Initial Mechanisms of the Development of Hypertonic Heart

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In rabbits, arterial hypertension was simulated according to Goldblatt. One, 2, 4, and 6 weeks after surgery, the hearts of control and experimental animals were extirpated for morphological examination. In semithin sections of the left and right ventricles, morphometry was performed using an Avtandilov grid. Ultrathin sections of these organs were examined under an electron microscope. It was found that the initial signs of myocardial hypertrophy appeared soon after hypertension modeling, and more early in the right ventricle. Activation of apoptosis was noted in cardiomyocytes of both ventricles, and its intensity correlated with the degree of myocardial hypertrophy. It is hypothesized that apoptosis limits the development of hypertrophy in the myocardium.

Key Words: *myocardium; arterial hypertension; hypertrophy; apoptosis*

The early stage of arterial hypertension provide the basis for the development of not only myocardial hypertrophy, but also hypertrophic heat exhaustion complex [3]. In this respect, it was interesting to study morphological changes in the myocardium at the very early stages of "hypertrophied heart" and to assess the intensity of apoptosis in cardiomyocytes playing an important role in intramyocardial processes [5-8].

MATERIALS AND METHODS

Experiments were performed on 18 male Chinchilla rabbits weighing 3.0-3.5 kg. The animals were subdivided into six groups. In five experimental groups, one-clip Goldblatt arterial hypertension was modeled ($^1/_3$ narrowing of the abdominal aorta above the renal artery orifice). This model ensures reliable increase in both systolic and diastolic pressure as early as one week postoperation [3]. One, 2, 4, and 6 weeks after surgery, the thorax was opened under narcosis and the heart was perfused via the ascending aorta with 2.5% glutaraldehyde. The fragments of papillary muscles were excised from the left and right ventricles, processed by routine methods, and embedded in Araldite. Semithin and ultrathin sections were prepared on a Reichert-Jung-Ultracut microtome. The semithin sections were stained [4] and examined under a light immersion microscope. In each series, morphometry was performed in 30 vision fields using an Avtandilov grid. The presence of muscle fibers, cell nuclei, collagen, blood vessels, muscle fiber destruction sites were assessed together with the volume of extracellular space (in volume percents). The intensity of apoptosis was assessed by our original method. The total number of cell nuclei was counted. Among them, the nuclei situated in completely destructed cells, outside cells, or even in the blood vessels were counted (Fig. 1). These nuclei were conventionally termed as free-drifting nuclei (FDN). The percentage of FDN in respect to total number of nuclei was taken as the index of apoptosis.

The data were processed statistically by Student's t test at $p \leq 0.05$ and correlation analysis using original

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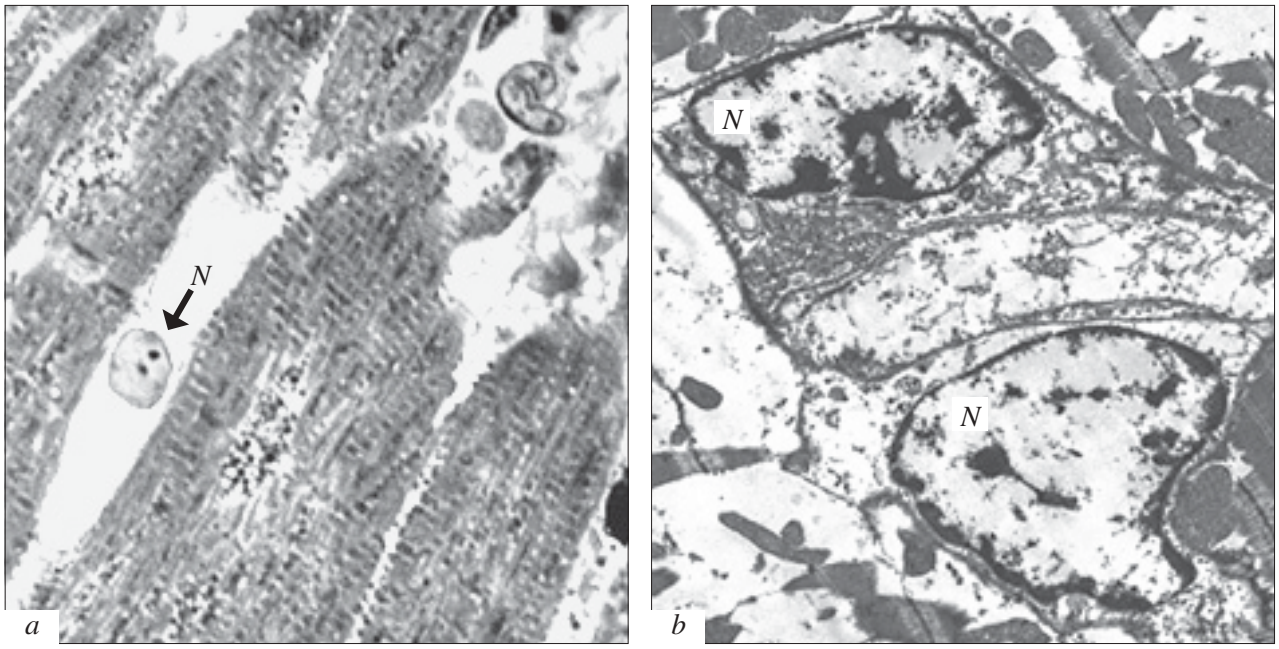

