Cardiac Output in Rats During the Development of Cardiac Hypertrophy

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Cardiac output, reserve force of the heart, total peripheral resistance and weights of the heart and other organs were determined in normal rats, and in rats at different times after their aortas were narrowed just below the diaphragm. Although the output of the hypertrophied heart was normal, its reserve force was greater.

AORTIC constriction causes an increase in heart weight and blood pressure in intact, but not in hypophysectomized rats. The cause of this lack of cardiac hypertrophy after hypophysectomy is unknown. Before some insight can be gained into the changes occurring after hypophysectomy, it seemed important to elucidate as many as possible of the hemodynamic events which precede and accompany cardiac hypertrophy in normal rats. The changes in heart weight and blood pressure that occur at different times after aortic constriction have already been described. In the present series of experiments we determined the cardiac output in normal rats and in rats whose aortas had been constricted for varying periods. We also made an attempt to assess the reserve force of the heart by determining the extent to which cardiac output could be raised by increasing inflow into the heart.

METHODS

Male albino rats, Wistar strain, weighing 180 to 240 Gm., were used under pentobarbital anesthesia. Cardiac output was determined by means of the direct Fick principle. A catheter of no. 100 polyethylene tubing (Clarke Adams Co.) was introduced through the right external jugular vein into the right heart. The position of the catheter was verified at autopsy. In the majority of cases its tip was found in the right atrium, in a few cases in the right ventricle. Venous samples were withdrawn through this catheter, arterial samples through a catheter in the right femoral artery. Oxygen content of these samples was determined by the micromethod of Roughton and Scholander.

Blood pressure was recorded in the left carotid and left femoral arteries with Hathaway pressure gages connected with shortened needles inserted directly into the vessels. A T-cannula was introduced into the trachea. One side of this was connected to a small Benedict-Roth apparatus, constructed for rats. From this the rats inspired pure oxygen and expired back through a carbon dioxide absorber. The other side of the T-cannula was connected to a Hathaway gage for recording respiration.

The rats were heparinized and after the introduction of the catheter blood samples were withdrawn for oxygen analysis. The catheter in the right heart was then connected to a Palmer slow infusion pump. This was so adjusted that it delivered 7.5 ml. of 3.5 per cent polyvinylpyrrolidone (PVP) in 5 min. (one infusion unit). Following each infusion unit, blood samples were taken. Up to 8 units could be infused into normal rats before heart or respiration failed. Most of the infused fluid was found as free fluid in the abdominal cavity, in the lumen of the intestines and the bladder. All organs (liver, spleen, kidney, heart, brain, lungs, skin, fat) contained more fluid than those of normal rats.

Evans blue dye was given intravenously at the beginning of the experiment and the initial blood volume was determined. Blood volume could not be followed continuously because of the great loss of fluid and dye from the circulatory system throughout the course of the experiment. Some idea of the blood volume at the end of the experiment was arrived at in the following way. A sample of blood was taken, a second dose of Evans blue was injected, and another sample was taken after 1 to 2 min. The absorption maximum was determined at 615 μ in a Beckman spectrophotometer. From the absorption of the second sample that of the first sample was subtracted.

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and the blood volume was calculated from the standard curve. From these determinations it seemed that about twice the initial blood volume, about 30 ml., was contained in the circulatory system, and all excess fluid above this had left it. In an attempt to decrease fluid outflow, a 5-times more concentrated PVP solution was used in a few experiments but this did not alter the results significantly.

Constriction of the aorta was carried out under ether anesthesia, as described elsewhere. It involved application of a silver ring, 0.8 mm. in diameter, just below the diaphragm. The above determinations were performed at various selected intervals after aortic constriction.

After the experiment the amount of free fluid in abdominal and thoracic cavities was measured, and the wet and dry weights of the heart and different organs were determined.

RESULTS

Figure 1 shows the mean values of the results obtained from groups of 6 to 10 rats examined at the following intervals after aortic occlusion: 1 to 2 hours, 1 to 2 days, 6 to 8 days and 21 days.

The cardiac hypertrophy which developed in this series was due entirely to the hypertrophy of the left ventricle, which was enlarged by 45 per cent of its original weight in 3 weeks.

The blood pressure rose as the hypertrophy developed and reached a definitely hypertensive level, not only above the stricture but also below it.

