GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Experimental Study of Myocardial Collagen during Nifedipine Therapy of Arterial Hypertension

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Light and electron microscopy of the left-ventricular myocardium obtained from spontaneously hypertensive SHR rats showed a pronounced increase in collagen content. These changes were more pronounced in animals treated with nifedipine in the mean therapeutic dose for 8 weeks. Collagen accumulated between muscle fibers and often formed perivascular cuffs. Hence, nifedipine promotes the formation of scleroproteins in the myocardium.

Key Words: *collagen; myocardium; arterial hypertension; nifedipine*

Many recent studies showed that blockers of slow Ca^{2+}-channels (*e.g.* nifedipine) widely used for the treatment of hypertension produce a negative inotropic effect on the myocardium and augment the risk of heart attacks [5-8]. Chronic overload of the myocardium reduces its inotropism due to the formation of the so-called "complex of hypertrophic heart wearing" [1]; the development of this complex starts with intense formation of connective tissue in the myocardium. Here we investigated the formation of collagen determining the development of cardiac muscle sclerosis.

MATERIALS AND METHODS

Experiments were carried out on 20 spontaneously hypertensive SHR rats and 10 intact Wistar—Kyoto rats (control). Nifedipine in a dose of 0.5 mg/kg corresponding to the mean therapeutic dose in humans was daily injected intramuscularly to 10 hypertensive rats for 8 weeks, after which all animals (experimental and control) were sacrificed by heart extirpation under narcosis.

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The hearts were perfused with 2.5% glutaraldehyde. Fragments of the left papillary muscles were dissected, postfixed in osmium tetroxide (pH 7.2-7.4), and embedded in epon-araldite mixture. Semithin [4] and ultrathin sections were made using a Reicher-Jung-Ultracut ultramicrotome, contrasted with lead hydroxide and uranyl acetate, and examined under a Zeiss-10 transmission electron microscope. Morphometric analysis of semithin sections was carried out using G. G. Avtandilov grid. The content of collagen and the number of blood vessels were evaluated. Electron-microscopic study was carried out by the author at Laboratory of Electron Microscopy (Institute of Pathology, Heidelberg University, Germany).

RESULTS

In normal myocardium collagen forms narrow strata between muscle fibers (Fig. 1, *a*). The content of collagen in the myocardium essentially increases in arterial hypertension (Fig. 1, *b*) and increases still more after nifedipine therapy (Fig. 1, *c*, *d*). Large collagen layers were seen between muscle fibers and formed cuffs around blood vessels. The latter phenomenon was much more pronounced after nifedipine therapy.

Electron microscopy showed the same picture (Fig. 2). It is noteworthy that collagen fibers prevent

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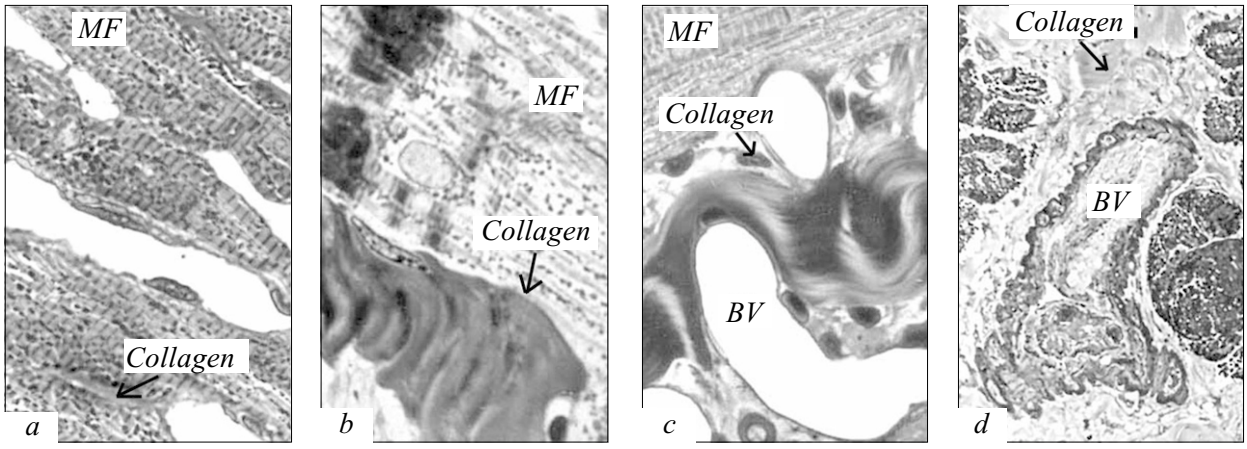

Fig. 1. Semithin sections of left ventricles from control (*a*), spontaneously hypertensive (*b*) rats, and spontaneously hypertensive rats treated with nifedipine (*c*, *d*), ×452. *MF*: muscle fibers; *BV*: blood vessel.

