Myocardial Hypertrophy in Rabbits with Renovascular Hypertension under Pharmacological Blockade of Angiotensin II Synthesis and Its Interaction with Specific Receptors

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The dynamics of blood pressure, the weight of the heart and its subdivisions, and morphology of myocardium were studied in the rabbits with experimental renovascular hypertension. Treatment with inhibitors of angiotensin II synthesis (lotensin) or its interaction with specific receptors (valsartan) decreased blood pressure and the weight of the left ventricle, but did not affect the interrelations between structural elements in the heart, which remained the same as in hypertension-induced myocardial hypertrophy. In addition, these drugs impaired some parameters of cardiac activity attesting to myocardial overload, increase in collagen content in the myocardium, and decrease in the ratio of the numbers of capillaries and mitochondria to the weight of myofibrils.

Key Words: *hypertension; treatment; myocardial hypertrophy; regression*

Clinical and experimental data indicate that treatment of hypertension with antihypertensive drugs induces regression of myocardial hypertrophy [3-9,11]. However, significance of this phenomenon for cardiac function remains unclear [10]. Our aim was to study the effect of regression of myocardial hypertrophy on the structure and function of "hypertensive heart".

MATERIALS AND METHODS

Experiments were performed on 40 male Chinchilla rabbits weighing 2.5-3.5 kg. The animals were divided into four groups of 10 rabbits: controls (sham-operated) and rabbits with renovascular hypertension modeled according to P. Page untreated and treated with lotensin, an inhibitor of plasma angiotensin-converting enzyme blocking synthesis of angiotensin II (Ciba, 50 mg *per os* daily for 6 weeks) or valsartan, a blocker of angiotensin receptors (10 mg *per os* daily, Ciba). In acute experiments carried out 6 weeks after surgery, blood pressure was measured with an electromanometer in the proximal part of the carotid artery. In addition, the peak systolic pressure was measured in both ventricles under normal conditions and under isovolumic contractions caused by a 5-sec occlusion of the ascending aorta (for left ventricle) and pulmonary artery (for right ventricle). Wet and dry weights of the left and right ventricles and right atrium were determined. The data were used to calculate the duration of systolic phases and the real and maximum intensity of ventricular function (IVFr and IVFm, respectively) as the ratio of real (or maximum) isovolumic peak systolic pressure in the corresponding ventricle to its weight [1]. The samples were embedded in Araldite. The semithin and ultrathin sections prepared with a Reichert-Jung Ultracut ultramicrotome were examined under light and Zeiss-10 electron

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TABLE 1. Weight of Left Ventricle and Its Correlation with Diastolic Blood Pressure (BP_{min}) in Hypertensive Rabbits Treated with Lotensin and Valsartan (*M±m*)

Indices	Control	Hypertension	Lotensin	Valsartan
Weight, g	1.65±0.03	2.44±0.05*	2.00±0.07*	1.89±0.04*
Dry weight, g	0.95±0.05	1.44±0.07*	0.81±0.03*	0.77±0.02*
ρ (BP_{min} — weight)	+0.70+	+0.73+	+0.52	+0.26
ρ (BP_{min} — dry weight)	+0.69+	+0.72+	+0.53	+0.22

Note. $p \leq 0.05$: *compared to the control, +significant correlation.

microscopes, followed by morphometric analysis in order to determine the content of myocardial structures (in volume percents). The differences between the indices were significant at $p \leq 0.05$. The degree of relations revealed by the correlation analysis were strong at $r \geq 0.70$, moderate at $r = 0.69$-0.30, and weak at $r \leq 0.29$.

RESULTS

Both lotensin and valsartan significantly decreased systolic and diastolic pressure in rabbits with renovascular hypertension (Fig. 1, *a*). It is noteworthy that valsartan decreased diastolic pressure below the control values. Both drugs significantly decreased weight of the heart and left ventricle in comparison with the control and did not affect the weight of the right ventricle (Fig. 1, *b*). Thus, both drugs reduced the weight of hypertrophic heart. The morphometric analysis showed that lotensin and valsartan practically did not change the interrelation between morphological elements in the myocardium (Fig. 1, *c*) and in cardiomyocytes (Fig. 1, *b*). Thus, the antihypertensive drugs decreased myocardial weight, but did not induce re-

