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THE IMPORTANCE OF RENAL VASCULAR TONE IN DETERMINING THE SEVERITY OF RENAL ARTERY STENOSIS IN DOGS

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SUMMARY

1. The effects of the state of renal vascular tone during induction of renal artery stenosis on the subsequent systemic blood pressure and renin responses have been studied in chronically instrumented, conscious dogs.

2. In one group of dogs, renal vascular tone was altered by brief (2–3 min) renal artery infusions of ACh, saline, methoxamine or angiotensin II during narrowing of the renal artery to reduce distal pressure to 40 mmHg. The infusions were turned off 1 min later.

3. The more vasoconstricted the kidney at the time of stenosis, the slower was the restoration of distal renal artery pressure and the greater the rises in systemic blood pressure, plasma renin activity (PRA) and effective stenosis resistance. At the end of 1 hr of stenosis, the rises in systemic blood pressure were $4 \cdot 3 \pm 3 \cdot 3$, $11 \cdot 3 \pm 3 \cdot 3$, $28 \cdot 9 \pm 3 \cdot 3$ and $26 \cdot 3 \pm 2 \cdot 8$ mmHg for the ACh, saline, methoxamine and angiotensin II-infused dogs respectively; rises in PRA were $0 \cdot 3 \pm 0 \cdot 24$, $1 \cdot 18 \pm 0 \cdot 42$, $5 \cdot 09 \pm 1 \cdot 38$ and $4 \cdot 02 \pm 0 \cdot 74$ ng/ml. per hr respectively.

4. In another group of dogs a given aortic–renal artery pressure gradient was produced on two occasions: (i) with the animal conscious; (ii) under brief sodium pentobarbitone anaesthesia and preparation for surgery. After 24 hr systemic blood pressure had risen by $15 \cdot 7 \pm 3 \cdot 6$ mmHg above initial values when stenosis was induced under anaesthesia ($P < 0 \cdot 05$) and only by $1 \cdot 2 \pm 3 \cdot 6$ mmHg (N.S.) when it was induced with the animal conscious. Corresponding rises in PRA were $1 \cdot 29 \pm 0 \cdot 42$ ($P < 0 \cdot 05$) and $0 \cdot 25 \pm 0 \cdot 11$ (N.S.) ng/ml. per hr. Establishment of a given gradient in the high vascular resistance kidney of the anaesthetized dog thus requires greater narrowing of the renal artery than in the lower resistance renal bed of the conscious animal.

5. The tone of the renal vascular bed is a major determinant of the severity of renal artery stenosis.

INTRODUCTION

In a previous study, we postulated that the vascular tone of the kidney was a major determinant of the effective resistance to blood flow of a renal artery stenosis (Anderson, Johnston & Korner, 1979*a*). In those experiments on conscious dogs, we observed that induction of renal artery stenosis resulted in an initial transient phase of renal vasodilatation which accentuated the aorta–renal artery pressure gradient and increased the effective stenosis resistance. This was followed by a phase of

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angiotensin II-mediated renal vasoconstriction which restored renal artery pressure distal to the stenosis, thereby reducing both the aorta–renal artery pressure gradient and the stenosis resistance. When angiotensin II formation was inhibited, the kidney remained vasodilated with maintenance of a high stenosis resistance (and pressure gradient). This dependence of stenosis resistance on the tone of the distal vascular bed is in accord with recent analysis of the haemodynamic behaviour of arterial stenoses in other organs (Gould, Lipscomb & Hamilton, 1974; Mates, Gupta, Bell & Klocke, 1978; May, Van de Berg, DeWeese & Rob, 1963; Schwartz, Carlyle & Cohn, 1979; Walinsky, Santamore, Wiener & Brest, 1979; Young, Cholvin, Kirkeeide & Roth, 1977).

