Influence of Hypertension on Aortic Atherosclerosis in the Watanabe Rabbit

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The effects of one-kidney, one clip Goldblatt hypertension on aortic atherosclerosis have been studied in the Watanabe heritable hyperlipidemic (WHHL) rabbit. Renovascular surgery was performed on WHHL rabbits at 3 months of age, and the rabbits were followed for periods of 3–6 months. Aortic atherosclerosis was assessed by measurement of intimal surface involvement with atherosclerotic lesions, determination of aortic free and ester cholesterol content, and microscopic examination. Systolic blood pressure increased by approximately 40–60 mm Hg in the renovascular surgical group as compared with the sham-operated group, but body weight, heart rate, serum cholesterol, and serum triglyceride were unaffected. Aortic atherosclerosis was increased in the hypertensive rabbits, even after 2–3 months of hypertension. At 3 months after renovascular surgery, the aortic surface area covered by atherosclerotic disease averaged 77 ± 4.4% in hypertensive as compared with 16 ± 3.3% in control rabbits. At 6 months after surgery, the values were 62 ± 8.2% and 30 ± 5.3% in the hypertensive and control rabbits, respectively. The differences in surface involvement and cholesterol content as a result of hypertension were particularly prominent in the descending thoracic aorta. Atherosclerotic lesions in the descending thoracic and abdominal aortic regions of normotensive WHHL rabbits were localized primarily to the ostia of branch vessels, but in the hypertensive rabbits, the involvement was typically very diffuse. No major differences in the nature of atherosclerotic lesions of comparable size were apparent by light microscopy. The results indicate that hypertension accelerates atherogenesis in the WHHL rabbit and suggest that this model may be valuable for studying the mechanisms by which such acceleration is induced. (Hypertension 1989;14:203–209)

Clinical data have indicated that hypertension accelerates the complications of atherosclerosis. The incidences of myocardial infarction, angina pectoris, sudden death, and peripheral vascular disease are all increased more than twofold in hypertensive as compared with normotensive individuals.1 Atherogenesis in humans also may be enhanced in the hypertensive population. Postmortem investigations have demonstrated that the extent of both fatty streaks and fibrous plaques and the degree of arterial stenosis are increased in several arterial beds including the coronary, cerebral, and peripheral circulations.2,3

Circulating plasma lipoprotein levels appear to influence the development of atherosclerosis in response to hypertension. Studies in several species including the rat, rabbit, and monkey have indicated that atherosclerotic lesions rarely develop as a result of hypertension alone.4 In addition, populations such as those in the Orient, with high incidence of hypertension but relatively low levels of plasma cholesterol, continue to have low incidence rates for the clinical complications of atherosclerosis. Investigation of the relation between hypertension and atherosclerosis has been limited by the lack of a suitable animal model for study. Studies in cholesterol-fed baboons and in cholesterol-fed rabbits with renovascular hypertension have suggested an increased rate of development of atherosclerotic disease in hypercholesterolemic-hypertensive animals,5,6 but no similar data are available in the absence of elevated dietary cholesterol intake.

The current study was initiated to examine the effects of one-kidney, one clip renovascular hypertension on the development of aortic atherosclerosis in the Watanabe heritable hyperlipidemic (WHHL) rabbit, which has spontaneous hypercho-
lesteerolemia as a result of a defect in the cellular receptor for low density lipoproteins. The animals were made hypertensive at 3 months of age and were followed for periods of approximately 3 and 6 months.

Materials and Methods
Watanabe Heritable Hyperlipidemic Rabbits

The WHHL rabbits were bred from homozygous animals kindly provided by Dr. Russell Ross of the University of Washington School of Medicine and Dr. Alan Fogelman of the University of California School of Medicine in Los Angeles. The breeding animals were kept in rooms equipped with laminar flow filters at a temperature of approximately 22°C and with a 12-hour light/dark cycle. They were fed 120 g/day Agway Prolab High Fiber Rabbit Chow (Syracuse, New York), except for pregnant and nursing females, who were fed ad libitum. All animals had free access to water.

The litters were housed in large breeding cages containing plastic nesting boxes and bedding and with small gauge grates inserted into the cage floor to prevent injury to the pups. The pups were weaned at 8 weeks of age. After weaning, they were housed in a room separate from the breeders.

