EFFECT OF PRELIMINARY LOCAL HYPOXIA ON DEVELOPMENT OF IMMUNE MYOCARDIAL INJURY

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Different types of organic injury to the myocardium are accompanied by the appearance of large quantities of anticardiac autoantibodies and their accumulation in patients' blood [7]. It was shown previously that reproduction of the antigen–antibody reaction in a limited area of the heart, stimulated by injection of anticardiac antibodies into one branch of the left coronary artery, is accompanied by the development of macrofocal injury to the heart and by marked disturbances of cardiac function and the systemic hemodynamics [2, 5, 6]. Meanwhile the problem of the conditions for realization of an immune reaction of this type, in the presence of high circulating blood titers of anticardiac antibodies remains unsolved. One factor promoting contact between antibodies and cardiac antigens may be myocardial hypoxia [3], when because of increased permeability of the vascular wall penetration of immunoglobulins to myocardial antigens is facilitated.

In the investigations described below the effect of preliminary local hypoxia of the myocardium on changes in the cardiodynamics and hemodynamics, contractility of the heart muscle, and the degree of development of myocardial injury following immunologic challenge to the heart were studied.

EXPERIMENTAL METHOD

Experiments were carried out on 27 mongrel dogs anesthesized with chloralose and urethane (0.07 and 0.3 g/kg respectively) without thoracotomy and with preservation of natural breathing. There were two series of experiments. In series I local immune injury to the myocardium chiefly of the left ventricle was induced by injecting anticardiac cytotoxic serum into the circumflex or descending branch of the left coronary artery (details of the method were described previously [2, 5]). In the experiments of series II immunologic challenge to the heart took place against the background of local hypoxia of the left ventricular myocardium. Local hypoxia was induced by perfusion of the descending or circumflex branch of the left coronary artery with blood undersaturated with oxygen (the animal's own venous blood) for 10 min, after which anticardiac antibodies were injected into the same coronary artery and arterial perfusion was restored. Anticardiac cytotoxic serum (ACS), obtained from rabbits immunized with dog heart homogenate (titer in the CGT 1:800) was injected in a volume of 0.1 ml/kg body weight. Changes in the cardio- and hemodynamics and contractility of the left ventricular myocardium were assessed on the basis of the following parameters: pressure in the left ventricle (LVP) of the heart and the rate of its changes (RC), cardiac ejection and systemic arterial pressure (SAP), and indices of contractility (IC) $\left(\frac{dp/dt_{max}}{IP}, \frac{dp/dt_{max}}{IIT}, V_{pm}\right)$, which were calculated beat by beat, in the course of the reactions, by means of a specially designed "Indeks" specialized computer system [7]. Indices of contractility and other parameters of the cardiodynamics were recorded with the ink-jet writer of an "Elema" (Sweden) Mingograf. Resistance to the blood flow in the coronary vessels was determined during autoperfusion of a branch of the coronary artery with constant blood volume. The partial pressure of oxygen in arterial and venous blood was determined by means of an Lp-7e polarograph (Czechoslovakia). The contracting heart was removed from the chest