Our results in trained quietly recumbent conscious dogs indicated that, in mild to moderate stenosis, the angiotensin II-mediated renal vasoconstriction minimized the stenosis resistance sufficiently to prevent development of chronic systemic hypertension (Anderson, Korner & Johnston, 1979*b*). In order to produce chronic hypertension reliably severe stenosis to produce a large pressure gradient was required (Anderson *et al.* 1979*b*). Our results appeared at variance with those of other workers who have observed hypertension after experimentally creating relatively modest aorta–renal artery pressure gradients (e.g. Ayers, Katholi, Vaughn, Carey, Kimbrough, Yancey & Morton, 1977; Ayers, Vaughn, Yancey, Bing, Johnson & Morton, 1974; Conway, 1968; Ferrario & McCubbin, 1973; Liard, Cowley, McCaa, McCaa & Guyton, 1974). In the above and other experimental studies stenosis has been produced either at surgery under anaesthesia, when renal vascular resistance is often elevated, or under more stressful conditions (e.g. standing up in a harness) than in our trained conscious recumbent dogs. In view of our previous observations it seemed likely that such experimental conditions would require greater narrowing of the renal artery diameter to produce a given reduction in distal pressure than would be the case in conscious, recumbent dogs in which renal vascular tone was low.

We have therefore performed two sets of experiments to test the hypothesis that the renal vascular tone at the time of the stenosis is a major determinant of the stenosis resistance, and hence of the systemic blood pressure and renin responses. Firstly, we have briefly altered renal vascular tone in conscious dogs by infusing vasoactive drugs at the time of narrowing of the renal artery. In the second set of experiments, we have compared the responses after establishing a given stenosis pressure gradient in the conscious animal with those occurring in the same dog under sodium pentobarbitone anaesthesia.

METHODS

Preparation of dogs

The experiments were performed on trained dogs prepared at a preliminary operation under halothane and nitrous oxide anaesthesia, as described previously (Anderson *et al.* 1979*a*, *b*). One kidney was removed and a Doppler flow probe and a Silastic balloon cuff or a wire snare were placed around the other renal artery and a catheter inserted with its tip distal to the cuff or snare. Catheters were also placed in the abdominal aorta and vena cava. The dogs were allowed to recover for at least 2 weeks before the first experiment. They visited the laboratory every day for catheter flushing and were thoroughly accustomed to laboratory procedures before the first experiment. Daily dietary Na^+ intake was 50–60 m-mole.

Intrarenal infusion of vasoactive drugs

After a control period (20 min) the vascular resistance of the kidney of the conscious dog was altered by brief infusion of a vasoactive substance into the renal artery. During the brief period of infusion, distal renal artery pressure was rapidly lowered to 40 mmHg, the infusion turned off and observations continued over the next hour while stenosis was maintained (for further details see Results). The drugs used were methoxamine hydrochloride (1·5–3 μg/kg per min; Burroughs Wellcome), angiotensin II (2–5 ng/kg per min; Hypertensin, Ciba), acetylcholine bromide (0·5–1·5 μg per min, Sigma) and saline (150 mM NaCl solution) vehicle. The drugs were dissolved in saline and infused at 0·1–0·4 ml./min. Drug doses were adjusted to increase or decrease renal blood flow by about 30% from resting.

The dogs were assigned to the four treatments in random order, with at least 5 days between experiments. Four dogs received all four treatments, and five other dogs only received some of the treatments because of technical mishaps (e.g. breakage of flowmeter wires, etc.).

Anaesthesia experiments

Renal artery stenosis was induced in five dogs on two occasions at least 1 week apart with the animal conscious on one occasion and anaesthetized on the other. The order was alternated in successive dogs. Each experiment lasted 24 hr. On the first day control measurements were made for 20 min with the dog fully conscious. The dog was then either anaesthetized with sodium pentobarbitone I.V. or injected with a 'placebo' dose of saline while remaining conscious. The dose of pentobarbitone was sufficient to just abolish the eyelid reflex and the limb withdrawal reflex in response to moderate pinching of the toe web; jaw muscle tension was almost absent. The dose was adjusted over the first 5 min and averaged 31 ± 3 mg/kg. No additional anaesthetic was given and 10 min later the hind limb was gently retracted and towel clips attached to the skin as if to prepare the dog for renal surgery. After completing these procedures there followed a second 20 min period of measurements before inducing renal artery stenosis. The latter was produced by inflating the renal artery cuff to reduce distal renal artery pressure over a period of 30 sec by 50 mmHg compared to the value just preceding cuff inflation. The haemodynamic and renin responses to stenosis were followed for 1 hr and the dog then returned to its metabolic cage with the renal artery cuff remaining inflated. All dogs ate their normal meal (presented about 3 hr later) before the next morning when urine was collected and the dog returned to the laboratory for measurements 24 hr after initial induction of stenosis. The renal artery cuff was deflated at the end of the experiment.