Surgical Procedure

Surgery to induce hypertension was performed at 3 months of age according to a modification of the method originally described by Goldblatt et al. Rabbits of approximately 2.0–2.2 kg body wt were anesthetized by intramuscular injection of 5 mg/kg xylazine and 35 mg/kg ketamine. Doses were repeated at 20–40-minute intervals as needed. The rabbits were placed in dorsal recumbency, and the skin was shaved and scrubbed with betadine and 95% ethanol. Under sterile conditions, a midline incision was made. The viscera was wrapped in moist gauze and drawn out of the cavity, and the kidney and renal arteries were exposed. A right nephrectomy was performed. A silver restriction clip with a gap of 0.508 mm was placed on the left renal artery. Operative and postoperative mortality from surgery was approximately 20%. Mortality was related either to renal failure due to excessive constriction of the renal artery or to the development of stroke because of severe hypertension. Approximately two thirds of the operated rabbits developed hypertension as defined by increases in systolic blood pressure to average levels exceeding 140 mm Hg. The remaining rabbits were excluded from the study. Sham rabbits were surgically prepared in the same manner, except that nephrectomy and renal artery clipping were not performed.

Systolic blood pressure and heart rate were measured at monthly intervals using the tail-cuff method previously developed in our laboratory. The averages for the final 3 months of the study were used for comparisons between groups. The systolic pressure was determined with an IITC Model 59 preamplifier (IITC Life Science Instruments, Landing, New Jersey) and a Narcotrace 40 physiograph (Narco Bio-Systems, Houston, Texas). Heart rate was measured at a chart speed of 2.5 cm/sec. Body weight was determined monthly. Approximately 2 ml blood was removed monthly from the central ear artery, and total serum cholesterol, triglyceride, and blood urea nitrogen were assayed using enzymatic techniques (Sigma Diagnostics Kits, Sigma Chemical Company, St. Louis, Missouri, numbers 352, 336, and 66, respectively). The animals were fasted overnight before bleeding.

The rabbits were killed with an intravenous injection of sodium pentobarbital (100 mg/kg body wt). The tissues were fixed by a whole body perfusion technique using either 10% phosphate-buffered formalin or 3% paraformaldehyde and 0.25% glutaraldehyde. A cannula was placed in the ascending aorta, and approximately 600 ml fixative was perfused at approximately the final measured mean blood pressure. The heart was perfused retrogradely through a second aortic cannula placed 5 mm distal to the aortic valve.

Aortic Photography

The entire aorta from the heart to the bifurcation was removed, and the adventitia was dissected away. The aorta was opened along the middorsal line to expose the intimal surface. It was arranged in a manner to fill a photographic frame, pinned to a black tar dissecting plate, and covered with saline to avoid glare and drying. Photographs were taken with a 50 mm macro lens at a minimal possible distance using Ektachrome 160 professional film (Figure 1). Segments representing grossly normal, minimally atherosclerotic, and severely atherosclerotic areas of the aortic arch, and thoracic and abdominal regions, respectively, were removed for examination by light microscopy, and the photographs were repeated.

The microscopic sections were stained with hematoxylin and eosin and evaluated with respect to lesion thickness, foam cell content, lipid crystals, calcification, and necrosis.

Assessment of Aortic Surface Involvement

Segments without lesions were semitransparent and appeared bluish against the black background without the use of staining. Fatty lesions appeared bright white, and predominantly fibrocellular lesions were grayish-white. Histologic examination confirmed that intimal lesions as thin as three cell layers could be recognized on projected macrophotographs, provided that adventitial fat and tissue were removed. The photographs were projected onto the magnetic tablet of a manually operated image analyzer (MOP, Carl Zeiss Instruments, Oberkochen, FRG). The areas with lesions were traced and their areas were expressed as a percentage of the total areas and also separately for the arch, thoracic, and abdominal segments, respectively.
Arterial Lipids

The aorta was divided into three segments by cutting it circumferentially approximately 1.0 cm proximal to the first pair of intercostal arteries and also just proximal to the celiac artery. The adventitia was removed, and the intima-media layer was weighed and homogenized with a motor-driven, glass-glass homogenizer in 10 volumes 0.25 M sucrose, 10 mM HEPES, pH 7.4. The lipids were extracted from each segment according to the method of Folch et al.9 Free and esterified cholesterol were separated in aliquots of the extract by thin layer chromatography as previously described.10 Free and esterified cholesterol were eluted off the silica gel using chloroform:methanol (2:1, vol:vol) and quantitated according to the method of Rudel and Morris.11 Recovery of the lipids exceeded 90%.