Tachycardia was present one day after the constriction, as in our earlier experiments. Heart rate returned to normal within the first week. Three weeks after constriction, however, it was again increased.

Cardiac output dropped sharply 1 to 2 hours after narrowing and then gradually returned to normal, but it did not exceed this even 3 weeks after constriction though the left ventricle had hypertrophied by 45 per cent. Cardiac output of our normal rats averaged 48 ± 4 ml./min. This value checks reasonably well with that of 46.5 ± 2.2 ml./min. given by Blood, Smith and D'Amour for their "University of Denver strain" rats.

The maximum to which the output could be raised (reserve force of the heart) showed roughly similar changes. By increasing inflow into the heart, the output of 48 ml./min. of normal rats could be raised to 131 ± 13 ml./min. One to two hours after constriction, however, the maximum output reached was only 83 ± 10 ml./min. Three weeks later, though the resting output was not above normal, it could be raised to 178 ± 11 ml./min., instead of the normal 131 ml./min.

The total peripheral resistance rose from its normal level of 210,000 dynes/sec./cm. to 320,000 immediately after constriction, probably for mechanical reasons. It then gradually fell to 265,000 and later rose again to 310,000.

The systemic arteriovenous oxygen difference increased from the normal 10.6 ml./100 ml. blood to 13.5 ml. immediately after constriction of the aorta. Since there was only a slight drop in oxygen consumption, the tissues evidently compensated for the diminished cardiac output by removing more oxy-
gen from the blood. The arteriovenous oxygen difference was still above normal a day later, but as cardiac output again reached normal levels, it also returned to normal.

Figure 2 shows the hemodynamic changes that took place at these characteristic time intervals when the heart was loaded by an increased fluid return. The figure shows the changes in blood pressure, cardiac output, total peripheral resistance and heart rate after each infusion unit. The broken lines show the changes observed in normal rats and the solid lines show the influence of aortic narrowing on these changes.

In normal rats, infusion of the first unit of 7.5 ml. in 5 min. caused a rise in cardiac output. This was associated with a rise in systolic blood pressure, with no change in the diastolic. Total peripheral resistance fell sharply to less than half its original value after the first infusion period.

With the next 2 infusion units, cardiac output rose further and then remained at a sustained high level for the next 2 to 3 infusions. At the same time peripheral resistance fell to a sustained low level. Blood pressure (both systolic and diastolic) declined slowly with repeated infusions. The heart rate decreased from the beginning, leading to greatly increased stroke volumes until a terminal decline in cardiac output set in with relatively little change in heart rate.

One to two hours after narrowing, the cardiac output was less (31 ± 5 ml./min.) than in normal rats. In spite of the lower output the blood pressure behaved much as it did in normal rats, doubtless because of the increased peripheral resistance. The fall in heart rate on infusion was very sharp and sudden, even while the output remained relatively high, so that the stroke volume was increased throughout infusion. None of the
rats of this group survived more than 4 infusion units.

One to two days after narrowing, the blood pressure was already increased in the carotid (above the stricture) and its changes at this higher level paralleled those seen in normal rats after infusion. Cardiac output was still below normal and peripheral resistance was increased. The heart rate was increased at this time, but it began to fall on infusion to a level comparable with the heart rates of normal rats.

Seven days after narrowing there was a considerable hypertension above the stricture and a nearly normal pressure below it. As was shown in figure 1, a considerable heart (left ventricular) hypertrophy was present at this time. Cardiac output (41 ± 3 ml./min.) was near the normal level and so were its responses to infusion. The already high blood pressure had risen further and it fell to a normotensive level only after 4 to 5 infusion units. The higher blood pressure—though cardiac output was practically the same as in normal rats—corresponds with the slightly higher total peripheral resistance during the first infusion. Heart rate changes were not significantly different from those of normal rats.

Three weeks after narrowing the hypertension was very considerable and there was a left ventricular hypertrophy of 45 per cent. Since cardiac output (50 ± 5 ml./min.) was practically the same as in normal rats, this high blood pressure was due to the much higher peripheral resistance. Cardiac output increased more after infusion than in normal rats and it only fell back to normal values after several infusions, together with the blood pressure. Apart from the initially higher heart rate, these changes were similar to those in normal rats, leading at one time, when cardiac output was very high, to very greatly increased systolic outputs.

