Contribution of stenosis resistance to the rise in total peripheral resistance during experimental renal hypertension in conscious dogs

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Summary

1. Mild, moderate and severe renal artery stenosis was induced in uninephrectomized conscious dogs by inflating a renal artery cuff to lower distal pressure to 60, 40 or 20 mmHg respectively. The renal artery was narrowed progressively over the next 3 days by further inflation of the cuff to relower the distal renal artery pressure to the initial values.

2. Graded progressive stenosis produced graded progressive rises in blood pressure, plasma renin activity and total renal resistance to flow over the 3 day period, followed by a return to control values 24 h after cuff deflation.

3. The rise in total renal resistance to flow was almost entirely due to the stenosis, with only small changes occurring in renal vascular resistance.

4. In moderate and severe stenosis cardiac output did not alter significantly and thus increases in blood pressure were due to increases in total peripheral resistance. In these groups the resistance to blood flow of the stenosis accounted respectively for about 36 and 26% of the rises in total peripheral resistance. Vasoconstriction of the other non-renal vascular beds accounted for the remainder of the increase in total peripheral resistance.

5. In mild stenosis the changes in both cardiac output and total peripheral resistance were variable and not statistically significant. In this group the rise in stenosis resistance was compensated by vasodilatation of the non-renal vascular beds.

6. In all groups rises in plasma renin activity and blood pressure correlated with the haemodynamic severity of the stenosis.

7. Thus the resistance to blood flow of the moderate and severe renal artery stenoses accounted for one-quarter to one-third of the increases in total peripheral resistance. The remainder of the increase in total peripheral resistance was due to vasoconstriction of non-renal beds.

Key words: cardiac output, Goldblatt hypertension, renal blood flow, renin.

Introduction

In 1934 Goldblatt and his colleagues reported that narrowing the renal arteries resulted in arterial hypertension, whereas narrowing the femoral or splenic arteries did not [1]. These results suggested that the kidney provided some specific stimulus to increase blood pressure and 5 years later the discovery of the potent pressor hormone angiotensin II was reported [2, 3]. This hormone has generally been considered to be the major participant in the development of Goldblatt hypertension [4]. So far the possibility has not been considered that the renal artery stenosis resistance itself might make a significant contribution to the rise in total peripheral resistance in this type of hypertension.

We have shown previously that very marked narrowing of the renal artery was required to
achieve chronic sustained hypertension in conscious dogs [5]. This observation, together with the fact that the kidney receives a substantial proportion of the cardiac output, suggested that the stenosis itself might possibly exert a considerable resistance to blood flow. Goldblatt and his colleagues had shown that stenosis of the femoral and splenic arteries did not produce hypertension, but these arteries receive much lower proportions of the cardiac output than the kidney.

To assess the direct contribution of the stenosis to the increase in total peripheral resistance, we measured cardiac output, total renal blood flow and the blood pressures above (aorta) and below (renal artery) the renal artery stenosis. The relative magnitudes of the changes in total peripheral and stenosis resistances were then measured during 3 days of graded progressive narrowing of the renal artery in conscious dogs.

**Methods**

**Preparation of dogs**

Trained dogs were prepared at a preliminary operation at least 10 days before the first experiment [5]. With the dog anaesthetized with nitrous oxide and halothane, one renal artery was prepared with a perivascular silastic balloon cuff (1 cm length × 0.8 cm internal diameter, Hazen Everett, NJ, U.S.A.), an intravascular renal artery catheter distal to the cuff and a Doppler flowmeter (internal diameter 5 mm) either distal or proximal to the cuff. Catheters were also placed in the aorta and vena cava. The other kidney was removed. The chest was opened at the third intercostal space and a loose-fitting padded electromagnetic flowmeter transducer (1.8-22 mm internal diameter) was applied to the aortic arch. Wires and catheters were exteriorized on the left chest.

**Experimental protocol**

Control measurements were made on separate days with the trained dog lying on a padded table in a quiet laboratory. After measurements on the morning of day 2 the renal artery cuff was inflated to lower distal renal artery pressure to 60, 40 or 20 mmHg and the haemodynamic and renin changes followed for the next 1 h. Subsequently the cuff was adjusted by inflating it further to produce the same distal renal artery pressure (60, 40 or 20 mmHg) twice daily (in the morning after measurements and in the evening) for 3 days. The renal artery was thus progressively narrowed over 3 days and throughout this period steady-state haemodynamic measurements were made 18 h after the preceding cuff adjustment. After measurements on day 3 of stenosis, the cuff was deflated and recovery day measurements made at 24 h.

