be reduced to stabilization of the frequency of its spontaneous excitation. This improves atrial function, making it more regular.

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# MYOCARDIAL HYPERTROPHY IN YOUNG AND OLD ANIMALS WITH EXPERIMENTAL HYPERTENSION


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Clinical investigations have shown an increase in mortality with age among patients with hypertension accompanied by marked myocardial hypertrophy [10]. One reason for this may be narrowing of the range of adaptive and compensatory powers of the heart muscle in old age [5, 7] as a result of slowing of protein synthesis, a decrease in the RNA concentration and a decrease in its renewal in the cardiomyocytes [4, 8]. These data have been obtained in experiments on a model of acute hemodynamic overloading of the heart (coarctation of the aorta). The character of possible structural changes in the old heart in chronic hypertension has virtually not been studied morphologically.

The aim of this investigation was, by using morphological and graphic methods, to supplement the information obtained by physiological studies [1] by studying the morphogenesis of the "hypertensive" heart in old animals and to compare it with young animals with chronic hypertension.

## EXPERIMENTAL METHOD

Renal (renovascular) hypertension was induced in rabbits of two age groups (6-10 months and 3.5-4.5 years) by bilateral operations (with an interval of 2-3 weeks) to produce stenosis of the renal arteries by 1/3-1/4 of their initial diameter, by Gorev's method [2]. The control group consisted of nine old and 14 young animals, the experimental group of nine old and 16 young animals. Control and experimental rabbits with hypertension (4 months after the second operation) were killed by air embolism. After autopsy of the animal, the heart and its parts were weighed separately [3]. Samples of tissue from the left ventricular myocardium for electron microscopy were treated in the usual way. Longitudinal and transverse sections of heart muscle were cut on an LKB ultramicrotome, stained with uranyl acetate and lead citrate, and examined in the IEM-100B electron microscope. For light microscopy, heart tissue was fixed in neutral 10% formalin, paraffin sections were stained in the usual way with hematoxylin and eosin, and the diameter of muscle fibers of the circular layer of the myocardium was measured with an MOV-15 ocular micrometer under a magnification of 700 (100 fibers in each case).

## EXPERIMENTAL RESULTS

The results showed that the rabbit's heart undergoes hypertrophy with age. This was shown by the increase in the weight of the heart, the cardiac index (the ratio of the weight of the heart to body weight), and also the ratio of the weight of the left ventricle to body weight in the old animals (Table 1). Corresponding to the increased weight of the heart there


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TABLE 1. Weight of Heart and Derivative Parameters (M ± m) in Young and Old Rabbits under Normal Conditions (control) and in Experimental Hypertension (renal form)

| Parameter | Young rabbits | | Old rabbits | |
|---|---|---|---|---|
| | control (n = 14) | hypertension (n = 16) | control (n = 9) | hypertension (n = 9) |
| Weight of heart, g | 6,311±0,240 | 8,997±0,435 a | 11,020±0,669 c | 11,605±0,715 c |
| Weight of left ventricle, g | 3,704±0,135 | 5,517±0,249 a | 6,246±0,422 c | 6,757±0,352 c |
| Cardiac index, g/kg | 1,912±0,083 | 2,561±0,091 c | 2,502±0,180 c | 2,954±0,126 c |
| Percent of left ventricle | 58,8±0,76 | 61,5±0,62 b | 56,5±0,89 | 58,6±1,68 |
| Weight of left ventricle/body weight, g/kg | 1,096±0,041 | 1,572±0,052 a | 1,415±0,107 c | 1,753±0,106 d |

Legend: a) P < 0.01, b) P < 0.05 compared with normal (control) animals of same age; c) P < 0.01, d) P < 0.05 compared with young animals of corresponding group.

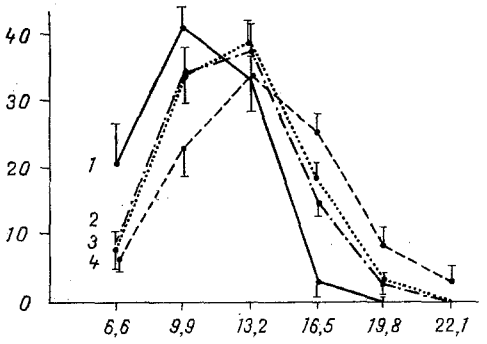


Fig. 1. Distribution of muscle fibers by diameter in middle layer of myocardium in young (1) and old (4) rabbits in control and in young (2) and old (3) rabbits with experimental renal hypertension. Abscissa, diameter of muscle fibers (in μ); ordinate, number of fibers (in %).

was an increase in the number of muscle fibers with diameters of 16.5, 19.8, and 22.1 μ, and a decrease in the number of cells of small diameter compared with young animals. The number of average sized cardiomyocytes remained unchanged at 34% of the total population (Fig. 1). Age hypertrophy of muscle cells took place on account of a balanced increase in the number of myofibrils and mitochondria. Despite marked heterogeneity of the cardiomyocytes, muscle cells of the old control animals differed from those of young animals in a number of features: 1) edema in the perimeter zone, a sharp decrease in the number of mitochondria and an increase in the number of lysosomes and the lipofuscin content in that zone; 2) the appearance of giant mitochondria and of mitochondria with various structural disturbances (edema of the matrix, destruction of cristae or their complete disappearance in individual zones) among the myofibrils; 3) widening of the interfibrillary spaces, with a resulting increase in diameter of the cells with age. The weight of the myocardium increased not only through hypertrophy of the cardiomyocytes but also through an increase in volume of the connective tissue. Many workers have made similar observations.