**DISCUSSION**

A decrease in cardiac output was observed by Alexander, Hinshaw and Drury\(^1\) one to three days after severe aortic constriction in rabbits. Authors suggest that aortic constriction increases the vascular bed distal to the stricture which is only gradually compensated by expansion of total plasma volume. In accordance with the above findings, cardiac output decreased in our rats, immediately after aortic constriction and only gradually returned to the normal value. We could, however, not ascertain an increased plasma volume at any time after constriction. The reason for this may be that we compared averages of groups of rats, whereas Alexander et al. compared postoperative and preoperative values in the same animal.

The actual stimulus for the observed cardiac hypertrophy was not revealed by our experiments. The heart muscle was stretched, its output and reserve force were diminished and the arteriovenous oxygen difference was increased. All of these, together with other parameters not yet investigated or identified, may be responsible for the onset of hypertrophy. The experiments, however, clearly show that one week after aortic constriction the hypertrophied heart maintains a near-normal hemodynamic situation.

There seems to be no apparent reason for any further change. Yet further changes occurred. Three weeks after constriction the heart was still further enlarged, with normal resting output and increased reserve force. A great hypertension had developed, which affected the blood pressure above and below the constriction.

The cause for the hypertension and further cardiac enlargement is probably the rise in peripheral resistance. Since no further change occurred in the silver ring around the aorta, it must be supposed that a general constriction of the peripheral vessels took place. That this is indeed the case is borne out by the fact that carotid and femoral pressures rise together. The greatly increased left ventricle maintains a normal output against this great peripheral resistance, which leads to a blood pressure around 250/170 mm. Hg. The hypertrophied ventricle is a strong ventricle: not only can it maintain a normal output, but its reserve force is also increased.
It seems probable that the mechanism which offsets the equilibrium attained about a week after constriction is of renal origin. It is known that the fall in pressure, particularly pulse pressure, can initiate such a mechanism.8-11 In our experiments a great reduction in femoral pulse pressure took place after aortic constriction, in accordance with the results of Sealy,12 Gupta and Wiggers13 and Alexander.14

The maximum to which cardiac output can be raised by infusion is used in this paper as a measure of the "reserve force" of the heart. While such a procedure gives information about myocardial functioning ability, it must be borne in mind that cardiac output is also influenced by changes in peripheral circulation. That such changes occur after occlusion of the aorta was shown by Barcroft15 and similar changes are indicated by the behavior of total peripheral resistance in our experiments.

Infusion of PVP caused a transitory rise in blood pressure and cardiac output, a fall in total peripheral resistance and a slowing of the heart. The great fall in total peripheral resistance remains unexplained, but was also observed by Gowdey and Young18 in dogs following large infusions of dextran.

The gradual slowing of the heart observed in all groups as PVP is infused can be explained by two mechanisms. It may be due partly to the action of the pressoreceptors stimulated by the rise in pressure following infusion, and partly to the large amounts of PVP infused at room temperature. Though the temperature of the rats was not measured, it seems reasonable to expect a reduction which can slow the heart. Mainwood17 showed that the effect of the two mechanisms is more than additive, i.e., cold causes vagal facilitation. This may be the reason for the particularly sharp fall in heart rate 1 to 2 hours after aortic constriction. As was shown earlier4 the pressoreceptors are active at this time and their effect would then be further facilitated by the infusion of cold PVP.

These experiments furnish clear experimental proof that the cardiac hypertrophy which develops after aortic constriction leads to a heart which is not only enlarged but which is also stronger than it was before hypertrophy set in. It has to be borne in mind that this cardiac hypertrophy resembles most closely a "training" hypertrophy, taking place in normal, undamaged heart muscle. It would thus correspond to a pure "tonogen" hypertrophy in the terminology of Moritz.18

SUMMARY

Cardiac output in normal rats was 48 ± 4 ml/min. and could be raised to 131 ± 10 ml. by infusion of 3.5 per cent polyvinylpyrrolidone. Immediately after aortic narrowing, cardiac output fell to 31 ± 5 ml. and the reserve force was also diminished (83 ± 10 ml). At this time total peripheral resistance was 320,000 dynes/sec./cm.5 instead of the normal 210,000. One week later the heart became enlarged and its output and reserve force were back to normal. Three weeks after aortic narrowing, aortic hypertension extended above and below the constricted area, and calculated resistance was increased; although the output of the heart was normal, its reserve force was greater.

SUMMARIO IN INTERLINGUA

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