Methods of producing renal artery stenosis

The inflatable renal artery cuff and wire snare have been described previously, and also the tests for ensuring that the cuffs maintained their inflation (Anderson *et al.* 1979*a*, *b*). The cuffs are simpler to use than the snares; they can be inflated without disturbing the dog and can be readily deflated at the end of the experiment. Cuffs were used in seven out of nine dogs in the first set of experiments and in all the dogs in the second set of experiments on the effects of anaesthesia. The two dogs with snares in the first set of experiments showed identical responses to the dogs with cuffs, in agreement with previous findings (Anderson *et al.* 1979*a*).

Measurements

Systemic and renal artery blood pressures and renal blood flow (Doppler flowmeter) were measured as described previously (Anderson *et al.* 1979*a*, *b*). Plasma renin activity was measured by radioimmunoassay from samples of arterial blood (Anderson *et al.* 1979*a*). Creatinine concentrations in plasma and urine were measured using the Boehringer Creatinine Kit, and urinary Na^+ by flame photometry. Renal vascular resistance was calculated as renal artery blood pressure/renal blood flow. Stenosis resistance was calculated as (aortic pressure − renal artery pressure)/(renal blood flow as % of pre-stenosis value).

RESULTS

Effects of infusing vasoactive drugs at the time of stenosis

After a control period, the dogs were infused (i) with ACh to produce renal vasodilatation (n = 7); (ii) with methoxamine or angiotensin II to produce renal vasoconstriction (n = 5, 6); or (iii) with normal saline (n = 7). Acetylcholine increased renal flow by 34 ± 7% and methoxamine and angiotensin II reduced it by 30 ± 4% and 29 ± 3% respectively. There were no significant changes in systemic blood pressure or heart rate during the infusion of these drugs, except during methoxamine

