AN EXPERIMENTAL STUDY OF THE REVERSIBILITY OF CARDIAC HYPERTROPHY

Yu. M. Repin

Laboratory of the Physiology and Pathology of the Heart, Institute of Normal and Pathological Physiology (Director – Active Member AMN SSSR Professor V. V. Parin) of the AMN SSSR
(Presented by Active Member AMN SSSR V. V. Parin)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 57, No. 3, pp. 37-40, March, 1964
Original article submitted March 18, 1963

As a result of the fact that in some cases it is now possible to correct organic defects of the heart, to restore the normal arterial pressure in hypertensive patients, and so on, a problem of much current importance is the subsequent fate of changes in the heart acquired in the course of a disease after the factors causing them have been removed.

The reversibility of myocardial hypertrophy has not been investigated systematically until very recently. The few clinical observations [1, 3, 7, 9, 13] which have been reported indicate that the roentgenological dimensions of the heart may be reduced after successful treatment of diseases associated with hypertrophy of the myocardium. However, roentgenological methods are not sufficiently precise to allow differentiation between a reduction in the dimensions of the heart as a result of disappearance of its hypertrophy and a contraction of the volume of the chambers as a result of an increase in myocardial tone and disappearance of dilatation. The few attempts which have been made to solve this problem experimentally [11, 12, 14, 15] likewise are incomplete, for their conclusions regarding the disappearance of hypertrophy were based entirely on comparison of the mean weight of control and experimental animals sacrificed at various intervals after the creation and subsequent removal of factors causing permanent hyperfunction of the heart, and were not supported by the results of histological investigation of the heart muscle.

An important obstacle retarding the experimental study of this problem has been the lack of sufficiently simple and reliable techniques for creating a marked degree of hypertrophy of the myocardium in a short time and allowing the cause to be removed at any stage of development of the process. In the experimental studies cited above the development of cardiac hypertrophy for the purpose of studying its reversibility was brought about by one of the following methods: prolonged administration of adrenalin, prolonged physical exertion, constriction of one of the renal arteries with subsequent removal of the corresponding kidney after stabilization of the arterial pressure at a high level, and the formation of an anastomosis between the right carotid artery and the right jugular vein, and its removal by ligation of the carotid artery after the development of cardiac hypertrophy. As a rule these methods did not provide a high enough degree of functional overloading of the myocardium, and did not result in the development of a high enough degree of hypertrophy.

Marked changes in the heart have been produced by the formation of experimental stenosis of the mouth of the aorta. The character and dynamics of these changes have been studied fully [6, 5]. A method of removing experimental aortic stenosis was suggested for the first time by F. Z. Meerson [6, 5], but proved to be technically difficult, especially if a long time had elapsed after formation of the stenosis on account of the development of adhesions.

D. S. Sarkisov and co-workers [2], who first began to make an extensive study of the problem of the reversibility of acute and chronic changes in internal organs, suggested an experimental model of graded and removable stenosis of the aortic orifice in rabbits. Despite its reliability, this model has certain disadvantages and, in particular, it cannot be used in small laboratory animals and requires repended surgical operations in the region of the heart.

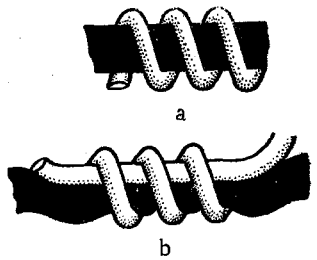

Fig. 1.

We propose herewith a method of removable and graded coarctation of the aorta in albino rats which is simpler and more suit ble for use in large-scale investigations. In the present paper we describe the results of a morphological study of the reversibility of the sequelae of persistent hyperfunction of the heart produced by the use of this method.

