min after the operation. During the next six days these animals were subjected to one session of HBO daily. Of the 14 with MI, both treated and untreated by HBO, seven rabbits began one day before coronary occlusion to receive the antioxidant ionol by intraperitoneal injection in a sessional dose of 20 mg/kg, using Tween-80 as emulsifier. The control consisted of seven intact rabbits. The antioxidant activity (AOA) of the cardiac lipids was determined on a model of oxidation of the methyl ester of oleic acid [4] and superoxide dismutase (SOD) activity was determined by a method based on the ability of the enzyme to inhibit autooxidation of adrenalin, mediated by the superoxide anion [2], in the intact and ischemic zones

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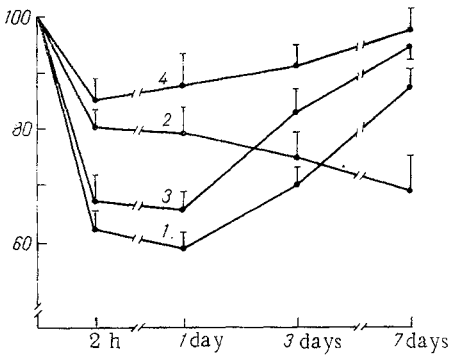

Fig. 1. Dynamics of left ventricular contractility after production of MI. Abscissa, time after operation; ordinate, developed pressure when aorta compressed, relative to control level taken as 100%. 1) MI, 2) MI + HBO, 3) MI + ionol, 4) MI + HBO + ionol.

of the left ventricle 2 h and 1, 3, and 7 days after ligation of the coronary artery. The contractile function of the heart was assessed from the pressure in the left ventricle recorded electromanometrically on a "Mingograph-82" apparatus under conditions of relative rest, and during total occlusion of the ascending aorta for 5 sec in animals anesthetized with hexobarbital and artificially ventilated.

EXPERIMENTAL RESULTS

The development of experimental MI was accompanied by inhibition of the contractile function of the heart, most marked 2 and 24 h after coronary occlusion (Fig. 1). Later contractility began to recover partially, but even on the 7th day after ligation it had not regained the control level. The use of HBO partially prevented depression of cardiac contractility developing after 2 and 24 h, but after three days HBO not only did not improve, but actually worsened cardiac function compared with untreated animals.

Preliminary administration of ionol prevented disturbance of cardiac contractility by ischemic necrosis of the myocardium; this protective effect of ionol was exhibited most clearly starting with the third day after coronary artery occlusion.

Combined use of HBO and the antioxidant was the most effective way of preventing disturbances of cardiac function in MI. In this case the preventive effect of combined HBO and ionol could be observed at all times of the investigation.

The study of SOD activity and AOA of lipids in the course of MI revealed depression of these parameters of antioxidant protection both in the ischemic zone and in the nonischemic zone of the myocardium. This depression was most marked in the zone of ischemia, where it was found during the first day with a gradual tendency toward normalization at subsequent times of observation. These results agree with those obtained previously showing that in MI and total cardiac ischemia AOA of lipids [3] and SOD activity [5, 10] decline. The fall in SOD activity in cells damaged by hypoxia is perhaps one of the principal factors initiating lipid peroxidation [6].

The action of the therapeutic measures adopted in these experiments on the components of antioxidant protection of the heart was manifested most clearly in the intact zone of the myocardium. HBO, especially in combination with ionol, considerably reduced the severity of injury to these important components of antioxidant cell protection in MI (Figs. 2 and 3) and contributed to the earlier recovery of cardiac function. Partial prevention of the fall in SOD activity under the influence of HBO may be the result of a decrease in the degree of hypoxia in cardiomyocytes which remained viable. If HBO alone was used, impairment of myocardial contractility on the 7th day after the operation (Fig. 1) was in good agreement with the fall in AOA of the lipids and SOD activity in the intact zone.

