Regression of Left Ventricular Hypertrophy in Two-Kidney, One Clip Goldblatt Hypertension

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SUMMARY The effect of regression of left ventricular hypertrophy (LVH) on ventricular performance was studied in two-kidney, one clip Goldblatt hypertensive rats (2K1C) treated with methyldopa or by unclipping. Sham operations were performed in a total of 21 rats; 12 and nine were studied after 4 and 6 weeks, respectively. Hypertension was induced in 38 additional rats. Of these, 11 were studied at 4 weeks. Cardiac index was measured by electromagnetic flowmetry under light ether anesthesia, and ventricular performance was assessed by rapid intravenous saline infusion. Of the remaining 27 hypertensive rats at 4 weeks postclipping, 10 were treated with methyldopa (400 mg/kg/day) and nine were unclipped; eight were left untreated as controls. Two weeks thereafter, ventricular performance was determined as described above. When expressed as the relationship between cardiac index and LV end-diastolic pressure, ventricular performance tended to be depressed in 2K1C. Ventricular performance, mean arterial pressure, and LV-to-body weight ratio returned to control in unclipped rats. Whereas methyldopa resulted in regressed LVH, its effect on mean arterial pressure and total peripheral resistance was not as marked as unclipping, both remaining significantly increased (p < 0.001). The disparate effects of unclipping and methyldopa on systemic hemodynamics indicate that the improved ventricular performance with methyldopa was related more to its effect on LVH, suggesting that in these animals regression of LVH was associated with improved ventricular performance.

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KEY WORDS • Goldblatt hypertension • left ventricular hypertrophy • regression of hypertrophy • antihypertensive treatment • unclipping • ventricular performance

RECENT studies have demonstrated that left ventricular hypertrophy (LVH) may regress with certain antihypertensive therapy in experimental or clinical forms of hypertension. These reports have demonstrated that some antihypertensive drugs will regress hypertrophy even though their hemodynamic effects may not be as beneficial as other agents. For example, certain vasodilating agents that significantly reduce arterial pressure, total peripheral resistance, and LV work will not regress hypertrophy; other agents, however, will diminish ventricular mass despite lesser reduction in arterial pressure and total peripheral resistance. This study was designed to determine the effects of regression of LVH on systemic hemodynamics and LV performance in rats with two-kidney, one clip Goldblatt hypertension (2K1C). Regression of hypertrophy was produced by two means: pharmacologic therapy with methyldopa and surgical removal of the clip.

Materials and Methods

Ventricular Performance (After 4 Weeks)

Hypertension (2K1C) was produced in 11 Wistar rats by placing a tantalum clip (0.2 mm gap) around the right renal artery under ether anesthesia; the left kidney remained untouched. In 12 other Wistar rats, a sham operation was performed, and after the renal artery was handled with forceps, the incision was closed and the animal permitted to recover. At the time of surgery the rats were 10 weeks old and weighed 246 (± 6.5) g. They were housed in polyethylene cages for the remainder of the study and were provided with standard rat chow and water ad libitum.

Over the ensuing 4 weeks, systolic pressure was measured twice weekly using tail-cuff plethysmography. Rats were considered hypertensive only if systolic pressure exceeded 180 mm Hg during Weeks 3 and 4 of the follow-up period. By the end of the fourth week, the average weight of the 1K1C rats was 376 ± 16 g, and that of the sham-treated rats was 399 ± 6 g.

At the conclusion of the 4-week follow-up period, polyethylene tubing was inserted into a femoral artery and exteriorized through a tunnel to the back of the neck to provide direct recording of arterial pressure.
Three hours thereafter, when the rat had fully recovered from anesthesia, pressures were measured by a Statham P23Db strain gauge connected to a multichannel polygraph, and the rat was once again anesthetized with ether for systemic hemodynamic studies. At this time a femoral vein was also cannulated with polyethylene tubing for intravenous infusion; and a precalibrated electromagnetic flow probe (2.5 mm diameter) was placed around the ascending aorta through a midsternal incision using a technique previously reported from this laboratory.10 Before the chest was opened, the trachea was intubated with PE-240 tubing, and the rat was ventilated artificially using a Harvard small-animal respiratory apparatus. In addition to measuring ascending aortic blood flow, a catheter was inserted through the left atrium into the LV for recording LV pressures by means of another Statham transducer (P23Db) placed at chest level. Thus, arterial and LV pressures were recorded directly; ascending aortic blood flow was obtained by electromagnetic flowmetry; heart rate was determined from beat-to-beat analysis of the arterial pressure pulse; and the appropriate hemodynamic indices were calculated from these measurements. Stroke index was derived by dividing the cardiac output by heart rate, expressing this volume as ml/beat/kg body weight; total peripheral resistance index (TPRI), by dividing mean arterial pressure by the cardiac index and expressing this as TPR units; and LV end-diastolic pressure was derived directly using the appropriate zero references for each measurement.

