J. Physiol. (1979), **287**, *pp.* 231–245
With 7 text-figures
Printed in Great Britain

ACUTE RENAL HAEMODYNAMIC AND RENIN-ANGIOTENSIN SYSTEM RESPONSES TO GRADED RENAL ARTERY STENOSIS IN THE DOG

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(*Received 20 June 1978*)

SUMMARY

1. The acute renal haemodynamic and renin-angiotensin system responses to graded renal artery stenosis were studied in chronically instrumented, unanaesthetized dogs.

2. Stenosis was induced over 30 sec by inflation of a cuff around the renal artery to lower distal pressure to 60, 40 or 20 mmHg, with stenosis maintained for 1 hr. This resulted in an immediate fall in renal vascular resistance, but over the next 5–30 min both resistance and renal artery pressure were restored back towards prestenosis values. Only transient increases in systemic arterial blood pressure and plasma renin and angiotensin levels were seen with the two milder stenoses. Despite restoration of renal artery pressure, renal blood flow remained reduced at all grades of stenosis.

3. Pre-treatment with angiotensin I converting enzyme inhibitor or sarcosine[1], isoleucine[8] angiotensin II greatly attenuated or abolished the restoration of renal artery pressure and renal vascular resistance after stenosis, and plasma renin and angiotensin II levels remained high. Renal dilatation was indefinitely maintained, but the normal restoration of resistance and pressure could be simulated by infusing angiotensin II into the renal artery.

4. The effective resistance to blood flow by the stenosis did not remain constant but varied with changes in the renal vascular resistance.

INTRODUCTION

In their classic paper describing experimental renal hypertension Goldblatt, Lynch, Hanzal & Summerville (1934) stressed the difficulty of standardizing the degree of renal artery stenosis. Recent authors have endeavoured to achieve this by establishing a stable pressure gradient of about 30–50 mmHg or more across the stenosis at the time of application of the constrictive device (Ferrario & McCubbin, 1973; Ayers, Vaughan, Yancey, Bing, Johnson & Morton, 1974; Liard, Cowley, McCaa, McCaa & Guyton, 1974; Tagawa, Gutmann, Haber, Miller, Samuels & Barger, 1974). In these studies the exact method of establishing the gradient has not been described, though some of the descriptions imply that it is necessary to tighten the stenosis several times over the first ½–2 hr after initial application (e.g. Ayers

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et al. 1974; Bianchi, Fox, Pagetti, Caravaggi, Baer & Baldoli, 1975). Some 'autoregulation' of blood flow following initial application of stenosis is suggested by the considerable restoration of renal blood flow that has been observed within minutes after acute stenosis in the dog (Lupu, Maxwell, Kaufman & White, 1972; Watkins, Davis, Hanson, Lohmeier & Freeman, 1976). Furthermore, Anderson, Korner, Johnston, Angus & Casley (1978) showed recently in conscious dogs that renal artery pressure also begins to recover within minutes after production of stenosis.

The evaluation of the haemodynamic events after acute stenosis has been difficult, because in none of the above studies have there been simultaneous and continuous measurements of distal renal artery pressure and renal blood flow. This is particularly important in view of experimental and theoretical studies of the haemodynamic interrelationships in arterial stenosis (Shipley & Gregg, 1944; May, Van de Berg, De Weese & Rob, 1963; Thomas, Brockman & Foster, 1968; Berguer & Hwang, 1974; Gould, Lipscomb & Hamilton, 1974; Young, Cholvin, Kirkeeide & Roth, 1977). These indicate that in addition to the resistance offered by the arterial stenosis, the vascular resistance of the distal bed is an important determinant of both the pressure gradient across the stenosis and the blood flow.

The purpose of the present experiments was to study the effects of several grades of renal artery stenosis on the time course of the simultaneously measured changes in renal artery pressure, renal blood flow, renal vascular resistance and aortic pressure in unanaesthetized, trained dogs. The changes in renal haemodynamics were related to changes in plasma renin activity and angiotensin II (AII) concentration. In addition, we examined the role of the renal effects of angiotensin II on the changes in renal blood flow, renal artery pressure and renal vascular resistance.

METHODS

Animals and operations

The experiments were performed in male mongrel dogs weighing from 18 to 30 kg. A preliminary operation took place at least 2 weeks before the first experiment, using halothane-N_2O anaesthesia after acepromazine premedication (100 μg/kg). One kidney was removed and a polyvinyl chloride catheter was inserted through the wall of the renal artery of the remaining kidney (Herd & Barger, 1964). The catheter tip was distal to an inflatable saline-filled silastic cuff of 5 mm i.d. (Hazen Everett, Mahway, N.J., U.S.A.). A cuff type Doppler flow probe was placed around the renal artery, and polyvinyl chloride catheters were inserted into the abdominal aorta and inferior vena cava. The catheters and flowmeter wires were exteriorized on the chest and protected by a canvas jacket. The dogs received streptomycin (250 mg/day) and penicillin (250 mg/day) given intramuscularly for 1 week after the operation. They had free access to water and were fed on a diet of canned dog food and dry biscuits, with a consequent high daily sodium intake of about 110 m-equiv/day (see O'Connor, 1977).

Protocol

The dogs were trained to lie quietly on a padded table and had become thoroughly familiar with the laboratory by daily visits for flushing of their catheters before the start of the experiment. At each time any small additional air bubbles that had accumulated were removed by applying suction to the cuff and tubing using a 0.9% NaCl-filled syringe. The cuffs and tubing were checked post-mortem and appeared to be completely free of bubbles. On the day of the experiment the dogs rested 30 min before the start. The experiments on the acute effects of stenosis consisted of a control period followed by a period of stenosis. When more than one experiment was performed in a given dog, at least 5 days were allowed between experiments.