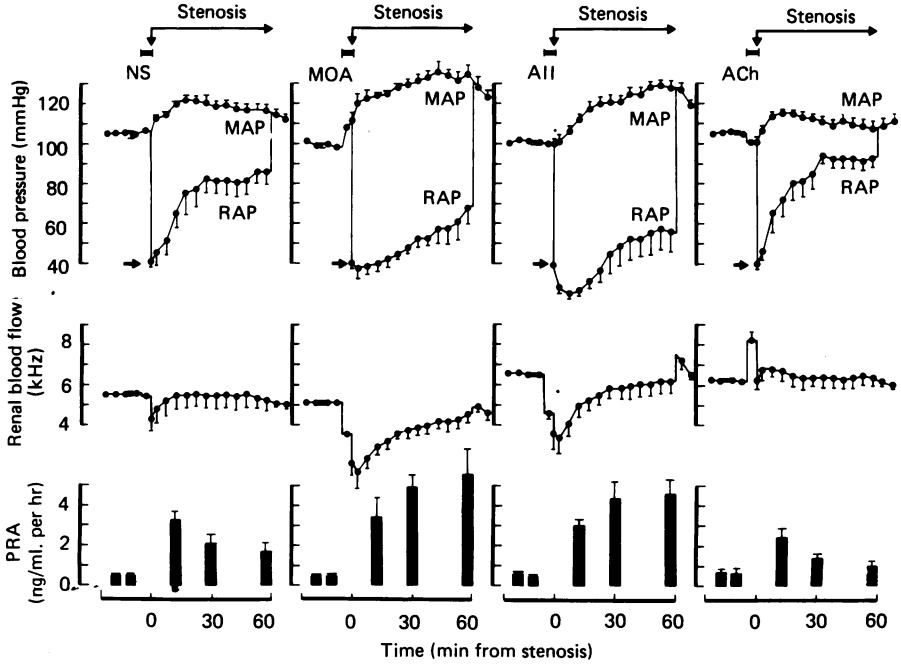

Fig. 1. Average responses to renal artery stenosis produced by acutely lowering renal artery pressure to 40 mmHg at the vertical arrow, during brief infusions (shown by bar at top) of 0·9% saline (NS, n = 7, left panel), methoxamine (MOA, n = 5, 2nd panel), angiotensin II (AII, n = 6, 3rd panel) or acetylcholine (ACh, n = 7, right panel). Values shown for blood pressures and renal blood flow are means averaged over 5 min except value at end of stenosis. Time at 0 min corresponds to completion of the stenosis production by lowering renal artery pressure to 40 mmHg. Bars are standard errors of means during control period and standard errors of difference from control within dogs after stenosis. PRA: plasma renin activity.

infusion when blood pressure rose by 6·4 ± 2·5 mmHg. When blood flow had become stable for 1 min, the renal artery was narrowed over a period of 30 sec to reduce distal renal artery pressure to 40 mmHg in all instances. The infusion was then stopped and the changes in haemodynamics and in plasma renin activity (PRA) were studied over the next hour, at the end of which the stenosis was released. Each dog was studied again with one of the other drugs at least 5 days later (see Methods).

There were marked differences in the rates of restoration of distal renal artery pressure and in responses of systemic arterial blood pressure and PRA, depending

on the tone of the renal vascular bed at the time of stenosis (Fig. 1). Restoration of distal renal artery pressure was most rapid and complete and the elevations in mean arterial pressure and PRA were smallest after stenosis was induced with the kidney dilated with ACh. By contrast, infusing either methoxamine or angiotensin II into the renal artery at the time of stenosis was associated with slow recovery of distal renal artery pressure and marked and well sustained elevations in arterial pressure and PRA. In these dogs, the small recovery of distal renal artery pressure appeared to be mainly secondary to the elevation in systemic arterial pressure. The kidneys with normal tone (saline infusion at the time of stenosis) showed less rapid restoration of renal artery pressure than seen when the dogs were infused with ACh. For example, it took $16{\cdot}3 \pm 3{\cdot}2$ min for renal artery pressure to reach 60 mmHg in the former group, compared to $9{\cdot}1 \pm 1{\cdot}5$ min in the latter. However, the same general patterns in arterial pressure and PRA were seen, in contrast to dogs infused with angiotensin II or methoxamine. The peak rise in mean arterial pressure was greater in the saline-treated dogs than in the ACh-treated dogs ($19{\cdot}2 \pm 2{\cdot}9$ compared to $11{\cdot}9 \pm 1{\cdot}7$ mmHg, $P < 0{\cdot}05$) and the rise in PRA was smaller ($0{\cdot}1 > P > 0{\cdot}05$ at 30 min).

Averaged over the period 40–60 min after induction of renal artery stenosis during infusions of either ACh, saline, methoxamine or angiotensin II, the mean systemic arterial pressure had increased above control period values by $4{\cdot}3 \pm 3{\cdot}3$, $11{\cdot}3 \pm 3{\cdot}3$, $28{\cdot}9 \pm 3{\cdot}3$ and $26{\cdot}3 \pm 2{\cdot}8$ mmHg respectively. At 1 hr, PRA values had risen by $0{\cdot}30 \pm 0{\cdot}24$, $1{\cdot}18 \pm 0{\cdot}42$, $5{\cdot}09 \pm 1{\cdot}38$ and $4{\cdot}02 \pm 0{\cdot}74$ ng/ml. per hr above control values. Pressure gradients across the stenoses were respectively 12 ± 4, 29 ± 9, 68 ± 11 and 65 ± 13, with the last two gradients not significantly different to those created initially at the time of stenosis during infusion of methoxamine and angiotensin II (i.e. 67 ± 5 and 58 ± 5 mmHg respectively).