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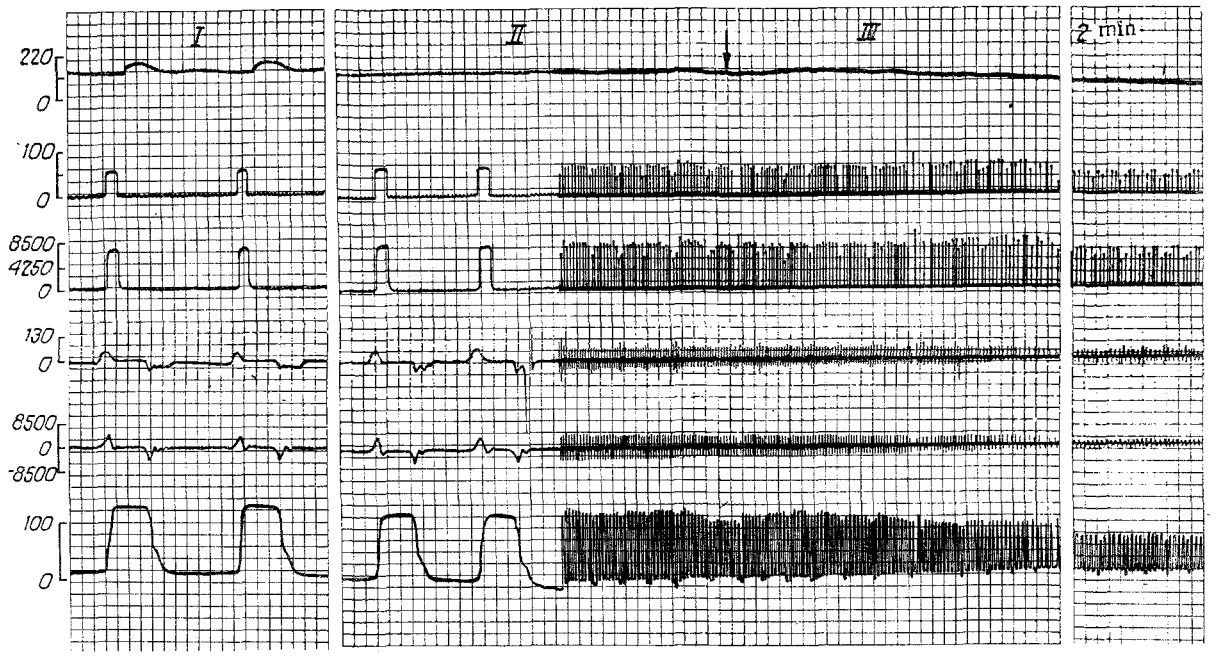

Fig. 1. Changes in hemo- and cardiodynamics and myocardial contractility during immunologic challenge to the heart after preliminary hypoxia. I) Control, II) hypoxia, III) ACS. From top to bottom: SAP, indices of contractility $\left(\frac{dp/dt_{max}}{IP}, \frac{dp/dt_{max}}{IIT}, V_{pm}\right)$, rate of change of pressure in left ventricle, and pressure in left ventricle.

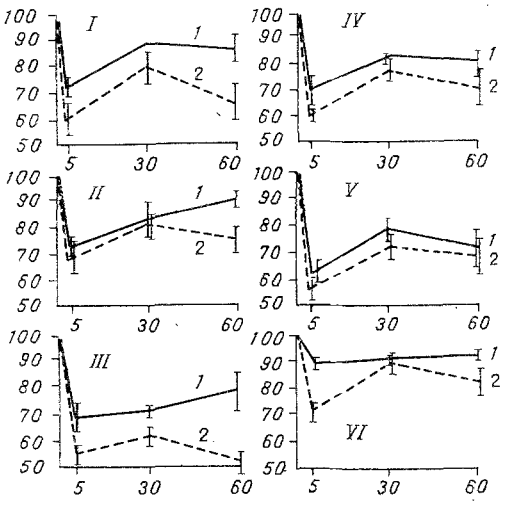

Fig. 2. Changes in hemo- and cardiodynamics and myocardial contractility in response to immunologic challenge to the heart alone (1) and preceded by hypoxia (2). Abscissa, time (in min); ordinate, percent of original value, I) SAP, II) LVP, III) RC, IV) dp/dt_{max}, V) dp/dt_{min}, VI) IC.

60-90 min after injection of the ACS, immersed in ice-cold KCl solution until total arrest, and blocks of tissue were excised from the intact and injured areas of left ventricular myocardium. Areas of injury were detected from the change in total dehydrogenase activity in the muscle fibers and the volume of injury was determined macroscopically [11]. The concentrations of glycogen [8] and phosphorylase [13] were determined histochemically. The size of the focal lesions of the heart was estimated by a histostereometric method using an ocular grid [1].

