METHOD OF PRODUCING HEART HYPERTROPHY IN ALBINO RATS BY NARROWING THE AORTA ASCENDENS.*

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(With 1 Figure and 4 Tables in the text.)

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To be able to work out the physiology and sphere of activity of the hypertrophized cardiac muscle we must have methods by which heart hypertrophy can be produced experimentally.

In our previous experiments (Hajdu and Beznák 1943; Beznák and Hajdu 1944) we produced heart hypertrophy by narrowing the aorta with a silver ring of a suitable diameter just below the diaphragm. (This stricture caused 30—50% hypertrophy in 5 days). From about the third day after the narrowing we found transsudation in the pleural cavity and possibly edema of the brain, which were not caused by heart failure. Only part of the deaths occurring were due to heart failure, the majority probably being caused by the mechanical effect of the great quantity of pleural fluid and by edema of the brain. We decided to seek another method, by which we could avoid the effects not caused by the changed haemodynamic conditions which made interpretation of the results more difficult. The new method consisted of narrowing the aorta just as it leaves the heart, before the branching of the great vessels. We hoped thus, by imitating the aortic stenosis more carefully, to avoid the disturbing factors above mentioned.

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METHODS.

We worked on albino male rats, inbred for 4 years in our laboratory, weighing 185 ± 15 gs. The operation was performed in ether anaesthesia. After a median incision and stripping off the chest muscles we cut the sternum vertically at its joint with the IInd rib and, having freed it from the joint with the Ist rib and the clavicle, removed it. After the blunt separation of the deeper muscles and the thymus, the brachiocephalic artery came into sight. We prepared this artery down to the aortic arch. By slightly pulling the brachiocephalic artery we freed the ascending aorta so that we could get under it with a fine pair of crooked forceps. We put a silver ring (which was made previously and opened a little) under the aorta so prepared and closed it by mild pressure. After letting the aorta go we controlled the position of the ring and pushed it a bit down towards the heart. The wound was closed by skin suture. The operation can be performed after some practice without the opening of either pleural cavity; that is, without pneumothorax. Special care should be taken that the cutting of the sternum does not take place below the joint of the IInd rib (pneumothorax). The cutting of the Ist rib and the collar bone should be performed on a 45° inclined operating bank illuminated by a reflector. The rings were made of 0.8 mm wide silver wire. This wire was wound in tight spirals round a small steel cylinder possessing the required diameter. The spiral so prepared was sawed on one side along the axis and fell into as many rings as the wire was wound round the cylinder. We smoothed the edges of the rings and somewhat opened them. We tried rings with different diameters, using 10 animals for each diameter, to find the most suitable size. We found the best width to be 1.45 mm. The experiments here reported were all performed with this size. We made an electrocardiogram of the animals before the operation, just after it, and later once a week. The results thus obtained are published in the following paper. We dissected the animals immediately after their death, or after their being killed. First the atria and auricles of the hearts were cut off, opened, freed from blood and weighed. The right ventricle was cut off from the septum with a pair of fine scissors, dried and freed from blood. Then we cut off the left ventricle from the septum and weighed ventricle and septum separately. The measurements were performed on a torsion balance with an accuracy of ± 1 mg. We made determinations of dry weight and ash content in the right part of the heart (right ventricle, septum and atria) and in the left part (only the wall of the left ventricle.).

EXPERIMENTAL RESULTS.

We narrowed the aortae of 95 rats in the above described way. The mortality curve of 82 rats is shown in Figure 1. Eight fur-

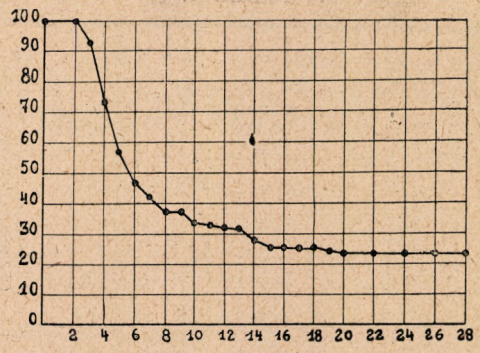

Figure 1. Survival of rats after the narrowing of their aorta ascendens. X-axis: days after the operation. Y-axis: survival of rats in %.