During the induction of stenosis in the dogs receiving ACh the elvated renal blood flow was reduced back to initial pre-infusion control values and remained near these values for the next 1 hr (Fig. 1). During induction of stenosis in the dogs receiving methoxamine or angiotensin II the reduced renal blood flow was lowered even further, but gradually returned over the 1 hr stenosis period towards pre-infusion control. In saline-infused dogs flow was also initially reduced during induction of stenosis but rapidly returned close to control (Fig. 1).

The calculated stenosis resistance immediately following reduction of distal renal artery pressure to 40 mmHg was lowest in the ACh-infused dogs, followed by the saline-, angiotensin II- and methoxamine-infused dogs, in that order. Five minutes later after the infusion had been turned off, stenosis resistance fell in the saline- and ACh-infused dogs, but rose further as the effects of the vasoconstrictor agents methoxamine and angiotensin II wore off (Table 1). At 1 hr, stenosis resistance had fallen in all instances, but was still ranked in the same order as obtained initially (Table 1).

Stenosis produced during infusions of the vasoconstrictor agents methoxamine and angiotensin II resulted in similar elevations in blood pressure and PRA above initial (pre-infusion) control. However, methoxamine, infused into the renal artery to reduce renal blood flow by about 30%, caused a rise in systemic blood pressure even before stenosis. By contrast, the brief angiotensin II infusion before stenosis caused

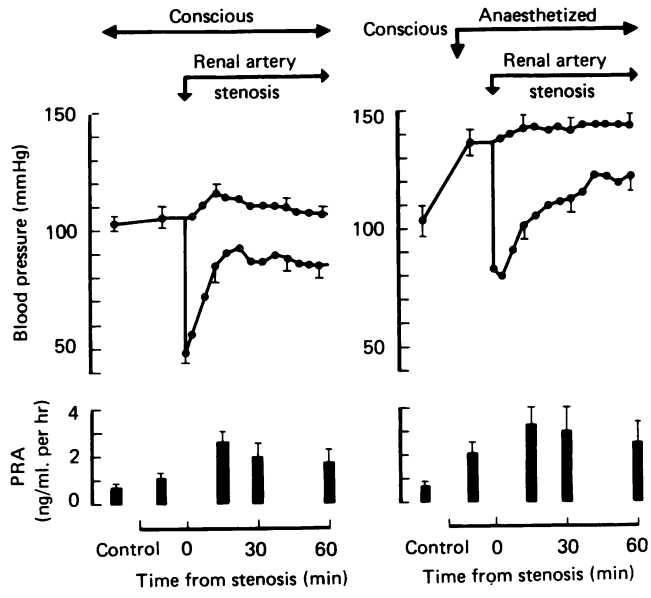

Fig. 2. Acute changes in response to pentobarbitone anaesthesia (or saline injection), and renal artery stenosis to reduce distal renal artery pressure by 50 mmHg. Left panel: dogs conscious throughout. Right panel: dogs anaesthetized with pentobarbitone (31 ± 3 mm/kg) at first vertical arrow. Values shown are means averaged over 20 min before stenosis and averaged over 5 min after. Error bars as for Fig. 1. PRA: plasma renin activity.

TABLE 1. Effective resistance to flow by renal artery stenosis following reduction of distal pressure to 40 mmHg during brief infusion of different vasoactive agents into the renal artery at the time of stenosis

	Effective stenosis resistance		
Infusion	Immediately after stenosis induction	5 min later*	1 hr later
ACh	$0{\cdot}62 \pm 0{\cdot}05$	$0{\cdot}49 \pm 0{\cdot}09$	$0{\cdot}16 \pm 0{\cdot}10$
Saline	$0{\cdot}93 \pm 0{\cdot}17$	$0{\cdot}75 \pm 0{\cdot}16$	$0{\cdot}38 \pm 0{\cdot}14$
Angiotensin II	$1{\cdot}24 \pm 0{\cdot}20$	$1{\cdot}83 \pm 0{\cdot}33$	$0{\cdot}68 \pm 0{\cdot}14$
Methoxamine	$2{\cdot}67 \pm 0{\cdot}84$	$3{\cdot}55 \pm 0{\cdot}77$	$0{\cdot}81 \pm 0{\cdot}20$

* 4 min after end of drug infusion.

no change in arterial pressure. These different effects on blood pressure probably accounted for the different effects of the two constrictor agents on the stenosis resistances immediately after cuff inflation (Table 1).

