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Role of Adrenergic Mechanisms in the Development of Cardiac Hypertrophy[1] (39127)

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(Introduced by I. H. Chaudry)

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Several hypotheses have been proposed to explain the cardiac hypertrophy that develops on increasing the afterload (14). Meerson has suggested that the genetic apparatus is activated by an early increase in myocardial O_2 consumption and the ATP depletion due to the increased cardiac work demands (11). The validity of the hypothesis has not been tested by other workers.

The role of catecholamines in the development of hypertrophy is also unclear (3). Hypertrophy occurs in rats given 6-hydroxydopamine to deplete cardiac sympathetic nerve endings (3). However, a definitive statement regarding the role of catecholamines could not be made since 6-hydroxydopamine did not deplete all the nerve endings and the adrenal medullae (3). In the present study, we have attempted to validate the Meerson hypothesis, and secondly, to determine the possible role of catecholamines in the development of cardiac hypertrophy following an increase in the afterload.

Methods. Adult Sprague–Dawley (Holtzman) rats of both sexes weighing between 210 and 280 g (mean weight 252 ± 5 g) were anesthetized with ether. Following a midline abdominal incision, a 0.5-cm segment of the suprarenal abdominal aorta was isolated. A uniform degree of constriction around the aorta was produced by tying 3-0 surgical silk around the blunt end of a curved needle having an external diameter of 0.5 mm. The needle was carefully withdrawn from the ligature so that diameter of the constriction approximated that of the needle. The abdomen was closed and the animals were allowed food and water *ad libitum*. A total of 36 rats were sacrificed 1, 2, 3, 4, 5, and 6 days following the banding procedure. Twenty sham-operated control rats of the same weight and strain served as controls for the 6 days. In the control group of rats, the posterior wall of the peritoneum was incised, the aorta was isolated but not constricted. The postoperative care of these animals was similar to that of the rats that were banded.

Another group of 36 rats were banded in a similar manner, and as in the earlier group, six rats were sacrificed 1, 2, 3, 4, 5, and 6 days following the banding. However, these rats were given ip injections of 2.0 mg/kg body weight of practolol (Ayerst Labs.) dissolved in 1 ml of normal saline, at the time of the banding and every 12 hr after the banding until the sacrifice. There was no observable loss of the drug through the abdominal incision. A group of 20 sham-operated rats subjected to a similar stress and given similar injections of practolol for 6 days served as the control group. Preliminary experiments in normal rats established that the cardio-selective adrennergic blocking action of 2 mg/kg of practolol injected ip could be maintained for the 12-hr period.

Simultaneous pressure measurements were taken in the carotid and femoral arteries in banded rats to determine the pressure gradient across the band at the time of the sacrifice. In the sham-operated rats, only the carotid artery pressures were recorded. Pressures were obtained using the Hewlett–Packard 7700 recorder and Hewlett–Packard 1830 C transducers.

Following sacrifice, the hearts were excised and the atria, valves, and epicardial fat were removed from the ventricles. The

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TABLE I. EFFECTS OF PRACTOLOL ON THE SYSTOLIC (S), DIASTOLIC (D), MEAN (M) ARTERIAL PRESSURES, AND HEART RATE (HR) IN THE RAT[a]

	Resting			Isoproterenol		
	S/D	M	HR	S/D	M	HR
Control	115/110	110	440	90/85	88	560
Practolol (2 mg/kg)						
0.25 hr	113/110	111	320	90/87	88	340
4 hr	108/100	104	310	60/50	54	340
12 hr	95/78	85	325	65/55	61	345

[a] Values are in mm Hg and beats per min, during a 12-hr period. The effectiveness of the cardioselective beta-adrenergic blockade was tested with injections of isoproterenol at various times.

free wall of the right ventricle was dissected in the form of a curved triangle at its insertion into the ventricular septum. The remaining cone-shaped portion of the heart included the ventricular septum and the free wall of the right ventricle, and this portion was weighed separately from the free wall of the right ventricle. The weights of the two cardiac samples were normalized per gram body weight at the time of sacrifice. The lung and liver weights were also determined at the time of sacrifice. Each organ was gently blotted on filter paper before being weighed on the H51 Mettler balance.