Ventricular function data were obtained after baseline hemodynamic measurements had remained stable for at least 10 minutes. Isotonic saline was then infused rapidly over a 1-minute period through a femoral venous catheter at a rate of 40 ml/min/kg. Previous studies had demonstrated that this infusion rate produced a rapid increase and plateau in cardiac output within 60 seconds.11 Left ventricular end-diastolic pressure and cardiac output were recorded continuously during this infusion. Ventricular function curves were then obtained by plotting the LV end-diastolic pressure against cardiac output (at 2.5, 5, 10, 15, 17.5, and 20 mm Hg pressure).

Ventricular Performance (After 6 Weeks)

This group of animals was subdivided into four subgroups. The first subgroup of nine rats received a sham operation after 4 weeks and was followed for 2 more weeks. The second subgroup of 27 animals underwent the procedure for developing 2K1C as described above. Of these, eight rats remained untreated for the entire 6-week period; nine rats had a second operation for removal of the right renal arterial tantalum clip after 4 weeks and were followed for an additional 2 weeks. The remaining 10 2K1C rats were treated for 2 subsequent weeks with methyldopa (400 mg/kg/day) in divided daily doses by gastric tube feeding. Thus, there were three groups of 2K1C rats that were followed for 6 weeks: one group was left untreated; a second group had their renal arteries unclipped; and a third group treated for 2 weeks with methyldopa. At the conclusion of 6 weeks, hemodynamic measurements and ventricular performance studies were carried out in a fashion similar to that described above for the 4-week group of rats.

Heart Weight

At the conclusion of the hemodynamic study, the heart was removed and the atria carefully cut away. The right ventricular free wall was carefully dissected from the left. The intraventricular septum was thus included in the left ventricular weight.

Statistical Analysis

Student's nonpaired t test was used for analysis of data. Multiple analysis of variance was used to analyze for differences in ventricular performance data. Significance of difference was established at p < 0.05.

Results

Ventricular Performance (After 4 Weeks)

Following placement of the renal arterial clip, arterial pressure progressively increased as compared with the sham controls. At the end of 4 weeks, systolic, diastolic, and mean arterial pressures were significantly elevated (p < 0.001) and in direct proportion to the increased total peripheral resistance index (p < 0.01; table 1). Heart rate was faster in these 2K1C (p < 0.01), but cardiac index remained normal. Cardiac mass was directly related to the arterial pressure recorded in the unanesthetized rats prior to these hemodynamic studies (r = 0.794; p < 0.001) (fig. 1). Ventricular performance of the 2K1C rats was impaired compared to that of the sham-treated rats, but the difference in curves was only significant at the highest LV end-diastolic pressures. Thus, none of the sham-treated rats demonstrated a decrease in cardiac index as LV end-diastolic pressure increased. But, in contrast to the sham-operated rats, the 2K1C rats all increased LV end-diastolic pressure in excess of 17.5 mm Hg, and this was associated with a fall in cardiac index. During rapid volume infusion, systolic blood pressure (SBP) fell from 166 ± 16 to 141 ± 8 mm Hg and from 118 ± 5 to 113 ± 6 mm Hg in 2K1C and sham groups, respectively.

Ventricular Performance (After six weeks)

Whether the rats were treated by removal of the clip or with methyldopa, arterial pressure was reduced; this pressure reduction was associated with a regression of cardiac mass (table 2). However, there was no
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TABLE 1. Comparison of Systemic Hemodynamics and Cardiac Mass in Two-Kidney, One Clip Goldblatt Hypertensive Rats and Rats with Sham-Operations after 4 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Sham-operated rats</th>
<th>Renal hypertensive rats</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>399 ± 6</td>
<td>376 ± 16</td>
<td>ns</td>
</tr>
<tr>
<td>Arterial pressure (mm Hg):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>128 ± 4</td>
<td>175 ± 0.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diastolic</td>
<td>68 ± 3</td>
<td>99 ± 5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean</td>
<td>87.8 ± 3</td>
<td>124 ± 5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>330 ± 10</td>
<td>369 ± 9</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Cardiac index (ml/min/kg)</td>
<td>222 ± 10</td>
<td>203 ± 15</td>
<td>ns</td>
</tr>
<tr>
<td>Total peripheral resistance index (U)</td>
<td>0.41 ± 0.03</td>
<td>0.65 ± 0.07</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Stroke work index [(mm Hg) (ml/beat/kg) (0.136)]</td>
<td>117 ± 7</td>
<td>130.6 ± 10.5</td>
<td>ns</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>2.5 ± 0.4</td>
<td>3.6 ± 0.4</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>LV weight (g)</td>
<td>0.99 ± 0.02</td>
<td>1.12 ± 0.05</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>LV weight/body weight (mg/g)</td>
<td>2.47 ± 0.06</td>
<td>3.08 ± 0.11</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Each value represents the mean (± standard error). LV = left ventricular.