Effects of anaesthesia

The effect of pentobarbitone anaesthesia plus hind-limb retraction and insertion of towel clips prior to the induction of stenosis was to increase systemic blood pressure $+35 \pm 6$ mmHg while renal blood flow fell $-9{\cdot}2 \pm 5{\cdot}0\%$; renal vascular resistance rose by $+52 \pm 14\%$ and PRA rose by $1{\cdot}36 \pm 0{\cdot}42$ ng/ml. per hr (compared to mean

pre-anaesthesia control values). Renal artery stenosis was established by producing a 50 mmHg aorta – renal artery pressure drop. In the anaesthetized dogs renal artery pressure was reduced to 81 ± 9 mmHg. After 1 hr of stenosis, distal renal artery pressure had risen to 122 ± 7 mmHg, while arterial pressure, already elevated by anaesthesia (see above), rose only slightly further (7 ± 4 mmHg, N.S.). PRA also showed a further increase in response to stenosis, with a maximum value at 15 min (Fig. 2). The dogs had fully recovered from anaesthesia 24 hr later, but the systemic

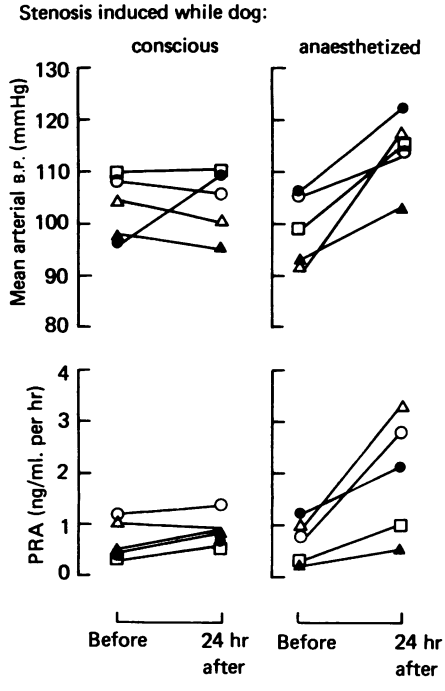

Fig. 3. Individual responses of five dogs to renal artery stenosis. Left panel: renal artery stenosis induced while dogs were conscious. Right panel: stenosis induced while dogs were under pentobarbitone anaesthesia. All values shown were made with the dogs fully conscious, before and 24 hr after renal artery stenosis which reduced distal renal artery pressure by 50 mmHg in all dogs.

arterial blood pressure was still 15·7 ± 3·6 mmHg above the initial pre-stenosis pre-anaesthesia values ($P < 0{\cdot}025$) (Fig. 3). PRA was also significantly raised by 1·29 ± 0·41 ng/ml. per hr ($P < 0{\cdot}05$) (Table 2).

By contrast, production of the same aorta – renal artery pressure gradient without anaesthesia in the same dog resulted in a more rapid restoration of renal artery pressure, even though the absolute distal renal artery pressure at the production of stenosis was lower (47 ± 3·3 mmHg) than when the same gradient had been established under anaesthesia. The magnitude of the changes in PRA in response to stenosis was similar to that seen in anaesthesia, but started from a lower value. Systemic arterial blood pressure rose only transiently at about 15 min after stenosis, and at 1 hr and 24 hr after stenosis was not significantly different to initial control (+ 3·6 ± 2·4 mmHg

and $+1{\cdot}2 \pm 3{\cdot}6$ mmHg respectively). Plasma renin activity at 24 hr was only slightly elevated ($+0{\cdot}25 \pm 0{\cdot}11$ ng/ml. per hr, N.S.).