The mean control values of the ventricle, lung, and liver weights and pressures obtained in the sham-operated controls were compared with mean values obtained on the 6 days following the banding using Student's t test. The comparisons were carried out in the untreated rats, as well as in the rats given practolol.

Results. Table I shows the cardiac beta-adrenergic blocking effects of ip injection of 2 mg/kg practolol in an anesthetized rat during a 12-hr period. Isoproterenol (0.2 μg/min/kg) given in the control period resulted in decrease in the arterial pressures and in tachycardia. Isoproterenol given 0.25, 4, and 12 hr after practolol injection resulted in marked hypotension, but a marked tachycardia was not observed (Table I).

Figure 1 shows the development of left

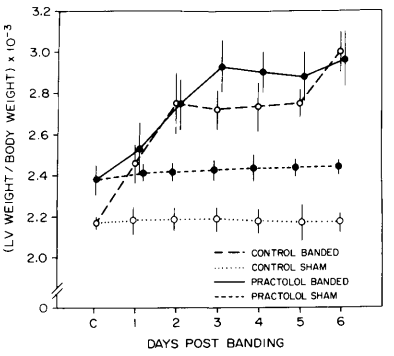

FIG. 1. Increase in left ventricular wt-body wt ratio in untreated banded rats and banded rats given practolol. C represents values obtained in sham-operated rats. Mean values are shown with ± 1 SEM.

ventricular hypertrophy following the banding of the suprarenal abdominal aorta in the untreated rats and rats given practolol. The control value for left ventricular wt–body wt ratio in the untreated group of $(2.18 \pm 0.043) \times 10^{-3}$ was lower than the control value $(2.34 \pm 0.12) \times 10^{-3}$ in the rats given practolol (Fig. 1). This may reflect the slightly higher arterial pressures observed in the rats given practolol. In the untreated group, the significant increase ($P < 0.05$) in the left ventricular wt–body wt ratio was evident 1 day postbanding (Fig. 1). In the rats given practolol, significant ($P < 0.05$) increases in left ventricular weights occurred on 2 days postbanding (Fig. 1). In both cases, maximal increases in left ventricular weights were attained 2 days after the bandings since the left ventricular wt–body wt ratios on the second day were not significantly different from the values on the sixth day (Fig. 1). The left ventricular–body weight ratios did not change during the 6 days in the sham-operated untreated rats and sham-operated rats given practolol (Fig. 1).

Figure 2 indicates the significant ($P < 0.05$) increases in the right ventricular free wall–body weight ratio following the banding of the suprarenal aorta in the untreated rats and rats given practolol. Maximal increases in right ventricular free wall also occurred 2 days postbanding. The increases in the two groups were not significantly different from each other (Fig. 2). The right

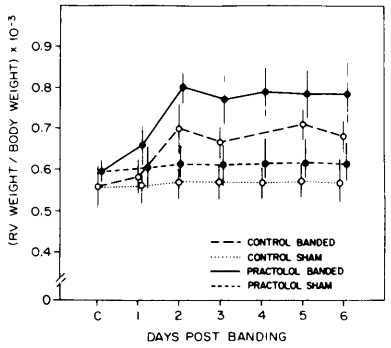

FIG. 2. Increase in right ventricular free wall wt–body wt ratio in untreated banded rats and rats given practolol.

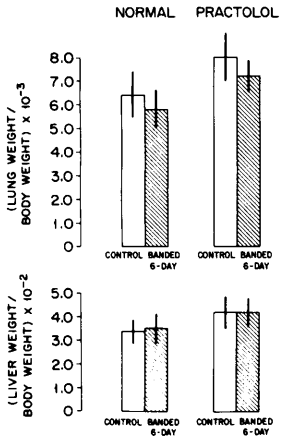

FIG. 3. Lung wt–body wt ratio and liver wt–body wt ratio in untreated rats and banded rats given practolol. Mean values ± 1 SEM of the sham-operated control are shown with values for the 6-day banded rats.

ventricular weights did not change during the 6 days in the sham-operated untreated rats and sham-operated rats given practolol.

