Hypertension and Increased Hindlimb Vascular Reactivity in Experimental Coarctation of the Aorta

By Juan Nolla-Panades, M.B.

The cause of hypertension in human coarctation of the aorta is not well understood. The proponents of a mechanical hypothesis suggest that the increase in blood pressure is due to the resistance offered by the coarctation and the collateral circulation, whereas those favoring a humoral explanation postulate the existence of a generalized increase in peripheral resistance such as occurs in renal hypertension. Evidence for the increase in peripheral resistance is the finding, in some instances, of an elevated diastolic pressure below as well as above the aortic stricture.

Experimental coarctation of the aorta has raised a similar problem. The results of Barcroft, Brotchner, and Gupta and Wiggers are in agreement with a purely mechanical origin of the hypertension. However, these workers used acute experiments, and there is evidence suggesting that in more prolonged studies the situation is different. Goldblatt et al. postulated a renal origin for the hypertension. Other authors have arrived at a similar conclusion.

McQueen has shown an increased vascular reactivity in the hindquarters of hypertensive rats with renal artery constriction. If the hypertension in experimental coarctation of the aorta were of renal origin, similar results could be expected. However, there is an interesting hemodynamic difference between renal artery constriction and aortic coarctation. In the latter, while the blood pressure above the constriction is elevated, the blood pressure below is close to normal, and sometimes fully normal. Therefore, since the hindquarter vessels are protected from the high blood pressure, it follows that any change in the reactivity of these blood vessels in experiments in which the blood pressure below the constriction is normal could not be attributed to exposure of the blood vessels to high blood pressure.

The present work was planned to investigate further the possible renal origin of the hypertension in experimental coarctation of the aorta and to study the effect of local blood pressure on the reactivity of a vascular bed. Coarctation of the aorta has been produced in rats, and heart weights and blood pressures above and below the constriction have been measured. The responses of the isolated, perfused hindquarters of these animals to noradrenaline have also been studied.

Methods

Female white Wistar rats of the Otago colony, 2 months old and mostly weighing between 140 and 180 Gm., were used throughout. Coarctation of the aorta was produced, under ether anesthesia, by applying a silver clip of 0.825-mm. diameter which completely encircled the abdominal aorta. The animals were divided into three groups. In group A, of 28 animals, the clip was applied above the origin of both main renal arteries. In group B, of 8 animals, the clip was placed below the origin of both main renal arteries. Group C, of 36 animals, underwent a dummy operation.

Systolic blood pressures were measured by a photoelectric method in the fore- and hindlimbs. The blood pressure was taken on three separate days: before the operation, on the day of the operation, and on the next day. Thereafter the blood pressure was taken at weekly intervals until the animals were killed.

The preparation used for the study by perfusion of the vascular bed has been previously described by Fastier and Smirk. This preparation permits perfusion of the isolated hindquarter vessels of the rat at constant rate using an artificial medium.
TABLE 1

Perfusion Medium

<table>
<thead>
<tr>
<th>mM Cation/L.</th>
<th>NaCl</th>
<th>KCl</th>
<th>MgSO₄ • 7H₂O</th>
<th>NaHCO₃*</th>
<th>CaCl₂*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>118.8</td>
<td>5.36</td>
<td>1.20</td>
<td>25.1</td>
<td>2.55</td>
</tr>
</tbody>
</table>

*Treated with CO₂ beforehand until pH = 7.4.

Results

There was no significant difference in body weight for the three groups of animals (table 2).

BLOOD PRESSURE

The preoperative blood pressures were similar in the three groups (table 2). The preoperative forelimb blood pressures were 10 to 15 mm Hg lower than the hindlimb blood pressures.

In the three groups of animals, there was an immediate fall in blood pressure after operation. In group A (fig. 1), from the day following the operation there was a progressive increase in blood pressure above and below the constriction. The forelimb blood pressure attained a hypertensive level about 10 days after clipping of the aorta, while the hindlimb blood pressure returned to the preoperative level over the same period of time. In group B (fig. 2), the forelimb blood pressure returned to preoperative levels within 24 hours after the operation, while the hindlimb blood pressure remained 10 to 15 mm Hg below that in the forelimb. This difference persisted until the end of the experiment. Group C regained preoperative levels in both fore- and hindlimb blood pressures in the next 24 hours.

Table 2 shows the average blood pressure for each group one month after the operation. There was a highly significant difference in forelimb blood pressure between group A and both other groups (P < 0.001). There was no significant difference between group B and group C. The hindlimb blood pressure was similar for groups A and C and it was lower in group B, but the difference was not significant (0.1 < P < 0.05).
TABLE 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean body weight (Gm.)</th>
<th>Mean hindquarter weight*</th>
<th>Mean heart weight*</th>
<th>Blood pressure (mm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Before operation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Forelimb</td>
</tr>
<tr>
<td>Group A</td>
<td>108.03 ± 21.1</td>
<td>32.1 ± 3.6</td>
<td>418.00 ± 47.3</td>
<td>103.0</td>
</tr>
<tr>
<td>Group B</td>
<td>177.50 ± 16.3</td>
<td>31.3 ± 1.6</td>
<td>366.12 ± 17.7</td>
<td>112.3</td>
</tr>
<tr>
<td>Group C</td>
<td>159.86 ± 26.2</td>
<td>29.0 ± 1.3</td>
<td>382.47 ± 22.6</td>
<td>105.5</td>
</tr>
</tbody>
</table>

*As percentage of body weight.
± = Standard deviation of the mean.

