Metaischemic (Post-Goldblatt) Hypertensive Vascular Disease in Rats

FRANCISCO PELTIER QUEIROZ, M.D., PH.D., JOSE-MANUEL ROJO-ORTEGA, M.D., PH.D., AND JACQUES GENEST, C.C., M.D.

SUMMARY Malignant hypertension was induced in rats by aortic ligation above the left renal artery. After 7- and 28-day periods of hypertension, the characteristics of the vascular disease were studied and the kidney below the aortic ligation was removed. The blood pressure and the vascular disease were reexamined at the end of the first and fourth weeks after nephrectomy. The evolution of the vascular disease was assessed in the contralateral kidney, in the heart, and in the superior mesentery. The results obtained allowed the following conclusions: 1) when the predominant lesions are of fibrinoid necrosis and moderate intimal hyperplasia without fibromucoid changes (initial phase), the hypertension and the hypertensive vascular disease are completely reversible after the nephrectomy; 2) when the predominant lesions are proliferative endarteritis with fibromucoid changes (chronic phase), neither the hypertension nor the vascular disease are reversible after the left nephrectomy and during the period of follow-up. Therefore, the type of vascular lesion seems to be one important determinant of the reversibility of the hypertensive process after nephrectomy.

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KEY WORDS • malignant hypertension • renovascular hypertension • hypertensive vascular disease

In the one-kidney, one clip hypertensive state of rats, removal of the remaining kidney usually does not interfere with blood pressure.1-2 Conversely, removal of the renal artery constriction results in lowering or normalization of blood pressure.3-4

In the two-kidney, one clip hypertensive model, removal of both kidneys usually does not lower blood pressure.1-2,4 The effect of the removal of the ischemic kidney in this model depends upon the duration of hypertension. If hypertension is from 1/2 to 3 weeks duration, removal of the ischemic kidney results in the return of blood pressure to normal,1-4 whereas hypertension from 2 to 8 weeks' duration usually results in continuously elevated blood pressure.3-4 In this model, removal of the clip at 4 weeks resulted in lowering of the blood pressure,2 while the same maneuver at 8-46 weeks failed to affect the blood pressure.7 Furthermore, removal of the previously ischemic kidney 1 to 3 weeks after removing the clip did not lower blood pressure, but removal of the contralateral, untouched kidney at this time did.7

These results vary when different animal species or different models of hypertension are compared.10-11 The reasons for sustained hypertension after removing the ischemic kidney (metaischemic hypertension) are controversial. The vascular disease itself could contribute to sustaining hypertension.8 A point of issue is the type of vascular disease, and the present experiments were designed in an attempt to answer this question. The model of Rojo-Ortega and Genest14 was used since vascular disease in this model is severe, consistent and may be tested after manipulating the ischemic kidney.

Material and Methods

Hypertension was induced in 32 adult male Sprague-Dawley rats, by a complete aorta ligation just above the left renal artery. The characteristics of hypertension in this model have been described elsewhere.12-14 An especially important aspect of this model is that after an initial phase of high plasma renin activity and fibrinoid necrotic vascular lesions, a chronic phase ensues in which plasma renin activity returns to normal and the vascular lesions are...
predominantly of the proliferative type. The chronic phase begins around the third week after aortic ligation.

**Experiment I**

Fifteen animals were subjected to aortic ligation. Seven days after the surgical procedure, six animals were sacrificed, and a left nephrectomy was performed in the remaining nine animals. Of these, five were sacrificed at the end of the first week and four at the end of the fourth week following nephrectomy. Weights and blood pressures were measured during the course of this experiment. After aortic ligation, blood pressure was determined directly from the carotid artery with a catheter attached to a pressure transducer Statham (P-23), connected to a Grass polygraph model 7P1-A. All of these procedures were performed under light pentobarbital anesthesia (5 mg/100 g of body weight). At necropsy, the heart, superior mesentery, and kidneys were processed by routine methods for histological examination. Sections were stained with hematoxylin-eosin, periodic acid Schiff and Weigert-Van Gieson. Six rats of similar initial body weight were sham-operated and served as controls.