EXPERIMENTAL METHODS

Profiting by the method of constriction of vessels in small laboratory animals using a wire spiral, suggested by A. Kh. Kogan [4], and by the observations of Beznak [10] and M. G. Pshennikova [8], who obtained marked hypertrophy of the heart as a result of constriction of the abdominal aorta in albino rats, we wrapped a wire spiral made of unoxidizable metal around the aorta immediately below the diaphragm (laparotomy was performed through a midline incision, in layers, with the animal lying on its back). The internal diameter of the turns of the spiral corresponded to the external diameter of the aorta, so that the spiral did not compless the aorta (Fig. 1A). Next, under the turns of the spiral, between them and the aorta, was inserted the end of a thick Kapron thread, causing constriction of the aorta, narrowing its lumen by an amount equal to its cross-sectional area (Fig. 1B). The degree of coarctation of the aorta may be graded by varying the thickness of the thread or the diameter of the turns of the spiral. The free end of the thread was brought out through the cranial end of the operation wound. The abdomen was closed in layers without drainage. The free end of the thread was left beneath the skin, where it was fixed to the sutures inserted into the muscles. The operations were carried out under ether anesthesia and were completed by sprinkling penicillin solution into the abdominal cavity. To remove the coarctation at the end of the required interval after its creation, the end of the Kapron thread was palpated through the skin, a small incision made above it, and the thread pulled out of the abdominal cavity, releasing the space beneath the spiral. The spiral was left around the aorta.

For albino rats weighing 250-300 g a spiral with an internal diameter of its turns of 1.35 mm and a thread with a diameter of 0.6 mm were used, resulting in an average degree of narrowing of the cross section of the lumen of the aorta of 25%.

A morphological investigation was made of the heart of animals sacrificed 30 days after creation of coarctation of the aorta (20 rats), and also 4 months after removal of the coarctation which had been in existence for 30 days (10 rays). As controls, investigations were made of intact animals (50 rats) and animals sacrificed 4 months after the creation of a removable coarctation of the aorta (10 rats). In each rat the relative weight of the heart (ratio between the weight of the heart and live weight of the animal) was determined and a histotopographical investigation made of total sections of the myocardium stained with hematoxylin-eosin and by Van Gieson's method.

EXPERIMENTAL RESULTS

In the animals sacrificed 30 days after creation of a reversible coarctation of the aorta, the relative weight of the heart was increased and lay within the range 0.0037-0.0069 (mean 0.0047). In the intact rats at the same time it varied between 0.0027 and 0.0031 (mean 0.0029). Hence the creation of coarctation of the aorta led after one month to an increase in the mass of the heart, on average by 60%.

Total transverse sections of the hearts of these animals revealed a considerable enlargement of the chambers of the heart and thickening of the walls of the ventricles, especially the left. Histotopographical investigation revealed hypertrophy of the muscle fibers, most marked near the endo- and epicardium and in the papillary muscles (Fig. 2b). The volume of the nuclei of the fibers was increased, and individual nuclei contained vacuoles. In some areas of the myocardium, mainly at the sites of maximal development of hypertrophy, groups of fibers were seen to be undergoing degenerative changes, with areas of necrosis. These fibers were indistinct in outline, and here and there they were thinned and deformed. Their sarcoplasm was devoid of longitudinal and cross striation and appeared structureless, glassy, and homogeneous, and in some places it was broken up into granules and fragments of different shapes and sizes. These fibers stained a more intensive shade of orange-yellow with picrofuchsin, and when stained with hematoxylin-eosin they exhibited basophilia. Their nuclei were darker and structureless, and sometimes they were elongated and rod-shaped. Death of the muscle fibers was accompanied by profileration of the loose connective tissue and accumulation of lymphoid cells, with the formation of recent scars. The stroma, mainly in the perivascular spaces, and also beneath the endo- and epicardium and, to a lesser degree, in the intermuscular spaces,

