CHANGES IN THE ULTRASTRUCTURE OF THE "INTACT" ZONE OF HEART MUSCLE AND CONTRACTILE ACTIVITY OF THE HEART IN ACUTE MYOCARDIAL ISCHEMIA

V. S. Paukov, V. A. Frolov, and T. M. Yudakova

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Acute myocardial ischemia of the left ventricle was produced in 20 chinchilla rabbits. The contractile activity of the left ventricle was determined after 5, 20, and 40 min and 3 days, and the energy deficit and potential working capacity of the cardiac muscle were calculated. Quantitative analysis of the ECGs was carried out and the coefficient of energy efficiency of the mitochondria calculated. Signs of hyperfunction of the ultrastructures of the muscle cells appeared 5 min after occlusion of the coronary vessel in the unaffected areas of the myocardium; destruction and formation of the ultrastructures followed in the course of 40 min of energy deficit of the heart muscle. On the 3rd day the changes in the ultrastructures gave evidence of the development of compensatory and adaptive processes leading to increased production of energy and enabling the heart to perform its real function.

Most workers who have studied the ultrastructure of the myocardium in infarction have described only the lesions in the zone of necrosis of the heart muscle. The so-called intact zone, i.e., myocardium not within the zone of the occluded coronary artery, has received far less study.

The object of this investigation was to study the state of the intact zone of heart muscle in the early stages of myocardial infarction and to establish the connection between the morphological changes and the contractile activity of the heart.

EXPERIMENTAL METHOD

Twenty chinchilla rabbits were used. In acute experiments under hexobarbital anesthesia and with artificial ventilation, the background ECGs were recorded after which the descending branch of the left coronary artery was ligated. Parameters of contractile activity of the heart were than determined 5, 20, and 40 min and 3 days later: the true systolic pressure in the left ventricle (VP_r) and the maximal intraventricular pressure (VP_m); the duration of mechanical diastole was calculated from the records of intraventricular pressure and the pressure in the carotid artery, and by means of special equations [7, 8] a coefficient characterizing the potential working capacity of the myocardium (η) and the energy deficit (ED) of the heart muscle was calculated.

At each stage of the experiment pieces of tissue were excised from the intact myocardium (posterior wall of the left ventricle) of 5 rabbits for electron-microscopic study. The material was fixed in a 1% buffered solution of O_sO_4 and embedded in Araldite. The sections were examined in the UÉMV 100K electron microscope. Thirty electron micrographs for each stage of the experiment were subjected to

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TABLE 1. Parameters of Mechanical Activity of Left Ventricle and Ultrastructure of Intact Zone in Acute Focal Myocardial Ischemia (M ± m)

Parameters	Normal	5 min	20 min	40 min	3 days
VP_r (in mm Hg)	109±5*	109±4*	112±4*	92±3†	90±3 †
VP_m (in mm Hg)	147±7*	130±3*	126±4 †	126±3†	138±3*
η (in %)	100*	78 †	73†	73†	89*
ED (in %)	0	40	41	25	11
No. of mitochondria per electron micrograph	13±0,45*	11±1*	9±0,08*	10±1†	9,4±0,5*
No. of cristae per mitochondrion	5±0,2	3±0,3	3±0,2	3±0,1	5±0,2
Mean area of 1 mitochondrion (in μ^2)	0,44±0,02*	0,53±0,06*	0,73±0,06	0,74±0,05	0,54±0,8*
CEEM (in %)	100	58*	58*	73	60*

Legend. The signs *, † in the horizontal rows denote mean values between which the difference is not significant.

