STRUCTURAL AND FUNCTIONAL HETEROGENEITY OF CARDIOMYOCYTES DURING HEMODYNAMIC OVERLOADING OF THE RAT HEART

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UDC 616.12-008.615-092.9-07:616:127-008.9-092.18

KEY WORDS: cardiomyocytes; ultrastructure; heterogeneity; hemodynamic overloading.

Polymorphism and mosaicism of structural changes in cardiomyocytes are observed in electron-microscopic studies [9, 13]. The discovery of the essential nature of typical reactions of cardiomyocytes under exposure to extremal conditions is particularly interesting from this point of view, and the investigation described below was devoted to its study.

EXPERIMENTAL METHOD

Experiments were carried out on 78 noninbred albino rats of both sexes weighing 150-220 g. Hemodynamic overloading of the heart was created by graded constriction of the abdominal aorta. The rats were decapitated 10 min, 1, 2, and 24 h, 2 and 30 days, and 3 and 9 months after the operation. The myocardium of four animals killed 30 min and 2 h after a mock operation served as the control. Material for electron microscopy was processed by the usual methods and embedded in a mixture of Epon and Araldite or of butyl and methyl methacrylates. Activity of succinate (SDH) and lactate (LDH) dehydrogenases was determined by the method of Kerpel–Fronius and Hajos. A mixture of Epons was used as embedding media. Ultrathin sections were stained in solutions of uranyl acetate and lead citrate and examined in the UÉMV-100B electron microscope. Some sections intended for ultrahistochemical investigation were studied in the unstained state.

EXPERIMENTAL RESULTS

The study of cardiomyocytes at different stages of the experiment showed that the morphological and metabolic heterogeneity of the cells was apparent after the first day of the experiment. Depending on the state of the organoids several principal types of cells, responding differently to overloading, were distinguished.

Cells of type I, with swelling of the mitochondria and dilatation of the tubules of the sarcoplasmic reticulum. Swelling of the mitochondria was characterized by rarefaction of the matrix and focal or diffuse lysis of the cristae (Fig. 1a). Higher SDH activity was observed in such mitochondria (Fig. 1b). LDH activity in the membranes of the sarcoplasmic reticulum also was increased (Fig. 1c). The structure of the myofibrils and other cell organoids was largely preserved, but the glycogen content was depressed. In the existing view swelling of the mitochondria associated with their overloading, excitation, and change into the "energized state" [1, 12, 15], is evidence of overstrain of the cell and mobilization of its energy reserves under conditions of hyperfunction [6, 8, 9].

Type II – cells with changes mainly in the myofibrils, expressed as contractures and lysis of myofibrils. The most frequent form of destruction of the myofibrils was lysis, and in most cases it was unaccompanied by changes in the structure and typical localization of other organoids. Two variants of myofibrillolysis were distinguished: partial lysis, connected with selective lysis of I disks (Fig. 2a), and total lysis of myofibrils with simultaneous destruction of all parts of the sarcomere (Fig. 2b). Irrespective of the original localization,

Laboratory of Pathomorphology and Electron Microscopy, L. A. Oganesyan Institute of Cardiology, Ministry of Health of the Armenian SSR, Erevan. (Presented by Academician of the Academy of Medical Sciences of the USSR D. S. Sarkisov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 96, No. 7, pp. 117-120, July, 1983. Original article submitted December 17, 1982.

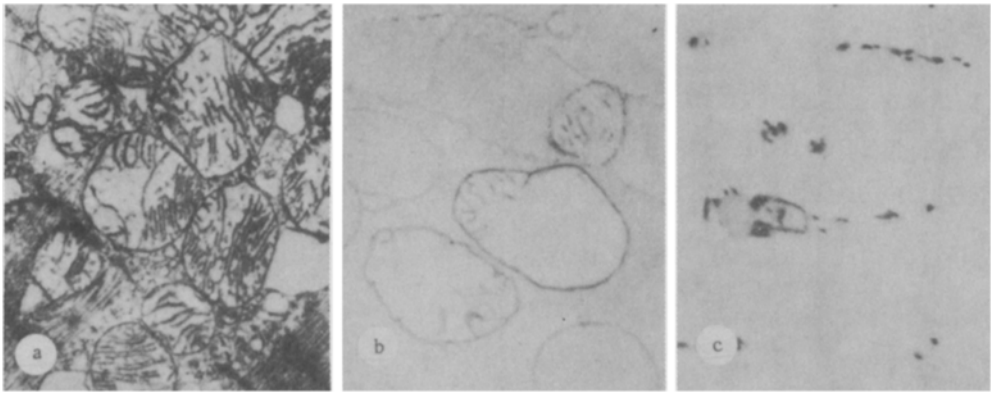

Fig. 1. Swelling of mitochondria and dilatation of tubules of sarcoplasmic reticulum. a) General view, 20,000×; b) SDH activity in mitochondrial membranes. Kerpel–Fronius and Hajos reaction, 22,000×; c) LDH activity in membranes of sarcoplasmic reticulum. Kerpel–Fronius and Hajos reaction, unstained preparation, 18,000×.