HEART WEIGHT

Heart weight expressed as a percentage of body weight was significantly higher in the animals of group A than in those of the other two groups (table 2). The heart weights of groups B and C did not differ significantly.

There was a highly significant regression line of heart weight on forelimb blood pressure for group A (r = 0.70, P < 0.001). This regression line was not significant for the other two groups.

PERFUSION OF ISOLATED HINDQUARTER PREPARATION

The hindquarter weights after separation from the upper parts of the rats were similar for the three groups (table 2). With constant-rate perfusion, the initial perfusion pressure in group A was higher than in group B or C (table 3). The differences were significant. There was no significant difference between group B and group C.

The response of the hindquarters to norepinephrine was also significantly higher in group A as compared with either of the other two groups (table 3). The responses of groups B and C did not differ significantly.

The regression line of hindlimb norepinephrine responses on hindlimb perfusion pressure for group A (fig. 3) was highly significant, but it was not significant for the other two groups.

There was a significant regression line of perfusion pressure on heart weight for group A (r = 0.45, 0.02 > P > 0.01), and the regression line of hindlimb norepinephrine responses on heart weight was also significant (r = 0.48, P < 0.001). Those regression lines were not significant for the other two groups.

The regression line of hindlimb norepinephrine responses on forelimb blood pressure was significant for group A (r = 0.41, 0.01 > P > 0.001), but the regression line of hindlimb perfusion pressure on forelimb blood pressure was not significant in this group. No correlation was found between either hindlimb norepinephrine responses or hindlimb perfusion pressure and hindlimb blood pressure for group A. None of these regression lines was significant for groups B and C.

Eight animals of group A, with the highest heart weights, were compared with the same number of animals of group C, of equal body weights. The hindlimb perfusion pressure and hindlimb norepinephrine responses were significantly higher in group A (table 4).

Discussion

In the present investigation, only the animals with coarctation of the aorta above the renal arteries developed hypertension and hypertrophy of the heart. Rytand et al. found that if, after constricting the aorta between both renal arteries, the kidney below the constriction was extirpated, there was no increase in heart weight. Scott et al. have shown, in dogs with coarctation of the thoracic aorta, that after transplanting one kidney to the neck and removing the other, the carotid blood pressure returned to the initial level. These experiments support the view that the kidneys play an important part in the development of the hypertension that follows constriction of the aorta.

The blood pressure changes are in agreement with the results of Goldblatt et al., Steele, Page, and Ogden et al. in dogs; Rytand and Beznak in rats; and Sealy et al. in rabbits. In the present study, only
systolic blood pressures were measured. The animals of group A showed a significant increase in forelimb blood pressure, while the average hindlimb blood pressure was normal. Other papers have reported increases in diastolic blood pressure above and below the coarctation. This elevation in diastolic blood pressure has been taken as evidence for a generalized increase in peripheral resistance. Some authors have contested this conclusion. The elevation in diastolic blood pressure in the lower limbs could be explained by the mechanical effects of the constriction. There is no doubt that in acute experiments constriction of the aorta produces changes in blood pressure due to purely mechanical factors. The greater the degree of stenosis, the greater is the rise in blood pressure above, and the greater the fall below, the stenosis. However, it seems difficult to explain the slowly progressive elevation in blood pressure in the animals of group A as being due only to mechanical factors. If this increase in blood pressure were due to further narrowing of the aorta caused, for example, by a fibrotic reaction to the clip, a further decrease in blood pressure below the constriction could be expected. Figure 1 shows that the progressive increase in forelimb blood pressure and the recovery of hindlimb blood pressure take place in a parallel way. Harris et al. arrived at similar conclusions. Ogden et al. concluded from their experiments, carried out in cats and dogs, that complete occlusion of the aorta above the renal arteries produced two types of pressure rises: an immediate increase from mechanical factors and a slow increase due to renal ischemia. It is perhaps of interest to point out that the time course of the blood pressure elevation produced by constricting the aorta is similar to the time course of the hypertension produced by constricting a renal artery.

In conclusion, it seems that the hypertension in experimental coarctation of the aorta cannot be explained solely as a result of the mechanical effect of the lesion, and that the kidneys are essential for the development of the hypertension.

The initial hindlimb perfusion pressure and the responses to norepinephrine were significantly higher in the isolated hindquarters of rats of group A as compared with groups B or C. If the animals of group A were smaller, this might be an explanation, but table 2 shows that the body weights were similar for the three groups. When a number of animals from group A were compared with the same number of animals from group C, matched for body weight, the hindlimb perfusion pressure and the norepinephrine responses were significantly higher in group A.