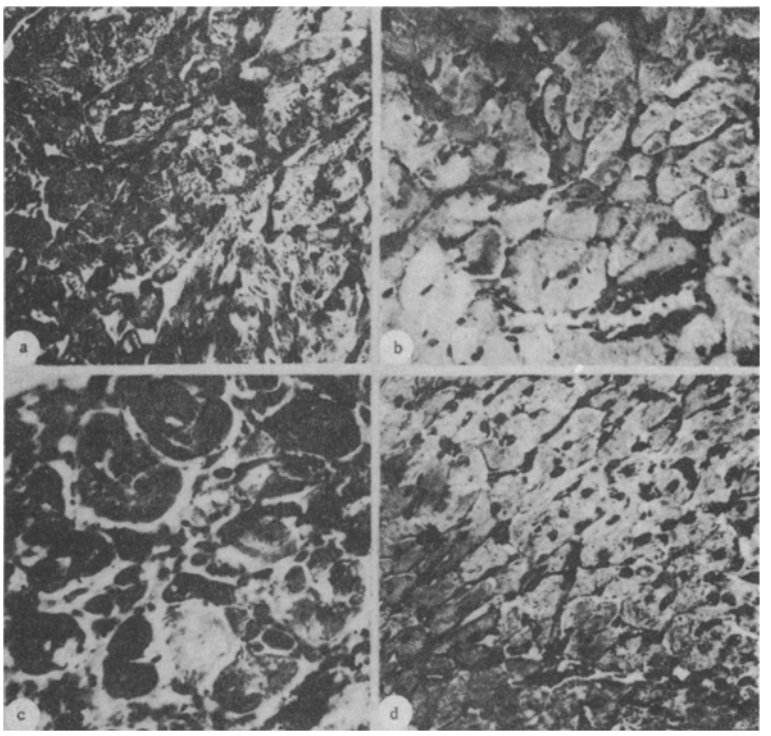

Fig. 2. Changes in the degree of hypertrophy of the muscle fibers of the myocardium in the subendocardial layer of the left ventricle. a) Control rat; b) 30 days after creation of coarctation of the aorta; c) 4 months after creation of coarctation; d) 4 months after removal of coarctation of the aorta. Photomicrograph. Stained by Van Gieson's method. Magnification 290.

appeared edematous and contained large numbers of young connective-tissue cells. The walls of the coronary vessels had cuff-like thickenings resulting from proliferation of the adventitia and slight thickening of the intima.

In the animals surviving 4 months after creation of coarctation of the aorta a further increase in the mass of the heart was observed (in the rats of this series of experiments the relative weight of the heart lay within the limits of 0.0046-0.0069, with a mean value of 0.0054, i.e., 185% of the normal value), accompanied by more profound changes in the heart muscle: marked and, in some places, giant hypertrophy of the muscle fibers (Fig. 2c) in all layers of the myocardium, and many fibers showing pathological changes – from early stages of degeneration to severe atrophy and necrosis. Extensive proliferation of connective tissue was observed, both as zones of proliferation of young connective-tissue cells and as sheets of adult tissue, mainly in the perivascular spaces and to a lesser degree beneath the endo- and epicardium, and finally, as numerous tiny scars, scattered throughout the myocardium. The walls of the vessels were thickened and sclerotic, with thinning and coarsening of the muscular layer in the arteries and signs of proliferation of the endothelium in the arterioles.

Four months after removal of the coarctation of the aorta after it had been in existence for 30 days, the mass of the heart had almost returned to its original value: the relative weight of the heart in the 10 animals of this group varied between 0.0030 and 0.0034, with a mean value of 0.0032, i.e., 110% of normal. The volume of the chambers and thickness of the walls of the heart were the same as in the control animals. Histotopographical investigation showed disappearance of the hypertrophy of the muscle fibers of the myocardium and restoration of their normal volume (Fig. 2d). A few groups of atrophied, tortuous, and thin muscle fibers with abnormal staining properties were seen, surrounded by wide zones of dense, connective tissue. Mature connective tissue, stained an intense crimson color with picrofuchsin, was abundant in the dilated perivascular spaces and below the endo- and epicardium, and present in smaller amounts as filaments in the intermuscular spaces and as multiple tiny scars at the sites of the dead fibers. The vessel walls were sclerotic.