**Measurements**

Recordings of mean arterial pressure, renal artery pressure, renal blood flow (Doppler flowmeter) and cardiac output (electromagnetic flowmeter) were begun about 30 min after the dog had settled in the laboratory. Cardiac output and renal blood flow were then measured alternately four times for 5 min each. Arterial blood samples were taken for radioimmunoassay for plasma renin activity and plasma angiotensin II concentration [6].

Cardiac output (excluding coronary blood flow) was measured as ascending aortic root blood flow by means of an electromagnetic flowmeter (Biotronix 622 pulsed logic flowmeter). Zero flow was taken as end-diastolic flow and continuously checked by monitoring the integrated stroke-volume trace for zero integration during diastole before resetting for the following flow-pulse wave. The transducers were of a C-coiled coreless design incorporating platinum/gold alloy electrodes [7]. They were cushioned in reinforced silastic sheeting (0.02 inch thick, Dow Corning) and calibrated in vitro with NaCl solution (150 mmol/l) before implantation.

Renal blood flow was measured by the Doppler flowmeter around the renal artery, as described previously [6, 8]. The advantages of the Doppler flowmeter in this situation include the linear relationship between Doppler shift and volume flow over a wide range of pressure (Fig. 1a; [9]) and the stability of electronically determined flowmeter zero which was checked by brief inflation of the renal artery cuff 2 days before and again at the end of the 6-day experiment (e.g. Fig. 1b). Five Doppler flowmeters were calibrated by implanting them around the carotid artery of an additional dog and then pump-perfusing the carotid arteries at autopsy 2 weeks later. Two other Doppler flowmeters were pump-perfused in situ around the renal artery, but this proved impossible in most dogs due to the extensive scar tissue around the artery. The relationship between kHz Doppler shift and volume flow was linear (Fig. 1a) in agreement with previous findings in the rabbit [8]. There were small differences in individual slopes of the calibration lines, but the intercepts were not significantly different from
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665

0 100 200 300
Flow (ml/min)

0 1 2
Doppler shift (kHz)

0 1 2
3

FIG. 1. (a) Calibration of a renal artery Doppler flowmeter by pump-perfusion of the renal artery at autopsy. The artery was perfused at two pressures, 150 (■) and 90 mmHg (○). The regression line is for 90 mmHg. (b) Comparison in one dog of occlusion of the renal artery for 1 min to obtain zero blood flow and the electronic zero of the Doppler flowmeter. BP = Aortic blood pressure; RBF = renal blood flow.

zero. The average value for blood flow/kHz Doppler shift for the seven flow probes was 103 ml/min (range 95–108). We have used the average slope 103 ml min⁻¹ kHz⁻¹ to express renal blood flow in the different groups.

Seven dogs were subjected to each grade of severity of renal artery stenosis and to the control experiment (no renal artery stenosis, measurements made over the same number of days). Cardiac output was successfully measured in four dogs in mild stenosis group, five dogs in the moderate group and four dogs in the severe group. The electromagnetic flowmeter probes failed in the remaining dogs due to entry of body fluids.

Resistance to blood flow was calculated as pressure/flow neglecting venous pressure; total peripheral resistance (TPR) = mean arterial pressure (MAP, mmHg)/cardiac output (ml/min); total kidney resistance = MAP/renal blood flow (RBF, ml/min); renal vascular resistance (RVR) = distal renal artery pressure (RAP, mmHg)/RBF; renal artery stenosis resistance = (MAP – RAP)/RBF. To assess the contribution of the kidney to the rise in total peripheral resistance it was more convenient to assess the changes in conductance units (flow/pressure). Total peripheral conductance (TPC), renal vascular conductance and total kidney conductance (TKC) were calculated and non-renal (i.e. rest of body) conductance (NRC) was derived from the relationship TPC = TKC + NRC.

Renal artery occlusion

The acute changes in blood pressure after complete occlusion of the renal artery were studied in a separate group of anaesthetized dogs [pentobarbitone, 30 mg/kg, intravenous (i.v.)]. In these dogs an inflatable cuff and electromagnetic flowmeter were placed around the left renal artery. The blood pressure response to a 10 min occlusion of the renal artery was studied in four untreated dogs and five dogs pretreated with [Sar¹,Ile⁸]angiotensin II (5 mg/kg, i.v.).