Statistical analyses were made using the Student’s t test for independent samples.

Results

Clinical Characteristics

Rate of weight gain or final body weight did not differ significantly in the normotensive and hypertensive WHHL at either 3 or 6 months after surgery (Table 1).

Systolic blood pressure in the 3-month hypertensive WHHL group averaged 180±5.4 mm Hg (mean±SEM) as compared with 123±3.5 mm Hg in the sham-operated controls (p<0.001) (Table 1 and Figure 1). At 6 months after surgery, systolic blood pressures averaged 174±8.7 mm Hg versus 127±0.8 mm Hg (p<0.001) in the renovascular and control groups, respectively. The major rise in blood pres-
sure usually occurred between 2 and 4 weeks after renal artery clipping. Heart rate did not differ significantly between any of the groups.

No significant differences were present between hypertensive and normotensive groups in either total serum cholesterol or triglyceride levels (Table 1). Blood urea nitrogen was increased somewhat in hypertensive as compared with normotensive WHHL rabbits (Table 1).

**Arterial Cholesterol**

Both free and ester cholesterol were usually greater in the ascending aorta and arch than in the descending or abdominal aorta in all WHHL groups (Table 2). Three months after surgery, significantly greater levels of aortic free and ester cholesterol were present in the descending thoracic and the abdominal aorta of hypertensive as compared with normotensive WHHL rabbits (Table 1).

**Intimal Surface Involvement**

A marked increase in intimal surface area covered by atherosclerotic lesions was apparent in the hypertensive as compared with the normotensive WHHL rabbits. The differences were highly significant statistically despite the relatively small number of rabbits studied in each group. At 3 months after renovascular surgery, the total lesion area averaged $77\pm4.4\%$ in the hypertensive and $16\pm3.3\%$ in the normotensive WHHL rabbits ($p<0.00001$) (Table 3). At 6 months after surgery, the values for the hypertensive group were $62\pm8.2\%$ versus $30\pm5.3\%$ in the control group ($p<0.01$). The greatest differences were observed in the descending thoracic aorta.

In the normotensive WHHL rabbits, the lesions were distributed primarily around the ostia of vessels, whereas in hypertensive WHHL rabbits, the aortic involvement tended to be very diffuse. Representative photographs of aorta from a normal and a hypertensive WHHL rabbit are shown in Figure 1A and 1B.

**Microscopic Examination**

The atherosclerotic lesions in both normotensive and hypertensive rabbits showed a wide range of severity. However, advanced lesions were more frequently observed in the hypertensive rabbits. Figure 2A illustrates typical intercostal ostial lesions in a control WHHL rabbit with mostly cellular intimal plaques, and Figure 2B shows an advanced lesion with many foam cells in the same rabbit.

Figure 3 illustrates representative sections in hypertensive WHHL rabbits. In Figure 3A, there is a luminal fibrocellular cap with underlying foam cells and a relatively acellular core with necrosis. In Figure 3B, there is also seen intimal calcification and a heavy deposition of cholesterol crystals.

**Table 1. Effects of One-Kidney, One Clip Goldblatt Hypertension on Body Weight, Blood Pressure, Heart Rate, Blood Urea Nitrogen, and Serum Lipids in Watanabe Heritable Hyperlipidemic Rabbits**

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Body weight (kg)</th>
<th>Systolic BP (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>BUN (mg/dl)</th>
<th>Serum cholesterol (mg/dl)</th>
<th>Serum triglyceride (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (5)</td>
<td>3.00±0.15</td>
<td>123±3.5</td>
<td>233±13</td>
<td>18±1</td>
<td>670±106</td>
<td>389±69</td>
</tr>
<tr>
<td>3 months after surgery (4)</td>
<td>2.62±0.14</td>
<td>180±5.4*</td>
<td>253±12</td>
<td>27±4tt</td>
<td>755±57</td>
<td>308±35</td>
</tr>
<tr>
<td>Control (4)</td>
<td>3.10±0.19</td>
<td>127±0.8</td>
<td>247±9</td>
<td>17±1</td>
<td>809±61</td>
<td>304±31</td>
</tr>
<tr>
<td>6 months after surgery (6)</td>
<td>2.96±0.13</td>
<td>174±8.7*</td>
<td>252±9</td>
<td>24±2tt</td>
<td>925±64</td>
<td>356±89</td>
</tr>
</tbody>
</table>

Values represent mean±SEM. BP, blood pressure; BUN, blood urea nitrogen.