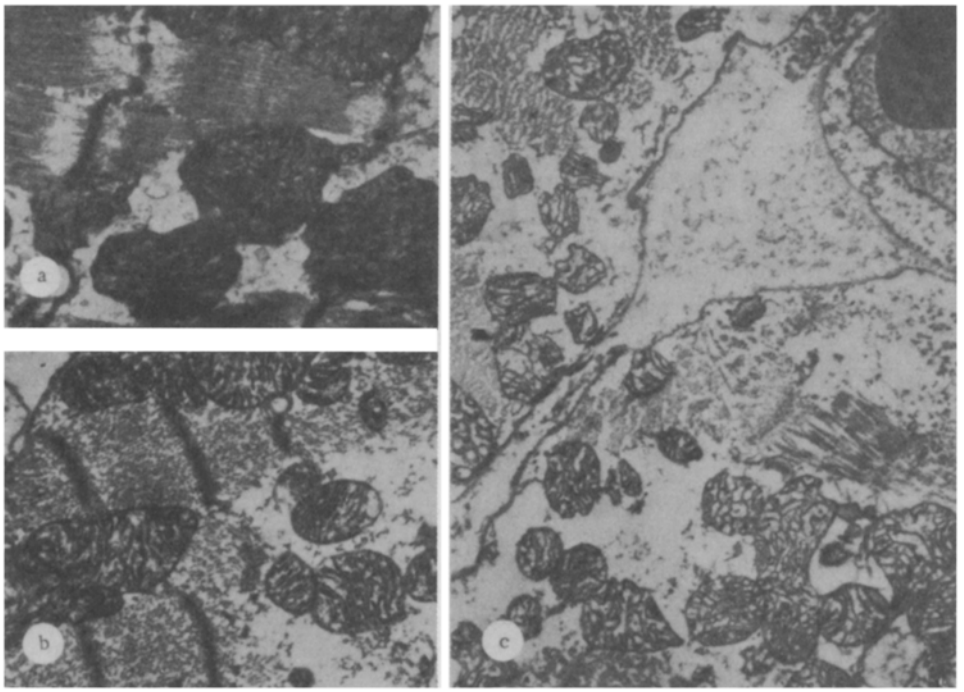

Fig. 2. Variants of lesions of cardiomyocytes. a) Selective lysis of I disks of myofibrils (22,000 ×); b) simultaneous destruction of all parts of the sarcomere (18,000 ×); c) disintegration of ultrastructures on account of edema (12,000 ×).

the structural changes were focal or diffuse in character and could end with disappearance of the contractile structures in individual areas or throughout the territory of the cardiomyocyte. Contractural lesions of the myofibrils were manifested as various degrees of shortening of the sarcomeres and thickening of the corresponding Z lines, and in some cases by disturbance of continuity of the myofibrils. Relaxation of the sarcomeres was combined quite frequently with lysis of the I disks. All forms of lesions of the myofibrils could be interpreted as evidence of depression, or in some cases complete cessation, of the specific contractile function of the cardiomyocytes.

Type III – cells with widespread disintegration of ultrastructures on account of edema. Cells of this type were characterized by general rarefaction of the cytoplasm, separation of the organoids, and a reduction in the glycogen content. As the pathological process progressed, these features were joined by structural disturbances in the organoids (Fig. 2c). The changes noted above could be evidence of weakening of the contractile function of the cardiomyocyte.