Results

Haemodynamic effects of progressive stenosis

After control measurements were obtained on 2 days, renal artery stenosis was induced on the second morning by lowering distal renal artery pressure to either 60, 40 or 20 mmHg by inflating the renal artery cuff rapidly over a period of 30 s. The cuff was then securely clamped. In each dog distal renal artery pressure was lowered again to the specified value that afternoon (6 h later). The next set of haemodynamic measurements were made 18 h later at the end of day 1. Distal renal artery pressure was then lowered again to the specific value, by further cuff inflation and the cuff clamped again, the procedure repeated again that afternoon and measurements were made again 18 h later (i.e. next day, day 2). After lowering distal renal artery pressure, as on the previous day, we obtained another set of measurements after another 18 h, on day 3. When these were completed the cuff was deflated and another set of "recovery" measurements made 24 h later (Fig. 2). Another group of instrumented dogs was studied daily with an identical protocol, except that no stenosis was induced (sham
FIG. 2. Haemodynamic and renin response to graded progressive stenosis of the renal artery. After 2 control days (C1, C2) the renal artery cuff was inflated to lower distal pressure to 60 ('mild'), 40 ('moderate') and 20 mmHg ('severe') twice daily (23 and 18 h before readings on days 1, 2 and 3 of stenosis). The cuff was deflated after day 3 measurements and recovery (R) measurements made 24 h later. The left hand panel shows dogs subjected to the same protocol, except that there was no inflation of the renal artery cuff. AP = Arterial pressure, RBF = renal blood flow (kHz Doppler shift), CO = cardiac output and PRA = plasma renin activity. Bars show ±SEM of each measurement within dogs for 2 control days and ±SE of difference from mean control value (i.e. within dogs) for the 3 days of stenosis and recovery day. The number of animals was seven in each group. Cardiac output measured in dogs: n = 5, 4, 5 and 4 respectively in the groups from left to right.

There were no significant changes in any of the haemodynamic variables in this latter group (Fig. 2).

Repeatedly lowering distal renal artery pressure to a given value resulted in progressive narrowing at each grade of stenosis and was associated with corresponding rises in systemic mean arterial pressure (Fig. 2). By day 3 the increase was 19.4 ± 5.2 mmHg in the group with mild stenosis, 33.9 ± 11.2 in those with moderate stenosis and 52.3 ± 15.9 mmHg in those with severe stenosis. The cardiac output responses varied somewhat in individual dogs in each group, but there were no significant time-related changes in any of the groups (Fig. 2).

Renal blood flow remained unchanged in mild stenosis, but fell significantly over the 3 day period in the other two groups (Fig. 2). By day 3 it had fallen by 27.3 ± 6.7% of the control value in progressive moderate stenosis and by 45.6 ± 14.6% in progressive severe stenosis. By day 3 distal renal artery pressure was also below the control value in all groups, with average reductions of 8.8 ± 6.0 mmHg (mild), 23.6 ± 8.5 mmHg (moderate) and 25.4 ± 4.0 mmHg (severe stenosis) (Fig. 2). In the severe progressive stenosis group three of the seven dogs developed symptoms of malignant hypertension on day 3 (reduced plasma volume, very severe hypertension, some haemolysis).

Total kidney resistance (renal vascular resistance plus stenosis resistance) increased progressively in all groups with the increases almost entirely due to the progressive elevation of the stenosis resistance in all cases (Fig. 3). By day 3 the rise averaged about 20, 90 and 330% of initial
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Control respectively in the mild, moderate and severe stenosis groups. The renal vascular resistance fell slightly during mild stenosis (P = 0.05, days 2, 3), remained unchanged in moderate stenosis and increased slightly by day 3 in severe stenosis (N.S.) (Fig. 3).

Conductance changes

These were calculated from a subset in each grade of progressive stenosis in which cardiac output and renal blood flow were both measured (mild stenosis n = 4; moderate stenosis n = 5; severe stenosis n = 4).

In progressive mild stenosis changes in total peripheral conductance were variable and not significant over the 3 days of stenosis (Fig. 4). However, there was a small fall in total kidney conductance, which averaged 0.89 ± 0.21 litre s⁻¹ kPa⁻¹ × 10⁻⁴ on day 3 (P < 0.05). This fall was entirely due to the stenosis. In contrast non-renal conductance tended to increase slightly but not significantly over the 3 day period (Fig. 4).

In progressive moderate stenosis total peripheral conductance fell by day 3 by an average of 6.08 ± 1.37 litre s⁻¹ kPa⁻¹ × 10⁻⁴ (Fig. 4). This was associated with a fall in total kidney conductance of 2.34 ± 0.33 litre s⁻¹ kPa⁻¹ × 10⁻⁴ and a fall in non-renal conductance of 3.73 ± 1.31 litre s⁻¹ kPa⁻¹ × 10⁻⁴. Similar conductance changes were observed in progressive severe stenosis (Fig. 4).

