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Research Article

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Dissociations between increments of GFR and sodium excretion occurred. Equivalent increments of GFR in the ischemic kidney in dogs receiving either 5% glucose in water or 10% mannitol in 0.3% saline were associated with natriuresis only in the latter group: *a*) as an initial response of the contralateral kidney to renal arterial constriction (RAC) in spite of a concomitant reduction in RBF and an unchanged GFR; *b*) in the ischemic kidney on giving angiotensin. The natriuresis produced by angiotensin was independent of the magnitude of elevations in blood pressure, altered filtration fraction, and was associated with a further reduction in RBF. After release of RAC in the dogs receiving mannitol, an […]

Some Determinants of the Effects of VAL-5-Angiotensin II Amide on Glomerular Filtration Rate and Sodium Excretion in Dogs

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ABSTRACT In 12 dogs anesthetized with chloralose, angiotensin (angiotensin II amide) given intravenously increased the glomerular filtration rate (GFR) of an ischemic kidney while simultaneously having little effect on the GFR of the contralateral kidney. In the ischemic kidney, in 14 of 30 observations, increments of GFR greater than 100% of mean control GFR (9 ml/min) occurred in response to angiotensin. The magnitude of the increase in GFR produced by angiotensin was independent of dose (range 0.005–0.050 μg/kg per min), the degree of accompanying pressor response, and alterations in renal blood flow (RBF) (electromagnetic flowmeter). In the ischemic kidney, increments of GFR could be produced by sub-pressor doses of angiotensin.

Dissociations between increments of GFR and sodium excretion occurred. Equivalent increments of GFR in the ischemic kidney in dogs receiving either 5% glucose in water or 10% mannitol in 0.3% saline were associated with natriuresis only in the latter group: *a*) as an initial response of the contralateral kidney to renal arterial constriction (RAC) in spite of a concomitant reduction in RBF and an unchanged GFR; *b*) in the ischemic kidney on giving angiotensin. The natriuresis produced by angiotensin was independent of the magnitude of elevations in blood pressure, altered filtration fraction, and was associated with a further reduction in RBF. After release of RAC in the dogs receiving mannitol, an antinatriuresis was again observed in response to angiotensin.

The presence of unilateral renal ischemia allowed the demonstration of a differential action of angiotensin on the GFR of an ischemic and nonischemic kidney. The natriuresis in response to angiotensin requires, in addition to mannitol, the participation of undefined factors invoked by unilateral renal ischemia.

INTRODUCTION

The renin-angiotensin system has been proposed to regulate glomerular filtration rate (GFR) (1, 2). The privileged location of the juxtaglomerular apparatus at the vascular pole of the glomerulus suggested to Goormaghtigh that it participated in regulating glomerular blood flow (3). In relating activity of the renin-angiotensin system to the control of GFR, assignment of the dominant action of angiotensin [1] to the pre- or postglomerular arteriole is a necessary first step. Thus, a primary action of angiotensin on the postglomerular arteriole was proposed by Schmid (1) and Leyssac (4). In contrast, Thurau considers the preglomerular arteriole to be the dominant site of action of angiotensin, thereby regulating the tubular load of sodium (2). GFR is usually reduced in response to doses of angiotensin II having moderate pressor effects (5). Predictable increases of GFR in response to angiotensin II have not been shown. The observation of the attenuation or loss of the renal vasoconstrictor action of angiotensin II during renal ischemia (6) suggested to us that the effect of angiotensin II on GFR may be altered in a similar manner.

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[1] Angiotensin (without roman numerical designation) shall denote angiotensins I and II, for they are probably both present within the kidney. It is impossible presently to distinguish their separate effects either intrarenally or systemically (see reference 19). Angiotensin II refers to the commercially available form (Asp^1-NH_2-Val^5-angiotensin II).

This consideration may be relevant to the proposals that angiotensin participates in the regulation of GFR.