Three grades of severity of stenosis were studied in the main series of experiments. The renal

artery was narrowed by inflating the cuff over a period of 30 sec to lower distal renal artery pressure to the predetermined value of either 60, 40 or 20 mmHg in a given experiment, and then clamping the cuff tubing to maintain inflation for the next 30–60 min. The dogs gave no signs of distress at any time during the experiment and appeared to be unaware of the cuff being inflated. The pressure in the cuff during inflation is high, 700–800 mmHg, so that the inflated cuff is taut and fairly rigid. Because of the rapid renal vascular resistance changes occurring after initially inflating the cuff (see Results) the properties of the cuff system were examined *in vitro* in a number of experiments using a thin walled rubber tube as a renal artery model. The system was perfused at constant flow by means of a roller pump, with a pressure gradient across the stenosis of about 60 mmHg, and resistance remained constant over the entire 3 hr observation period. In addition, in three dogs stenosis was induced by tightening a wire snare similar to that described by Harris & Ayers (1972) which had been previously implanted around the renal artery.

In some experiments restoration of renal artery pressure was prevented by maintaining the renal artery pressure at the predetermined value after rapidly lowering it as described above. In other experiments the dogs received angiotensin I (A1) converting enzyme inhibitor (CEI: SQ 20,881; Squibb Corp., U.S.A.) in the form of a 20 μg/kg bolus (1 ml.) into the renal artery followed by a continuous infusion of 0·5–1·0 μg/kg.min. In some dogs pre-treated with converting enzyme inhibitor, angiotensin II (2·5–5·0 ng/kg.min) was infused into the renal artery soon after induction of stenosis. AII renal artery infusions were given at 0·2 ml./min. In other experiments, dogs were given the angiotensin II receptor antagonist sarcosine^1, isoleucine^8 angiotensin II (Sar^1, Ile^8 AII) in the dose of 5 μg/kg.min I.V. The degree of competitive blockade produced by the latter was tested by comparing the effects of bolus doses of intravenously administered AII on the systemic blood pressure with those obtained before giving the antagonist. A dose of AII at least 100 times larger was required during infusion of Sar^1, Ile^8 AII to produce a given rise in blood pressure. The significance of the various changes were mostly assessed within dogs by standard statistical methods including paired t tests and analysis of variance (Snedecor & Cochran, 1967).

Circulatory measurements

Phasic and mean aortic and renal artery pressures, and phasic and mean renal blood flows were recorded on a Devices recorder (Fig. 1). Pressures were measured using Statham P 23 Dc transducers and renal blood flow was measured by the Doppler ultrasonic flowmeter technique described in detail previously (White, Angus, McRitchie & Porges, 1974; West, Angus & Korner, 1975; Fletcher, Korner, Angus & Oliver, 1976). We have previously observed in rabbits and confirmed it here again in preliminary experiments in dogs that there is a linear relationship between Doppler shift and volume flow over a wide range of pressures (West *et al.* 1975). Two days before an experiment flowmeter zero was checked against electronically determined zero by 2 sec inflation of the renal artery cuff. The electronically determined flowmeter zero was stable, with no detectable shifts over a period of months. Electromagnetic flowmeter studies by others have shown that there is no backflow in the renal artery under a wide variety of conditions including renal artery stenosis (Spencer & Denison, 1963; Ferrario & McCubbin, 1973), so that the non-directional recording of flow by the Doppler method does not introduce errors. Because of the difference in sensitivity of individual Doppler flowmeters (Fletcher *et al.* 1976) we have expressed renal blood flow in our experiments as kHz of Doppler shift. In the present study all flow comparisons during stenosis were based on the *change from control* in Doppler shift, and assessed in relation to the standard error of the difference within dogs. Previously the results of West *et al.* (1975) and Fletcher *et al.* (1976) had suggested that the between animal variation in sensitivity of calibration lines was randomly distributed about a group mean, since the means of individual slope values and calibration lines of groups of five to ten rabbits were closely similar. This also seems to be the case in the present study in dogs, since the mean values of the Doppler shifts for renal blood flow were similar in different groups of dogs (e.g. Fig. 2), and the findings of a relatively uniform response to stenosis between dogs (e.g. Table 1). From calibration studies performed in 5 dogs an approximate conversion factor is 160 ml./min.kHz Doppler shift. Renal vascular 'resistance' was calculated as (distal renal artery pressure, mmHg)/(renal blood flow, kHz Doppler shift) and expressed in arbitrary units. Effective stenosis resistance was calculated as (mean arterial–distal renal artery pressures, mmHg)/(renal blood flow, kHz) arbitrary units.

Renin and angiotensin assays

Blood samples of 10 ml. were collected for renin and AII assays by allowing blood to flow freely from an aortic catheter into 1 ml. cold BAL/EDTA solution (2,3-dimercaptopropanol, 0·1 M-disodium EDTA, 0·1% neomycin sulphate buffered to pH 7·4 with 0·66 M-phosphate buffer). After collection the blood was centrifuged immediately and 2 × 0·5 ml. aliquots of plasma were frozen for later estimation of plasma renin activity. This was measured enzymatically by radioimmunoassay of the AI generated after 2 hr incubation at 37 °C (Johnston, Mendelsohn & Doyle, 1972). AII was extracted from 5 ml. of the remaining plasma onto Fuller's Earth, washed first in 7 ml. distilled water and then in 5 ml. ethanol. AII was washed off the Fuller's Earth with 2 ml. 40% NH_4OH solution in ethanol, decanted and stored for later assay. Cross-reactivity of angiotensin I with AII was 0·1%, and < 1% for Sar^1, Ile^8 AII with AII.