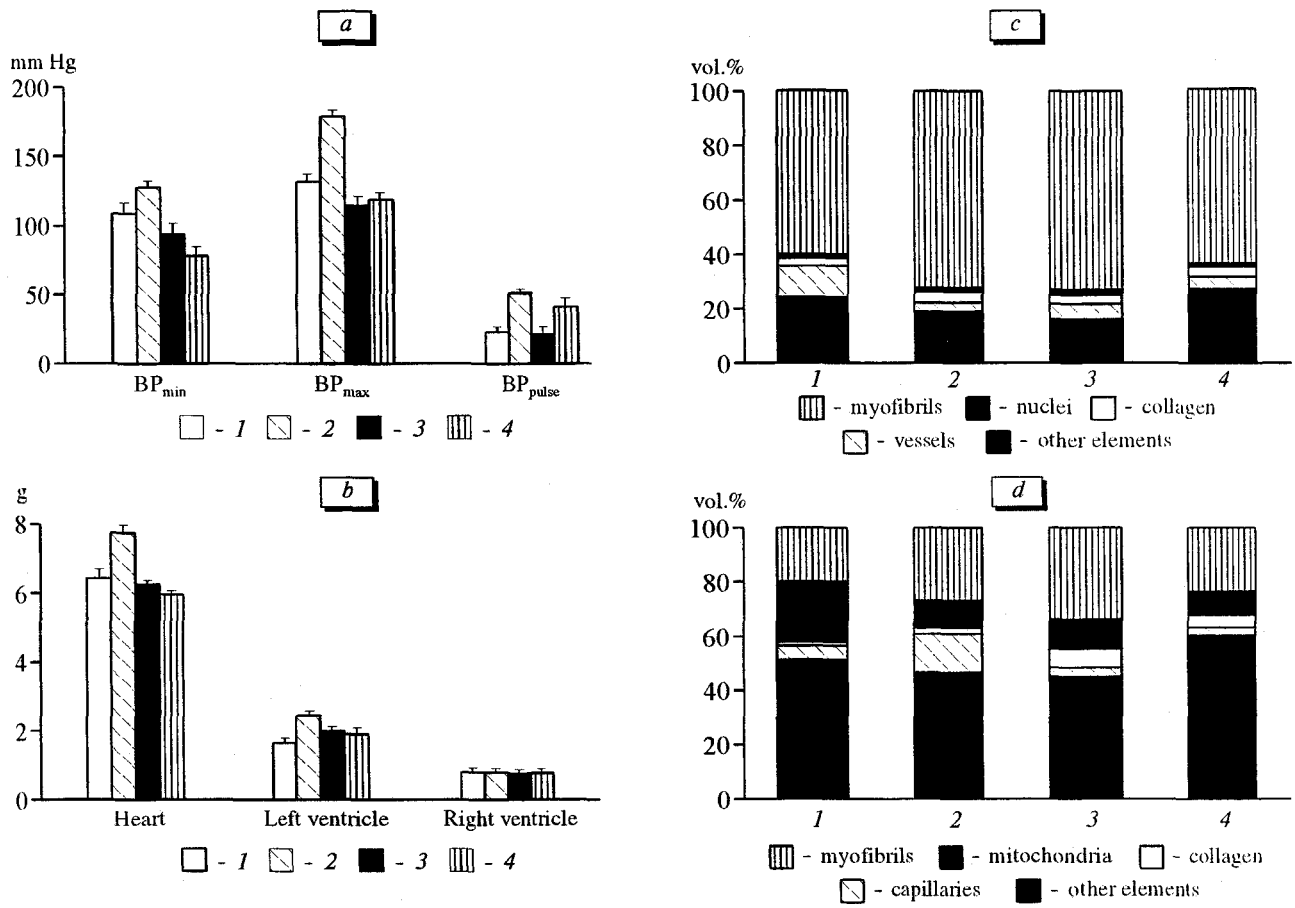

Fig. 1. Blood pressure (*a*), weight of the heart and its subdivisions (*b*), relationships between some myocardial structures in semithin (*c*) and ultrathin (*d*) sections of the left ventricle in control (*1*), under conditions of renovascular arterial hypertension (*2*), and after treatment with lotensin (*3*) and valsartan (*4*).