Figure 3 shows that the wet lung wt– and liver wt–body wt ratios are not significantly altered on the sixth day postbanding in untreated rats and in rats given practolol. However, the lung and liver weights were slightly higher in the rats given practolol, reflecting the higher arterial pressures in these animals (Fig. 3); nevertheless, the weight values were in the normal range. Practolol did not predispose the banded rats to any higher incidence of mortality than the untreated banded rats.

Table II indicates the changes in the arterial pressures and heart rate in the untreated rats and rats given practolol. The values are shown for control rats, and for rats banded 1 and 6 days. In the control rats given practolol, the heart rate was significantly reduced ($P < 0.05$), while pressures, although higher in the rats given practolol, were not statistically different. On first day after the banding, the heart rates in both groups were not different from the control rats. The systolic pressures in the carotid artery were elevated ($P < 0.05$) in both groups, while the diastolic and mean pressures were not significantly different from the untreated rats (Table II). The pressures in the femoral artery distal to the band were damped in both cases (Table II). On Day 1, the systolic arterial pressure gradient across the band averaged 70 ± 5 mm Hg in the untreated banded rats, and 73 ± 5 mm Hg in the rats given practolol. On the sixth day after banding, the heart rates in the two groups were not significantly different from the control values (Table II). However, the carotid and femoral arterial pressures increased ($P < 0.05$) in the untreated banded rats and in the banded rats given practolol (Table II). The peak systolic arterial pressure gradient across the band of 73 ± 4 mm Hg in untreated rats and of 79 ± 6 mm Hg in the rats given practolol in the 6-day banded rats were not different from gradients of 70 ± 5 mm Hg and 73 ± 5 mm Hg in the 1-day banded rats.

Discussion. The heart responds to increased cardiac work by increasing its mass (14). Little is known about the mechanisms initiating the increase in protein synthesis. Meerson (9, 10, 11) has suggested that the increase in cardiac work leads to increase in the myocardial O_2 consumption and decrease in the high-energy phosphate stores which stimulate increase in protein synthesis. In support of this hypothesis, Meerson (11) has indicated that the common link in cardiac hypertrophy resulting from cold, increased cardiac work secondary to aortic stenosis, decreased coronary flow, and isoproterenol is the initial decrease in high-energy phosphate stores. Cardiac hypertrophy secondary to banding the aorta did not occur in rats in which ATP production had been increased by prior exposure

TABLE II. ARTERIAL PRESSURES AND HEART RATE IN NORMAL RATS AND RATS GIVEN PRACTOLOL[a]

	Normal			Practolol		
	S/D (mm Hg)	M (mm Hg)	HR (beats/min)	S/D (mm Hg)	M (mm Hg)	HR (beats/min)
Control	134 ± 5[b]/114 ± 6	120 ± 7	443 ± 12	146 ± 7/120 ± 4	128 ± 8	310 ± 9
1 day						
Proximal	145 ± 5/110 ± 3	122 ± 4	420 ± 11	155 ± 5/112 ± 4	127 ± 5	332 ± 7
Distal	75 ± 3/72 ± 4	73 ± 2		82 ± 2/79 ± 4	80 ± 2	
6 days						
Proximal	178 ± 5/135 ± 7	148 ± 7	410 ± 14	180 ± 5/148 ± 6	157 ± 3	312 ± 8
Distal	105 ± 3/100 ± 2	103 ± 2		101 ± 3/88 ± 4	90 ± 4	

[a] Control values and 1 and 6 days postbanding are indicated for both groups. In the banded rats pressures were recorded proximal to the band (carotid artery) and distal to the band (femoral artery).
[b] Values are ± 1 SEM.

to hypoxia (17). In addition, rats exercised over long periods developed cardiac hypertrophy but not hypertrophy of the gastrocnemius muscle (12). The gastrocnemius mitochondria had an increased ability to generate ATP while cardiac mitochondrial function was not altered (12). These findings suggested that increased ATP production by the gastrocnemius prevented its hypertrophy. The reasons why ATP production did not increase similarly in the myocardium have not been explained. Other studies on isolated perfused hearts have shown that diminution of high-energy stores inhibit rather than stimulate protein synthesis (2, 5). In addition, in several studies the decreases in high-energy phosphate contents during moderate to severe overload have been small or nonexistent (4, 13, 15).