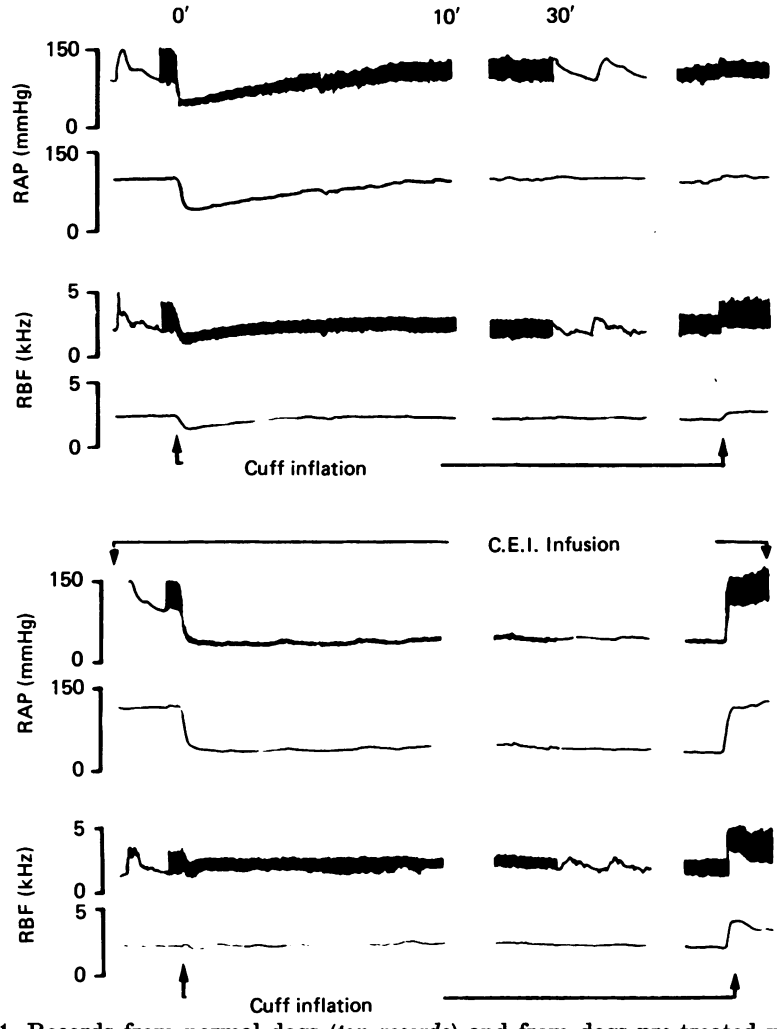

Fig. 1. Records from normal dogs (*top records*) and from dogs pre-treated with converting enzyme inhibitor (CEI) (*lower records*) showing time course of changes in phasic and mean renal artery pressure (RAP) and phasic and mean renal blood flow (RBF) before and at various times after start of renal artery stenosis induced by lowering distal RAP to 40 mmHg at first arrow; cuff deflated at second arrow.

RESULTS

Effects of graded stenosis

The cuff was inflated to the predetermined value of distal renal artery pressure (60, 40 or 20 mmHg; n = 8, 8, 13 respectively), the tubing was then clamped to maintain stenosis and observations were continued for 1 hr (Figs. 1, 2). Renal artery pressure returned rapidly towards control reaching a plateau from 5 to 30 min after the start of stenosis, at a rate that was inversely related to stenosis severity. Recovery

