Experimental Unilateral Renal Artery Constriction in the Dog

By Andrei N. Lupu, Morton H. Maxwell, Joseph J. Kaufman, and Fred N. White

ABSTRACT

Chronic hypertension caused by unilateral constriction of the renal artery in the presence of the opposite untouched kidney can be produced in the dog by progressive plication of the renal artery over a period of several hours. Twenty-three female dogs were studied. Mean arterial blood pressure was measured in the unanesthetized recumbent dog by direct puncture of the femoral artery. Reproducible control blood pressure readings were obtained only after daily training of the animals for at least 2 months. Mean arterial blood pressure for the whole group of animals was 98.25 ± 7.45 (sd) mm Hg prior to constriction. Three months after constriction, the mean arterial blood pressure of the group of dogs with a 50-63% reduction in renal blood flow was 132.4 ± 5.51 (sd) mm Hg (P < 0.001); for the group with a 78-86% reduction in renal blood flow it was 144.68 ± 10.68 (sd) mm Hg (P < 0.001). Six dogs from these two groups underwent ipsilateral nephrectomies 4-16 months after constriction, and their elevated arterial blood pressures returned to preconstriction normal values. It was concluded that this type of experimental hypertension in the dog is renal dependent in both the acute and the chronic stages.

KEY WORDS
chronic hypertension ipsilateral nephrectomy normal arterial blood pressure animal training graded constriction renal artery plication

It is generally believed that constriction of one renal artery in the presence of the opposite untouched kidney results in only a transient increase in systemic arterial blood pressure in the dog. Data from different laboratories indicate that the time course of spontaneous return to normotension after constriction is variable ranging from 10 days (1) to 6 weeks (2, 3). The present report demonstrates that unilateral constriction of the renal artery may result in a prolonged sustained increase in arterial blood pressure in the dog and that ipsilateral nephrectomy performed as long as 16 months after constriction consistently results in the return of elevated arterial blood pressure to preconstriction normal values.

Methods

Twenty-three female shepherd dogs weighing 16-40 kg were studied. Prior to constriction of the renal artery the dogs were trained to lie quietly on their backs to have mean arterial blood pressure (MABP) determinations performed in the unanesthetized state by direct needle puncture of the femoral artery. Despite daily training, it took at least 2 months before stabilization of control arterial blood pressure was achieved. Before and after renal artery constriction, MABP readings were obtained 1-3 times a week by direct puncture of the femoral artery with a 25-gauge needle connected to a Statham P23Db pressure transducer and an Electronics-for-Medicine recorder. In a preliminary study comprising 30 animals (A. L., unpublished data) it was found that use of large-bore needles frequently resulted in the formation of hematomas which led to
periarterial fibrosis. Apparently, under these conditions the arterial puncture was painful; the animals became restless during the procedure. As a result, no reliable pressure readings could be obtained.

The method used to constrict the renal artery has been previously reported (4, 5). It consisted of progressive plications of the renal artery wall with 6-0 silk vascular sutures until a predetermined reduction of renal blood flow was achieved as measured with an electromagnetic flowmeter. The flowmeter probe was placed around the renal artery proximal to the region of constriction. The flowmeter probes were calibrated in vitro against normal saline by using an arterial segment. Figure 1A and B depicts the method of constriction. In the anesthetized animal (pentobarbital 30 mg/kg) the renal artery was exposed through a retroperitoneal flank incision and gently freed from the surrounding tissues by blunt dissection. After placing the flowmeter probe around the renal artery, the wound was covered, and renal blood flow was allowed to stabilize for 20-30 minutes. Generally, during this time renal blood flow increased 10—15%. The renal artery was then manipulated with vascular forceps without interrupting renal blood flow, and the needle of the vascular suture was passed through the arterial lumen to reduce the luminal area by approximately 20—30% and tied in place. A similar plication was then made on the opposite side of the renal artery. By repeated further plications with the same sutures, renal blood flow could be reduced to a predetermined value. Because of the necessity for repeated periods of equilibration between plications for stabilization of renal blood flow, the procedure generally took at least 2 hours. After an equilibration period of 10—30 minutes following the final constriction, pressure determinations were obtained by direct needle puncture of the aorta and of the poststenotic renal artery, using the same equipment described above.

