A MODEL OF OCCLUSION-REPERFUSION ARRHYTHMIAS OF THE TRANSPLANTED RAT HEART

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Key Words: heart transplantation; model of arrhythmia.

The usefulness of rats as effective models of arrhythmias and for the study of mechanisms of action of arrhythmic drugs has been demonstrated by several investigators [1-3]. The most widely used model of arrhythmias in rats is that of temporary ligation of the coronary artery in situ, developed in [4]. In this model, up to 40% of the animals die from ventricular fibrillation after ligation of the coronary artery [2], because the fall of the systemic blood pressure leads to irreversible heart failure, or more precisely, to electromechanical dissociation. Nervous regulation of the heart, which in this model of ischemia and reperfusion of the myocardium, remains intact, has a considerable influence on the development of arrhythmias. Finally, this model can be used only once.

In order to abolish nervous control and to improve the reliability of the model as a result of greater reproducibility of the arrhythmias coupled with minimal activity of the animals, and the possibility of reusing them many times in experiments, a model of occlusion-reperfusion arrhythmias was developed on the heterotopically transplanted rat heart.

EXPERIMENTAL METHOD

The heart was transplanted into the neck. The method of transplantation was worked out on 22 male Wistar rats. The animals were chosen so that the recipient weighed about twice as much as the donor (350-450 and 150-200 g, respectively). In this way it was possible to avoid difficulties connected with covering the graft with the recipient's skin and to match the diameters of the brachiocephalic artery of the transplant and the recipient's carotid artery, which were to be anastomosed. Intraperitoneal injection of pentobarbital (40 mg/kg) was used for anesthesia. The vessels were isolated and sutured by means of the Soviet kit of microvascular instruments, produced by the "Medinstrument" Research and Production Combine (Kazan'), under the "Olympus 3M" binocular stereoscopic microscope (Japan). The suture material consisted of 10/0 thread on an atraumatic needle ("Ethicon," Great Britain). The ECG was recorded on a 6-channel EK-36 polygraph ("Hellige," West Germany) by means of subcutaneous needle electrodes. The operation consisted of three stages: dissection of the recipient's vessels, preparation of the graft, and its revascularization. Stage I: the skin of the sternomastoid muscles was divided. The jugular vein was dissected for a distance of 7-8 mm, sufficient for clipping and the formation of an anastomosis with the pulmonary artery of the grafts. The sternomastoid was retracted to the side to gain access to the carotid artery. The carotid artery was dissected as far as possible to its bifurcation, taking care to avoid injuring nerve trunks in the vicinity. The artery was ligated immediately proximally to the bifurcation. Stage II: the ribs were divided by two incisions along the anterior axillary lines and the resulting thoracic wall flap was retracted cranially. The ascending part of the aorta, its arch, and the brachiocephalic trunk were dissected. The aorta was separated from the pulmonary artery. The venae cavae, arch of the aorta at the level of origin of the left carotid artery, and the brachiocephalic and pulmonary arteries at the level of their bifurcation were ligated and divided. The pulmonary veins were ligated en masse. The heart was excised and placed in cold physiological saline. Stage III: after 5-10 min, necessary to allow the graft to cool and to prepare the vessels for anastomosis, the graft was placed into the wound on the recipient's neck. The jugular

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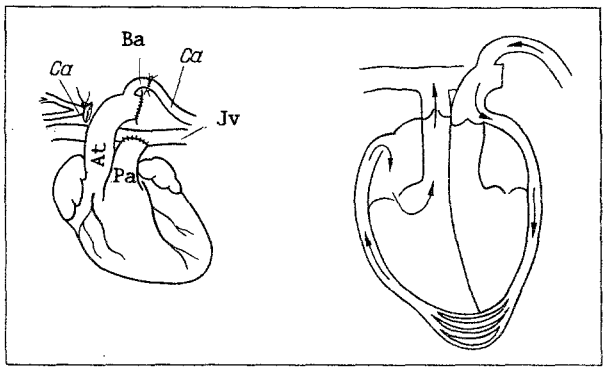

Fig. 1. Diagram showing transplantation of heart into the neck and hemodynamics of graft. Ca) Carotid artery of recipient, Ba) brachiocephalic artery of graft, Jv) jugular vein of recipient, Pa) pulmonary artery of graft, At) aorta.