In the present study, we have attempted to validate the Meerson hypothesis that increase in cardiac work secondary to increase in afterload, and the resulting increase in myocardial O_2 consumption lead to the development of cardiac hypertrophy. We have used the cardio-selective beta-antagonist practolol, which reduces the myocardial O_2 consumption by its negative inotropic and chronotropic effects (6, 8). Myocardial O_2 consumption is reduced because heart rate and contractility are major determinants of myocardial O_2 utilization (1). Practolol administered to banded rats did not alter the rate of development of cardiac hypertrophy. Left and right ventricular hypertrophy occurred in a fashion similar to the control rats exposed to a similar increase in afterload. The results in both groups were obtained from hearts without cardiac failure as evidenced by lung wt–body wt and liver wt–body wt ratios in the normal range. The results also indicate that the arterial pressures in both groups increased significantly 6 days after the banding while the pressure gradient across the band was not altered. The pressure changes may be related to the development of hypertrophy. Therefore, hypertrophy may be a compensatory mechanism that enables the heart to generate increased pressure to overcome the effects of increased resistance. These observations are not consistent with the Meerson hypothesis. By using a selective cardiac beta-adrenergic blocking agent that reduces cardiac O_2 consumption by reducing contractility and heart rate, we observed that hypertrophy occurs in a manner similar to control banded rats.

In addition, these studies indicate that cardiac sympathetic mechanisms also are not involved in the development of cardiac hypertrophy. Cohen (3) observed that 6-hydroxydopamine used to induce depletion of

cardiac sympathetic nerve endings did not alter the increase in cardiac weight due to arterial hypertension. However, a definitive statement regarding the role of cardiac sympathetics could not be made since 6-hydroxydopamine does not result in depletion of all the nerve endings and the adrenal medulla (7). In the present study in which the level of blockade was sufficient to block the effects of injected isoproterenol, the results confirm Cohen's conclusion that sympathetic mechanisms are not involved in the development of hypertrophy.

The present studies do not indicate a mechanism for the development of hypertrophy. However, the finding that hypertrophy also occurred in the free wall of the right ventricle in rats in which the suprarenal aorta was banded and in which there was no evidence of pulmonary edema, suggests that humoral mechamisms may be involved. Recent observations suggest that the renin–angiotensin system may play a permissive role in the development of hypertrophy in spontaneously hypertensive rats (16). Although the renin and angiotensin levels were not measured, they may be elevated since the band was placed proximal to the renal arteries, and hence, the renal perfusion pressure was reduced. However, a conclusion regarding the role of renin cannot be drawn since renin release can be inhibited by beta-adrenergic blocking agent propranolol (16) and may have been reduced by practolol, suggesting that renin–angiotensin mechanisms are not involved. Therefore, studies of humoral factors are necessary for the elucidation of mechanisms involved in development of cardiac hypertrophy.

Summary. This experiment was designed to study the role of cardiac beta-adrenergic mechanisms in the development of hypertrophy in rats. The suprarenal abdominal aorta was banded, resulting in an increase in cardiac wt–body wt ratio. A group of rats received a sham operation. Half of the banded rats were treated with practolol, 2.0 mg/kg intraperitoneally every 12 hr for the 6 days after banding. The effectiveness of cardiac beta-adrenergic blockade was confirmed by absence of an increase in heart rate following intravenous isoproterenol at various times between practolol injections. Practolol did not affect the gradient in the banded groups. Six animals in each banded group were sacrificed daily for 6 days. The right and left ventricles were dissected separately and weighed. RV–body weight ratios increased similarly in both banded groups. LV–body weight ratio (g/kg) was 2.17 ± 0.043 in sham rats, and it attained maximal levels of 3.03 ± 0.10 within 6 days in banded untreated rats and 2.96 ± 0.14 in banded rats receiving practolol. Therefore, beta-adrenergic mechanisms were not involved in the development of hypertrophy due to increased afterload. Also, these findings are not consistent with the Meerson hypothesis, since hypertrophy occurred despite the reduction in myocardial O_2 consumption due to practolol.

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