Fig. 4. Vascular conductances during progressive mild (n = 4) moderate (n = 5) and severe (n = 4) renal artery stenosis. C = Average of 2 control day measurements; 1, 2 and 3 = days of stenosis; R = recovery day. Total peripheral conductance (■), 'rest of body' conductance (▲), renal vascular conductance (●) and total kidney (stenosis and vascular) conductance (○). The shaded area represents the stenosis resistance.

Fig. 5 summarizes the relative contributions of the different circulatory sections to the total peripheral conductance changes. In progressive mild stenosis there appeared to be 'compensation' by non-renal beds for the fall in total kidney conductance, the fall in the latter being entirely due to the stenosis. In moderate stenosis the renal artery narrowing accounted for a substantial fraction of the overall fall in total peripheral conductance (43 and 30% on days 2 and 3 of the period of stenosis respectively) (Fig. 5). In severe
TABLE 1. Plasma angiotensin II concentration (pmol/l) during mild, moderate and severe progressive renal artery stenosis

Values are means ± SEM (control days) and ±SE of mean difference from control (for stenosis and recovery days). (*Values too high for assay.)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Days of stenosis</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mild</td>
<td>9 ± 3</td>
<td>8 ± 2</td>
<td>15 ± 5</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 ± 1</td>
<td>33 ± 11</td>
<td>52 ± 31</td>
</tr>
<tr>
<td>Severe</td>
<td>4 ± 1</td>
<td>32 ± 6</td>
<td>103 ± 41</td>
</tr>
</tbody>
</table>

stenosis the stenosis accounted for a slightly smaller proportion (37 and 17% on days 2 and 3 respectively).

Plasma renin activity

In progressive mild stenosis plasma renin activity was still close to control values on day 1, but thereafter increased on each of the other 2 days (Fig. 2). In both moderate and severe stenosis plasma renin activity increased each day, with average levels higher in severe compared with moderate stenosis. Angiotensin II concentration changes followed an essentially similar pattern to the changes in plasma renin activity (Table 1).

Relationships of stenosis resistance to blood pressure and plasma renin activity changes

The progressive daily increases in systemic blood pressure and in plasma renin activity correlated closely with the increase in stenosis resistance (Fig. 6). The relationship of each variable to the stenosis resistance was adequately described by a common regression line over the entire range of the three grades of stenosis.

Occlusion of the renal artery

Complete occlusion of the renal artery in conscious dogs, for periods of up to 1 min (to obtain zero flow to check the Doppler flowmeter electronic zero) were without effect on arterial pressure (e.g. Fig. 1b).

Occlusion of the renal artery in anaesthetized dogs caused an initial increase in blood pressure of 3.0 ± 1.2 mmHg with a further small rise of 2.0 ± 2.5 mmHg at 10 min, and similar rises of 4.4 ± 1.6 mmHg and 2.0 ± 3.8 mmHg in dogs pretreated with [Sar, Ile8]angiotensin II respectively.

Discussion

Graded progressive narrowing of the renal artery over 3 days increased total renal resistance to blood flow in the three groups of dogs. The elevation in resistance was almost entirely due to the renal artery stenosis, with only minimal changes in the resistance of the intrarenal vasculature. Total peripheral resistance also increased progressively in the moderate and severe groups and was responsible for almost the entire elevation of arterial pressure, since cardiac output did not change significantly. The values for total kidney resistance on days 2 and 3 of moderate stenosis were closely similar to those calculated from the data of Harris & Ayers [10] and Ferrario & McCubbin [11] and in our previous study in chronic hypertension [5]. Thus, had no further narrowing of the renal artery been made, a stable type of benign Goldblatt hypertension would probably have resulted. In this group the hypertension was entirely due to increased total peripheral resistance, with the stenosis accounting for about one-third of that rise. The other two-thirds of the rise in total peripheral resistance was due to vasoconstriction of other non-renal vascular beds, presumably due to the increased plasma levels of angiotensin II. There was no vasoconstriction of the vasculature of the kidney in this moderate stenosis group, possibly due to the presence of opposing local autoregulatory factors.
resulting from the reduced distal renal artery pressure and renal blood flow or because of the intrarenal shifts in flow.