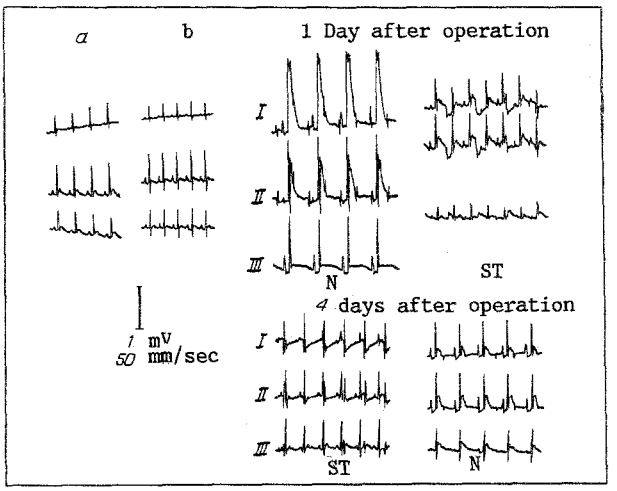

Fig. 2. Dynamics of electrical activity of transplanted heart. N) Neck leads, for which electrodes were located on then neck around the graft, ST) standard leads from limbs; a) recipient before operation; b) donor before operation. 1, 2) 1st and 4th days after operation, respectively.

vein was clipped and its lumen opened longitudinally. An anastomosis was formed with a continuous suture between the pulmonary artery of the graft and the recipient's jugular vein, end-to-side. The dissected carotid artery was then clipped and divided. Using interrupted sutures an anastomosis was formed between the brachiocephalic artery of the graft and the recipient's carotid artery, end-to-end. After restoration of the blood flow to the graft, the latter was placed in a subcutaneous pouch. An occluder was applied to the carotid artery and brought out onto the skin of the animal's withers. The wound was sutured. The hemodynamics of the grafted heart was maintained as follows (Fig. 1). Blood from the recipient's carotid artery entered the aorta of the graft and thence its coronary arteries. The coronary venous blood flowed from the myocardium into the right atrium, and right ventricle, from which it was returned to the recipient's jugular vein. The graft did not perform any pumping function.

EXPERIMENTAL RESULTS

Changes characteristic of myocardial ischemia, in the form of an increase in voltage of the R waves and elevation of the ST segments were observed on the ECG of the graft during the first hours after transplantation. These changes became less frequent toward the end of the 1st day (Fig. 2).

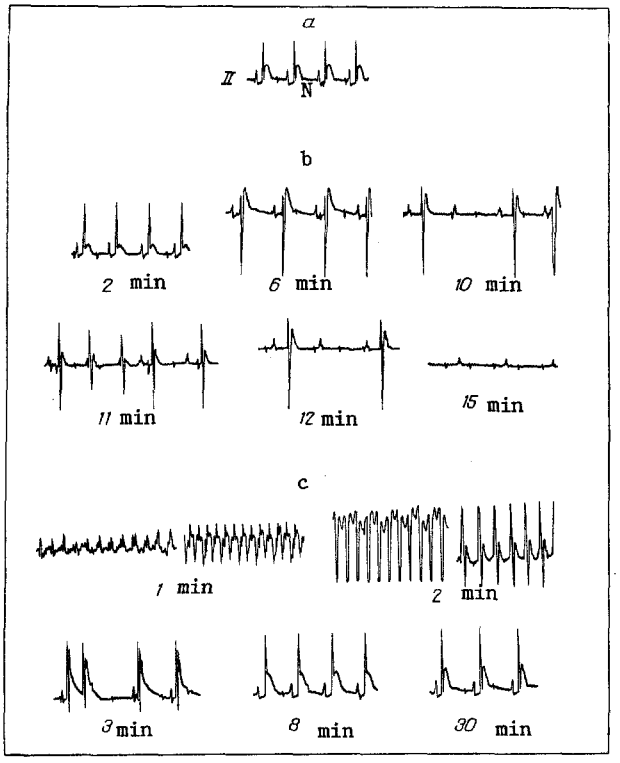

Fig. 3. Electrical activity of the transplanted heart, recorded during experimental modeling of occlusion-reperfusion arrhythmias. a) ECG before occlusion; b) after occlusion of artery; c) after reperfusion of myodardium.