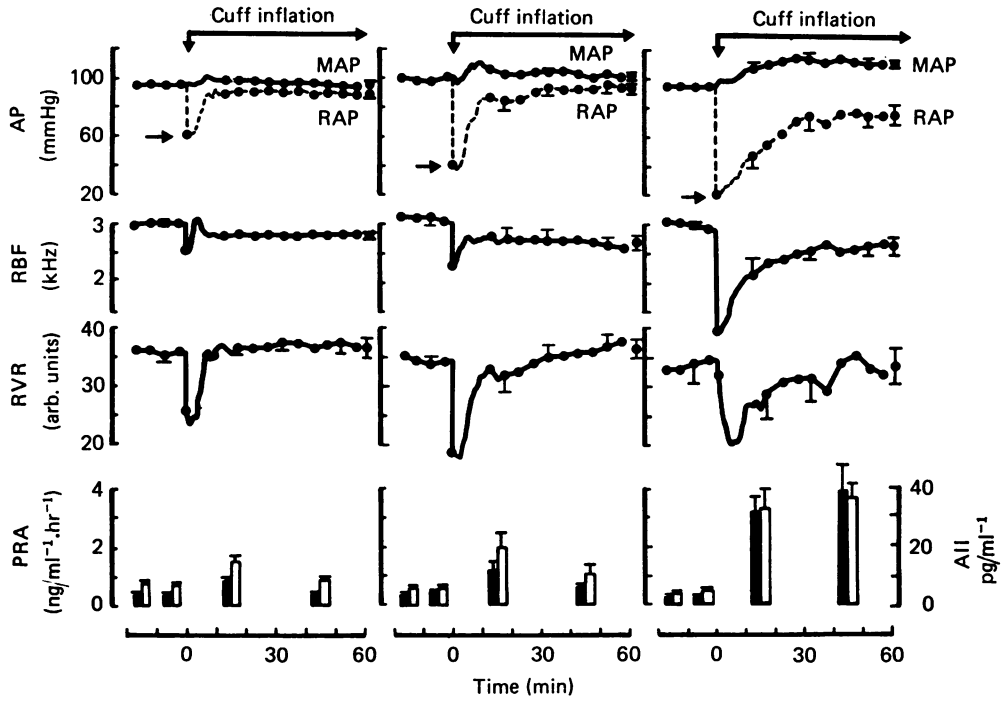

Fig. 2. Average effects of graded renal artery stenosis produced by acutely lowering renal artery pressure to 60 mmHg (left panel, n = 8), 40 mmHg (middle panel, n = 8), and 20 mmHg (right panel, n = 13), on arterial pressure (AP; mean arterial pressure, MAP = continuous lines; renal artery pressure, RAP = interrupted lines), renal blood flow (RBF), renal vascular resistance (RVR). Values shown are means averaged over 5 min at different times before and during stenosis except for the first 15 min after completing inflation when values were averaged every minute. Lowest row shows mean and S.E. of mean of plasma renin activity (PRA, filled rectangles) and arterial angiotensin II concentration (AII, open rectangles). Values at 0 min correspond to completion of cuff inflation (horizontal arrow). Bars are standard errors of means during control period and standard errors of difference from control within dogs at selected time intervals during stenosis.

was almost complete with the two mildest levels of stenosis and the steady-state values (40–60 min from the start) were not significantly different from initial control. However, in the group where renal artery pressure had been lowered to 20 mmHg 'steady-state' renal artery pressure remained $16 \pm 7{\cdot}1$ (S.E. of mean) mmHg below control ($P < 0{\cdot}05$).

Renal blood flow reached minimum values in all groups at the end of 30 sec cuff inflation (Fig. 2). In the mildest grade of stenosis this was followed by a brief period during which flow rapidly returned to control. At about the time the renal artery pressure began to recover flow fell again to reach its steady-state value $6{\cdot}8 \pm 1{\cdot}9\,\%$ ($P < 0{\cdot}01$) below control. In the other two groups the initial rate of restoration of flow was also more rapid than that of pressure (Fig. 2). During the 'steady-state'

TABLE 1. Renal blood flow (kHz Doppler shift) in eight dogs during control period (C, average value over 20 min) immediately after stenosis (I, one reading at 30 sec) and during 'steady-state' phase (S.S., averaged between 40–60 min after stenosis)

Dog	C	I	(C−I)	S.S.	(C−S.S.)
1	2·56	2·2	0·36	2·55	0·01
2	2·21	2·2	0·01	2·15	0·06
3	2·98	2·3	0·68	2·58	0·40
4	3·24	2·5	0·74	2·9	0·34
5	2·89	2·4	0·49	2·11	0·78
6	4·11	3·0	1·11	3·95	0·16
7	4·59	2·0	2·59	3·51	1·08
8	2·35	1·8	0·55	1·82	0·53
Mean	3·12	2·3	0·82	2·69	0·42
S.E.	0·30	0·13	—	0·26	—
S.E. of difference	—	—	0·28	—	0·13

TABLE 2. Stenosis resistance variation at different cuff pressures

Renal artery pressure reduced to	Number of dogs	Effective stenosis resistance (arbitrary units) Time after inflating cuff (min) 0	40–60
60 mmHg	8	$16{\cdot}3 \pm 2{\cdot}3$	$1{\cdot}36 \pm 0{\cdot}51$
40 mmHg	8	$27{\cdot}0 \pm 2{\cdot}0$	$3{\cdot}65 \pm 0{\cdot}90$
20 mmHg	13	$65{\cdot}0 \pm 8{\cdot}5$	$14{\cdot}7 \pm 4{\cdot}0$

renal blood flow was $13{\cdot}2 \pm 3{\cdot}7\,\%$ below control in the '40 mmHg' group and $12{\cdot}3 \pm 5\,\%$ in the '20 mmHg' group ($P < 0{\cdot}05$ in each group). The immediate and 'steady-state' changes in blood flow during stenosis were reasonably uniform, as shown in Table 1 for dogs in which renal artery pressure was acutely lowered to 40 mmHg. With all levels of stenosis the amplitude of the renal blood flow pulse was significantly reduced (e.g. Fig. 1).

Renal vascular resistance fell immediately during cuff inflation. Because of the difference in phasing of renal artery pressure and blood flow changes it reached its minimum from 1 to 6 min after clamping the tubing (Fig. 2). It then gradually increased to a steady-state value not significantly different from initial control at all grades of stenosis. Effective stenosis resistance declined from its initial maximum to levels of about 8–20 % of this value during the steady-state phase (Table 2). Even at the mildest grade of stenosis the 'steady-state' stenosis resistance was still significantly greater than zero ($P < 0{\cdot}05$).

Systemic mean arterial pressure rose only slightly and transiently at the two milder levels of stenosis, but in the most severe grade it reached a 'steady-state' value of $18{\cdot}2 \pm 2{\cdot}5$ mmHg above control ($P < 0{\cdot}001$) (Fig. 2). The aortic–renal artery

pressure gradients of the three groups were in order of increasing severity of stenosis: $2{\cdot}7 \pm 1{\cdot}5$ mmHg (N.S.), $8{\cdot}6 \pm 2{\cdot}2$ mmHg ($P < 0{\cdot}01$) and $29 \pm 8{\cdot}5$ mmHg ($P < 0{\cdot}01$), 40–60 min after stenosis.