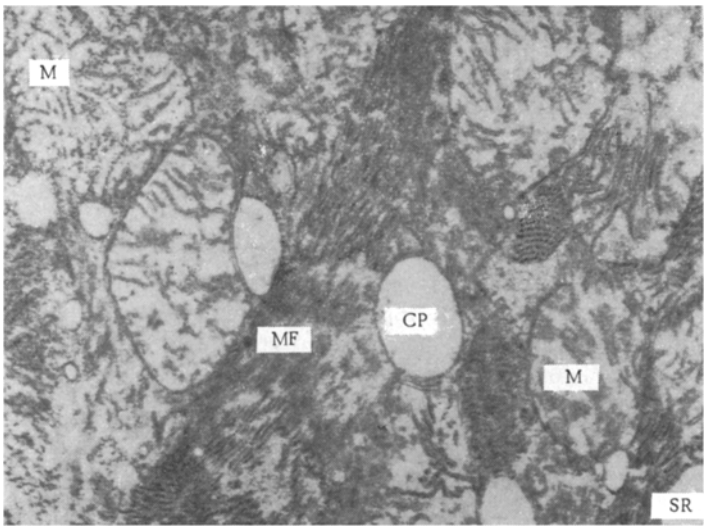

Fig. 1. Intact zone, 5 min after occlusion of coronary artery: severe swelling and destruction of mitochondria (M), focal destruction of myofibrils (MF), dilatation of tubules of sarcoplasmic reticulum (SR), disappearance of cell granules (21,000×).

quantitative analysis and the coefficient of energy efficiency of the mitochondria (CEEM) calculated by the authors' own method [5]. Statistical analysis of the numerical data was carried out by Student's method. The level of significance of differences between the means was $P \leq 0.05$.

EXPERIMENTAL RESULTS

Marked intracellular and intercellular edema and areas of separation of the fibers with homogenization and lysis of the myofibrils were observed in the cells of the intact myocardium of the left ventricle 5 min after ligation of the coronary artery. The number of mitochondria was much less than normal, they were considerably swollen, the matrix of the organelles showed spots of reduced density, the cristae were fragmented, and their number was sharply reduced (Fig. 1). Frequently homogenized mitochondria completely without cristae were seen. The outer membrane of many mitochondria no longer appeared double. The number of granules in the sarcoplasm was sharply reduced. All these changes were more marked after 20 min of the experiment. Many small lipid inclusions in contact with the mitochondria appeared. The tubules of the sarcoplasmic reticulum were dilated. The nuclei had sharply indented outlines

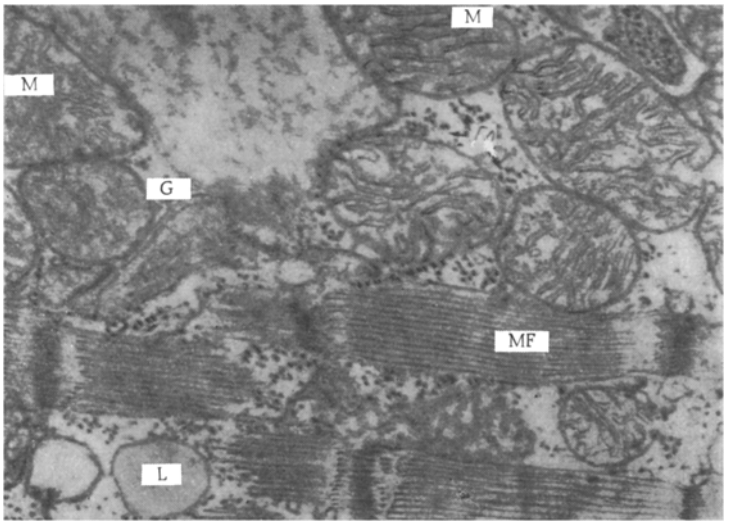

Fig. 2. Intact zone, 3 days after occlusion of coronary artery: focal hyperplasia of mitochondria (M), increased number of cristae, restoration of normal structure of myofibrils (MF), sharp increase in number of granules of glycogen (G) and lipids (L) (21,000×)

and an increased chromatin content. Edema of the cells was reduced 40 min after ligation of the coronary artery, the number of mitochondria was slightly increased, union of the fragments of their cristae was observed and the heterogeneity of the myocardial cells was increased. After 3 days focal hyperplasia of the mitochondria was found in the intact zone, they were less swollen, and the cristae were more numerous. They were irregularly arranged and severely fragmented, curved in shape, and with multiple anastomoses between the fragments. The cell edema had disappeared and the glycogen content was sharply increased (Fig. 2). Many lipid inclusions were present. The normal structure of the myofibrils was restored. The outlines of the nuclei were still indented.

