Possible Mechanism of Regression of Myocardial Hypertrophy

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Structure of the myocardium was studied in rabbits with renovascular hypertension during the development of myocardial hypertrophy and its regression under the effect of β-adrenoceptor antagonist lopressor. Myocardial hypertrophy was associated with ultrastructural changes in cardiomyocytes, while lopressor therapy led to their regression and normalization of cardiomyocyte ultrastructure. Regression of hypertrophic changes was accompanied by a marked increase in the number of extracellular nuclei, which indicated enhanced apoptosis of cardiomyocytes.

Key Words: *myocardial hypertrophy; regression; β-adrenoceptor antagonist; apoptosis*

Our previous studies demonstrated pronounced regression of myocardial hypertrophy (MH) in animals with experimental renovascular arterial hypertension (RVAH) treated with inhibitors of angiotensin-converting enzyme (ACE) and calcium channel blockers [1,2]. Similar effect was produced by propranolol [6]. The mechanisms of this regression remain unclear. It is believed that changes in the intensity of apoptosis play an important role in both the development and regression of MH [4,5], but these data are controversial. The aim of the present study was to evaluate the effect of selective β-adrenoceptor antagonist lopressor on the regression of MH and intensity of apoptosis in cardiomyocytes isolated from RVAH rabbit.

MATERIALS AND METHODS

Experiments were performed on 40 male Chinchilla rabbits weighing 2.5-3.0 kg. The animals were divided into four groups (10 rabbits per group): sham-operated rabbits (control 1); sham-operated rabbits treated with lopressor (0.5 mg/day intramuscularly) for 2 weeks (control 2); rabbits with experimental RVAH and hypertension modeled according to P. Page (experiment 1); and rabbits with experimental RVAH treated with lopressor (0.5 mg/day intramuscularly) for 2 weeks starting from the 6th week after surgery (experiment 2). Eight weeks after surgery the rabbits were sacrificed, the hearts were extirpated and perfused with glutaraldehyde (2.5%), papillary muscles were excised, postfixed in OsO_4 (pH 7.2-7.4), and embedded in Epon-Araldite. The semithin and ultrathin sections were prepared with a Reicher-Jung Ultracut ultramicrotome. The semithin sections were stained [3] and examined under a light microscope. The morphometric analysis was performed using G. G. Avtandilov eyepiece grid (30 visual fields in each case). Ultrathin sections were contrasted with uranyl acetate and lead citrate and examined under a Zeiss-10 transmission electron microscope. The morphometric analysis (×2500) was carried out on a monitor with morphometric grid similar to that used in light microscopy. The results were analyzed statistically using Student's t test at $p \leq 0.05$.

RESULTS

RVAH was accompanied by pronounced MH, which regressed under the effect of lopressor (Fig. 1, *a*, *b*). Lopressor also reduced the weight of myocardium in intact heart. By contrast to ACE inhibitors inducing regression of MH without structural normalization [1],