Figure 2A–D demonstrates the necessity for equilibration periods between plications and emphasizes the importance of renal blood flow measurements as a criterion of constriction. In this experiment the first two sutures did not modify the renal blood flow, although a thrill could be felt in the poststenotic renal artery. The third and fourth stitches (Fig. 2A and B) each reduced the blood flow by approximately 37—40%. However, renal blood flow returned to or close to preconstriction values in 10 and 20 minutes, respectively. The fifth stitch initially reduced the flow by up to 90% (Fig. 2C). But 1 hour later the blood flow had stabilized at a value two times higher (Fig. 2D). (At present we monitor renal blood flow for 1 hour after application of the last stitch. Optimal reduction in renal blood flow resulting in a sustained increase in MABP without the occurrence of collateral circulation seems to range from 0% to 30% as recorded 1 hour after constriction.) In 7 of 70 experimental animals, spontaneous return of elevated MABP to control values occurred during the first month after constriction; renal arteriography showed that the constriction was absent in all of these 7 animals. Direct inspection of the site of constriction showed that the sutures were outside the renal artery, suggesting spontaneous erosion through
the arterial wall or loosening of the ties in these experiments.

Following renal artery constriction the animals were divided into four groups. In the six animals of group 1, constriction of the renal artery resulted in no decrease in renal blood flow but in a measurable pressure gradient ranging from 15 to 45 mm Hg. In the seven animals of group 2, renal blood flow was reduced 50–62% and a pressure gradient of 99.40 ± 11.58 (SD) mm Hg developed. In the six animals of group 3, renal blood flow was reduced by more than 90% and a pressure gradient ranging from 15 to 25 mm Hg developed. In the four animals of group 4, renal blood flow was reduced by more than 90% and a pressure gradient of 130.00 ± 4.08 (SD) mm Hg developed.

Results

The results are summarized in Table 1. In group 1 (0% flow reduction) two animals demonstrated an increase in MABP at 1, 2, and 3 months after constriction, but in the remaining four animals MABP was unchanged. In the two animals with increased blood pressure, the pressure gradients after constriction were 35 and 45 mm Hg, respectively. These two animals were followed for 9 and 11 months after constriction, and over this time both demonstrated a sustained increase in MABP.

All the animals in group 2 (50–62% flow reduction) and group 3 (78–86% flow reduction) demonstrated an increase in MABP (Table 1). When compared to the control base-line MABP, the changes in MABP 1, 2,