* $p<0.001$; $t_p<0.05$ comparing hypertensives vs. controls.

**Table 2. Effects of One-Kidney, One Clip Goldblatt Hypertension on Aortic Cholesterol Content in Watanabe Heritable Hyperlipidemic Rabbits**

<table>
<thead>
<tr>
<th>Group</th>
<th>Ascending and arch</th>
<th>Thoracic</th>
<th>Abdominal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FC</td>
<td>EC</td>
<td>FC</td>
</tr>
<tr>
<td></td>
<td>(mg/g wet wt)</td>
<td></td>
<td>(mg/g wet wt)</td>
</tr>
<tr>
<td>3 months after surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>4.75±1.21</td>
<td>7.71±2.76</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>5</td>
<td>6.60±1.26</td>
<td>7.77±1.93</td>
</tr>
<tr>
<td>6 months after surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4</td>
<td>8.72±1.86</td>
<td>15.9±3.09</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>6</td>
<td>12.6±1.39</td>
<td>13.3±2.04</td>
</tr>
</tbody>
</table>

Values represent mean±SEM. FC, free cholesterol; EC, ester cholesterol.

* $p<0.05$; † $p<0.001$; ‡ $p<0.01$ comparing hypertensives vs. controls.
TABLE 3. Effects of One-Kidney, One Clip Goldblatt Hypertension on Extent of Aortic Surface Atherosclerosis in Watanabe Heritable Hyperlipidemic Rabbits

<table>
<thead>
<tr>
<th>Aortic region</th>
<th>3 months after surgery</th>
<th>6 months after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (mean±SEM)</td>
<td>Hypertensive (mean±SEM)</td>
</tr>
<tr>
<td>Total aorta</td>
<td>16±3</td>
<td>21±3</td>
</tr>
<tr>
<td>Ascending &amp; arch</td>
<td>47±15</td>
<td>99±15</td>
</tr>
<tr>
<td>Descending thoracic</td>
<td>6±1</td>
<td>89±5</td>
</tr>
<tr>
<td>Abdominal</td>
<td>15±2</td>
<td>37±11</td>
</tr>
</tbody>
</table>

Values for 3 months after surgery represent the mean±SEM for five control and four hypertensive Watanabe heritable hyperlipidemic rabbits (WHHL).

Values for 6 months after surgery represent the mean±SEM for four control and six hypertensive WHHL.

*p<0.0001; †p=0.02; ‡p=0.06; §p<0.01; ‖ p<0.05.

Discussion

These studies were designed to develop a new practical model for studying the relation between hypertension and atherosclerosis and to help delineate the mechanisms whereby hypertension may accelerate atherosclerosis. Previous studies from our own and other laboratories have suggested marked similarities between the arterial effects of hypertension and the development of atherosclerosis induced by cholesterol feeding. These have included increased arterial permeability, endothelial changes, stimulation of smooth muscle migration and proliferation, increased adherence of circulating leukocytes to the endothelial surface, accumulation of monocytes/macrophages in the intima, and accumulation of connective tissue constituents. However, what is lacking with hypertension alone in the absence of hypercholesterolemia is the intimal accumulation of lipid. Therefore, we postulated that in the WHHL rabbit with genetically determined hyperlipoproteinemia, hypertension should accelerate the development of atherosclerosis. Such a hypothesis has been supported by prior studies using cholesterol-fed rabbits, but in this latter model, other changes associated with the very high circulating levels of cholesterol and the marked tissue accumulation of lipid could possibly influence the results.

The one-kidney, one clip Goldblatt model was selected because of the relative ease and consistency in inducing hypertension. All rabbits studied had relatively intact renal function, and serum cholesterol and triglyceride levels of the rabbits were...
FIGURE 3. Photomicrographs of hypertensive Watanabe heritable hyperlipidemic (WHHL) rabbits. Left panel: Representative lesion in the thoracic aortic arch of a hypertensive WHHL 3 months after renovascular surgery. A large, partially necrotic, sparsely cellular core of the intimal lesion is compromising the thinned media. Foam cells are clustered underneath a luminal fibrocellular cap, where longitudinal and cross-sectional profiles of smooth muscle cells are a predominant component. Hematoxylin-eosin stain, original magnification ×100. Right panel: Advanced lesion in the aortic arch of a WHHL 6 months after renovascular surgery. The core of the intimal lesion is relatively acellular, necrotic, calcified, and rich in cholesterol crystals. Compression and erosion of the tunica media are visible on the bottom of the micrograph. Small clusters of foam cells are present underneath and within the longitudinal profiles of the smooth muscle cells forming the luminal fibrocellular cap. Focal appearances of cartilagelike or bonelike formations in the extracellular matrix are also seen. Hematoxylin-eosin stain, original magnification ×100.

unaffected by the surgery. Plasma renin activity may increase initially in this model, but it typically returns to normal or subnormal levels with time.