In young animals with experimental hypertension of 4 months' duration hypertrophy of the heart developed. The weight of the left ventricle and cardiac index were considerably higher than the age control (Table 1), the peak of distribution of the cardiomyocytes was shifted from fibers with a diameter of 9.9 μ to those with a diameter of 13.2 μ (Fig. 1). By contrast with hypertrophied cardiomyocytes of intact old and young animals without hypertension, the fine structure of the cells showed signs of increased activity of the genetic apparatus and the systems for protein synthesis and energy metabolism. A reduction in density of the chromatin network and an increase in the number of ribosomes, of nuclei with 2-3 nucleoli and nucleolar pores, swelling, budding, and hypertrophy of mitochondria, hypertrophy of myofibrils (Fig. 2a), and organization of tubules of the endoplasmic reticulum into spiral systems close to the nucleus were observed in this case. Lysosomes and lipofuscin, together with lipid inclusions, appeared in most cells. Degenerative changes, in the form of marked swelling and

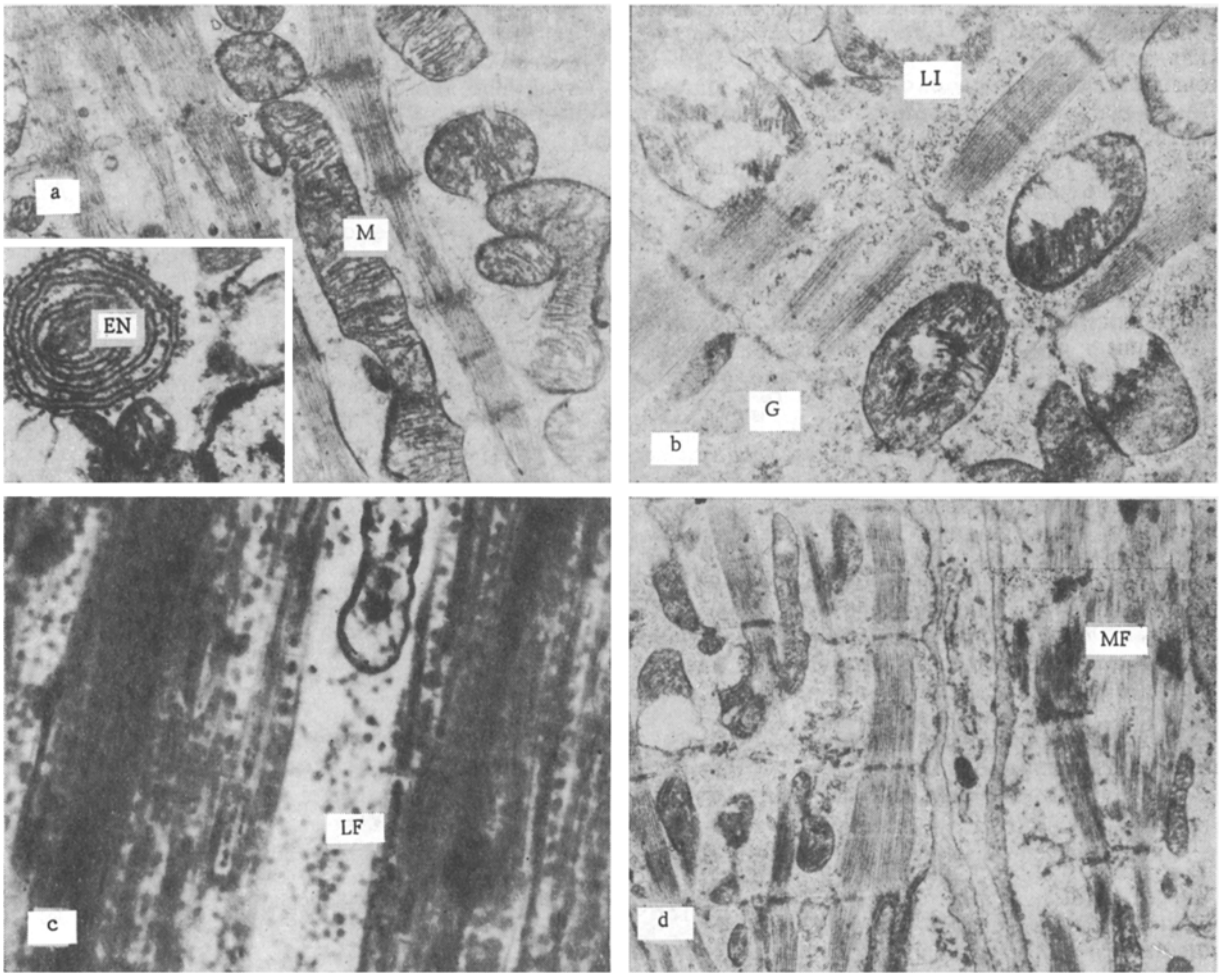


Fig. 2. Structural changes in cardiomyocytes of young (a, b) and old (c, d) rabbits with renal hypertension: a) hypertrophy of mitochondria (M) and rough endoplasmic reticulum (EN); b) accumulation of glycogen (G) and lipid inclusions (LI); c) edema in perinuclear zone, accumulation of lipofuscin (LF) — semithin section stained with methylene blue and fuchsine; d) necrosis of myocytes, disintegration of myofibrils (MF). Magnification: a) 17,424, b) 18,240, c) 2000, d) 1120.

destruction of mitochondria and accumulation of glycogen, were observed in some cardiomyocytes (Fig. 2b). Similar changes have been described previously in the heart of young rabbits with hypertension [6].

Unlike in the young animals, the development of hypertrophy in old animals with hypertension was accompanied by only small changes in the weight of the heart compared with the control (Table 1). Only the increase in the ratio of weight of the left ventricle to body weight was statistically significant; the degree of that increase, however, was only half of that observed in young animals with hypertension (relative to the corresponding control): 23.9% in old and 43.4% in young rabbits.

The destructive changes were intensified in the cardiomyocytes of old rabbits with hypertension, along with the same features of activation of the intracellular systems as in young animals. In the end, an increase in the number of cells with degenerative and necrotic changes was observed in the myocardium. Cells of the first type were characterized by edema of the mitochondria, accumulation of lipofuscin and myelin-like structures, and sequestration of this material, cells of the second type by lysis of myofibrils, death of the majority of mitochondria, swelling and vesiculation of the T and L systems, edema of the sarcoplasm, glycogen accumulation, and a sharp decrease in the diameter of the cardiomyocytes (Fig. 2c, d). Enlargement of the foci of replacement sclerosis in the middle layer of the myocardium and of the trabecular and papillary muscles compared with those in intact rabbits of the same age, observed under these circumstances, points to selective damage to the myocytes in zones with the maximal functional load.