The experiments reported in this paper demonstrate that the effect of angiotensin II on GFR was dependent on the control level of GFR. Thus, angiotensin II administered during renal ischemia invariably increased the depressed GFR of the ischemic kidney, while simultaneously, having no effect or decreasing the GFR of the contralateral kidney. If mannitol was administered, a natriuresis occurred *a*) as an initial response to renal arterial constriction (RAC) in the contralateral kidney, and *b*) in the ischemic kidney in response to angiotensin II during RAC.

METHODS

Twelve male mongrel dogs weighing from 19 to 26 kg were anesthetized with morphine sulfate (2 mg/kg, subcutaneously) and chloralose (100 mg/kg, intravenously). The abdominal cavity was entered through a transverse incision. The renal arteries were dissected free; care was taken not to disturb their innervation. A polyethylene catheter was introduced in a retrograde direction into each ureter and secured in place at the ureteropelvic junction. The dead space of each catheter was less than 1.1 ml. A multichannel direct writer (Sanborn Co., Waltham, Mass.) was used to record mean aortic blood pressure (MABP) as measured by a transducer (model P23Db, Statham Instruments, Inc., Los Angeles, Calif.) via a catheter inserted in a retrograde direction into a femoral artery, and renal blood flow (RBF) as measured by electromagnetic flowmeters (Statham model M-4001). Electromagnetic flowmeter sensors with openings of 2.5–3.5 mm, selected according to the size of the artery, were placed on each renal artery. The flowmeters were calibrated in two ways: perfusing blood through an excised renal arterial segment, and collecting femoral arterial blood for timed intervals while observing changes on the electromagnetic flowmeter with the flowmeter sensor placed proximal to the collecting site. The two methods for calibrating flowmeters were used for each sensor and were shown to agree within 5%. Previously, in three experiments, renal arterial blood flow measured with an electromagnetic flowmeter was compared simultaneously over a wide range of RBF with renal venous outflow measured by a Shipley-Wilson rotameter or directly by a T tube inserted in the renal vein; the values agreed within 10% (7). Zero flow was established by briefly occluding the renal artery, immediately distal to the flowmeter sensor, at the time of sensor placement and at the end of the experiment.

The renal artery was constricted by narrowing the aperture of a plastic screw clamp placed distal to the flowmeter sensor. The clamp was tightened without displacing the blood vessel from its bed; care was taken to avoid traction upon the renal artery.

In six experiments, a sustaining infusion of 5% glucose in water was administered at 6–8 ml/min. After two to three control periods of 10 min each, the renal artery was constricted and a period of 10-15 min was allowed for stabilization. Two clearance periods of 10–15 min duration were obtained during renal ischemia before administration of angiotensin II. Angiotensin II [2] (α-asparaginyl form of angiotensin II) was given intravenously by a Braun continuous infusion pump (model Unita 1) in appropriate concentrations so that the volume did not exceed 1 ml/min. Angiotensin II was administered in ascending dosage at rates of 0.005, 0.010, 0.025, and 0.050 μg/kg per min. Each dose of angiotensin II was given for 15–17 min, during which interval clearance periods of 10–15 min duration for each dose were obtained. At least three periods were obtained during infusion of angiotensin II. In one experiment in which 0.20 μg/kg per min of angiotensin II was given, a 10 min interval between this period and the preceding angiotensin period was observed, to prevent tachyphylaxis to the renal vascular action of angiotensin II (5, 8). The duration of the period of drug administration allowed stabilization of RBF values which occurred within 3 min after a new dose of angiotensin II was started. Renal vascular tachyphylaxis to angiotensin II was not observed under these experimental conditions.