**Experiment II**

Seventeen animals were subjected to aortic ligation. Twenty-eight days after surgery, seven animals were sacrificed for vascular study and a left nephrectomy was performed in the remaining 10 animals. Of these, five were sacrificed at the end of the first week and five others at the end of the fourth week following nephrectomy. All procedures regarding weight, blood pressure and histological studies on experimental and on six control rats were similar to those described above.

Results are expressed as means ± standard errors.

**Results**

**Experiment I**

Seven days after aortic ligation or sham operation, body weights of the control rats had increased from 315.2 ± 7.9 to 337.7 ± 13.2 g whereas it had decreased from 315.7 ± 4.1 to 226.8 ± 7.1 g in animals with aortic ligation. After the left nephrectomy, the increase in animal body weight was greater in those with aortic ligation than in those sham-operated (fig. 1). Blood pressure of the controls, 7 days after the initial surgery, was of 132.5 ± 5.3 mm Hg, whereas it was of 180.7 ± 8.0 mm Hg (p < 0.02) in animals with aortic ligation (fig. 2). After the left nephrectomy, the blood pressure of the hypertensive animals declined and reached normal values within four weeks (fig. 2). Histological studies on tissues of all animals sacrificed 7 days after aortic ligation revealed ischemic tubular atrophy in the left kidneys and malignant hypertensive vascular disease — mainly represented by fibrinoid necrosis — in the heart, superior mesentery, and contralateral kidney (fig. 3). Periarteritis-nodosa-like lesions and mitotic figures in cells of media and intima of vessels were occasionally observed. Proliferative endarteritic lesions were present in 17 to 33% of animals, depending on the vascular territory examined. In all these animals, lesions decreased in frequency 1 week after left nephrectomy and none were found at the fourth week (table I). Histological studies were normal for controls both before and after nephrectomy.

**Experiment II**

Twenty-eight days after aortic ligation or sham operation, body weight of controls had increased from 292.2 ± 4.1 to 383.7 ± 13.0 g whereas it had decreased from 300.5 ± 3.8 to 282.2 ± 16.9 g in animals with aortic ligation. After the left nephrectomy, the percent increase in body weight was similar...
FIGURE 2. Blood pressure follow-up after the left nephrectomy in rats with one and four weeks of malignant hypertension.

FIGURE 3. Arteriolar fibrinoid necrosis, seven days after aortic ligation. Superior mesenteric territory of the rat. PAS X 400.
TABLE 1. Incidence of Vascular Lesions in Rats with Metaischemic Hypertension After a Short and Long Period (1 and 4 weeks) of Malignant Hypertension Induced by Complete Aorta Ligation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. of rats</th>
<th>Percentage of rats with hypertensive vascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Heart (FN, PE)</td>
</tr>
<tr>
<td>Aorta ligation (7 days)</td>
<td>6</td>
<td>100 33</td>
</tr>
<tr>
<td>One week after R-xp</td>
<td>5</td>
<td>40 20</td>
</tr>
<tr>
<td>Four weeks after R-xp</td>
<td>4</td>
<td>0 0</td>
</tr>
<tr>
<td>Aorta ligation (28 days)</td>
<td>7</td>
<td>71 100</td>
</tr>
<tr>
<td>One week after R-xp</td>
<td>5</td>
<td>20 100</td>
</tr>
<tr>
<td>Four weeks after R-xp</td>
<td>5</td>
<td>0 80</td>
</tr>
</tbody>
</table>

R-xp = left nephrectomy; FN = fibrinoid necrosis; EP = proliferative endarteritis.

for these two groups (fig. 1). The blood pressure of controls 4 weeks after sham operation was 143.3 ± 5.9 mm Hg, whereas it was 195.6 ± 8.4 mm Hg in animals with aortic ligation (p < 0.01). Unlike Experiment I, after the left nephrectomy the blood pressure of animals with aortic ligation remained significantly high up to the fourth week (fig. 2). Histological studies were normal for controls both before and after nephrectomy. In animals with the aortic ligation, histological studies performed 28 days after the initial surgery showed ischemic tubular atrophy in the left kidneys and hypertensive vascular disease — mainly represented by proliferative lesions — in the heart, superior mesentery and contralateral kidney. Proliferative endarteritic lesions, when compared to those of Experiment I, were in a more advanced stage of development, with fibro-mucoid changes (fig. 4). Whereas such lesions remained and persisted through the fourth week after nephrectomy, the fibrinoid necrosis observed 4 weeks after aortic ligation were absent 4 weeks after left nephrectomy (table 1).