Plasma renin activity and AII concentration both increased above control 15 min after the start of stenosis, and the rise was proportional to the severity of the stenosis (Fig. 2). In the two milder grades of stenosis both variables had returned to levels not significantly different from control by 45 min, but in the most severe stenosis they remained significantly raised.

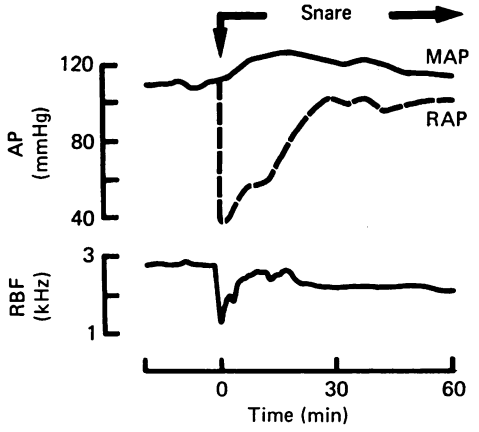

Fig. 3. Effects in one dog of tightening a wire snare around the renal artery on mean arterial pressure (MAP), renal artery pressure (RAP) and renal blood flow (RBF).

Effects of stenosis produced by a snare

Three experiments were performed in which renal artery stenosis was induced by lowering renal artery pressure to 40 mmHg by tightening a previously implanted wire snare. The time course of renal artery pressure after stenosis was virtually the same as that obtained after inflating the cuff, as shown in one representative experiment in Fig. 3. Results obtained in the other dogs were closely similar.

Pre-treatment with CEI and Sar^1, Ile^8 AII

The intermediate level of stenosis was chosen for detailed analysis. Pre-treatment with either CEI ($n = 5$) or with Sar^1, Ile^8 AII ($n = 3$) greatly reduced the restoration of renal artery pressure and renal vascular resistance after stenosis (Figs. 1, 4). Infusion of CEI into the renal artery during the control period resulted in only minimal changes in renal haemodynamics and renin-angiotensin system activity (Fig. 4). After the distal renal artery pressure had been reduced to 40 mmHg and the cuff had been clamped, there was a further lowering of renal artery pressure which eventually rose again to level off at about 50 mmHg. Renal blood flow first fell after induction of stenosis and then increased gradually to reach a value close to prestenosis control, i.e. it increased to a value during stenosis that was significantly greater than in the absence of CEI ($P < 0{\cdot}05$, signed rank test; Snedecor & Cochran, 1967) (cf. Fig. 2, middle panel, 20–30 min from start of stenosis). Renal vascular resistance remained low at 15 units (44% of control). In these experiments the stenosis was

maintained for only 30 min, but in two dogs it was maintained for up to 90 min on another day and there were no further changes after the first 15 min.

In three out of five dogs given CEI the effects of stenosis after pre-treatment with intravenously administered Sar[1], Ile[8] AII were studied on another day. Even by the I.V. route this drug produced considerable vasoconstriction during the prestenosis period (Fig. 4). During stenosis there were quantitative differences compared with

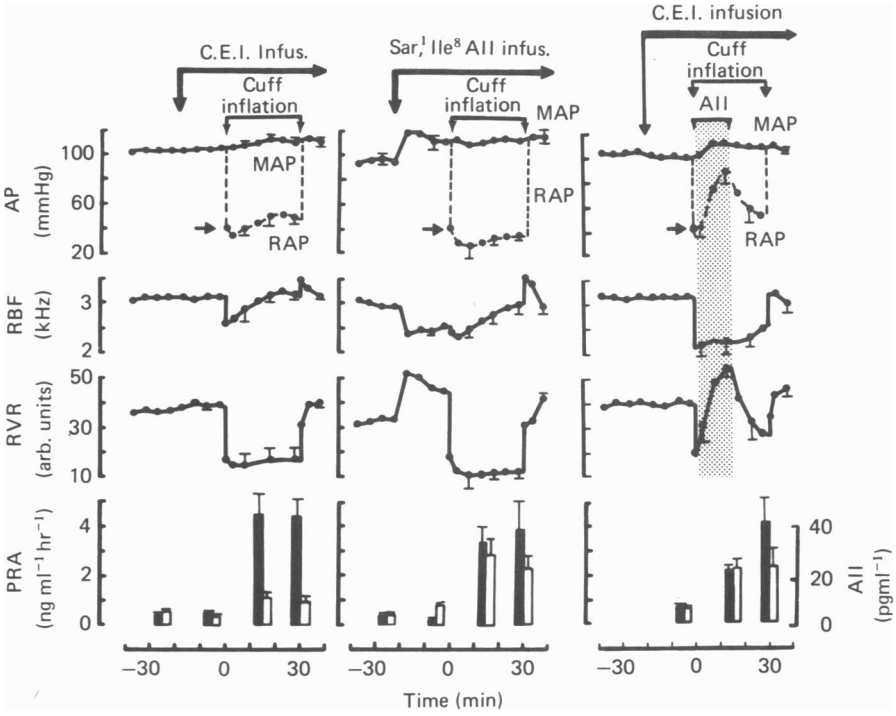

Fig. 4. *Left panel*: average effects of renal artery stenosis after pre-treatment with CEI on mean arterial pressure (MAP), renal artery pressure (RAP), renal blood flow (RBF), renal vascular resistance (RVR) and plasma renin activity (PRA) and AII concentration (n = 5); CEI was infused into the renal artery starting at the large vertical arrow. *Middle panel*: effects of stenosis on above variables after pre-treatment with Sar[1], Ile[8] AII (n = 3); intravenous infusion started at large vertical arrow. *Right Panel*: as in left panel, except that AII (2·5–5·0 ng/kg.min) was infused into the renal artery at times shown by shading (n = 5); stenosis was produced in all experiments by inflating cuff to lower renal artery pressure to 40 mmHg.