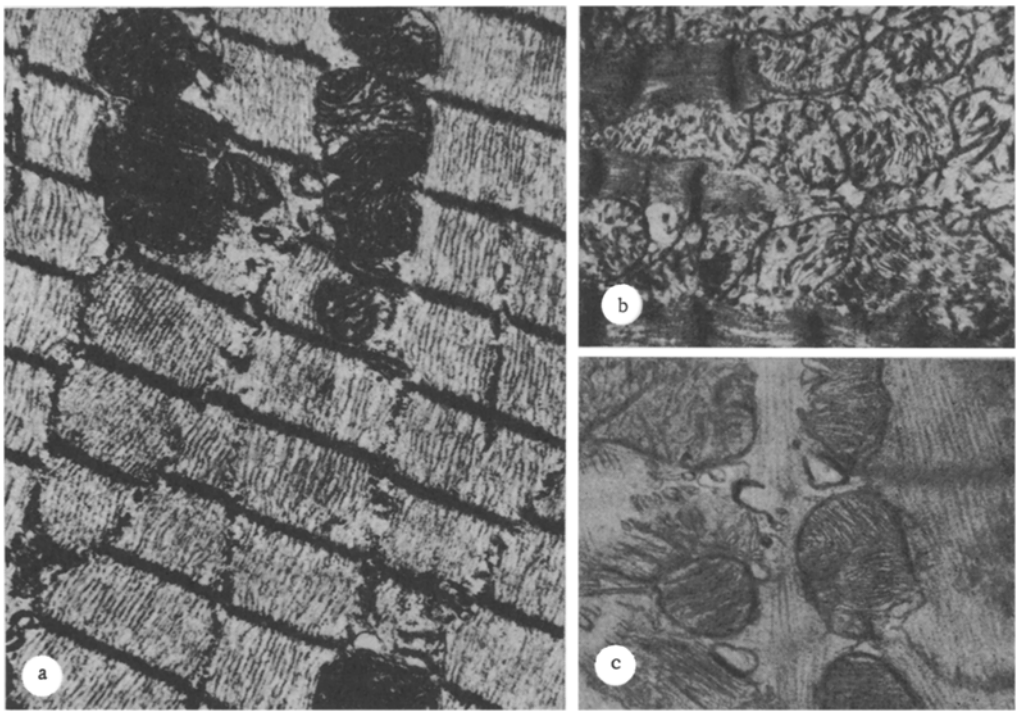

Fig. 3. Hypertrophy and hyperplasia of ultrastructures of cardiomyocyte. a) Splitting of myofibrils (20,000 ×); b) SDH activity in mitochondrial membranes. Kerpel–Fronius and Hajos reaction (18,000 ×); c) LDH activity in membranes of sarcoplasmic reticulum. Kerpel–Fronius and Hajos reaction. Unstained preparation (22,000 ×).

Type IV – cells with relatively unchanged organoids with evidence of activity of the nucleus and redistribution of the ultrastructures, with displacement of mitochondria and cytogranules toward the periphery beneath bulging regions of the sarcolemma. The unequal density of the matrix, differences in the packing density, and varying clarity of outlines of the mitochondrial cristae, as well as their unequal SDH activity will all be noted. These findings suggest that these cells were not intact but evidently constituted a functional reserve of the myocardium, activated during its development.

Starting with the 10th-14th day of the experiment, besides the types of cells described above, cardiomyocytes with predominance of synthetic processes leading to hypertrophy and hyperplasia of the ultrastructures, mainly mitochondria and myofibrils, also were found. Hyperplasia of the contractile structures took place through splitting of the hypertrophied myofibrils (Fig. 3a) or by their formation de novo. The formation of mitochondria was connected with processes of division and budding, and also with transformation of small vesicular formations. Hyperplasia of the organoids was accompanied by activation of aerobic oxidation, with an increase in SDH activity in the mitochondria (Fig. 3b) and lowering of the LDH level in membranes of the sarcoplasmic reticulum (Fig. 3c). The changes described above, which can be regarded as a manifestation of the intracellular form of regeneration [7], are the morphological equivalent of long-term hyperfunction and they lie at the basis of stable compensation of cardiac activity.

Cells with combined changes in mitochondria and myofibrils were distinguished by a broad spectrum of disturbances of their organoids. Injury to the myofibrils was reflected most frequently by lysis, whereas changes in the mitochondria were polymorphic in character, and were exhibited as swelling, detachment of the outer membrane, bead-like expansion, homogenization, and a reticular or dendroid arrangement of the cristae. Changes of this kind in the organoids were found most often against the background of hypertrophy and hyperplasia of the ultrastructures, associated with a chronic course of the pathological process.

The myocardium of the animals after a mock operation was characterized by absence of cardiomyocytes with injury mainly of the myofibrils, and also by weak expression of the process in the cells, with swelling of the mitochondria and dilatation of tubules of the sarcoplasmic reticulum.

In the light of modern views different types of structural changes in cardiomyocytes are regarded as a reflection of structural and functional heterogeneity, characteristic of the normal myocardium [3, 4]. This is

considered to be based on discrete and asynchronous functioning of the cells [2, 5], the subdivision of their vital activity into stages [11] connected with renewal cycles of intracellular structures [10], and also population differences in cardiomyocytes, confirmed in experiments with rat myocardial cells in culture [14]. It is these factors which determine the variability in the functional state of the cells at a time of stimulation, leading to differences in sensitivity and in the character of their response.

The ability of cardiomyocytes to respond differently to the same stimulus facilitates the development of changes of a compensatory and adaptive character in the myocardium simultaneously with destructive changes. The presence of so-called reserve cells in the myocardium, with relatively unchanged organoids, and of cells with structural changes of a compensatory and adaptive character promotes equalization and the establishment of the functional state of the heart muscle at the necessary level for the work of the heart under concrete extremal conditions. The facts described above suggest that structural and functional heterogeneity of the cardiomyocytes is one of the most important adaptive reactions on which adaptation in the broad sense of the term is based.

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