Experiments to create a model of reversible myocardial ischemia were carried out on eight rats with the heart transplanted into the neck at times of between 4 and 10 days after the operation (the minimal period of the experiments was determined by the time required to completely exhaust catecholamine reserves in the myocardium of the grafted, denervated heart, the maximal period by the frequent development of inflammation in the wound if the occluder remained in situ longer). Pulling on the threads of the occluder led to occlusion of the carotid artery supplying the graft, and to the development of total myocardial ischemia. Relaxation of the thread led to restoration of the blood flow along the artery and to reperfusion of the myocardium.

In all cases the pattern of the arrhythmias was quite uniform (Fig. 3). Occlusion arrhythmias in the form of extrasystoles and disturbances of atrioventricular conduction began at the 9th-10th minute, and by the 14th-15th minute electrical activity had disappeared. In none of the six cases (in two of the eight animals when an attempt was made to occlude the artery, it was damaged by the occluder) was fibrillation observed during occlusion of the carotid artery, i.e., during myocardial ischemia.

Restoration of the blood flow in the myocardium was accompanied in all cases by ventricular fibrillation, which lasted for 50 to 100 sec and was followed by ventricular tachycardia. At the 3rd-4th minute activity of the sinus node was restored against the background of AV blockade of a varied degree. The normal sinus rhythm was restored at the 5th minute. The ECG throughout the subsequent period reflected gradual disappearance of the signs of myocardial ischemia. By the 30th minute the ECG of the transplant was back to normal. Occlusion of the carotid artery for 30 min followed by reperfusion of the myocardium as a rule was not accompanied by ventricular conduction and sinus bradycardia were observed.

The maximal frequency of development of arrhythmias and, in particular, of ventricular fibrillation and ventricular tachycardia, was observed during reperfusion of the myocardium after its ischemia for 10-15 min. Occlusion of the artery for 10-15 min can therefore be regarded as optimal for a model of ventricular fibrillation, which is the one in greatest need by pharmacologists studying antiarrhythmic preparations.

Interest in reperfusion arrhythmias has increased steadily as their role in clinical practice has become clearer. Under clinical conditions the period of ischemia preceding the onset of reperfusion arrhythmias may differ very greatly and they vary in duration from a few seconds (spasm of the coronary artery) to several hours (removal of the clump from the aorta to the open heart operations, intracoronary thrombolysis, and baloon angioplasty of the coronary artery in acute myocardial ischemia).

The role of model investigations is particularly important in the study of such complex problems as sudden death. Since no single model can reproduce the natural course of coronary heart disease or give exhaustive information about its pathophysiology, we must rely on investigations conducted on a whole range of experimental models in order to elucidate problems connected with malignant arrhythmias, and to develop effective methods of their treatment and prevention.

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LIPID PEROXIDATION IN THE ADRENAL CORTEX IN EXHAUSTING STRESS

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Long-term exposures to extremal factors cause collapse of the adaptation process [4]. The reason for this phenomenon has not yet been explained. Nevertheless, it is logical to suggest that the collapse of adaptation may be connected with disturbance of the normal functioning of the endocrine system and, in particular, of the adrenal cortex. The adrenal cortex occupies a key position in the development of the adaptation syndrome, and the function of these glands is considerably depressed during prolonged, exhausting stress [4].

Lipid peroxidation (LPO), if activated excessively in many tissues, gives rise to destructive changes that are reflected in the rate of cellular metabolism and, consequently, in the specific function of tissue. In the adrenal cortex the existence of large amounts of biological antioxidants (ascorbic acid and α-tocopherol) evidently prevents the uncontrolled development of LPO [1, 6]. During exhausting stress, however, the situation may change.

The aim of this investigation was to determine the rate of LPO and the ascorbic acid and α-tocopherol levels in the adrenal cortex in the course of exhausting stress.

EXPERIMENTAL METHOD

Experiments were carried out on male rabbits (Soviet Chinchilla breed) weighing 2-2.5 kg and on noninbred male albino rats weighing 180-200 g. Stress was induced by immobilization by the limbs in the supine position for 6, 12, 24, 48, and 72 h. Each group consisted of six animals. After decapitation the adrenal cortex was separated from the medulla and used to determine concentrations of diene conjugates [7], α-tocopherol [12], and ascorbic acid derivatives [5]. 11-Hydroxycorticosteroids (11-HCS) in the blood plasma were determined by the method in [3].

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