EFFECT OF HYPERTROPHY ON THE CONTRACTILE FUNCTION OF THE HEART

(UDC 616.12-007.61-07:612.171)

F. Z. Meerson and M. G. Pshennikova

Laboratory of Myocardial Physiology and Pathology
(Head, Doctor Med. Sci. F. Z. Meerson), Institute of Normal and Pathological
Physiology (Dir., Active Member AMN SSSR Prof. V. V. Parin)
USSR Academy of Medical Sciences, Moscow
Presented by Active Member AMN SSSR V. V. Parin
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 59, No. 1,
pp. 36-40, January, 1965
Original article submitted October 13, 1963

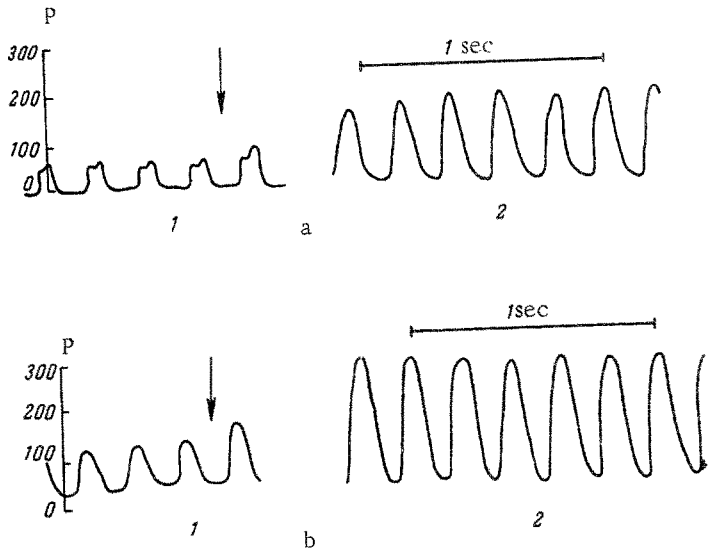
The question of whether the hypertrophied heart is more powerful [1, 9, 15, 24] or functionally defective [2, 16, 19, 21] has been for years and still is a subject of discussion. Several experimental investigations have been undertaken in recent years in an attempt to settle this question. Beznyak [13] and his colleagues and Alexander et al. [10] produced chronic experimental cardiac lesions. Six weeks later, when the animals were already showing marked myocardial hypertrophy, a maximum load was placed on the myocardium by ligation of the aorta or increase of the volume of fluid entering the heart. Progressive loading revealed that the hypertrophied heart could develop a higher systolic pressure in the cavity of the left ventricle and could maintain a larger minute volume than the normal heart.

In the evaluation of these results it must be remembered that they apply to a relatively early stage of hypertrophy with none of the features of the myocardial "wear and tear" complex which has been the subject of very careful study [3, 4, 11, 12, 27], and again, that the results of the investigations mentioned refer to the myocardium as a whole and do not depict the functional capabilities of the muscle tissue composing it. This follows from the fact that the parameters now used in cardiology to define the contractile function of the heart, namely the tension-time index (TTI) of Sarnoff and systolic pressure, actually depict the level of activity in a certain division of the heart and do not provide a means for assessment of the contractile powers of the muscle tissue of the myocardium.

Effect of Hypertrophy on the Contractile Function of the Myocardium

Index	Time of determination in relation to compression of aorta	Control	Hypertrophy of ventricle	P
P_{max} (mm Hg	Before	66±10	94±18.2	> 0.2
	During	247±8.1	295±13.3	< 0.02
ISF (from P_{max} mm Hg/g)	Before	84.9±11	65.3±8.36	> 0.1
	During	324±25	211.68±7.9	< 0.01
TTI (mm Hg × sec)	Before	5.65±0.76	6.54±0.99	< 0.2
	During	22.78±0.48	27.8±2.1	< 0.05
ISF (from TTI) (mm Hg × sec/g)	Before	7.21±0.43	4.54±0.37	< 0.01
	During	30.06±2.18	19.84±1.77	< 0.01
Absolute dry weight of ventricle (g)		0.79	1.40	—