There does not seem to have been serious consideration previously of the possible direct contribution of the renal artery stenosis to the elevation in total peripheral resistance in Goldblatt hypertension. Our experiments are the first to measure stenosis resistance and total peripheral resistance in the same experiments. In addition, the complexity of the hydraulic properties of arterial stenoses has only recently become recognized [12–14], particularly in relation to renal artery stenosis [6, 15]. It is now known that the tone of the vascular bed distal to the stenosis is a particularly important determinant of the resistance offered by a given degree of narrowing of the renal artery [15] and there is also a non-linear relationship between aortic pressure and blood flow through an arterial stenosis and distal vascular bed [12]. Although progressive narrowing of the renal artery would tend to reduce renal artery pressure per se, the associated elevation of arterial blood pressure offsets this by increasing the flow through the stenosis and kidney. The exact effects on flow are difficult to predict because of the non-linear relationship of flow to both arterial pressure and renal vascular resistance. We found that the kidney maintained a relatively high renal blood flow, not far below the fraction of cardiac output before moderate stenosis. The less the reduction in renal blood flow, the greater can be the contribution of the stenosis to the overall rise in total peripheral resistance. Thus renal blood flow fell more in the severe group than in the moderate group and the contribution of the stenosis to the rise in total peripheral resistance was less.

An extreme example to illustrate this phenomenon is the effect of complete occlusion of the renal artery. Only minimal and transient elevations in blood pressure were seen when the renal artery was occluded in anaesthetized dogs or during the brief occlusion performed to check electronic zero of the Doppler flowmeter in our conscious dogs. Similarly, only small and transient changes in blood pressure have been observed when an arteriovenous fistula with blood flow similar to the renal artery is opened or closed, although large changes occur in cardiac output [16].

The following formulation helps explain why complete occlusion of the vascular bed has a minimal effect on systemic blood pressure and total peripheral resistance. For convenience vascular conductance is used instead of resistance. Thus \( BP = Q_t / C_t \), where \( Q_t = Q_r + Q_o \) and \( C_t = C_r + C_o \) \( (BP = \text{arterial blood pressure}, Q = \text{flow}, C = \text{vascular conductance and subscripts } t, r \text{ and } o \text{ refer to total, renal and all other beds of the body respectively}) \). Then \( BP = (Q_r/C_r) + (Q_o/C_o) \). Thus, both \( Q_r \) and \( C_r \) of the last equation become zero on occlusion of the renal artery, and there are only minimal effects on blood pressure. Small changes that do occur are presumably buffered through baroreflex mechanisms. In our experiments on partial renal artery stenosis, elevation of arterial pressure maintains renal blood flow and the stenosis resistance becomes a considerable fraction of total peripheral resistance. The main cause of the elevation in blood pressure was vasoconstriction of non-renal vascular beds, presumably due to the high circulatory levels of angiotensin II. Expansion of plasma volume and increased cardiac output might also contribute to the hypertension subsequently [17]. This unique property of the kidney, to elevate indirectly blood pressure through its endocrine and body fluid regulatory properties, is in contrast with other vascular beds of the body. Goldblatt and colleagues [1] found for example that narrowing the splenic and femoral arteries did not produce hypertension. However, these vascular beds not only take a lower percentage of the cardiac output than the kidneys, but also lack means of indirectly elevating systemic blood pressure.

In the mild group there were variable changes in both cardiac output and total peripheral resistance within individual dogs responses. However, the stenosis increased the total kidney resistance in this group too, but compensatory vasodilatation tended to occur in non-renal vascular beds. We have previously shown that arterial baroreflexes suppress the blood pressure and renin rises during the first hour after renal artery stenosis and it is likely that similar mechanisms were acting here. This would also help to explain the lack of a rise in plasma renin activity after the first day of stenosis in this group.

In summary, it is possible to regard the stenosis of the renal artery as making two distinct contributions to the increase in peripheral resistance in Goldblatt hypertension. The first and quantitatively most important effect is to stimulate early renin release and our results show how strikingly the release of renin correlates with the severity of the stenosis resistance. Blockade of angiotensin II generation during this initial stage almost completely prevents the initial increase in blood pressure [4]. Secondly, the hydraulic resistance of the kidney contributes directly to the increase in total peripheral resistance, with this effect at least partially dependent on angiotensin...
II-mediated elevation of arterial pressure. That is, the stenosis resistance and the renin–angiotensin system are probably mutually dependent in their effects on arterial pressure initially. It remains to be shown whether angiotensin II is a critical part of the sequence or whether the stenosis can directly increase peripheral resistance and arterial blood pressure chronically.

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References