The clipping of the aorta could have interfered with the development of the hindquarter vascular bed. However, the fact that the hindquarter weights were similar for the three groups of animals, and that the perfusion pressure and norepinephrine responses of the
TABLE 4
Comparison Between Eight Animals of Group A and Eight Animals of Group C Matched for Body Weight

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean initial hindlimb perfusion pressure mm. Hg</th>
<th>Mean norepinephrine rise mm. Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>31.75</td>
<td>67.8</td>
</tr>
<tr>
<td>Group C</td>
<td>25.18</td>
<td>40.8</td>
</tr>
</tbody>
</table>

0.05 > P > 0.02
0.01 > P > 0.001

rats of group B did not differ significantly from those of group C, would suggest that the clipping itself had not decreased the development of the hindquarter. It is to be noted that the animals of group B had lower hindlimb blood pressures.

There is evidence for the existence of an increased responsiveness to pressor agents in both human and experimental hypertension. Several mechanisms have been postulated to explain this increased responsiveness: increased activity of vasoconstrictor fibers, increased amount of vasoconstrictor agents in the blood stream, increased reactivity of the vascular smooth muscle fibers to nervous or humoral influences, structural changes in the vessel walls. Smirk has already suggested that hypertrophy of the arterioles might produce an increased reactivity. Mendlowitz and Meyer found evidence of a higher resistance under conditions of maximal vasodilatation in the vessels of hypertensive, as compared with those of normotensive, subjects. Similar findings have been reported in both human and experimental hypertension. McQueen and Hodge and McQueen think that the cause of the increased vascular reactivity could be hypertrophy of the vessel walls. Tobian and Binion postulated an engorgement of the vessel walls with fluid. Either of these changes could produce a decrease in the initial size of the vascular lumen.

The results reported in the present study have shown that there is a significant correlation between hindlimb norepinephrine responses and initial hindlimb perfusion pressure for the animals of group A. The existence of structural changes in the vessel walls could produce an increased response to pressor agents without the need to postulate an increased sensitivity of the smooth muscle fibers, but the possibility of an increased sensitivity of the smooth muscle fibers cannot be dismissed. Redleaf and Tobian have shown that responses of rat aortic strips to norepinephrine were less in hypertensive than in normotensive animals, but their results do not necessarily apply to arteriolar smooth muscle. In the preparation used, the blood vessels were perfused with an artificial medium, and they showed no residual tone. Therefore, it is possible to rule out the existence of an increased neurogenic tone as the cause of the increased response to norepinephrine.

The increase in perfusion pressure and in norepinephrine responses found in the hindquarters of the animals of group A raises another interesting problem. It is well known that an elevated blood pressure can produce changes in the vessel walls. Follow considers that the increased resistance to flow found in hypertensive subjects under conditions of maximal vasodilatation is due to a secondary hypertrophy of the vessel walls as an adaptive process to a lasting increase in blood pressure. In coarctation of the aorta, the blood pressure below the constriction is usually normal or close to normal. Therefore, the changes in the vessels below the constrict-
tion cannot be secondary to an increased blood pressure, but there is some relationship between these changes and the hypertension above the constriction. The regression line in group A of either lower-limb norepinephrine responses or lower-limb perfusion pressure on heart weight is very highly significant. The relation with forelimb blood pressure is only significant for norepinephrine responses, but in our opinion heart weight is a more accurate indication of the degree of persistent hypertension than occasional measurements of the blood pressure.

It is not possible, in terms of the experiments made, to distinguish between a structural and a chemical (humoral) change in the blood vessels of the perfused hindquarters, but as the basic peripheral resistance and response to norepinephrine are increased without exposure of the blood vessels to a higher local blood pressure, it seems probable that the changes observed in the hindquarters are in some way related to the basic mechanism that produces the hypertension.

**Summary**

Experimental coarctation of the aorta has been produced in rats. Animals with the clip above both renal arteries have been compared with animals with the clip below both renal arteries and with dummy operated rats. The fore- and hindlimb blood pressures, heart weights and perfusion pressure, and norepinephrine responses of the isolated perfused hindquarters have been measured.

Only the animals with a clip above the renal arteries developed hypertension and hypertrophy of the heart. The increase in blood pressure was progressive, requiring about 10 days to reach hypertensive levels. Such animals showed an increase in the norepinephrine responses and in the perfusion pressure of hindlimb blood vessels when compared with either of the other two groups. The differences are statistically significant. In rats with clips above the renal arteries, there is a highly significant regression line of hindlimb norepinephrine responses on hindlimb perfusion pressure and of either of these values on heart weight.

It is considered: (a) that the hypertension in experimental coarctation of the aorta is not purely mechanical and the kidneys are essential for the development of this type of hypertension; and (b) that the increase in the norepinephrine responses and in the perfusion pressure found in the hindquarter vascular bed of rats with coarctation of the aorta above the renal arteries is not secondary to the hypertension as such, but in some way is related to the mechanism that produces the hypertension in experimental coarctation of the aorta.

**Acknowledgment**

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**References**

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VASCULAR REACTIVITY IN EXPERIMENTAL COARCTATION


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