Other significant differences in the responses to renal artery stenosis in anaesthetized dogs versus conscious dogs included lower 24 hr urine output, creatinine clearance and more water drunk ($P < 0{\cdot}05$ in each case, paired t test). No difference was seen in the first 24 hr urinary Na^+ loss. At 24 hrs renal blood flow was significantly elevated ($P < 0{\cdot}05$) and renal vascular resistance significantly reduced ($P < 0{\cdot}01$) in the conscious group. The renal haemodynamic responses were much more variable 24 hr after stenosis of anaesthetized dogs, with values not significantly different to pre-anaesthesia, pre-stenosis values.

TABLE 2. Average responses to 24 hr of renal artery stenosis. Haemodynamic and renin measurements made before and 24 hr after stenosis with dogs fully conscious; stenosis induced while dogs anaesthetized with pentobarbitone or conscious

	Conscious dogs	Anaesthetized dogs	Difference
Mean arterial pressure (Δ mmHg)	$+1{\cdot}2 \pm 3{\cdot}6$	$+15{\cdot}7 \pm 3{\cdot}6$*	$14{\cdot}5 \pm 4$†
Renal blood flow (Δ %)	$+29{\cdot}4 \pm 8{\cdot}8$*	$-2{\cdot}1 \pm 16{\cdot}4$	$31{\cdot}4 \pm 21{\cdot}2$
Renal vascular resistance (Δ %)	$-27{\cdot}9 \pm 5{\cdot}7$*	$17{\cdot}0 \pm 32{\cdot}8$	$-45{\cdot}0 \pm 33{\cdot}0$
Plasma renin activity (Δ ng/ml. per hr)	$+0{\cdot}25 \pm 0{\cdot}11$	$+1{\cdot}29 \pm 0{\cdot}41$*	$1{\cdot}06 \pm 0{\cdot}51$
24 hr H_2O intake (ml.)	520 ± 90	855 ± 70	$335 \pm 1{\cdot}20$†
24 hr urine output (ml.)	700 ± 130	510 ± 90	190 ± 75
24 hr water balance (ml.)	-175 ± 150	350 ± 110	510 ± 140†
24 hr Na^+ output (m-mole)	$28{\cdot}6 \pm 5{\cdot}8$	$25{\cdot}6 \pm 5{\cdot}5$	$3{\cdot}0 \pm 5{\cdot}9$
Average 24 hr creatinine clearance rate (ml./min)	$66{\cdot}2 \pm 11{\cdot}9$	$37{\cdot}0 \pm 6{\cdot}6$	$29{\cdot}2 \pm 7{\cdot}9$†

* $P < 0{\cdot}05$, paired t test on values before and 24 hr after stenosis in each dog.

† $P < 0{\cdot}05$, paired t test on the comparison of average responses within dogs to renal artery stenosis when induced with dogs conscious and under anaesthesia.

DISCUSSION

In the conscious dog, the state of renal vascular tone at the time of acute renal artery narrowing to reduce distal renal artery pressure to a given value markedly influenced the subsequent effective stenosis resistance, the rate of recovery of distal renal artery pressure and the systemic blood pressure and renin responses. In the present study we did not measure the reduction in renal artery diameter, but could rank the severity of stenosis from the magnitude of the effective stenosis resistance and the rises in systemic blood pressure and PRA. Our results suggest that less reduction in renal artery diameter was required to lower distal pressure to a set value when the kidney was dilated with ACh than when it was constricted with angiotensin II or methoxamine. Thus, in the 'low tone' kidney at the time of stenosis there was rapid restoration of distal renal artery pressure and only small transient increases in arterial pressure and PRA. On the other hand, in the 'high tone' vasoconstricted kidney at the time of stenosis the increases in systemic blood pressure and PRA were

large and well sustained and the elevation of systemic blood pressure contributed substantially to the restoration of distal renal artery pressure. The dogs which received a saline infusion instead of a vasoactive agent showed haemodynamic and renin responses between those with vasodilated and vasoconstricted renal vasculature, although the over-all pattern was closer to that of the low tone than to the high tone renal vasculature.