The results of the quantitative analysis of the electron micrographs and the results of physiological investigation of the heart are given in Table 1.

Clearly the ultrastructure and function of the heart, which were disturbed during the first few minutes after the onset of acute myocardial ischemia, by the 3rd day were showing a tendency to return to normal.

Comparison of the CEEM with the cardiac function and the value of ED (Fig. 3) suggests that in the period from 5 to 40 min the decrease in CEEM was due to destructive processes in the cells, giving a high ED and affecting the contractile function of the heart. On the third day, however, the decrease in CEEM could be evidence that the changes developing in the cells were of a compensatory and adaptive character (increased number and length of the cristae in the mitochondria, anastomosis between them, increased enzyme activity, and so on), enabling the ultrastructures of the heart to maintain a state of hyperfunction sufficient to provide the necessary energy. This view is supported by the decrease in ED and increase in the contractile function of the heart.

The results of comparison of the electron-microscopic data and the parameters of mechanical activity of the heart during acute focal myocardial ischemia indicate that the mitochondria of the intact zone of the myocardium are in a state of hyperfunction [2, 4, 6, 9, 11]. This is because the previous load (for 20 min there was no decrease in VP_r) is maintained by fewer myocardial cells (because the zone of ischemia was asystolic), so that they required an increased energy supply. Only when after 40 min the value of VP_r fell and, consequently, the energy expenditure to maintain the real function of the heart was reduced, was the value of ED lowered. This compensatory-adaptive reaction enables the myocardium to utilize energy not only to provide for its real function, but also for the resynthesis of its ultrastructural elements. As a result, on the 3rd day after the development of myocardial infarction, focal hyperplasia of the mitochondria was observed in the intact zone, the number of their cristae was increased, the ultrastructure of the muscle cells showed a marked tendency toward normalization, and the glycogen content was sharply increased.

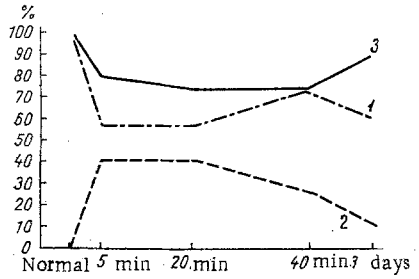

Fig. 3. Dynamics of changes in coefficient of energy efficiency of mitochondria (1), energy deficit (2), and potential working capacity of the myocardium (3).

The correlation between the changes in ED calculated for the left ventricle as a whole and in CEEM, calculated for the intact zone only, means that the changes in contractile activity of the ischemic heart, as least in the first 40 min, can be linked primarily with the changes taking place in the intact zone.

Data in the literature [1, 3, 10, 12] indicate that changes in the ischemic zone during the first hour after occlusion of the coronary artery develop much more slowly than those found in the intact zone. Consequently, acute overloading is more important for the state of the ultrastructures than interference with their oxygenation.

This investigation thus showed that 5 min after occlusion of a coronary artery evidence of hyperfunction of the ultrastructures of the muscle cells appears in the unaffected area of the myocardium, leading to their destruction and to an increase in ED of the heart muscle. The changes in the ultrastructure of the muscle cells of the intact zone 3 days after the onset of myocardial infarction are evidence of the development of compensatory and adaptive processes, leading to an increase in energy production and enabling the heart to perform its real function.

It can be concluded from a comparison of the results of the morphological and pathophysiological investigations that changes in the contractile activity of the heart and in its energy balance in acute focal ischemia are basically connected with changes in the ultrastructural elements of the intact zone of the myocardium.

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