In six experiments, a sustaining solution of 10% mannitol in 0.3% NaCl [3] was given at 4–6 ml/min while two or three clearance periods, each of 10 min duration, were obtained before and during an intervention. Control clearance periods were obtained before and 10 min after constriction of a renal artery. Angiotensin II was given to all dogs receiving mannitol at 0.025 μg/kg per min, intravenously, and in four of the six experiments, angiotensin II was also given at 0.010 μg/kg per min, intravenously, while RAC was maintained. In five of these experiments, 10 min after release of RAC, recovery values were obtained and the angiotensin II infusion (0.025 μg/kg per min) was repeated (two periods each).

A priming dose of inulin (50 mg/kg, intravenously) was given 1 hr before the first clearance period. A sustaining infusion containing inulin was given throughout the experiment to maintain plasma levels of inulin at 0.15–0.25 mg/ml. Venous blood samples for determination of plasma sodium, hematocrit, and inulin were removed at the midpoint of each collection period via a catheter inserted through a jugular vein into the superior vena cava. Plasma and urine samples were analyzed for inulin by the anthrone method (9). The hematocrits were determined by a microcapillary method. Sodium and potassium concentrations were determined by flame photometry (Instrumentation Laboratory Inc., Watertown, Mass., model 143). For calculation of filtration fractions, renal plasma flow was determined by: RBF $\times$ (1 $-$ hematocrit) = renal plasma flow. This experimental preparation eliminated the necessity for longer or more frequent clearance periods which may have resulted in the development of tachyphylaxis during an angiotensin II infusion (5, 8).

Since MABP (mean aortic blood pressure) and RBF were continuously recorded, any departure from the steady-state was immediately apparent. The clearance period was unacceptable, if changes in RBF ($>10\%$) occurred after allowing stabilization when the renal artery was constricted or angiotensin II was infused. Because of the minimal dead space (<1.1 ml/kidney) and continuous monitoring of MABP and RBF, the accuracy of the clearance periods was of a high order.

The data were transformed to natural logarithms to achieve approximate normality because the data appeared to be skewed and the standard deviation usually increased with the mean. A computer program was used in the analysis of variance for each response in a three-way classification: kidney, dog, and time. Because the interaction of treatment by kidney was significant, the data on each kidney were then analyzed separately by using an analysis of

[2] Hypertensin, CIBA Pharmaceutical Company, Summit, N. J.

[3] Osmitrol, Travenol Laboratories, Morton Grove, Ill.

TABLE I

*Summary of Changes in Contralateral and Ischemic Kidneys Produced by Angiotensin II Amide (0.005–0.050 μg/kg per min, i.v.) during Unilateral Renal Ischemia in Six Dogs Receiving 5% Glucose in Water**