The present authors have used an index to define the contractile power of the muscle tissue which they term intensity of myocardial structure functioning and which is the ratio of the functional activity of the myocardium as a



Pressure in left ventricle before (1) and 3 sec after (2) compression of the aorta in intact rabbits (a) and rabbits with cardiac hypertrophy (b). P) Pressure (mm Hg). Arrow indicates compression of aorta.

whole to its mass. It is the quantity of function performed by unit mass of cardiac muscle. To determine the true intensity of structure functioning (ISF) is a somewhat complicated task but for purposes of progressive or comparative examinations it is permissible to use an ISF index which is the ratio of systolic pressure, TTI or tension, to the mass of the corresponding ventricle. In the experiments of the authors mentioned above the functioning of the left ventricular myocardium as a whole was examined and the authors did not divide their indices of contractile function by the mass of the left ventricle and, therefore, were not in a position to assess the functional intensity of the muscle tissue forming the ventricle or, consequently, the effect of hypertrophy on the functional powers of myocardial tissue.

As the latter was also the purpose of the present investigation, the maximum level at which the hypertrophied left ventricle functioned was determined and the maximum level at which the muscle tissue forming the ventricle could function was then determined by dividing the values obtained by the weight of the myocardium.

METHOD

Stenosis of the commencement of the aorta, which was inevitably followed by considerable hypertrophy of the left ventricular myocardium, was produced in 12 male Chinchilla rabbits by a method which has been described in an earlier publication [4]. After 4.5-5 months, when the weight of the left ventricle in these animals had increased by 75-80%, acute experiments were carried out on equal numbers of surgically treated and control rabbits. Under urethane (1 g/kg) anesthesia, with artificial respiration, the thorax was opened and the left ventricle punctured for recording of the intraventricular pressure by means of a "Barovar" electromanometer and a "Kardiovar" ink-writing apparatus (Alvar). Pressure being recorded continuously, the ascending aorta was closed completely by compression for 10 sec. Ventricular contractions attained their maximum force in the 3rd or 4th second of compression and the intraventricular pressure was then at its maximum. Thereafter, the force of the contractions and the pressure level tended to decline. Two indices, read quite independently of one another, were used for determination of contractile function, namely maximum systolic pressure in the left ventricle (P_{max}) and TTI. These were both determined from the tracing of intraventricular pressure before and during compression of the aorta. The values before compression were the average values for 10 cycles but the values taken during compression were those for the most powerful contraction, i.e., those indicative of the highest level of contractile function attainable by the animal's left ventricle under these conditions. TTI was the product of the mean systolic pressure and the length of systole in that particular cycle. Maximum pressure and TTI were representative of the contractile functioning of the left ventricle as a whole. From these indices the maximum level of muscle tissue functioning was determined by dividing them by the dry weight of the ventricular muscle. The ISF, calculated from the maximum systolic pressure was P_{max} (mm Hg) / dry weight of ventricle (g) and calculated from TTI, TTI (mm Hg × sec) / dry weight of ventricle (g).

The table shows that the left ventricle was greatly hypertrophied (76% heavier than in control animals) in the rabbits with aortic stenosis. Before compression of the aorta, systolic pressure and TTI in the left ventricle were slightly higher and ISF slightly lower in the experimental than in the control animals. This might be taken to mean that the muscle tissue of the necessarily more active and hypertrophied left ventricle was functioning less perfectly than the left ventricle of the control animals. The table shows, however, that these differences were not always statistically significant; the main difference between the functioning of the hypertrophied and the functioning of the intact myocardium was seen after ligation of the aorta.

The contractile functioning of the hypertrophied ventricle then increased more than that of the control non-hypertrophied ventricle. Maximum systolic pressure in the former was 295 mm Hg and the comparative value for the ventricle in the control animals was 247 mm Hg, so that the former was 15.3% higher. TTI values were 22.7 for controls and 27.8 (or 22.5% higher) for the hypertrophied ventricles.