Discussion

In animals with severe hypertension induced by aortic ligation above the left renal artery, it was found that the removal of the left kidney during the acute, initial phase of the disease resulted both in progressive normalization of blood pressure and cure of hypertensive vascular disease. When a left nephrectomy was performed during the chronic phase of disease, no significant improvement of hypertension occurred and vascular hypertensive lesions persisted. These results are not surprising and were already observed in similar studies on hypertension.

Grollman et al. believed that the absence of a normal renal substance, resulting from organ removal or interference with it, could cause hypertension to develop and persist. The studies of Floyer suggested that residual hypertension, like initial hypertension, is directly related to abnormally functioning renal tissue and the production of a pressor substance. Using these results, Thai et al. performed a successful right nephrectomy upon a hypertensive young patient previously submitted for correction of a left stenosed renal artery which proved ineffective in lowering his blood pressure. It has been assumed for several years that the contralateral, untouched kidney would be progressively injured and that vascular lesions in it would act as small clips, i.e., after prolonged exposure to high blood pressure, this kidney would function as a Goldblatt kidney. Koletsky and Rivera-Velez showed that vasopressor activity in the contralateral kidney was not increased before or up to 5 months after the left nephrectomy. They concluded that widespread arteriolar disease was the important factor for maintaining the hypertension after the nephrectomy.

As suggested in previous studies, the initial lesions of malignant hypertension are predominantly fibrinoid necrosis. Progressively, a regenerative process is noted in these areas and several mitotic figures can be seen in the vascular wall. The use of colchicine some hours before necropsy in these animals facilitates this observation (Rojo-Ortega and Queiroz, unpublished data). It seems that proliferative lesions occur in the same areas of fibrinoid necrosis. The mitotic figures probably represent the initial stage of a regenerative phase. However, this regenerative process seems to be exacerbated in malignant hypertension. In fact, if high blood pressure is controlled in the initial phase, lesions of fibrinoid necrosis are repaired only to the point of restoring the integrity.
of the vascular wall. Four weeks after left nephrectomy and control of hypertension, histological studies performed on the animals of Experiment I were considered normal, regarding the state of the vascular wall. If hypertension is not controlled, the regenerative process continues and the lumen of the vessels becomes markedly reduced due to proliferative endarteritis with mucoid and fibrotic changes. Malignant hypertension is known to be associated with intravascular coagulation and factors that stimulate cellular proliferation have been isolated from platelets.

The processes of evolution and healing of vascular lesions in malignant hypertension are not clear. From our results, it seems that fibrinoid necrosis as well as initial proliferative lesions (proliferative endarteritis without fibromucoid changes) are able to heal, if blood pressure is lowered. If blood pressure remains high, as in Experiment II, the disappearance of fibrinoid necrosis could be interpreted either as a real healing process or as a progressive evolution of these lesions to proliferative ones. At this phase, the fully formed endarteritic lesions do not reverse.

The role of the contralateral kidney in maintaining hypertension in the chronic phase is also not clear, since it could be that the behavior of this kidney is different when the left kidney is removed or when its arterial stenosis is corrected. In the latter case, the presence of normal renal tissue could contribute to lower blood pressure. These aspects should be taken into account since they could help explain why removal of the contralateral kidney is effective in controlling hypertension after the removal of the left renal artery stenosis and why bilateral nephrectomy was ineffective. It could also help explain why in the one-kidney, one clip hypertensive model, irrespective of the duration of hypertension, removal of the remaining kidney was ineffective in lowering blood pressure, whereas the removal of the clip was largely effective.

Without excluding the potential roles of excretory and hormonal functions of the kidneys which result from several manipulations of these organs in renovascular hypertension, both diffuse vascular disease and the particular type of vascular disease seem to play an important role in determining the rate of reversibility of hypertension and of hypertensive vascular disease.
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