Fig. 1. Free drifting nuclei in cardiomyocytes during arterial hypertension. Semithin (*a*, ×100) and ultrathin (*b*, ×5000) sections of left heart ventricle after a 4-week arterial hypertension. Immersion magnification. N — nucleus.

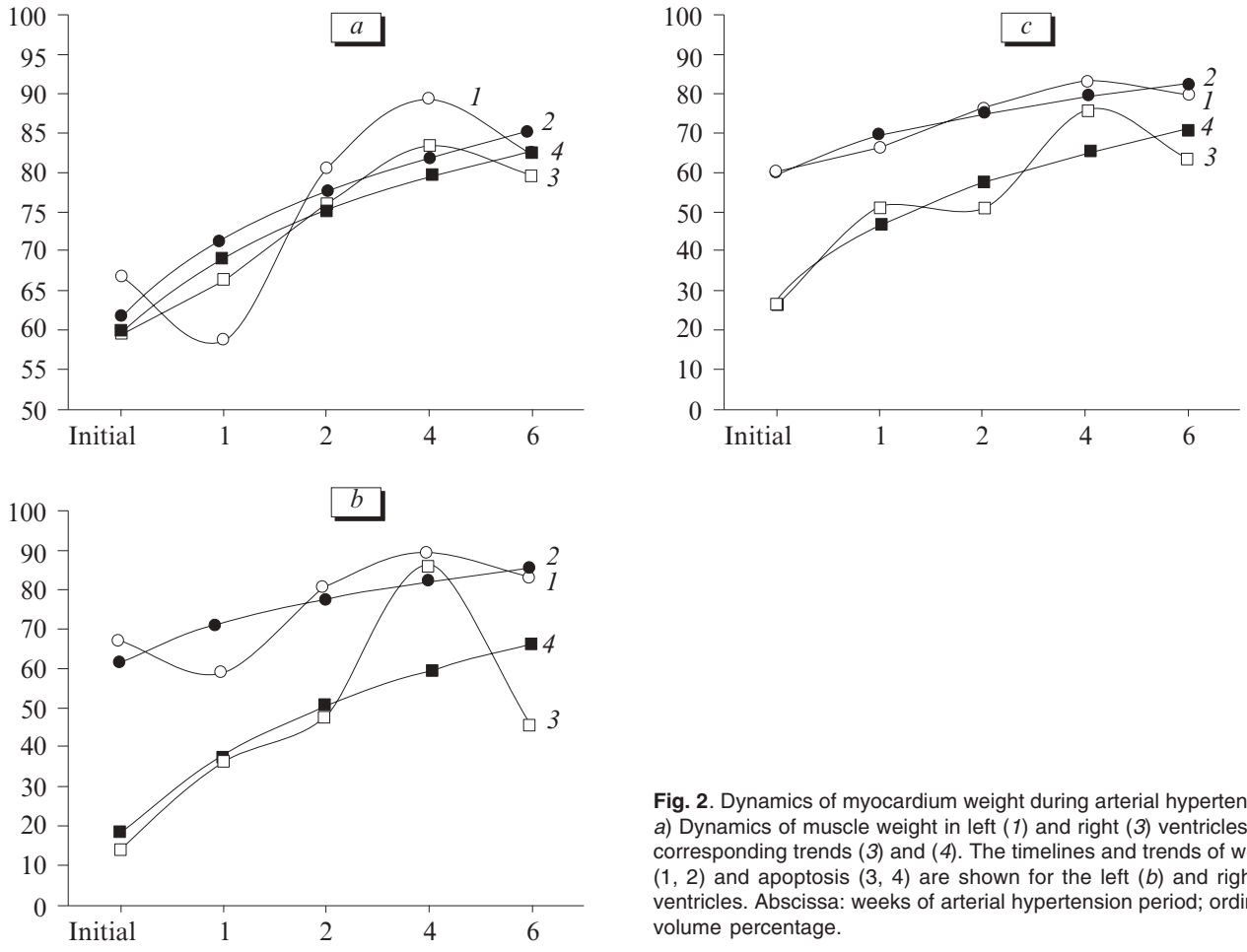

Fig. 2. Dynamics of myocardium weight during arterial hypertension. *a*) Dynamics of muscle weight in left (*1*) and right (*3*) ventricles with corresponding trends (*3*) and (*4*). The timelines and trends of weight (1, 2) and apoptosis (3, 4) are shown for the left (*b*) and right (*c*) ventricles. Abscissa: weeks of arterial hypertension period; ordinate: volume percentage.

TABLE 1. Morphometry of Semithin Sections of Left Ventricle (Volume Percents, *M*±*m*)

Timeline	Muscle fibers	Nuclei	FDN	Apoptosis index, %	Collagen	Vessels	Destruction sites	Extracellular space
Control	66.70±1.89	1.77±0.17	0.27±0.19	14±5	2.13±0.39	4.17±0.58	1.73±0.32	26.2±1.8
Week 1	58.70±1.23*	1.77±0.24	0.83±0.18*	36±7*	3.17±0.41	3.47±0.75	2.73±0.65	32.80±1.15*
Week 2	80.50±1.56*	2.60±0.41	1.50±0.34*	48±7*	2.52±0.57	4.07±0.72	5.80±0.51*	10.50±0.96*
Week 4	89.40±0.81*	3.73±0.42	2.93±0.28*	86±4*	2.00±0.37	1.13±0.17*	3.53±0.38*	3.73±0.39*
Week 6	82.5±1.09*	1.87±0.25	1.03±0.20*	45±9*	1.43±0.28	2.87±0.42*	3.33±0.34*	11.4±1.1*

Note. Here and in Table 2: *$p \leq 0.05$ compared to the control.

TABLE 2. Morphometry of Semithin Sections of Right Ventricle (Volume Percents, *M*±*m*)

Timeline	Muscle fibers	Nuclei	FDN	Apoptosis index, %	Collagen	Vessels	Destruction sites	Extracellular space
Control	59.70±1.67	2.90±0.37	0.60±0.15	26±7	2.20±0.39	7.83±0.93	2.33±0.35	27.5±1.5
Week 1	66.30±1.29*	1.53±0.19*	0.90±0.15	51±8	5.50±0.64*	4.33±0.59*	4.01±0.59*	22.30±1.35*