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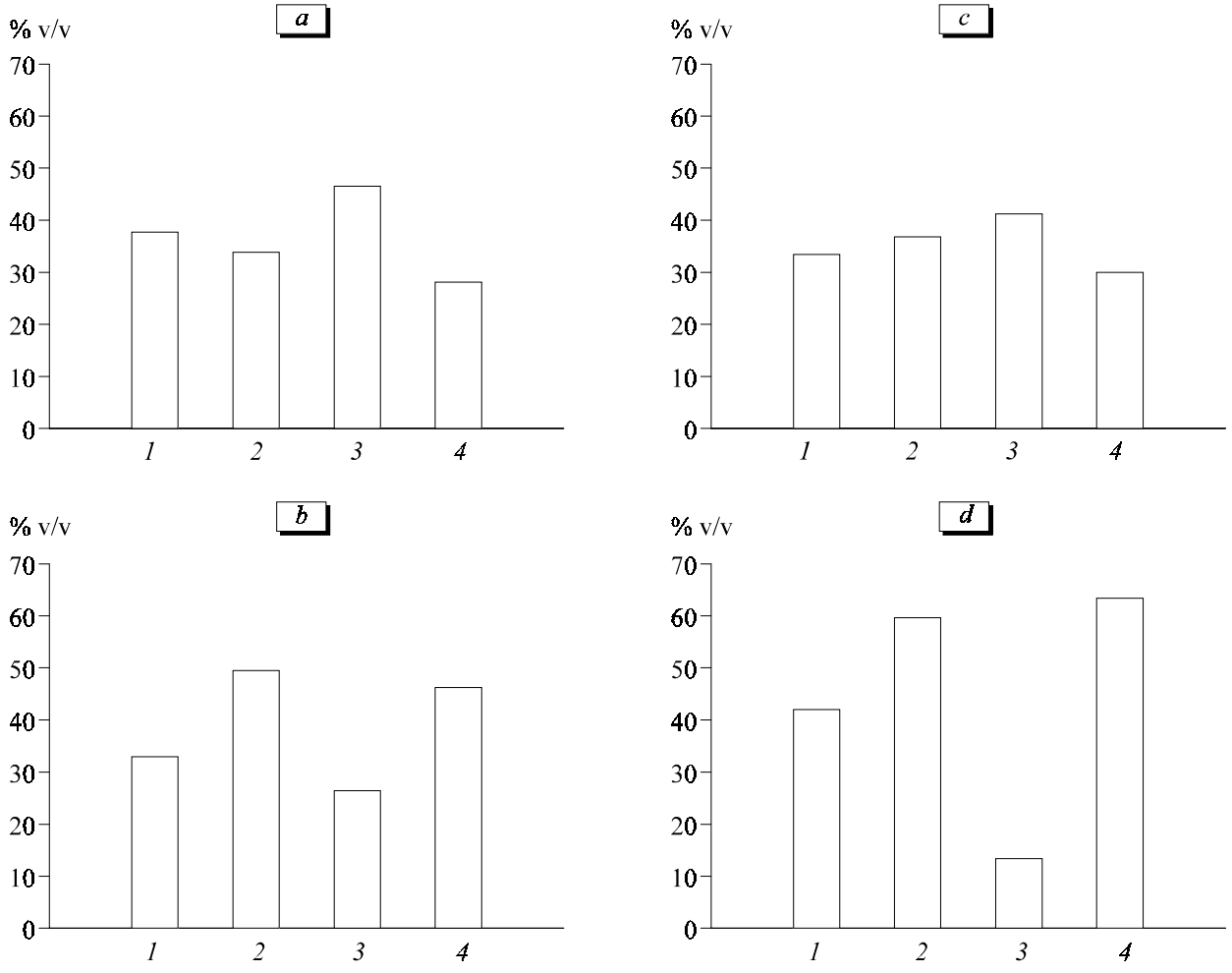

Fig. 1. Fraction of myofibrils (*a*, *c*) and the ratio of extracellular nuclei to the total number of nuclei (*b*, *d*) in the myocardium of the left (*a*, *c*) and right (*b*, *d*) ventricles (morphometry of semithin sections). Here and in Fig. 2: *1*) intact, *2*) intact+lopressor; *3*) hypertension; *4*) hypertension+lopressor.