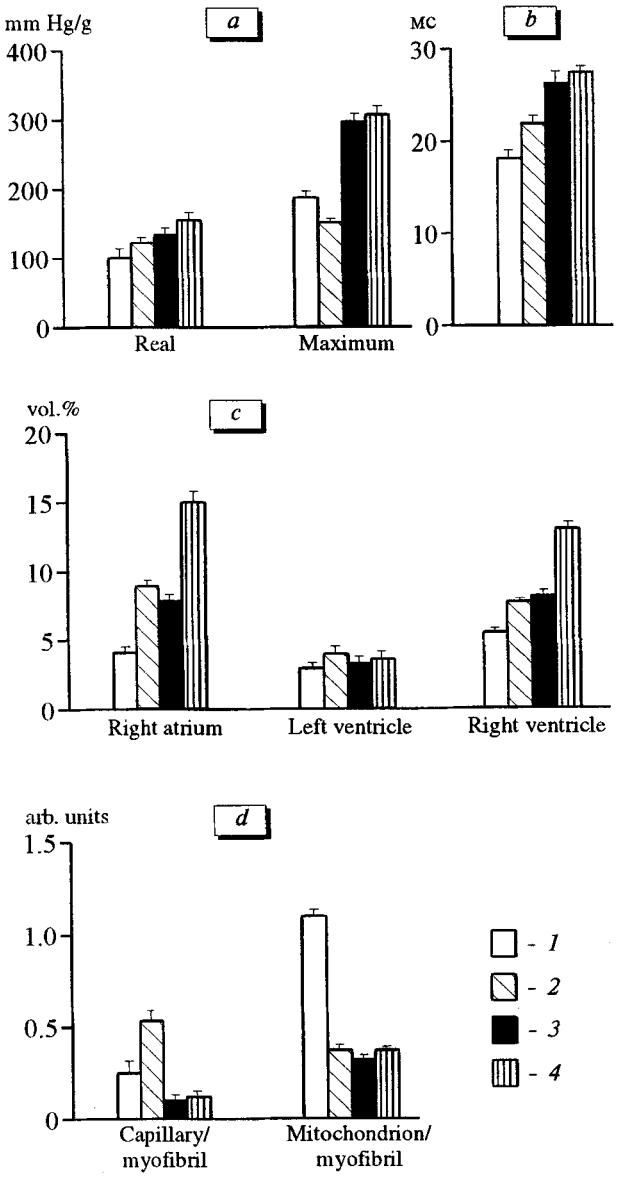

Fig. 2. Real and maximum intensity of left ventricle function (*a*), duration of isovolumetric contraction (*b*), collagen content (*c*), capillary/myofibril and mitochondrion/myofibril ratios (*d*) in the left ventricle in normal heart (*1*), under conditions of renovascular arterial hypertension (*2*), and after treatment with lotensin (*3*) and valsartan (*4*).

gression of myocardial hypertrophy. Since both wet and dry weights of the heart and left ventricle decreased, this phenomenon cannot be explained entirely by dehydration. It probably includes reduction of some structural elements without changing their proportions characteristic of the hypertrophic heart. The correlation analysis showed that both drugs drastically weakened the relationships between the weight of the left ventricle and diastolic blood pressure (Table 1). Therefore, the decrease in the weight of the left ventricle cannot be related entirely to the drop of peripheral resistance to cardiac output; presumably, these drugs directly affect plastic processes in the heart.

Both drugs significantly increased IVFr and IVFm (Fig. 2, *a*), which attests to improvement of potential capacity of the heart (IVFm) on the one hand, and indicates overload of myocardial elements, on the other (IVFr). Both drugs significantly prolonged the isovolumic contraction phase (Fig. 2, *b*), which indicates impairment of myocardial contractility. Valsartan increased collagen content in the right atrium and right ventricle in comparison with untreated hypertensive rabbits (Fig. 2, *c*). According to current views, capillary proliferation lags behind the growth of myocardial weight during hypertrophy development [1,2]. At a relatively early stage of hypertrophy we observed an increase in the capillary/myofibril ratio (Fig. 2, *d*), however both drugs drastically decreased this ratio (even below the control level), which is typical for the development of emaciation complex of hypertrophic heart. In all rabbits with renovascular hypertension the mitochondrion/myofibril ratio was far below the control value irrespective of treatment (Fig. 2, *d*).

Our data indicate that treatment of hypertension with the drugs blocking the renin-angiotensin II system decreases the weight of the myocardium without affecting structural signs of myocardial hypertrophy. This drop is accompanied by a decrease in myocardial contractility and vascularization.

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