CEI pre-treatment: with Sar[1], Ile[8] AII renal artery pressure and vascular resistance fell further after induction of stenosis and levelled off at somewhat lower absolute values (Fig. 4). For example, renal artery pressure levelled off at about 40 mmHg and vascular resistance at about 12 units (26 % of prestenosis control). Renal blood flow rose again above prestenosis control towards the end of the stenosis. Mean arterial pressure did not rise significantly during stenosis either with CEI or Sar[1], Ile[8] AII.

In both the above groups the rise in plasma renin activity was much greater than during the normal response, and there was no tendency for it to fall again in the course

of 30 min stenosis (Fig. 4). After pre-treatment with CEI AII increased significantly ($P < 0{\cdot}05$), but the rise was only one third of that observed in dogs pre-treated with Sar^1, Ile^8 AII.

Infusion of CEI during stenosis

In another four dogs infusion of CEI into the renal artery was started late, 30 min after induction of stenosis, when normal restoration of renal artery pressure was almost complete (Fig. 5). In contrast to the profound effects of pre-treatment with CEI, late administration of the drug had no effect on renal artery pressure. However, there was a small significant rise in blood flow ($P < 0{\cdot}05$) and renal vascular resist-

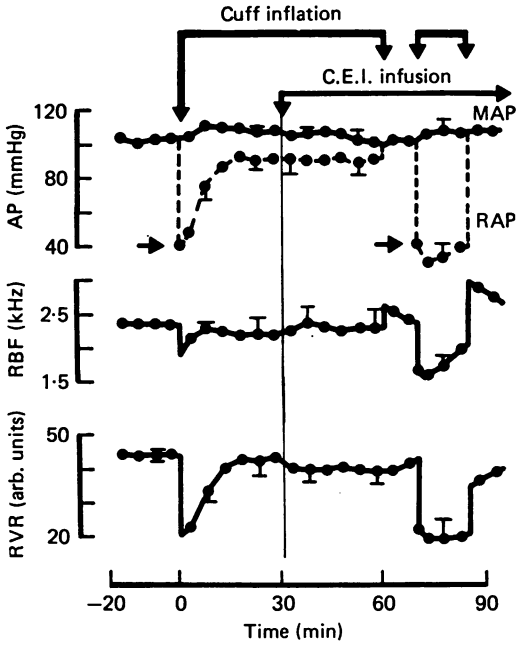

Fig. 5. Average effects of inflating the cuff to lower renal artery pressure to 40 mmHg, and then infusing CEI into the renal artery after 30 min ($n = 4$). At 60 min after the start of stenosis, the cuff was deflated and then after 10 min, reinflated to lower renal artery pressure to 40 mmHg. CEI infusion continued throughout. Abbreviations as in Fig. 2.

ance fell by $8{\cdot}8 \pm 2{\cdot}3\%$ ($P < 0{\cdot}05$). The results suggest that after 30 min only about one sixth of the maximal AII-mediated resistance change present during the first few minutes of stenosis still persisted (i.e. 8·8/56 units). In two dogs the dose of CEI was then increased tenfold without further effect. In all dogs, with CEI infusion continuing, the cuff was deflated for 10 min and renal artery stenosis was again induced. Now the recovery was greatly attenuated (Fig. 5, right), as in Fig. 4.

Infusion of AII after CEI pre-treatment

The experiments in Figs. 2 and 4 suggested that in normal dogs the intrarenal effects of AII contributed to early restoration of renal artery pressure and renal

vascular resistance. In the presence of CEI or Sar[1], Ile[8] AII renal vasodilatation persisted. Therefore, we tried to simulate the normal restoration processes in CEI-pre-treated dogs by infusing AII into the renal artery starting 1–2 min after induction of stenosis (Fig. 4, right). This produced rapid elevation of renal artery pressure and an increase in renal vascular resistance that was somewhat greater than in the normal response (cf. Figs. 2, 4). During AII infusion arterial plasma AII concentration rose in all dogs to levels higher than after CEI pre-treatment alone. When the infusion was turned off AII levels fell in three out of five dogs but increased in the other two. The doses of 2·5–5·0 ng/min of AII reduced renal blood flow in normal dogs in the absence of stenosis by 12–25% of control.