In our experiments, the renal artery was narrowed rapidly so that initial flow changes and estimation of effective stenosis resistance were not confounded by changes in systemic arterial pressure secondary to renin release. One exception to this was the experiments with methoxamine where arterial pressure rose before induction of stenosis despite the intrarenal route of administration, presumably due to passage through the kidney and vasoconstriction of other beds. This did not occur with angiotensin II which is rapidly metabolized by intrarenal enzymes (Oparil & Bailie, 1973). The resistance to blood flow exerted by a fixed-diameter arterial stenosis is not constant but varies with arterial pressure and distal vascular resistance (Anderson *et al.* 1979*a*; Gould *et al.* 1974; Mates *et al.* 1978; May *et al.* 1963; Schwartz *et al.* 1979; Walinsky *et al.* 1979; Young *et al.* 1977). In all groups in the present study, the calculated stenosis resistance fell from its initial value over the hour of stenosis. In the 'low' and 'normal' tone kidneys this was presumably mainly due to the secondary AII-mediated vasoconstriction (Anderson *et al.* 1979*a*) which follows the initial 'autoregulatory' vasodilation. In the dogs whose kidneys were vasoconstricted at the time of stenosis, stenosis resistance actually rose further over the first 5 min of stenosis as the effects of the methoxamine and angiotensin II wore off and the kidney dilated. In these two groups, the kidneys remained dilated for the next hour, but renal blood flow increased and stenosis resistance decreased as the result of the increase in systemic arterial pressure.

In the present study pentobarbitone anaesthesia plus preparation for surgery caused a marked rise in arterial pressure (in agreement with Fray, Siwek, Strull, Stellar & Wilson, 1976). Under these conditions renal blood flow was reduced and renal vascular resistance markedly elevated. Because of the different values of arterial pressure before stenosis in the conscious and anaesthetized dogs, a set pressure *drop* was established across the stenosis rather than the reduction of distal pressure to a set absolute value. Thus distal pressure was reduced to an average value of 47 mmHg in the conscious dogs compared to 81 mmHg in the anaesthetized dogs. Because of the different resting values in the two states it is difficult to interpret the initial blood pressure and renin responses to stenosis. However, the next day when the animals had completely recovered from the anaesthesia, both plasma renin and arterial blood pressure were elevated. This was in contrast to the absence of hypertension and the absence of a rise in PRA 24 hr after renal artery stenosis was induced while the dogs were fully conscious. The results thus suggest that creation of a set pressure gradient in anaesthetized dogs was associated with a more severe reduction in renal artery diameter than in conscious dogs.

These results probably explain why it is easier to produce 'Goldblatt' hypertension during surgery than in conscious dogs. The operative procedures required to expose the renal artery surgically are much more traumatic than the anaesthesia and simple manipulations performed here, and it is therefore likely that the kidney is even more

vasoconstricted. Thus the reduction in vessel diameter required to achieve a set pressure drop (or set % reduction in blood flow) would have to be even greater than required here.

In conclusion, the experiments reported here indicate that the state of the renal vascular tone is of critical importance in determining the degree of narrowing of the renal artery required to lower distal pressure to a given value and thus the blood pressure and renin responses to the stenosis. Because of the powerful capacity of the kidney to restore its vascular tone following the initial 'auto-regulatory' vasodilatation, a single renal artery narrowing to produce even quite low distal renal artery pressures in conscious animals is usually inadequate to cause permanent elevation of systemic blood pressure (Anderson *et al.* 1979*a*, *b*). We reported previously (Anderson *et al.* 1979*b*) and other investigators have also reported that several progressive adjustments of the constrictive device were often necessary to reliably achieve systemic hypertension (e.g. Lupu, Maxwell, Kaufman & White, 1972; Tagawa, Gutmann, Haber, Miller, Samuels & Barger, 1974; Ayers *et al.* 1974; Watkins, Davis, Hanson, Lohmeier & Freeman, 1976). The present experiments may point to another method; namely production of a moderate stenosis gradient while the kidney is vasoconstricted pharmacologically. Angiotensin II would be a suitable choice because of its potency on the renal vasculature (e.g. Hollenberg, Solomon, Adams, Abrams & Merrill, 1972).

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