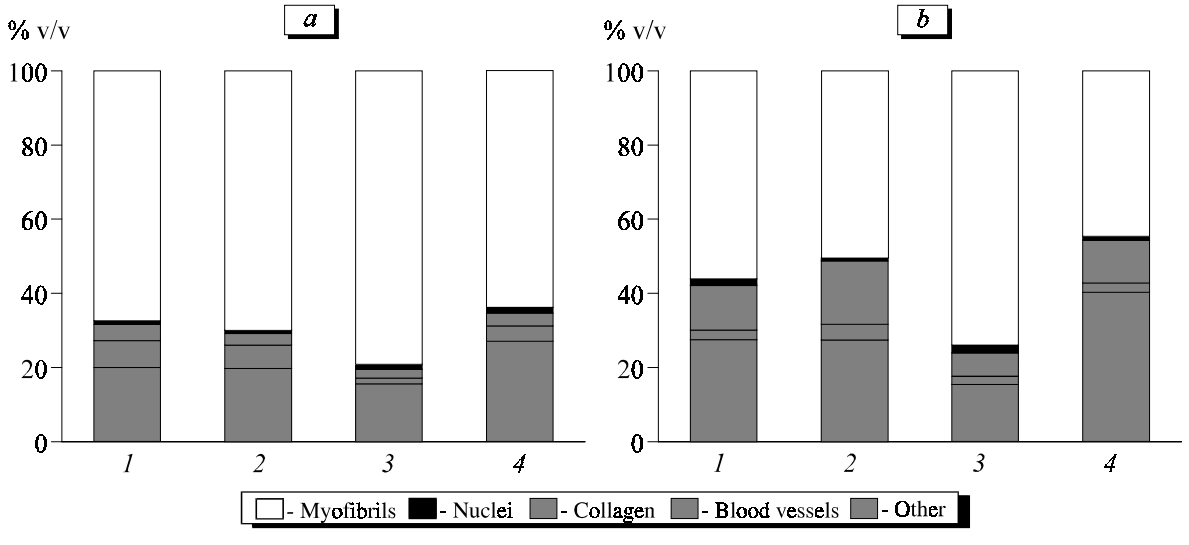

Fig. 2. Structural interrelations in the myocardium of the left (*a*) and right (*b*) ventricles (morphometry of semithin sections).

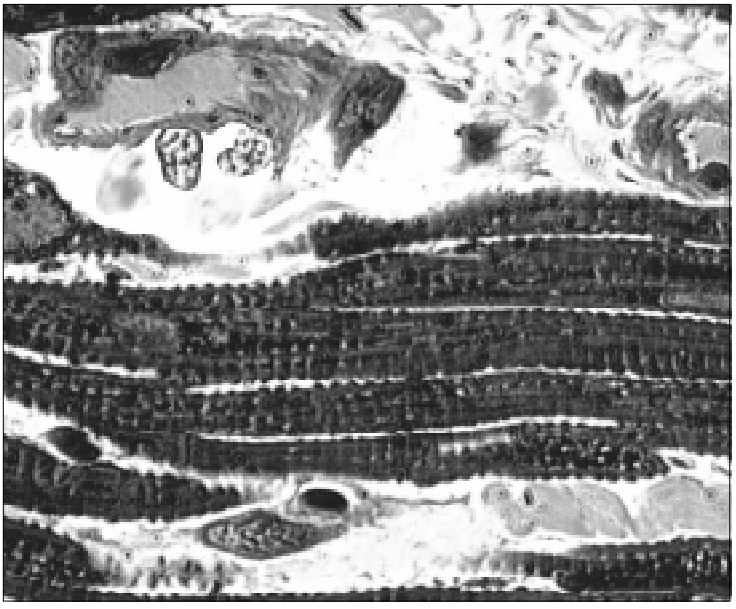

Fig. 3. Cardiomyocyte nuclei in the extracellular space. Semithin section of the left ventricle from a rabbit with arterial hypertension treated with lopressor, ×900.

lopressor normalized the structure of hypertrophic myocardium and ultrastructure of cardiomyocytes (Fig. 2).

Since the final stage of apoptosis is the release of the nucleus from the cell into extracellular space, the intensity of apoptosis was evaluated by the ratio of extracellular nuclei (Fig. 3) to the total number of nuclei per visual field. The morphometric data showed that this ratio markedly decreased during RVAH (especially in the right ventricle), but drastically increased under the effect of lopressor. The effects of lopressor on intact and hypertonic heart were similar (Fig. 1, *b*, *d*).

Thus, the intensity of apoptosis decreased during the development of MH, but increased under the effect of lopressor. It can be hypothesized that disturbance of apoptosis underlies MH development, while regression of MH under the effect of β-adrenoceptor antagonist results from stimulation of this process.

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