Week 2	76.1±1.0*	1.47±0.19*	0.83±0.16	51±7*	2.23±0.28	5.23±0.78*	3.43±0.40*	15.00±0.26*
Week 4	83.4±1.4*	3.40±0.36	2.47±0.33*	76±6*	2.20±0.39	2.67±0.62*	2.9±0.39	8.43±0.91*
Week 6	79.80±1.08*	1.77±0.31*	1.33±0.19*	64±10*	6.13±0.72*	3.80±0.43*	2.33±0.32	8.53±1.05*

software developed at the Department of Pathological Physiology, Russian University of People Friendship.

RESULTS

During the development of arterial hypertension, the weight of muscles in both ventricles increased (Tables 1, 2; Fig. 2, *a*). In the right ventricle, this process started earlier. These findings agree with previous reports [2], where analysis of the dynamics of heart electrical axis in hypertonic patients showed that under conditions of arterial hypertension, hypertrophy of the right ventricle was triggered earlier than in the left ventricle. Present morphometric data corroborate our conception on the leading role of the right ventricle in heart regulation under normal or pathological conditions [1,4].

It is worthy to note a strict correlation between the degree of increase in myocardium weight and apoptosis index, which was characteristic of both ventricles (Fig. 2, *b*, *c*). Since apoptosis cannot stimulate the increase in myocardium weight, we hypothesized that, on the contrary, apoptosis itself is triggered by the increase in myocardium weight. Thus, apoptosis can be a factor limiting the development of myocardial hypertrophy.

In conclusion, the development of myocardial hypertrophy during arterial hypertension begins at the very early stages of hypertension, while apoptosis of cardiomyocytes is a factor regulating hypertrophy of the heart.

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