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Blood flow reduction</th>
<th>Control MABP (mm Hg)</th>
<th>1st month MABP (mm Hg)</th>
<th>2nd month MABP (mm Hg)</th>
<th>3rd month MABP (mm Hg)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0%</td>
<td>101.58 (18)</td>
<td>105.0 (9)</td>
<td>105.0 (5)</td>
<td>103.2 (6)</td>
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<tr>
<td></td>
<td>0%</td>
<td>102.50 (10)</td>
<td>100.0 (5)</td>
<td>100.0 (5)</td>
<td>101.8 (5)</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>90.88 (17)</td>
<td>95.0 (10)</td>
<td>92.0 (5)</td>
<td>90.0 (8)</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>100.98 (44)</td>
<td>104.0 (8)</td>
<td>102.5 (8)</td>
<td>100.0 (6)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>101.0 ± 4.54</td>
<td>99.87 ± 5.63</td>
<td>98.75 ± 5.07</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>50%</td>
<td>100.00 (16)</td>
<td>126.0 (5)</td>
<td>117.5 (4)</td>
<td>122.5 (4)</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>100.62 (10)</td>
<td>121.67 (8)</td>
<td>126.0 (5)</td>
<td>124.29 (7)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>99.42 ± 4.27</td>
<td>123.86 ± 3.06</td>
<td>121.75 ± 6.01</td>
<td>123.39 ± 1.26</td>
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<tr>
<td>3</td>
<td>50%</td>
<td>103.17 (15)</td>
<td>130.14 (7)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>101.79 (17)</td>
<td>132.15 (5)</td>
<td>130.0 (5)</td>
<td>128.17 (5)</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>98.50 (10)</td>
<td>127.15 (4)</td>
<td>132.50 (4)</td>
<td>130.83 (6)</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>102.83 (40)</td>
<td>144.64 (10)</td>
<td>145.61 (8)</td>
<td>140.50 (10)</td>
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<tr>
<td>Mean ± SD</td>
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<td>98.42 ± 4.32</td>
<td>130.55 ± 8.18</td>
<td>128.63 ± 8.28</td>
<td>132.4 ± 5.11</td>
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<td>4</td>
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<td>100.82 (28)</td>
<td>147.86 (7)</td>
<td>131.67 (6)</td>
<td>130.13 (6)</td>
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<tr>
<td></td>
<td>50%</td>
<td>101.37 (15)</td>
<td>130.14 (7)*</td>
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<tr>
<td></td>
<td>50%</td>
<td>103.17 (15)</td>
<td>130.14 (7)*</td>
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<tr>
<td>Mean ± SD</td>
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<td>123.86 ± 3.06</td>
<td>121.75 ± 6.01</td>
<td>123.39 ± 1.26</td>
</tr>
<tr>
<td>5</td>
<td>50%</td>
<td>95.0 (18)</td>
<td>135.60 (9)</td>
<td>144.0 (11)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>95.10 ± 3.5</td>
<td>137.44 ± 8.18</td>
<td>138.63 ± 8.28</td>
<td>132.4 ± 5.11</td>
</tr>
<tr>
<td>6</td>
<td>50%</td>
<td>90.70 (14)</td>
<td>150.25 (8)</td>
<td>151.67 (6)</td>
<td>140.0 (9)</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>93.0 (10)</td>
<td>145.0 (6)</td>
<td>138.33 (5)</td>
<td>138.70 (4)</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>94.38 (18)</td>
<td>139.17 (6)</td>
<td>138.0 (5)</td>
<td>135.0 (4)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>94.90 ± 6.04</td>
<td>150.70 ± 10.02</td>
<td>148.0 ± 10.57</td>
<td>144.68 ± 10.68</td>
</tr>
<tr>
<td>7</td>
<td>50%</td>
<td>102.19 (16)</td>
<td>164.29 (7)</td>
<td>160.0 (6)</td>
<td>160.0 (6)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>100.49 ± 6.07</td>
<td>150.70 ± 10.02</td>
<td>148.0 ± 10.57</td>
<td>144.68 ± 10.68</td>
</tr>
<tr>
<td>8</td>
<td>50%</td>
<td>105.88 (38)</td>
<td>157.5 (12)</td>
<td>160.0 (6)</td>
<td>156.43 (8)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>100.70 ± 7.90</td>
<td>151.95 ± 11.10</td>
<td>148.21 ± 6.64</td>
<td>99.62 ± 7.88</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate the number of consecutive readings from which the base-line and the postconstriction monthly averages were calculated. The mean control MABP for all groups together was 98.25 ± 7.45 mm Hg.

*Ipsilateral nephrectomy after the 1-month control study.

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and 3 months after renal artery constriction were highly significant ($P < 0.001$).

In the animals of group 4 (>$90\%$ flow reduction) the average MABP for the whole group was increased by $24\text{ mm Hg}$ 1 month after renal artery constriction; MABP returned towards normal control values after this time (Table 1).

Figure 3 shows sections of a renal artery obtained 6 months after renal artery constriction from a dog in group 3. It can be seen that proximal to the constriction the renal artery appears to be normal (Fig. 3A). At the site of constriction (Fig. 3B) there is a medial hypertrophy. This represents a fibrous reaction probably due to the presence of the constric- tive sutures. The poststenotic dilated renal artery section appears in Figure 3C.

**EFFECT OF IPSILATERAL NEPHRECTOMY ON MABP**

As mentioned above, 7 animals underwent ipsilateral nephrectomies 1–16 months after renal artery constriction. Figure 4 depicts the time course of MABP response in 6 of these animals. (The pressure response of the animal whose kidney was removed 1 month after constriction is not plotted in the figure.) It can be seen that all animals responded to ipsilateral nephrectomy by a drop in MABP to values close to or below those recorded prior to constriction.