The highest level of contractile functioning attainable in the hypertrophied ventricle was thus greater than the corresponding level for the non-hypertrophied ventricle. This is illustrated by the tracings in the figure.

The position changes when we pass from these indices for the ventricular muscle as a whole to the index of the intensity of muscle tissue functioning. During the period of aortic compression the maximum intensity of muscle function attained was 324 mm Hg (based on maximum pressure) and 30 mm Hg × sec/g tissue (based on TTI) for the normal myocardium and 211 mm Hg and 19.8 mm Hg × sec/g tissue for the hypertrophied myocardium.

This means that the maximum level of muscle function in the hypertrophied ventricle was about one-third lower than the corresponding level for the intact ventricle.

The important fact determined by these experiments is that any considerable degree of hypertrophy of long duration, even if there is complete clinical compensation, significantly reduces the maximum quantity of function that can be performed by unit mass of myocardium.

This can best be understood by reference to general concepts on the relationship between hyperfunction and myocardial hypertrophy.

Compensatory hyperfunction of the heart in valvular disease, hypertension and other affections of the circulatory system precedes myocardial hypertrophy and, consequently, is achieved by increase in the intensity with which its structures function. At this stage of the process this increased intensity engenders more active energy production and protein synthesis in the myocardium, with greatly increased oxygen consumption [7, 17, 18, 26], and, under appropriate conditions, increased inclusion of tagged precursors in proteins and nucleic acids per unit mass of myocardium [6, 5, 8, 22]. This intensified synthesis of nucleic acids and protein resulting from the increased intensity of structure functioning becomes the basis of myocardial hypertrophy.

Myocardial hypertrophy leads in turn to distribution of its increased functioning over an increasing mass of muscle tissue so that the intensity at which the muscle of the myocardium functions tends to fall gradually to or below the normal level. Return of the intensity of functioning to the normal level means an end to more active synthesis and energy production: the inclusion of tagged precursors in proteins and nucleic acids and oxygen consumption per unit mass of myocardium again become normal [5, 8, 14, 20, 23]. Hypertrophy is now more or less an accomplished fact and hyperfunction of the organ as a whole is now achieved by increased mass with normal intensity of functioning.

Later, nucleic acid and protein synthesis in the hypertrophied myocardium undergoes gradual and ultimately profound disturbance in a manner which has been discussed in detail earlier [6]. This interference with the synthetic activity necessary for maintenance of the contractile function of the heart is, in fact, the development of the complex "wear and tear" process in the myocardium, the signs of which are reduction of DNA concentration, reduced intensity of protein synthesis in the myocardium, reduction of the adenosine triphosphatase activity of myofibril myosin, destruction and reduction of the mass of mitochondria with some reduction of ATP and phosphocreatine concentrations, vacuolation and fatty degeneration of a proportion of fibers, gradual atrophy of others and progressive cardiosclerosis [3, 4, 11, 12, 27]. Myocardial "wear and tear" complex would appear to be the most probable cause of the reduced functional capacity of myocardial muscle tissue associated, as shown in these experiments, with prolonged hypertrophy. A point of considerable importance is that the reduction of the maximum functional intensity attainable by the muscle tissue of the myocardium produced by "wear and tear" of the myocardium does not for some time lead to any reduction of the maximum level of contractile function of which the cardiac muscle as a whole is capable. The reason for this is that the increase in the mass of muscle in hypertrophy outweighs the disturbance of the

contractile capabilities of the muscle tissue. In other words, the larger muscle, consisting of less efficient tissue can contract as or even more powerfully than a smaller muscle of normal tissue. It is obvious, however, that as metabolism becomes increasingly disturbed and destructive processes progress, the intensity of functioning of the hypertrophied myocardium will ultimately fall to a level at which the increase in the mass of the myocardium will no longer be able to compensate for the decline in the functioning of the contractile structures. The load imposed on the heart may then prove more than it can deal with and it is at this point that insufficiency of the hypertrophied heart develops.