		Control	RAC	RAC + AT II, 0.005–0.010 μg/kg per min, i.v.	RAC + AT II, 0.025–0.050 μg/kg per min, i.v.	Probability levels: Intragroup significance‡	Control vs. RAC§	RAC vs. RAC–AT II, 0.005–0.010§	RAC vs. RAC–AT II, 0.025–0.050§	Interaction‖
	MABP, *mm Hg*	115 ±5	124 ±7	135 ±11	144 ±9	<0.01	NS	NS	<0.01	
	PNa, *mEq/liter*	130 ±2	122 ±3	120 ±5	118 ±4	<0.05	NS	NS	NS	
	HCT, %	37 ±2	37 ±2	37 ±2	38 ±2	NS	NS	NS	NS	
RBF/m², *ml/min*	C	191 ±20	152 ±15	136 ±19	98 ±10	<0.01	<0.05	NS	<0.01	NS
	I	171 ±18	111 ±23	134 ±30	98 ±26	<0.01	<0.01	NS	NS	
GFR/m², *ml/min*	C	27.0 ±1.8	28.7 ±1.8	29.4 ±3.1	26.7 ±2.6	NS	NS	NS	NS	<0.01
	I	28.7 ±2.7	9.5 ±3.7	19.2 ±5.2	17.7 ±3.6	<0.01	<0.01	<0.05	<0.01	
FF	C	0.22 ±0.02	0.31 ±0.03	0.38 ± 0.05	0.45 ±0.03	<0.01	<0.01	<0.05	<0.01	NS
	I	0.25 ±0.02	0.11 ±0.04	0.17 ±0.04	0.25 ±0.05	NS	NS	NS	NS	
UV/m², *ml/min*	C	1.4 ±0.4	3.0 ±1.0	5.2 ±2.4	4.2 ±2.1	NS	NS	NS	NS	<0.01
	I	1.4 ±0.4	0.6 ±0.4	2.2 ±1.2	1.9 ±1.0	<0.01	<0.05	NS	NS	
UNa/m², *mEq/liter*	C	12.8 ±5.3	8.7 ±3.0	6.2 ±1.8	7.0 ±3.1	NS	NS	NS	NS	NS
	I	15.7 ±5.2	9.8 ±3.5	5.6 ±2.0	5.5 ±2.8	NS	NS	NS	NS	
$U_{Na}V$/m², *μEq/min*	C	17.0 ±8.7	14.2 ±3.1	27.2 ±14.7	18.0 ±8.4	NS	NS	NS	NS	<0.01
	I	20.5 ±8.7	2.4 ±0.9	4.2 ±1.2	4.3 ±1.1	<0.01	<0.01	NS	NS	
UK/m², *mEq/liter*	C	31.5 ±8.4	25.8 ±9.5	12.2 ±4.6	17.0 ±7.9	<0.05	NS	NS	NS	NS
	I	33.3 ±9.5	32.8 ±12.3	21.6 ±9.0	26.3 ±12.0	NS	NS	NS	NS	
U_KV/m², *μEq/min*	C	31.8 ±5.4	38.3 ±5.1	34.8 ±9.0	30.2 ±8.0	<0.05	NS	NS	<0.05	<0.01
	I	34.5 ±6.4	9.4 ±3.3	18.8 ±6.7	19.2 ±4.8	<0.01	<0.01	NS	NS	

* The mean and its SE are indicated for each value. Values corrected for body surface area are indicated by —, m^2. AT II = angiotensin II amide; C = contralateral kidney; I = ischemic kidney; RAC = unilateral renal arterial constriction. MABP = mean aortic blood pressure; PNa = plasma sodium concentration; HCT = hematocrit; RBF = renal blood flow; GFR = glomerular filtration rate; FF = filtration fraction; UV = urinary volume; UNa = urinary sodium concentration; $U_{Na}V$ = urinary excretion of sodium; UK = urinary potassium concentration; U_KV = urinary excretion of potassium.

‡ Intragroup significance = over-all significance among all experimental periods for one kidney. Analysis of variance using a logarithmic transformation was employed to determine statistical significance for the differences among the four periods.

§ Dunnett's test was used to determine statistical significance in comparing RAC with the other periods (interventions).

‖ Interaction of treatment (or time) with the state of the kidney (clipped or unclipped) was determined by analysis of variance for each response in a 3-way classification: kidney, dog, and time.

NS indicates no statistical significance.

variance for a two-way classification. If the analyses showed a significant difference among times, Dunnett's test was used to compare the mean responses at each of the other times with the mean response obtained during RAC. The relationships between urinary excretion of sodium ($\Delta U_{Na}V$) and Δ GFR (Fig. 1) were determined by correlation coefficients and analyses of covariance. Differences in Δ GFR between clipped and unclipped kidneys (Fig. 3) were determined by *t* test based on paired observations. A *P* value of 0.05 or less was considered statistically significant. Statistical analyses were performed according to methods described by Steel and Torrie (10).