**Discussion**

A review of the published experiments of Goldblatt reveals that, although most dogs with unilateral renal artery constriction in the presence of an opposite untouched kidney demonstrated a spontaneous decrease in elevated arterial blood pressure to control values within 6 weeks or less (2, 3), in some animals hypertension persisted for the duration of the follow-up periods of 7 and 9 months (6, 7). Furthermore, removal of the clamp 9 months after constriction in one of these dogs resulted in return of the elevated arterial blood pressure to preconstriction values (7). However, this aspect of Goldblatt's work has been widely overlooked and at times erroneously interpreted. As an example, Braun-Menendez et al. in their authoritative treatise (8) stated: "When the ischemia is produced in one kidney only in dogs, the hypertension persists in general from several weeks to several months and then gradually returns to normal. In rats, however, persistent rises have been obtained by unilateral ischemia. The reason for the gradual disappearance of the hypertension in animals other than the rat has not been completely elucidated." This concept, which has since been perpetuated in the medical literature, was not in accord with available published data. At the time the book was written, the only animals in the literature which demonstrated an increase in arterial blood pressure lasting for more than 6 weeks were those of Goldblatt, cited above, and these animals did not return spontaneously to normotension. In fact, in reviewing the literature up to date, we have been unable to locate a single publication in which an increase in arterial blood pressure lasting for several months (3 or more) in a series of dogs has returned spontaneously to normal levels. In the publications of Fasciolo (9, 10), return to base-line pressure occurred in 17 days.

![FIGURE 3](attachment:image)

Microscopic sections of a constricted renal artery 6 months after constriction. A: Proximal segment; B: Segment at the level of the stenosis; C: Segment distal to the stenosis.

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MABP before and after renal artery constriction of six animals that underwent ipsilateral nephrectomies 4–16 months after unilateral renal artery constriction. Arrows indicate time of nephrectomy.

The work of Cerqua and Samaan (11) increased MABP lasted for less than 3 weeks, for Blalock and Levy (12) less than 4 weeks, and for Ebihara and Grollman (1) 10 days. A single exception might be the work of Kezdi published in 1960 (13). This series of five animals with unilateral main renal artery constriction demonstrated an increase in MABP 6 weeks after constriction, but at the time they were killed they had control MABPs. However, in this study the only postconstriction blood pressures reported were at 6 weeks and at the time of death. Thus, it is impossible to ascertain the precise time after constriction at which the drop in blood pressure occurred. Thus it would appear that the statement of Goldblatt, namely, that in most of the dogs arterial pressure returns to preconstriction values in 6 weeks or less after unilateral constriction, is a correct one (2, 3). It is considered, therefore, that increased MABP induced in the dog by unilateral main renal artery constriction and lasting 3 months or longer represents a chronic elevation in arterial blood pressure.

It is apparent that the present report is at variance with the results of most previous investigators. What then accounts for this difference? A first explanation may be the possibility that with the Goldblatt type of clamp there is a progressive thinning of the arterial wall in the region of the clamp, resulting in a lesser degree of stenosis (14). This view seems to have gained some support from the recent finding of Blair-West et al. (15) that in the sheep removal of the Goldblatt clamp resulted in an important dilatation of the renal artery at the level of the clamp, indicating a thinning of the arterial wall. It is known that for a single constriction the precise degree of reduction of the vascular cross-sectional area is highly critical (16, 17).
and that small increases in vascular radius of only a few hundred microns at the level of the constriction may return renal blood flow and the pressure distal to the constriction to normal values. Conversely, a slight decrease in radius may result in an important drop in blood flow and pressure. That this type of arterial wall thinning did not occur in the present series is shown in Figure 3. This interpretation, however, fails to explain why this same mechanism does not play an important role in the presence of unilateral constriction followed by contralateral nephrectomy or in the presence of bilateral renal artery constriction. It would suggest, nevertheless, that to evoke the same type of stimulus or stimuli leading to an increase in MAP the precise degree of constriction of the renal artery in the presence of an untouched opposite kidney is of critical importance.

A second possibility is the difference of “control” arterial pressures. Whereas in this study the base-line MAP for the whole group of animals was 88 mm Hg, in previous studies the value for normal MAP ranged from 120 to 150 mm Hg (7, 9-13, 18-20). Factitiously high base-line arterial pressure may mask significant pressor responses to experimental procedures. In other words, if the normal MAP is considered to be 140 mm Hg, as shown in Figure 4 by the horizontal solid line, an increase of 10-20 mm Hg above base line is statistically not significant. However, if in the same animal the base-line pressure is considered to be below 100 mm Hg, a change of 40-60 mm Hg in MAP becomes statistically highly significant.