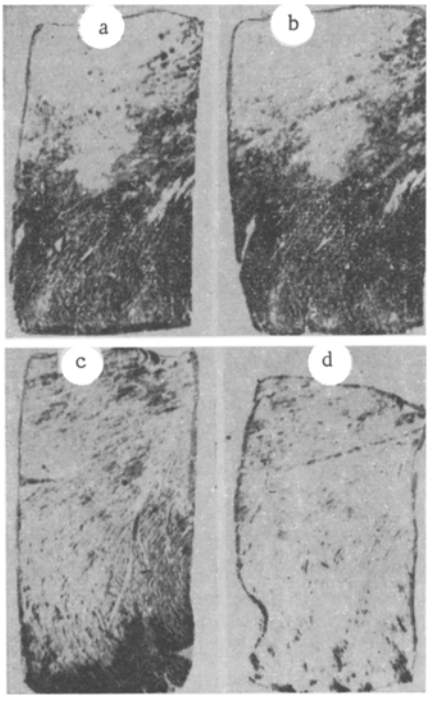

Fig. 3. Changes in content of glycogen (a, c) and phosphorylase (b, d) in injured area of left ventricular myocardium. a, b) Immune injury; c, d) immune injury preceded by hypoxia Magnification 5 ×.

EXPERIMENTAL RESULTS

Hypoxemic perfusion of one branch of the left coronary artery with mixed venous blood (the original arteriovenous difference in partial pressure of oxygen was 32 ± 5.6 mm Hg) led to dilatation of the coronary vascular system: The coronary vascular resistance fell from 146 ± 8.6 to 116 ± 12.6 mm Hg (on average by 21 ± 5.8% of the initial level). A short period of hypoxia did not induce the necessary changes in the heart muscle. No significant changes in dehydrogenase activity or their substrates, or the content of glycogen and its metabolic enzyme phosphorylase, were observed.

A typical example of the response to combined challenge of a limited area of myocardium is illustrated in Fig. 1. Perfusion with venous blood did not lead to any significant changes in systemic arterial pressure, the left ventricular pressure and the rate of its changes, and indices of myocardial contractility, but subsequent immunologic challenge induced a marked fall of these parameters even in the early stage (2nd minute of reaction). If ACS was injected against the background of hypoxia, more profound disturbances of the basic parameters of the cardio- and hemodynamics and myocardial contractility were observed, not only in the early stages of the reaction, but more especially after 60-90 min (Fig. 2).

It was shown previously that in immune injury to the myocardium the degree of disturbances of the cardio- and hemodynamics is largely determined by the volume and depth of injury to the heart muscle [4].

The volume of the focus of immune injury to the myocardium (experiments of series I), determined from the reduction in dehydrogenase activity, averaged 16 ± 2.9% and in some cases amounted to 20-28%. The volume of the injured area of myocardium when preceded by hypoxia (experiments of series II) averaged 34 ± 3.5%, and in some cases amounted to 40-75%.

The results of the histochemical investigations revealed more severe disturbances of energy metabolism in the injured region of myocardium in the experiments of series II. The content of glycogen and of its metabolic enzyme phosphorylase in the immunologically injured area of myocardium was reduced on average to 60%, but to 90% if immune injury was preceded by hypoxia (Fig. 3).

Injection of anticardiac antibodies into a limited area of the coronary vascular system, preceded by hypoxia of the same region of myocardium, thus had a more injurious action than

in the control series. This is shown by the greater fall in total dehydrogenase activity and in the content of glycogen and phosphorylase in the region of injury.

It can be concluded from these findings that moderate preliminary myocardial hypoxia considerably potentiates the effect of immune injury to the myocardium, increasing both the volume of injury and the severity of the metabolic disturbances in the focus of injury. This potentiation may be due to substantial dilatation of the coronary vessels during hypoxemia and an increase in area of the capillary vascular system exposed to the action of the injurious factor. The number of functioning capillaries rises significantly if the oxygen supply to the myocardium is insufficient [10], and this evidently creates conditions for potentiation of the injurious action of immune factors and for a substantial increase in the volume of injury to the myocardium. Preliminary hypoxia may also lead to changes in transcapillary transport [12] and may thus be conducive to the faster and deeper penetration of antibodies into structures of the myocardium. Myocardial hypoxia may evidently facilitate realization of the pathological action of anticardiac antibodies circulating in the blood.

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