Analysis of the morphometric data on the population structure of the cells revealed that no further increase in the thickness or number of the hypertrophied fibers beyond the maximal values characteristic of old hearts of intact animals took place in the old rabbits compared with young during hypertrophy (Fig. 1). On the contrary, there was a decrease in the number of hypertrophied cardiomyocytes from 16.5 to 22.1 μ in diameter. It is evidently this fraction of muscle fibers which undergoes degenerative changes and dies. Some relative increase in weight may take place on account of hypertrophy of fibers with small diameter, because an increase in the number of fibers 9.9 μ in diameter up to 35% was observed, although from the functional point of view this hypertrophy is not perfectly complete, for it takes place on account of an unbalanced increase in the number of myofibrils and mitochondria (slight hypertrophy of the myofibrils and well-defined hyperplasia of the mitochondria), on the one hand, and of edema of the cytoplasm on the other hand.

In young rabbits in the period of formation of compensation (the 16-week period), hypertrophy of the myocardium thus does not reach the limit observed in old animals, as regards either weight of the heart, diameter of its fibers, or the number of hypertrophied cardiomyocytes. During the period of this study, all intracellular systems in the heart of the young animals remained activated. However, as some workers postulate [9, 12], there exists a critical volume which cardiomyocytes may reach during hypertrophy in the process of ontogeny (in man and the rat) or in experiments on animals [12], namely $65 \times 10^3$ $\mu^3$. Meanwhile degenerative changes also develop. This has been demonstrated in various models of myocardial hypertrophy [11]. On the whole hypertension leads to aging of the myocardium as regards both the character of distribution of the muscle fibers by diameter and ultrastructural features and volume of connective tissue in the heart.

A distinguishing feature of formation of the "hypertensive" heart in old animals, as their arterial pressure rises, is a sharp decline in the ability of cardiomyocytes to undergo additional hypertrophy beyond that obtained during the whole period of ontogeny. The diameter and number of hypertrophied fibers also are critical. The decrease in the rate of protein and RNA synthesis with age [4, 8] is evidently the reason why repair processes lag behind the increasing volume of degenerative and necrotic changes taking place in the heart. This last state of affairs can explain the acceleration of decompensation of the hypertrophied myocardium in old people with hypertension.

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