It can be concluded from these results that when ischemic damage to the myocardium is present a combination of HBO with elevation of the tissue antioxidant level may constitute

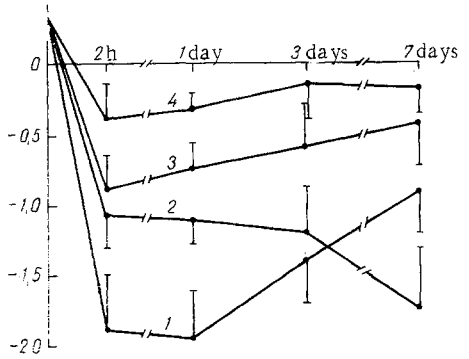

Fig. 2. Dynamics of AOA of lipids in periischemic zone of left ventricle after MI production. Abscissa, time after operation; ordinate, AOA (in h · ml/mg). 1) MI, 2) MI + HBO, 3) MI + ionol, 4) MI + HBO + ionol.

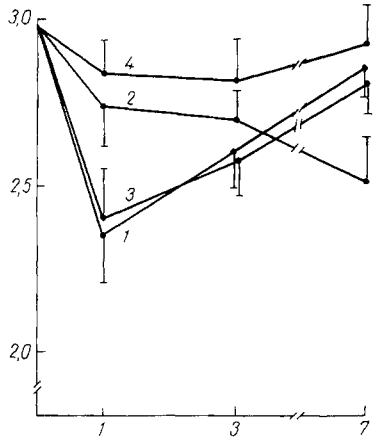

Fig. 3. Dynamics of SOD activity in periischemic zone of left ventricle after MI production. Abscissa, time after operation (in days); ordinate, enzyme activity (in units/mg protein). 1) MI, 2) MI + HBO, 3) MI + ionol, 4) MI + HBO + ionol.

an important principle for preservation of cardiac function. This two-component approach is perfectly consistent with the biological importance of oxygen, vitally essential for the cell yet a chemically aggressive agent. The universality of hypoxia in the pathogenesis of cell damage, on the one hand, and at the same time the existence of signs of free-radical oxidative destruction of the intracellular components, on the other hand, suggest that the dual approach (oxygen—antioxidant) used in this investigation for the correction of oxidative processes may be an essential adjunct to existing methods of treatment of hypoxic states. Prevention of the side effects of HBO may be a special indication for the use of inhibitors of free-radical processes.

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ELECTROMECHANICAL COUPLING DISTURBANCES IN MYOCARDIAL CELLS IN THE COMPRESSION SYNDROME

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KEY WORDS: myocardium; intracellular potentials; isometric contractions; blood plasma; compression syndrome.

The compression syndrome (CS) is accompanied by a marked decrease in cardiac output [2]. Marked changes have been demonstrated in electrical activity of the heart [5, 6] and a decrease in its contractility in CS [3]. According to one view, insufficiency of the cardiovascular system in CS is due to the toxic properties of the plasma [4, 5]. However, no direct investigations into the action of plasma on myocardial cell function have yet been undertaken.

The aim of this investigation was to study the action of plasma from rabbits with CS on myocardial electrical and contractile activity. The methods used were developed by the writers previously in order to study the action of "burn" plasma, isolated from the blood of animals exposed to burn trauma, on the myocardial cells [1].

EXPERIMENTAL METHOD

Intracellular transmembrane resting (RP) and action (AP) potentials and mechanical contractions in response to electrical stimulation of the capillary muscles of the heart were investigated in 17 rabbits: six preparations were taken from healthy rabbits, 11 from rabbits with CS. CS was induced by compression (90 kg) of the soft tissues of the thigh for 12 h. Blood and hearts from rabbits with CS were taken 1.5 h after decompression under urethane anesthesia (1 g/kg). The papillary muscles were isolated from the right ventricle. Isolation of the muscles, their arrangement in the working chamber, the conditions of stimulation, the method of obtaining blood plasma, details of the apparatus and composition of the Tyrode solution were all described previously. Contractions of the preparations were recorded during the experiments in response to stimulation at frequencies of 0.1, 0.2, 0.5, 1, and 2 Hz successively, and intracellular potentials of single myocardial fibers were recorded in response to stimulation at 1 Hz: 1) in Tyrode solution, 2) after replacement of the Tyrode solution by blood plasma from control (healthy) rabbits, 3) after replacement of normal plasma by blood plasma from animals with CS, and 4) after removal of the CS plasma and reperfusion with plasma from control animals. The plasma was diluted 1 : 1 with Tyrode solution. To prevent frothing of the plasma during oxygenation, "antifoam" was used.

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