RESULTS

Effects of angiotensin II during infusion of 5% glucose in water. Table I shows the values for renal function obtained during control periods, during periods of renal arterial constriction (RAC), and for periods during which angiotensin II was administered at two dose ranges while RAC was maintained. Plasma sodium showed a progressive fall while hematocrit remained constant. The responses to angiotensin II were indistinguishable for all parameters to each of the doses

within the lower (0.005 and 0.010 μg/kg per min) and higher (0.025 and 0.050 μg/kg per min) dose ranges. However, the lower and higher dose ranges of angiotensin II were separable on the basis of their effects on MABP and RBF. The division of Table I relative to doses of angiotensin II reflects these considerations. During RAC, before administration of angiotensin II, blood flow to the contralateral kidney decreased while GFR and $U_{Na}V$ were unchanged. In the ischemic kidney the expected reductions in RBF, GFR and $U_{Na}V$ occurred after induction of RAC. The blood flows of the ischemic and contralateral kidneys exhibited a differential response to the lower doses of angiotensin II. Thus, lower doses of angiotensin II frequently did not decrease blood flow to the ischemic kidney; in four of six experiments RBF was increased. In contrast, simultaneously determined blood flow to the contralateral kidney was decreased in all experiments. A bilateral reduction in RBF and greater pressor response was observed in response to the higher doses of angiotensin II. Angiotensin II at either dose did not reduce the mean GFR of the contralateral kidneys, whereas in the ischemic kidneys similar increases in mean GFR occurred in response to both the lower and higher doses of angiotensin II. Angiotensin II administered during renal ischemia did not modify sodium or potassium excretion from either kidney relative to those values initially observed after RAC. In seven observations in three experiments, repeated infusion of angiotensin II after release of RAC resulted in either bilateral reductions in GFR of 8–54% (five observations) or an unchanged GFR.

Fig. 1 shows the changes produced by angiotensin II on the simultaneously determined GFR and $U_{Na}V$ of ischemic and contralateral kidneys for 21 observations in six experiments. The effect of angiotensin II on GFR was independent of dose within the range of doses used in the present experiments. In spite of large changes in GFR, occurring in the ischemic kidney, concomitant changes in $U_{Na}V$ produced by angiotensin II were absent or small; viz., less than 10 μEq/min (Fig. 1). There was no significant correlation between the magnitude of the changes in $U_{Na}V$ and GFR in either the ischemic or contralateral kidney (correlation coefficients $r = 0.175$ and 0.407, respectively). An analysis of covariance in which changes in $U_{Na}V$ were adjusted for changes in GFR showed no significant difference between the ischemic and contralateral kidneys. In most instances, small increases and decreases of $U_{Na}V$ accompanied the changes in GFR in ischemic and contralateral kidneys, respectively. However, in two observations in response to angiotensin II, large changes in $U_{Na}V$ (40 and 66 μEq/min) which were not predicted by the accompanying changes in GFR occurred in the contralateral kidney (Fig. 1).