The relationship in these animals between arterial pressure and cardiac size ($r = 0.298$). Arterial pressures in the rats whose renal arteries were unclipped were at the same level as sham-operated rats (table 2), but arterial pressure and total peripheral resistance index in the methyldopa-treated 2K1C were higher ($p < 0.001$, each) despite regression of cardiac mass. Preinfusion cardiac index was depressed in 6-week 2K1C rats compared to the other three groups (table 2).

The LV function studies demonstrated normal cardiac performance curves in sham-operated rats, rats that had their renal artery unclipped, and rats that were treated with methyldopa (fig. 2 right). Therefore, despite the higher total peripheral resistance and arterial pressures, the methyldopa-treated 2K1C rats with regression of LVH had normal ventricular performance. None of the rats demonstrating regression of LVH increased ventricular end-diastolic pressure above 17.5 mm Hg during the rapid intravenous volume infusion. By comparison, rats with hypertension of 6 weeks' duration exhibited significantly reduced cardiac index at all LV filling pressures. In addition, when volume load was standardized to body weight, LV end-diastolic pressure rose more in the 6-week 2K1C rats, while at the highest filling pressure levels the LV performance curve exhibited a descending limb. There were no differences among groups in response of systolic pressure during infusion; SBP fell during the infusion from 112 ± 4 to 109 ± 4 mm Hg (sham); 128 ± 10 to 123 ± 10 mm Hg (unclipped); 135 ± 7 to 122 ± 8 mm Hg (methyldopa); and 166 ± 6 to 160 ± 6 mm Hg (2K1C).

In contrast to this abnormal LV performance of the 6-week 2K1C rats, analysis of the relationship of stroke work and LV end-diastolic pressure revealed an unchanged function. Thus, LV stroke work index was not significantly different among subgroups at any level of end-diastolic pressure (fig. 3).
### Table 2. Comparison of Systemic Hemodynamics and Cardiac Mass in Four Groups of Sham-Operated Rats

<table>
<thead>
<tr>
<th>Group 1 (sham)</th>
<th>Group 2 (clipped)</th>
<th>Group 3 (unclipped)</th>
<th>Group 4 (methyl-dopa)</th>
<th>Statistical comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of rats</td>
<td>9</td>
<td>9</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>427 ± 8</td>
<td>409 ± 10</td>
<td>406 ± 12</td>
<td>403 ± 13</td>
</tr>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>118 ± 5</td>
<td>174 ± 6</td>
<td>129 ± 7</td>
<td>148 ± 1</td>
</tr>
<tr>
<td>Diastolic</td>
<td>64 ± 3</td>
<td>97 ± 4</td>
<td>64 ± 4</td>
<td>75 ± 3</td>
</tr>
<tr>
<td>Mean</td>
<td>82 ± 3</td>
<td>122 ± 5</td>
<td>86 ± 5</td>
<td>99 ± 4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>287 ± 8</td>
<td>363 ± 13</td>
<td>322 ± 9</td>
<td>366 ± 11</td>
</tr>
<tr>
<td>Cardiac index (ml/min/kg)</td>
<td>238 ± 7</td>
<td>192 ± 14</td>
<td>250 ± 8</td>
<td>227 ± 9</td>
</tr>
<tr>
<td>Stroke index (ml/beat/kg)</td>
<td>0.83 ± 0.02</td>
<td>0.53 ± 0.04</td>
<td>0.78 ± 0.03</td>
<td>0.63 ± 0.04</td>
</tr>
<tr>
<td>Total peripheral resistance index (mm Hg/ml/min/kg)</td>
<td>0.35 ± 0.02</td>
<td>0.56 ± 0.05</td>
<td>0.35 ± 0.03</td>
<td>0.44 ± 0.03</td>
</tr>
<tr>
<td>Stroke work index (mm Hg) (ml/beat/kg) (1.36)</td>
<td>134.0 ± 7.5</td>
<td>117.1 ± 11.0</td>
<td>130.0 ± 6.5</td>
<td>125.4 ± 8.8</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>3.1 ± 0.3</td>
<td>4.8 ± 0.4</td>
<td>3.2 ± 0.3</td>
<td>3.1 ± 0.3</td>
</tr>
<tr>
<td>LV weight (g)</td>
<td>1.05 ± 0.06</td>
<td>1.23 ± 0.07</td>
<td>1.02 ± 0.03</td>
<td>1.04 ± 0.03</td>
</tr>
<tr>
<td>LV/body weight (mg/g)</td>
<td>2.44 ± 0.10</td>
<td>3.02 ± 0.16</td>
<td>2.52 ± 0.07</td>
<td>2.58 ± 0.06</td>
</tr>
</tbody>
</table>