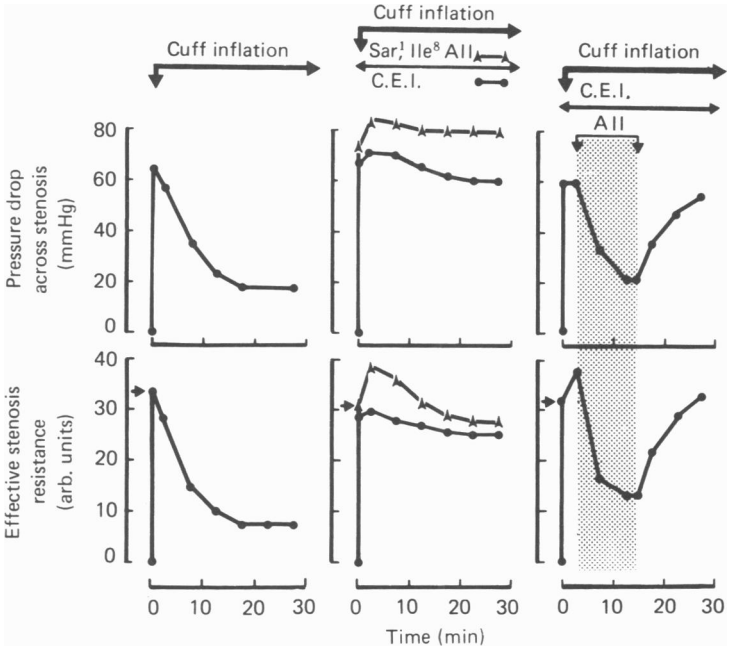

Fig. 6. Mean values of changes with time in pressure drop across stenosis and effective stenosis resistance following reduction of renal artery pressure to 40 mmHg. *Left panel*: normal response, $n = 8$. *Middle panel*: pre-treatment with Sar[1], Ile[8] AII (▲——▲), $n = 3$, or with CEI (●——●), $n = 5$. *Right panel*: pre-treatment with CEI, with AII infused into the renal artery during period shown by shading ($n = 5$).

Effective stenosis resistance

With the normal renal haemodynamic restorative processes the stenosis resistance fell rapidly from the initial maximum (Fig. 6, left). When these changes were prevented with Sar[1], Ile[8] AII (or with CEI) pressure gradient across the stenosis remained almost constant, and resistance rose slightly and then fell to a value similar to that attained at the end of cuff inflation (Fig. 6, middle). When renal vascular resistance was temporarily increased by intrarenal infusion of AII there was a fall in effective stenosis resistance (Fig. 6, right), similar to that observed during normal recovery (Fig. 6, left); when AII infusion was discontinued stenosis resistance again increased.

Another series of experiments was performed in normal dogs in which renal artery pressure was maintained constant for 1 hr of stenosis at a predetermined level of 30 mmHg (Fig. 7). It should be noted that the effective cuff resistance had to be increased over 1 hour's stenosis to maintain renal artery pressure, involving additional cuff inflation. This resulted in a small, time-related decrease in renal blood flow following an initial brief restorative phase. In these dogs there was a time-related increase in plasma renin activity as in the CEI experiments. However, in contrast to the latter mean arterial pressure now increased greatly by 34 ± 6·8 mmHg towards the end of the period.

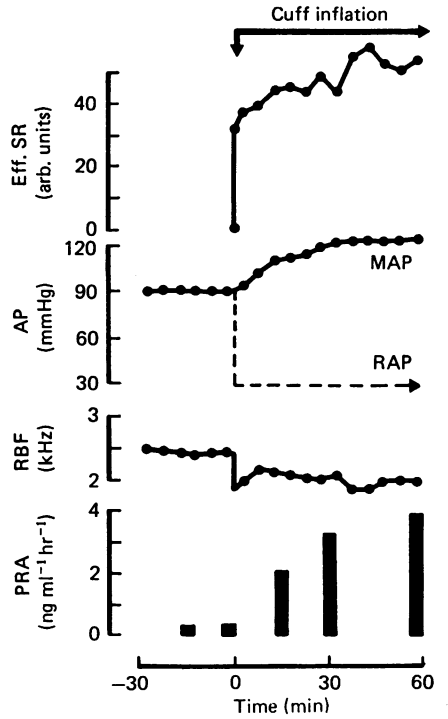

Fig. 7. Average effects on effective stenosis resistance (Eff. SR), mean arterial pressure (MAP), renal blood flow (RBF) and plasma renin activity (PRA) of reducing renal artery pressure to 30 mmHg by cuff inflation (vertical arrow) and subsequently maintaining renal artery pressure (RAP) at 30 mmHg by constant cuff adjustment for 1 hr.

DISCUSSION

The experiments have demonstrated that immediately after stenosis there is a complex series of renal vascular and hormonal changes, which have not to our knowledge been previously described. During stenosis there is reduction in renal vascular resistance followed by gradual restoration towards the initial resting value and a time-related change in effective stenosis resistance. This does not appear to depend on failure of the cuff to maintain constant the diameter of the stenosis, since identical changes were observed with a fixed wire snare. The possibility of leakage from the cuff has also been excluded by demonstration of the constancy of stenosis resistance in an *in vitro* system and by the *in vivo* demonstration of well maintained

stenosis resistance after pre-treatment with CEI or Sar[1], Ile[8] AII. These suggest that the normal haemodynamic transients are biologically determined and not artifactual. It is unlikely that development of renal collateral blood flow contributes to the restoration of renal haemodynamics, since others have shown that collaterals take many weeks to develop (Fekete, 1967; Watkins *et al.* 1976; Siegel & Levinsky, 1977).

Factors determining stenosis resistance

There has been extensive theoretical analysis of the determinants of the pressure drop across a fixed diameter stenosis (e.g. Berguer & Hwang, 1974; Young *et al.* 1977). These have indicated that the pressure difference across a constriction is not a linear function of flow, as it is for Poiseuille's relationship. Young *et al.* (1977) have suggested that an appropriate hydraulic model is a non-linear stenosis resistance in series with the resistance of the distal vascular bed.