This leads to a basic question with regard to experimental renovascular hypertension. What is the normal arterial blood pressure of a trained recumbent dog? Olmsted and Page (21) were the first to direct attention to the fact that the true resting arterial blood pressure of the dog was well below that previously reported. Our own experience, obtained from 13 animals with chronically implanted aortic catheters followed 20–120 days after implantation indicates that in a well trained dog systolic pressure ranges from 100 to 140 mm Hg and diastolic pressure from 50 to 80 mm Hg (MAP from 70 to 100 mm Hg) with a pulse pressure not exceeding 60 mm Hg (A. L., unpublished data). Characteristically an untrained anxious animal will display a wide pulse pressure with systolic values ranging from 200 to 240 mm Hg and diastolic pressures ranging from 80 to 100 mm Hg (MAP from 120 to 147 mm Hg). It would thus appear that determination of a reliable control arterial blood pressure in the animal under study is of the utmost importance in the evaluation of experimental hypertension. Furthermore, a sustained increase in MAP of 30-50 mm Hg (groups 2 and 3) is by no means negligible. Even in the human such an increase in MAP is highly significant. Recent unpublished data obtained from the National Cooperative Study of Renovascular Hypertension show that, for 250 patients who underwent ablative or corrective surgery for unilateral renal artery stenosis in the presence of a normal opposite kidney, the average systolic pressure prior to surgery was 180 ± 20 (SD) mm Hg and the average diastolic pressure was 108 ± 11 (SD) mm Hg. This would represent a MAP of approximately 132 mm Hg. Considering that the normal MAP in the human is 90 mm Hg, the mean increase in MAP for these 250 patients was 42 mm Hg, which is very close to the increment in pressure observed in the present series of animals.

A third possibility is that the method used differed somewhat from previous methods of renal artery constriction. None of the previous methods (Goldblatt clamp, cellophane perinephritis, figure-of-eight renal compression) were quantitatively standardized so as to define the functional significance of the stenosis. With regard to the Goldblatt clamp, Goldblatt (22) stated: “It follows that the degree of ischemia could not be standardized and the exact extent (of renal artery stenosis) was not known.” The prolonged periods of equilibration between successive renal artery plications (see Methods) to allow for delayed autoregulation (23) and subsequent stabilization of renal blood flow added even further quantification to the present method. An unknown
proportion of previously reported experimental animals may have had little or no reduction in blood flow, similar to the four animals in group 1, or conversely they may have had such an extensive degree of constriction that renal atrophy resulted, similar to the animals in group 4; neither of these two groups of dogs developed sustained hypertension.

A recent publication appears to be contradictory to the present results. Using the method proposed by Collins (24) (tying the renal artery around a stylet of predetermined diameter, which is subsequently removed), Ebihara and Grollman (1) reported that unilateral renal artery constriction in dogs with relatively normal control mean arterial blood pressures (100-105 mm Hg) resulted in only transient hypertension of less than 10 days duration. We therefore repeated these experiments in three animals, using the exact method of constriction used by these investigators, and in addition monitored renal blood flow with an electromagnetic flowmeter. For up to 3 hours of observation after renal artery constriction the renal blood flow remained at zero or close to zero. This indicated that the severity of the constriction was greater than that obtained in our animals of group 4 (greater than 90% reduction in flow) in which renal atrophy and only transient hypertension were observed. These findings seem to be supported by the previously published data of Murphy and Gagnon (25), who employed the same technique of renal artery constriction as that used by Ebihara and Grollman. Of eight animals followed 12-54 days after renal artery constriction, five demonstrated an atrophic nonfunctioning kidney.

The fact that two of our animals with no flow reduction (group 1) developed a sustained increase in MABP would lend support to the concept forwarded by Corcoran and Page (26, 27), namely that experimental hypertension can be obtained in the absence of renal "ischemia."

It is generally accepted that the acute phase of hypertension following renal artery constriction is renal dependent (due to liberation of renal pressor substance), whereas the chronic phase has been attributed to an extrarenal, possibly neurogenic, mechanism (28). These previous experimental models are not applicable to the human, since a number of clinical reports have demonstrated cure of unilateral renal arterial hypertension by nephrectomy even several years after the onset. The present experimental model more closely simulates human renal arterial hypertension, inasmuch as unilateral nephrectomy, performed as long as 16 months after constriction, regularly results in a decrease in arterial pressure to preconstriction levels. Recently, Fujii et al. (29) reported similar results in rabbits. These results suggest a unitary renal-dependent mechanism responsible for both the acute and the chronic phase of renal arterial hypertension.

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References


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