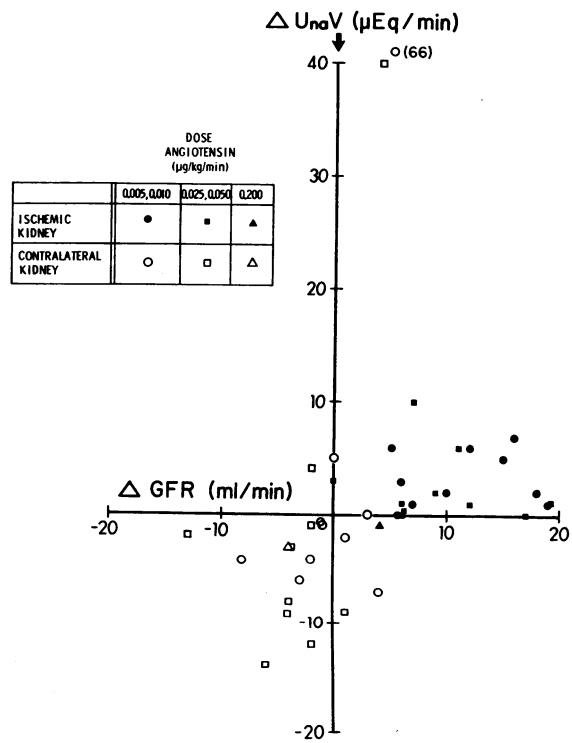

FIGURE 1 Relation between increase in glomerular filtration rate (GFR) and increase in sodium excretion ($U_{Na}V$) determined simultaneously for ischemic and contralateral kidneys in response to angiotensin II given intravenously to chloralose-anesthetized dogs receiving 5% glucose in water. The dose of angiotensin II is expressed in μg/kg per min. 21 observations in six experiments are plotted for the simultaneously determined increments in GFR and $U_{Na}V$ for ischemic and contralateral kidneys.

Effects of angiotensin II during infusion of 10% mannitol in 0.3% saline. In Table II, in dogs receiving 10% mannitol in 0.3% saline, control values for renal function obtained before and during RAC are contrasted to those obtained in response to a single dose of angiotensin II (0.025 μg/kg per min) infused intravenously while the RAC was maintained. As in the first six experiments, the most notable observation is that angiotensin II increased the mean GFR of the ischemic kidneys ($P < 0.01$), while the simultaneously determined mean GFR of the contralateral kidneys was not significantly changed. The major differences observed between the two groups of experiments were the natriureses which occurred in the dogs receiving mannitol both as an initial response of the contralateral kidneys to RAC and for the two kidneys in their response to angiotensin II during renal ischemia. A modest kaliuresis accompanied the natriuresis in response to angiotensin II given during renal ischemia. Angiotensin II in equivalent doses produced a pressor response and bilateral renal

TABLE II

*Summary of Changes in Contralateral and Ischemic Kidneys Produced by Angiotensin II Amide (0.025–0.050 μg/kg per min, i.v.) during Unilateral Renal Ischemia in Six Dogs Receiving 10% Mannitol in 0.3% NaCl**

		Control	RAC	RAC + AT II, 0.025 μg/kg per min, i.v.	Probability levels: Intra-group significance‡	Control vs. RAC§	RAC vs. RAC–AT II§	Interaction‖
	MABP *mm Hg*	108 ±3	115 ±4	142 ±8	<0.01	NS	<0.01	
	PNa, *mEq/liter*	139 ±1	138 ±1	138 ±1	NS	NS	NS	
	HCT, %	39 ±2	38 ±2	37 ±2	NS	NS	NS	
RBF/m², *ml/min*	C	143 ±18¶	122 ±14	77 ±10	<0.01	NS	<0.01	<0.01
	I	181 ±29	100 ±24	76 ±12	<0.01	<0.01	NS	
GFR/m², *ml/min*	C	21.8 ±1.6	23.5 ±1.5	22.3 ±1.5	<0.05	NS	NS	<0.01
	I	22.9 ±1.2	9.2 ±1.2	15.7 ±1.3	<0.01	<0.01	<0.01	
FF	C	0.24 ±0.03	0.30 ±0.03	0.45 ±0.05	<0.01	NS	<0.01	<0.01
	I	0.22 ±0.04	0.18 ±0.06	0.33 ±0.06	<0.01	NS	<0.01	
UV/m², *ml/min*	C	2.0 ±0.2	3.6 ±0.3	4.2 ±0.4	<0.01	<0.01	NS	<0.01
	I	2.3 ±0.1	1.0 ±0.2	2.8 ±0.2	<0.01	<0.01	<0.01	
UNa/m² *mEq/liter*	C	14.2 ±4.5	22.3 ±4.8	24.9 ±3.6	NS	NS	NS	<0.01
	I	21.8 ±8.4	8.4 ±3.2	21.5 ±3.3	<0.05	NS	NS	
$U_{Na}V$/m², *μEq/min*	C	28.6 ±9.0	85.5 ±24.8	108.8 ±23.5	<0.01	<0.01	NS	<0.01
	I	52.2 ±21.4	10.9 ±5.2	61.0 ±10.7	<0.01	NS	<0.05	
UK/m², *mEq/liter*	C	19.5 ±4.2	14.4 ±1.0	16.8 ±1.8	NS	NS	NS	<0.01
	I	19.7 ±4.3	12.1 ±1.8	17.6 ±1.9	<0.05	NS	NS	
U_KV/m², *μEq/min*	C	38.2 ±8.2	52.4 ±5.8	70.2 ±10.9	NS	NS	NS	<0.01
	I	45.8 ±11.6	13.6 ±3.2	48.9 ±6.3	<0.01	<0.01	<0.01	