Other investigators have found that flow (or distal arterial pressure) begins to fall at lesser degrees of vessel narrowing when the distal vascular bed is dilated than when it is constricted (Shipley & Gregg, 1944; May *et al.* 1963; Berguer & Hwang, 1974; Gould *et al.* 1974; Young *et al.* 1977). Most peripheral beds respond to stenosis by 'autoregulatory' peripheral vasodilatation which tends to accentuate the pressure gradient and the effective resistance of the stenosis. The kidney also responds to stenosis with an initial vasodilatation. However, the kidney has unique properties in that reduction in renal artery pressure elicits renin secretion and AII production (Davis & Freeman, 1976) which constricts the dilated renal bed and helps to restore distal renal artery pressure. Under these conditions a given degree of renal artery narrowing will produce less 'critical' stenosis (cf. May *et al.* 1963) than at the height of dilatation during cuff inflation. 'Effective' stenosis resistance decreases from the high value observed during the initial vasodilator phase. By contrast, when the vasoconstrictor effects of AII are prevented both the pressure gradient and the effective stenosis resistance remain high (Fig. 6). The vasodilator phase then becomes prolonged indefinitely, as would occur in other 'autoregulating' peripheral beds without a special vasoconstrictor mechanism. The experiments in which AII was infused during stenosis in dogs pre-treated with converting enzyme inhibitor provide good evidence that the effective stenosis resistance is to a large degree determined by the alterations of vascular resistance of the renal bed (Fig. 4, right).

Determinants of plasma renin activity in stenosis

Without pre-treatment with CEI or Sar[1], Ile[8] AII the plasma renin activity and AII concentration were increased only transiently. During mild and moderate stenosis plasma renin activity fell again during restoration of renal artery pressure and renal vascular resistance. It was only with more severe stenosis (20 mmHg, Fig. 2) or when renal artery pressure was actively held down in normal dogs (Fig. 7), or after administration of CEI that it continued to increase.

Ayers and colleagues have shown that in renal artery stenosis sufficiently severe to produce sustained hypertension, angiotensin II causes renal vasoconstriction and that the latter is a factor in turning off renin-angiotensin system activity over a period of several days after induction of stenosis (Ayers *et al.* 1974; Ayers, Katholi, Vaughan, Carey, Kimborough, Yancey & Morton, 1977). Our results suggest that

this mechanism is part of a more general response of the renal circulation regardless of whether the stenosis is severe enough to produce hypertension. It is at the two mildest levels of stenosis that the rapid time course of changes makes the reciprocal relationship between renal artery pressure and renin-angiotensin system most clearly apparent.

The experiments in which CEI was infused late suggest that once renal artery pressure has become restored mechanisms other than the renin-angiotensin system contribute largely to its continued maintenance. The nature of these has not been investigated here.

It is possible that this response could be accentuated by the renal hypertrophy that followed the preceding nephrectomy. However, the increase in blood flow during hypertrophy appears to be complete after about 7–10 days in dogs (Ferrario & McCubbin, 1973). The experiments reported here were performed 2 weeks to 2 months post-nephrectomy.

Renal constrictor action of AII

In the present study the recovery of renal artery pressure and vascular resistance has been slightly greater after pre-treatment with CEI than after pre-treatment with Sar^1, Ile^8 AII. The most likely reason is the renal effect due to the small increase in arterial AII, owing to failure of the dose of intrarenally administered CEI to inhibit completely the pulmonary conversion of AI to AII. We cannot say whether the AII which helps restore renal artery pressure in our experiments is formed in the kidney or in the lung. The former seems possible in view of the demonstration by others that such formation can occur (Granger, Dahlheim & Thurau, 1972; Hofbauer, Zschiedrich & Gross, 1976). As regards the site of action on the renal vasculature, it has been found that AII acts predominantly on the efferent arteriole (e.g. Corcoran & Page, 1940; Korner, Stokes, White & Chalmers, 1967; Krahe, Hofbauer & Gross, 1970; Hall, Guyton, Jackson, Coleman, Lohmeier & Trippodo, 1977; Jackson, Guyton & Hall, 1977). This would help to raise filtration fraction and maintain glomerular filtration rate.

Relation to other studies

Most of the work on experimental renal artery stenosis has been related to producing hypertension, and many workers appear to have increased the severity of stenosis during application of the constrictive device, as in Fig. 7, rather than study the haemodynamic transients during fixed stenosis (Fig. 2). Moreover, there have been no studies with continuous haemodynamic monitoring in unanaesthetized animals, and in many experiments the renal artery constriction has been applied during surgery under anaesthesia. When sodium pentobarbitone anaesthesia is used arterial pressure is often elevated (Fray, Siwek, Strull, Steller & Wilson, 1976) and there is some renal vasoconstriction (Ferrario & McCubbin, 1973). Both these effects mean that in order to achieve the same reduction in renal artery pressure or blood flow as in a quiet unanaesthetized dog, greater narrowing of the renal artery will be necessary. Furthermore, it is likely that the reduction in vascular tone following anaesthesia will make the stenosis still more 'critical' and reduce even further the pressure distal to the stenosis.

This work was supported by a grant from the National Health and Medical Research Council of Australia. We thank E. Anderson, M. Le Duc, J. Dixon and D. Casley for excellent technical assistance; Dr Z. P. Horowitz of E. R. Squibb & Sons Inc. for the gift of SQ 20 881 and Dr. J. Coghlan of the Howard Florey Institute, Melbourne, for Sar^1, Ile^8 AII.

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