Each value represents the mean (± standard error).

Group 1 = sham-operated; Group 2 = two-kidney one clip (2K1C) Goldblatt hypertensive rats; Group 3 = 2K1C rats with clip removed; Group 4 = 2K1C rats treated with methyl-dopa. LV = left ventricular.

### Figure 2.

Left ventricular performance in renovascular hypertensive rats. Left: Comparison of 4-week two-kidney, one clip (n = 11) Goldblatt hypertensive with sham-clipped rats (n = 12). Right: Comparison of treated (methyldopa, n = 10, or unclipped, n = 9) with 6-week clipped (n = 8) and sham-clipped (n = 9) rats. Values are means ± se. See text for further details.
Discussion

The results of these studies demonstrate that two-kidney, one clip Goldblatt hypertensive (2K1C) rats had increased arterial pressure produced by increased total peripheral resistance. This was associated with a normal cardiac index and a faster heart rate in the 4-week rats but a reduced resting cardiac index in the 6-week 2K1C. Resetting of the arterial baroreceptors (i.e., upward shift of both range and threshold of carotid sinus nerve activity leading to a faster heart rate) in renal hypertensive animals has been reported previously by McCubbin and coworkers. A tendency toward impaired LV performance was observed in rats with hypertension of 4 weeks’ duration as compared with sham-operated rats despite ventricular hypertrophy (fig. 2 left). This apparent functional deficit was even greater and reached statistical significance at all LV end-diastolic filling pressures in rats with untreated hypertension of 6 weeks’ duration (fig. 2 right). When hypertensive rats were treated either by surgical removal of the renal arterial clip or with methyldopa, there was rapid regression of LV mass to control levels within 2 weeks, associated with a normalization of ventricular performance. However, an analysis of the relationship of stroke work index to LV end-diastolic pressure indicates that there is no significant difference among the three 6-week 2K1C subgroups and their respective sham subgroup (fig. 3). The implication from these two findings is that the apparent functional deficit in LV performance at 6 weeks is related to the elevated arterial blood pressure in the untreated animals. Consequently, at all LV end-diastolic pressures the 6-week renal hypertensive rats were unable to maintain a normal cardiac index as indicated by a depressed LV function curve with a descending limb (fig. 2 right).

This study confirms the previous studies of Sen et al. demonstrating that methyldopa regresses LVH in hypertension. When spontaneously hypertensive rats with regression of LVH produced by methyldopa treatment were subjected to ventricular performance measurements, Spech and coworkers demonstrated a seemingly normal ventricular performance. In our present study, normal ventricular performance was observed in 2K1C rats treated with methyldopa despite the higher arterial pressure compared with sham rats. This difference may be in part related to the experimental model, genetic factors, and the rapidity with which the arterial pressure increases.

Factor(s) other than arterial pressure may be operative in the regression of cardiac hypertrophy following treatment with methyldopa. Angiotensin II and catecholamines may stimulate production of myocardial protein. Methyldopa decreases renal renin release and consequently plasma renin activity. It also reduces circulating catecholamines as a result of central alpha-receptor stimulation. Perhaps the effect of methyldopa on cardiac mass is partially mediated through these mechanisms. Additional effects of methyldopa, through specific action on myocardium, are also possible.

Methyldopa was the antihypertensive agent used in both this study and the above studies on spontaneously hypertensive rats. In the present study, however, the kidney was left in place after the renal arterial clip was removed, whereas in the myocardial biochemical study of Sen and coworkers the clipped kidney was excised. In any case, the present study demonstrates that LV performance was impaired with the development of the same type of renal hypertension associated with LVH (as indicated by the rightward shift and the descending limb of the ventricular performance curve). With treatment of hypertension, regression of LV mass was associated with a normalization of ventricular function even when arterial pressure and total peripheral resistance remained significantly elevated with methyldopa treatment.

Acknowledgments

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