* See Table I for explanation of abbreviations.

‡, §, ‖ See Table I for explanation of symbols specifying statistical treatment.

¶ In two experiments an accessory renal artery was present. Therefore, the RBF is underestimated by the amount of blood flow in the accessory renal artery (estimated 20–40% of total RBF) on these two experiments.

vasoconstriction which were indistinguishable from those occurring in dogs receiving glucose.

In Fig. 2, the effects of angiotensin II on MABP, RBF, GFR, and $U_{Na}V$ (average of two or three periods for the latter two parameters) of the separate kidneys before, during, and after constriction of the right renal artery are shown. Angiotensin II produced a differential effect on GFR during RAC; the GFR of the ischemic kidney was increased while that of the contralateral kidney was reduced. Sodium excretion increased bilaterally in spite of concomitant reductions in RBF. After release of the arterial constriction, angiotensin II reduced $U_{Na}V$ bilaterally relative to the values obtained in the period of recovery.

In five of the six experiments in which 10% mannitol in 0.3% saline was given, after release of the arterial constriction, recovery observations were made and the infusion of angiotensin II (0.025 μg/kg per min) was repeated (Table III). Angiotensin II increased MABP, reduced RBF, and produced an antinatriuresis in the postconstriction period which are the expected responses to this dose of angiotensin II in dogs (5).

For dogs receiving mannitol, there was no correlation between the magnitude of changes in GFR and the magnitude of changes in $U_{Na}V$ for ischemic ($r = 0.334$) or contralateral kidneys. Moderate to large increases in $U_{Na}V$ occurred in association with variable increases in GFR in the ischemic kidney, in contrast to those experiments in which 5% glucose in water was given. Comparable increases in $U_{Na}V$ occurred less frequently in the contralateral kidney. However, the mean values for $U_{Na}V$ preceding infusion of angiotensin II differed significantly; viz., 85.5 and 10.9 μEq/min for contralateral and ischemic kidneys, respectively (Table II).