Hence the formation of coarctation of the aorta by our technique, narrowing its lumen by 25%, after one month caused an increase of more than 50% in the mass of the heart, the development of hypertrophy of the muscle fibers with degenerative changes or even necrosis in individual groups, and also the appearance of initial sclerotic changes in the myocardium in the form of a reactive proliferation of young connective-tissue cells along the course of the vessels and at the sites of dying fibers.

A longer period (4 months) of coarctation of the aorta led to a further increase in the mass of the heart with a more marked and widespread hypertrophy of the muscle fibers and, at the same time, to the development of a severe, mainly perivascular, progressive myocardiofibrosis.

The removal of coarctation after an existence of 30 days resulted in the restoration of the original mass of the heart and disappearance of the hypertrophy of the muscle fibers. However, it evidently had no significant effect on the further development of the pathological changes arising during the period of functional overloading of the myocardium, as indicated by the presence of scars and proliferation of dense connective tissue in the heart muscle of the animals 4 months after removal of the coarctation of the aorta. Nevertheless, the cessation of cardiac hyperfunction 1 month after its onset interrupted the progressive development of myocardiofibrosis and considerably reduced the severity and extent of the pathological changes in the myocardium by comparison with those observed in animals with coarctation of the aorta for a period of 4 months.

SUMMARY

The author describes an original method of graded removable constriction of the abdominal aorta in albino rats and gives the data of morphological examination of the myocardium in 40 animals killed at various intervals after the creation of coarctation of the aorta, as well as after its removal. Constriction of the aortic lumen by 25% led in a month to a 60% increase of the mass of the myocardium, hypertrophy of the muscle fibers with development of dystrophic changes and necrosis of their individual groups and the appearance of initial signs of cardiosclerosis. The existence of a four-months old coarctation resoluted in further development of hypertrophy of the muscle fibers with an increase in the mass of the myocardium to 185 % and development of severe diffuse perivascular myocardiofibrosis. Elimination of the coarctation of the aorta of one months standing led (in 4 months) to the reduction of the myocardial mass to its initial level, as well as to the disappearance of the muscle fiber hypertrophy and arrest in the progress of myocardiofibrosis.

LITERATURE CITED

1. A. I. Abrikosov, Special Pathological Anatomy [in Russian], 2, Moscow-Leningrad (1947), p. 205.
2. A. A. Vishnevskii and D. S. Sarkisov (editors). Investigations of the Reversibility of Acute and Chronic Changes in Organs [in Russian], Moscow (1962).
3. S. A. Gadzhiev, Surgical Treatment of Mitral Stenosis [in Russian], Leningrad (1961).
4. A. Kh. Kogan, Byull. éksper. biol., 1, 112 (1961).
5. F. Z. Meerson and G. V. Kobozev, Byull. éksper. biol., 5, 50 (1955).
6. F. Z. Meerson, Compensatory Hyperfunction and Failure of the Heart [in Russian], Moscow (1960).
7. S. E. Popov, Klin. med., 11, 42 (1958).
8. M. G. Pshennikova, In book: Physiology and Pathology of the Circulation. Proceedings of a Conference [in Russian], Moscow (1962), p. 90.
9. A. D. Yanovskii, In book: Problems in the Pathology of the Cardiovascular System [in Russian], Kiev(1959), p. 319.
10. M. Beznak, J. Physiol. (Lond.), Vol. 120 (1953), p. 23.
11. A. Drury and K. J. R. Wightman, Quart. J. exp. Physiol., Vol. 30 (1940), p. 45.
12. A. Drury, Ibid., Vol. 33 (1945), p. 107.
13. W. Kempner, Am. J. Med., Vol. 4 (1948), p. 545.
14. H. Patton, E. Page, and E. Ogden, Surg. Gynec. Obstet., Vol. 76 (1943), p. 493.
15. H. Wipf and H. Brawner, Arch. Path., Vol. 48 (1949), p. 405.