ther rats were killed on the second day and 5 died during the operation (3 from pneumothorax, 2 from bleeding). It is seen from this Figure that the mortality is very high between the 3rd and 7th days. During that time 58% of all the animals die. During the 2nd and 3rd week after the narrowing, mortality becomes increasingly rare, so that during that time only 19% of the animals die. There is no mortality from the 3rd week to the end of our experimental period (28 days). Dissection of the 48 animals which died during the first week after the operation showed haemothorax or haemopericardium in 46, the cause of these being the rupture of the aorta just below the ring. In the animals which died during the 2nd and 3rd weeks we found the following symptoms: dilated heart filled with blood, plethoric, brownish lungs which were darker than normal and from which frothy liquid could be pressed out, a small amount of fluid in the thoracic cavity, swollen liver with well defined structure. These findings showed that the cause of death was cardiac failure. In the 18 rats which survived to the 28th day we found a small edema of the somewhat pigmented lungs and explicit hyertrophy of the heart; that is, findings corresponding to a state of compensated vitium. Very often we observed fusiform aneurysmata of the aortae below the stricture, the size of which varied from that of a coloured pinhead to that of a pea. The death statistics are therefore the following: of the 82 animals about 60% died in consequence of rupture of the aorta, 20% in consequence of decompensation, and 20 remained living in

a compensated state. As was stated, we killed 8 animals on the second day to decide the onset of hypertrophy in relation to time.

The weights of the hearts and their parts are given in Table I.

TABLE I.

Changes in wet weight of certain parts of the heart.

	No.	Weight of whole heart		Change in % compared with normal	Sign. diff.	Weight of left ventr.		Change in % compared with normal	Sign. diff.	Weight of right ventr.		Change in % compared with normal	Sign. diff.	Weight of atria		Change in % compared with normal	Sign. diff.
		mg.	± μ			mg.	± μ			mg.	± μ			mg.	± μ		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Normal	31	631	59	—	—	405	38	—	—	162	27	—	—	64	13	—	—
2 days after narrowing	13	717	106	+ 14	2.8	477	81	+ 18	3.1	160	27	− 1	0.2	80	17	+ 25	3.0
Aortic rupture (first week)	43	721	73	+ 14	5.9	479	87	+ 18	5.0	168	27	+ 4	0.9	74	16	+ 16	3.0
28 days after narrowing	18	812	161	+ 29	4.6	547	116	+ 35	5.0	172	36	+ 6	1.0	92	20	+ 44	5.4
Decompensation	16	83›	161	+ 32	4.9	530	99	+ 31	4.9	203	49	+ 25	3.1	102	31	+ 59	4.6

We divided the weight of the septum in proportion to the weight of the two ventricles and added that weight to the one measured. In this way we got the weights of the right and left ventricles. These weights are given in the Table. It is seen from columns 2 and 4 of this Table that the hearts show a hypertrophy of 14% on the 2nd day after the narrowing. This hypertrophy hardly increases till the end of the first week but is almost doubled by the end of the experimental period (28 days). Columns 6—17 show that the left ventricles and the atria are hypertrophized. Their hypertrophy, like that of the whole heart, hardly changes from the 2nd to the 7th day and is doubled by the 28th day. It is seen in columns 2—7 that the right ventricle does not take part in these changes.

Table II. shows what part the different portions of the heart play in the hypertrophy found at different times. It is seen that the left ventricles make up about 20% of the whole hypertrophy, and 20% is produced by the atria.

We discuss separately the findings of those animals where the cause of death was decompensation. These results are shown in the last line of Tables I. and II. In these animals the hypertrophy was

TABLE II.

The distribution of hypertrophy in %.			
	Left ventricle	Right ventricle	Atria
2 days after narrowing	81.4	0.0	18.6
7 days after narrowing	82.2	6.7	11.1
28 days after narrowing	78.9	5.5	15.6
Decompensation	61.3	20.1	18.6

rather great: 32%. It is seen that here not only the left ventricles (Table I. columns 6—9) and the atria (columns 14—17), but also the right ventricles show hypertrophy (columns 10—13). Of the 32% hypertrophy 60% is produced by the left ventricles, and 20—20% by the right ventricles and the atria. (Last line of Table II.)

The results in dry weight are shown in Table III. In this and the following Table "left side" means only the wall of the left

TABLE III.