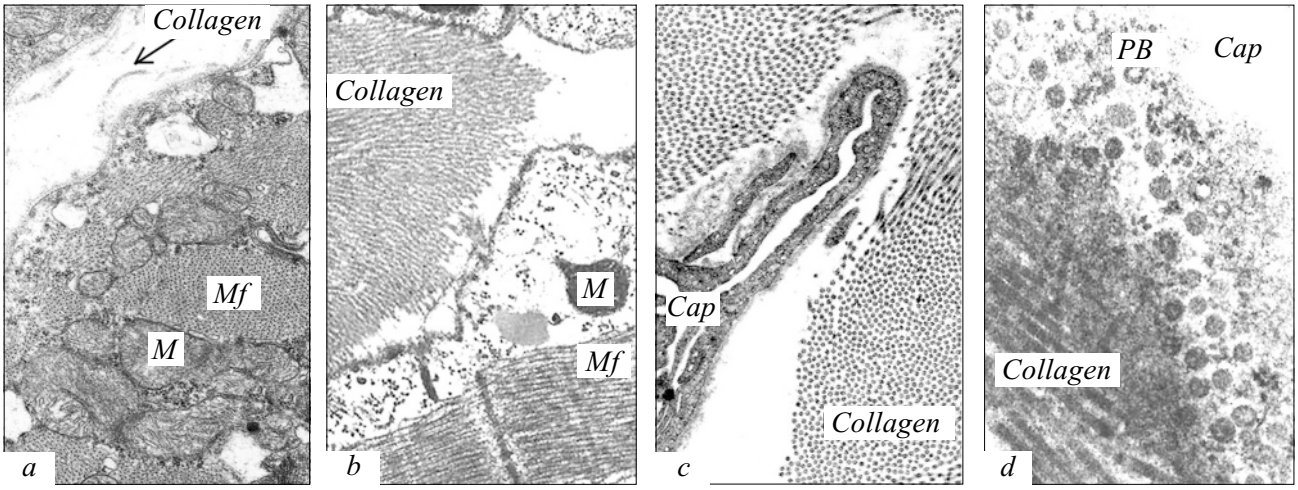

Fig. 2. Ultrathin sections of left ventricles from control (*a*), spontaneously hypertensive (*b*) rats, and spontaneously hypertensive rats treated with nifedipine (*c*, *d*). *a*, *b*: ×20,000; *c*: ×30,000; *d*: ×40,000. M: mitochondria; Mf: myofibrils; Cap: capillary; PB: pinocytous bubbles.

transport of pinocytotic vesicles from capillaries into myocardial tissue (Fig. 2, *d*).

The content of collagen in the myocardium of spontaneously hypertensive rats significantly surpassed the normal (Fig. 3), and tended to increase after nifedipine treatment. The collagen/blood vessels ratio changes similarly (Fig. 3, *b*). The increase of this coefficient after nifedipine treatment was more pronounced than in untreated animals with arterial hypertension.

Hence, the content of scleroproteins in the myocardium increases significantly in arterial hypertension. Collagen is synthesized not only by fibroblasts, but also by some other cells, for example endothelial, epithelial, and smooth-muscle cells [2]. Presumably, myocardial overload, disturbances in energy metabolism in the hypertrophic heart and myocardial hypoxia [1] trigger collagen hyperproduction. Localization of collagen around blood vessels after nifedipine treatment probably reflects defense and adaptive reaction

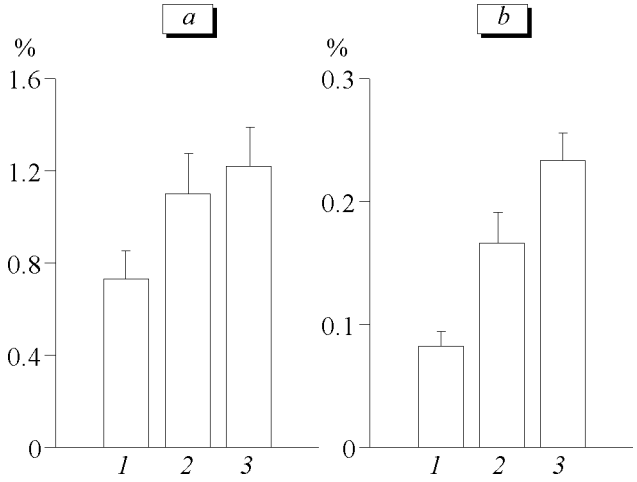

Fig. 3. Morphometric parameters of left-ventricular myocardium (semithin sections). *a*) collagen content; *b*) collagen/blood vessels ratio. *1*) controls; *2*) spontaneously hypertensive rats; *3*) spontaneously hypertensive rats treated with nifedipine.

[3], because collagen cuffs can prevent penetration of chemicals from vessels into tissue. On the other hand, these cuffs prevents penetration of oxygen and nutrients, which, no doubt, impairs myocardial trophy and promotes the development of "hypertrophic heart wearing complex". This fact should be taken into account in hypertensive patients receiving nifedipine for a long time.

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