The analyses of extent of aortic surface lesions and of free and ester cholesterol content were made in three separate segments of aorta: the ascending aorta including the arch, the thoracic region, and the abdominal aorta. The susceptibility to lesion development varies with these regions in both the cholesterol-fed and WHHL rabbit. In both normotensive and hypertensive rabbits, the extent of the intimal surface covered by lesions was much greater in the ascending aorta and arch than in areas further away from the heart. Any assessment confined to the total aorta might miss important regional changes induced by hypertension.

The hypertensive rabbits exhibited increases in aortic atherosclerosis in each area examined. The relative changes were particularly marked in the thoracic and abdominal aorta, where the intimal surface covered by grossly visible lesions in the hypertensive rabbits was more than double that in the controls. Free and esterified cholesterol content of these regions in the hypertensive was also greater than in the normotensive rabbits. In the ascending aorta and arch, the differences between hypertensive and normotensive WHHL rabbits were less marked with respect to both surface area and cholesterol measurements, presumably because of the extensive atherosclerosis that develops in these areas irrespective of the presence of hypertension.

The acceleration of aortic atherosclerosis could be demonstrated at both 3 and 6 months after surgery when the rabbits were approximately 6 and 9 months of age, respectively. The average period from the date of surgery to the development of significant hypertension was usually between 2 and 4 weeks. Thus, even after approximately 2–2.5 months of elevated blood pressure, there appeared to be adequate stimulus to cause increase in the extent of atherosclerosis. The degree of involvement by atherosclerosis did not differ significantly between the 3- and 6-month-old hypertensive groups. The blood pressures in the 3-month-old group turned out to be somewhat greater than for the 6-month-old hypertensives, and it is conceiv-
able that the slightly greater severity of hypertension could have counterbalanced any effect that longer duration might have caused. It is also possible that with more than one half of the total aortic surface already involved with atherosclerosis after 3 months, increased duration of hypertension might only affect the severity of lesions rather than their extent.

Hypertension appeared to induce a change in distribution of lesions in the aorta. In normotensive, relatively young WHHL rabbits (3–9 months of age), the majority of lesions appeared to be Y-shaped, just distal to the orifices of branch vessels. However, in the hypertensive animals, the atherosclerotic disease was much more diffuse, and the ostial predilection could not easily be appreciated. Hemodynamic stresses on the vessel wall could play a role in this regard by altering shear stresses on the endothelium, but the mechanisms remain unknown.

We and others\textsuperscript{12–14} have obtained evidence suggesting that hypertension may increase vascular permeability. Our data in normolipidemic New Zealand white rabbits have indicated that the flux of labeled albumin across the carotid artery studied in situ is increased markedly with one-kidney, one clip Goldblatt hypertension.\textsuperscript{14} In the presence of hyperlipoproteinemia, as seen with the WHHL rabbit, increased intimal permeability induced by hypertension might lead to exaggeration in rate of entry of lipoproteins into the intima. If the capacity for removing or degrading the lipoproteins were exceeded, then cholesterol accumulation might occur in the intima along with atherosclerotic plaque formation.

In this study, the lesions of normotensive and hypertensive WHHL rabbits were examined microscopically. Lesion severity was determined by gross inspection, and areas of comparable severity were compared by standard light microscopy. When controlling for similar levels of severity, no appreciable histological differences were apparent between normotensive and hypertensive WHHL rabbits. However, the disease in the hypertensives was generally more extensive and more severe than in the controls. More detailed analyses are now in progress to compare the cellular and extracellular composition of the atherosclerotic lesions in the two groups.

These studies indicate that the WHHL rabbit with renovascular hypertension is a potentially important model for examining the relation between hypertension and atherosclerotic vascular disease. Rapid acceleration of aortic atherosclerosis has been demonstrated in this model, thus providing opportunities for studying the mechanisms by which the enhancement of atherogenesis is affected by hypertension.

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