SUMMARY

A study was made of the effect produced by marked and prolonged hypertrophy of the myocardium on the contractile function of the heart. The authors proceeded from the concept that the myocardial functional level as a whole, and the functional level of the myocardial muscular tissue represent 2 different parameters inasmuch as the muscle of a considerable mass is capable of developing a high function with a comparatively low functional intensity of its structures; whereby the muscle possessing a relatively lesser mass, may develop the same function only at the expense of marked rise of the functional intensity of its structures. Therefore, the indices, characterizing the maximal function of the hypertrophic left ventricle, were related in the mentioned experiments to the mass of the ventricle. A significant and prolonged hypertrophy, caused by experimentally induced cardiac affection, reduced the functional level which could be carried out by a myocardial mass unit in conditions of maximal stress.

LITERATURE CITED

1. Yu. L. Arkusskii, Roentgenological Diagnosis of Diseases of Heart and Vessels [in Russian], Leningrad (1939).
2. N. A. Kevdin, Diagnosis of Cardiac Function and Functional Capacity in Normal and Pathological Conditions of the Circulatory System [in Russian], Smolensk (1928).
3. L. D. Krymskii, Vestn. Akad. Med. Nauk SSSR 12, 80 (1961).
4. F. Z. Meerson, Compensatory Hyperfunction and Cardiac Insufficiency [in Russian], Moscow (1960).
5. F. Z. Meerson and A. V. Pogosova, Vopr. Med. Khim. 6, 621 (1962).
6. F. Z. Meerson, The Connection between the Physiological Function and Genetic Apparatus of the Cell [in Russian], Moscow (1963).
7. F. Z. Meerson, L. I. Evnina, and N. G. Serdyuk et al., In: Physiology and Pathology of the Heart [in Russian], Moscow (1963), p. 142.
8. F. Z. Meerson and A. G. Bazardzhyan, Izv. Akad. Nauk. Armyansk. SSR Biol. Nauki 3, 19 (1963).
9. A. B. Fokht, Pathology of the Heart [in Russian], Moscow (1920).
10. N. Alexander, T. Goldfarb, and D. R. Drury, Circul. Res. 10: 11 (1962).
11. N. R. Alpert and M. S. Gordon, Am. J. Physiol. 202940 (1962).
12. A. Aras et al., Fed. Proc. 20: 1, 355 (1961).
13. M. Beznak, Circul. Res. 6: 207 (1958).
14. R. J. Bing et al., Am. J. Med. 15: 284 (1953).
15. J. Dieckhoff, Arch. Exp. Path. Pharmak. 182: 268 (1936).
16. A. Frank, Z. Ges. Exp. Med. 115: 312 (1950).
17. D. E. Gregg et al., Am. J. Physiol. 139: 726 (1943).
18. D. E. Gregg and R. E. Shipley, Am. J. Physiol. 142: 44 (1944).
19. C. V. Harrison and P. Wood, Brit. Heart J., 11: 205 (1949).
20. H. J. Levine and R. J. Wagman, Am. J. Cardiol. 9: 372 (1962).
21. A. J. Linzbach, Arch. Path. Anat. 314: 534 (1947).
22. T. Norman, Nucleic Acid and Protein Synthesis in Heart Hypertrophy. New York (1962).
23. R. E. Olson and W. B. Schwartz, Medicine (Baltimore) 30: 21 (1951).
24. E. Romberg, Lehrbuch der Krankheiten des Herzens und der Blutgefasse. Stuttgart (1921).
25. S. J. Sarnoff, E. Braumwald, and G. H. Welsh et al., Am. J. Physiol. 192: 148 (1958).
26. M. West, D. Gelb, and C. G. Pidz et al., Am. J. Med. Scie. 241: 350 (1961).
27. A. Wollenberger and W. Schultze, In: Physiology and Pathology of the Heart. Moscow (1963), p. 126.