Dry matter content in %.							
	1. No.	2. Left %	3. side ±	4. Signif. diff.	5. Right %	6. side ±	7. Signif. diff.
Normal	18	22.0	1.35		22.2	1.49	
2 days after narrowing	8	20.8	1.10	2.3	18.5	2.20	4.2
„Narrowed group"	28	21.9	0.75	0.3	20.8	1.20	3.1
Decompensation	7	21.8	1.14	0.4	21.1	1.88	1.3

ventricle as cut off from the septum, and "right side" means the wall of the right ventricle + the septum + the atria. The "narrowed group" contains all the animals which did not decompensate. We took as a separate group only those that we killed on the 2nd day after narrowing. It is seen from this Table that on the left side there is no appreciable difference in the content in dry material; that means that wet and dry materials take part in the resulting hypertrophy to about the same extent. The gain in wet weight somewhat over-rides that of dry matter on the 2nd day. (Table III. 2nd line, columns 2 and 4.) In spite of there being no change in the weight of the right side (right ventricle+septum+atria) on the 2nd day, there is a significant decrease in dry matter. (Table III, line 2, columns 5—7). Later on, when the weight of the right side increased (as we measured the hypertrophic septum and atria with the right side), the decrease in dry matter is less. In decompensated animals the right ventricle also hypertrophizes

(Table I, columns 12 and 13, last line) and then there is no change in dry matter. (Table III., columns 5—7, last line).

Table IV. shows the ash content in pro mille. It is seen that the ash content increases only on the 2nd day of the narrowing; later on it returns to normal. (Table IV, columns 4 and 7).

TABLE IV.

	Ash content in pro mille.						
	1. No.	2. Left %	3. side ±	4. Signif. diff.	5. Right %	6. side ∓	7. Signif. diff.
„Narrowed group"	18	10.6	0.80	—	10.0	1.40	—
2 days after narrowing	8	11.3	0.60	2.2	10.2	0.90	0.3
Normal	28	10.7	0.94	0.4	9.5	1.00	1.3
Decompensation	7	10.8	0.51	0.8	10.3	1.10	0.5

DISCUSSION.

In these experiments, we tried to work out a method by which we could imitate conditions of human aortic stenosis. The difference between our method and pathological conditions is only that in our case the coronary arteries originate below the stricture; that is, between the stricture and the heart; whereas in pathological conditions they originate after the stricture. With this method we could avoid those disturbing influences seen after the narrowing of the abdominal aorta (edema of the brain, great transsudation in the pleural cavity), and the deaths of those animals that were not killed by rupture of the aorta we knew to be due to heart failure. Our method is therefore well suited for producing heart hypertrophy in rats and for investigating the physiology of compensated and decompensated hearts.

Experimental aortic stenosis, just as that seen in pathological conditions, imposes work chiefly on the left ventricle. Thus the left ventricle shows a hypertrophy from the 2nd day on, so that it is responsible for 80% of the hypertrophy. The wet weight of the right ventricle, which at this stage does not perform plus work, does not change. The atria hypertrophize like the ventricles from the 2nd day on (15—20% of the hypertrophy). Under the influence of long-lasting stricture the hypertrophy may reach a very high value (44% of its original weight). In the animals that died in consequence of decompensation and where the circulation in the lungs was also hampered, there

was a marked hypertrophy of the right ventricle. In these cases the hypertrophy of the atria was even more marked (They increased by 60% of their original weight).

The dry weight in percentage and the ash content pro mille of the left ventricle do not change appreciably during the whole of its hypertrophy. The increase in fluid is a bit more than that of dry matter in the hypertrophy produced at the end of the 2nd day. (Table III., column 4. Sign. Diff.: 2.3). The right ventricle behaves somewhat differently. Though its weight does not change there is a significant diminution of dry elements. As at the same time the ash content $^0/_{00}$ is unchanged, the only possible explanation is that the right ventricle lost organic materials which were replaced by some fluid having the same ash-content as the heart. The greater the wet weight of the right ventricle becomes, the smaller the loss in organic compounds. In the case of decompensation where the right ventricle also hypertrophizes, this loss is altogether absent: in that case the dry matter in % has the same value as in normal hearts.

As was mentioned, in the beginning hypertrophies (2nd day) when the hypertrophy is caused by retention of water, the inorganic materials of the heart increase; this increase is only temporary, for in the later, real, phase of the hypertrophy it is again absent. This observation is in good agreement with that of Hitchings and Wearn (1941), who found that the electrolyte content of rabbits' hearts increases in the 3 first days of the hypertrophy but regains its normal level by the 6th day.

SUMMARY

1.) We publish a new method by which we can produce hypertrophy of the heart by artificial narrowing of the ascending aorta.

2.) 60% of the animals treated in that way (95 cases altogether) die within the first week in aortic rupture; 20% die in the course of the 2nd week in circulatory decompensation; 20% live on in a compensated state.

3.) Out of the total hypertrophy thus developed, 80% is that of the left ventricle, 20% that of the atria. The right ventricle hypertrophizes only in decompensation.

4.) The dry weight (in %) and the ash content (pro $]_0{}'^0$ increases during the first days of the hypertrophy; later on they both regain the normal level.

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