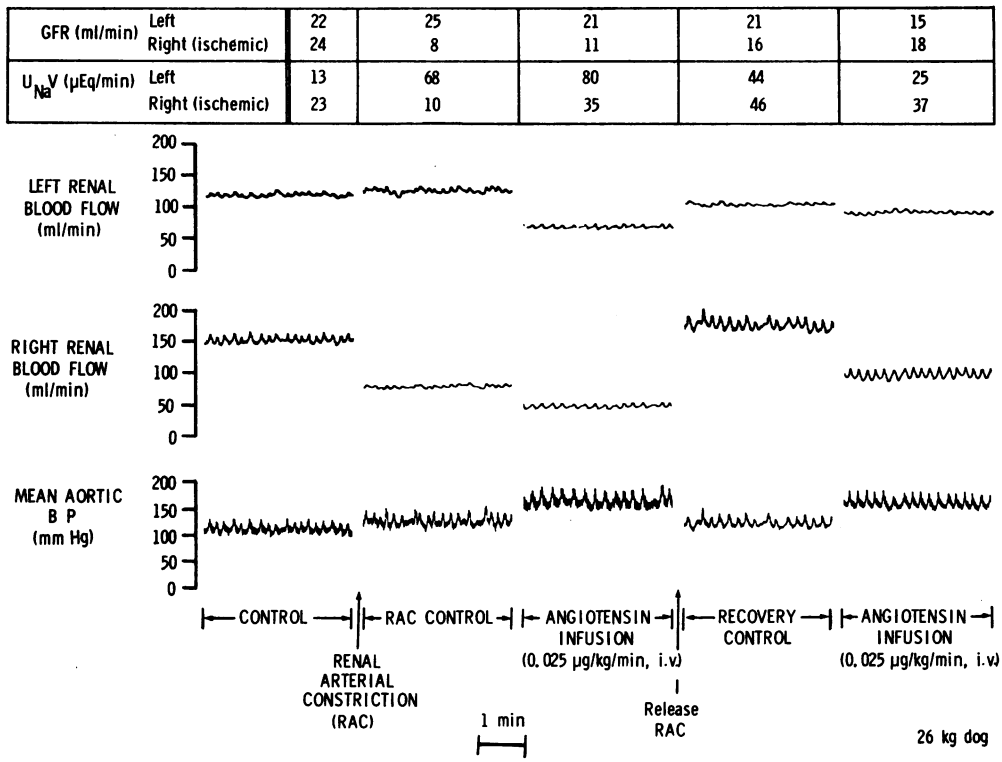

FIGURE 2 The effect of angiotensin II infused intravenously during right renal arterial constriction (RAC) and after release of RAC on mean aortic blood pressure, renal blood flows, glomerular filtration rates (GFR), and sodium excretion ($U_{Na}V$) for an ischemic and a contralateral kidney in a chloralose-anesthetized dog receiving 10% mannitol in 0.3% saline. The values for GFR and $U_{Na}V$ are the average of two or three periods. A smaller accessory left renal artery was present. The illustrated left renal blood flow is underestimated by the blood flow in the accessory vessel (20%–30% of total RBF).

An analysis of covariance adjusting changes in $U_{Na}V$ for changes in GFR showed no significant differences between the ischemic and contralateral kidneys. However, the ischemic and contralateral kidneys of each group (those receiving glucose or those receiving mannitol) could be differentiated on the basis of changes in GFR produced by angiotensin II ($P < 0.01$). The GFR of the ischemic kidney increased consistently, but showed little change and then usually a reduction in the contralateral kidney in each group (Fig. 3).

The effects of angiotensin II on the simultaneously determined GFR of ischemic and contralateral kidneys for all 12 experiments (30 observations) are shown in Fig. 3. The changes in GFR produced by angiotensin II in the contralateral or ischemic kidneys during infusion of 10% mannitol in 0.3% saline were similar to those changes in GFR observed when 5% glucose in water was administered; viz., increased GFR to the ischemic kidney and variable effects on GFR of the contralateral kidney. The changes observed in GFR in the ischemic kidney were much greater than could be accounted for by an error inherent in the anthrone method for measuring inulin (9). Thus, the standard error (obtained from the mean square for the residual in the analysis of variance) for the measurement of GFR was less than 2.5%. The capacity of angiotensin II to increase GFR in the ischemic kidney was most readily demonstrated when the GFR was reduced below 15 ml/min. On two occasions, when RAC resulted in a GFR which was within the range of GFR for the contralateral kidneys (20–30 ml/min), angiotensin II produced changes in the GFR similar to those observed in contralateral kidneys (Fig. 3). The coincident effects of angiotensin II on the GFR of the contralateral kidney were variable: moderate reductions of GFR were noted in 18 of 30 observations. The effects of angiotensin II on the simultaneously determined GFR for ischemic and contralateral kidneys were significantly different when the data were pooled ($P < 0.001$), or when considered with respect to dose; viz., $P < 0.05$ for 0.005 and 0.010 μg/kg per min, $P < 0.01$ for 0.025 and 0.050 μg/kg per min.

TABLE III

*Summary of Changes Produced by Angiotensin II Amide (0.025 μg/kg per min, i.v.) after Release of Renal Arterial Constriction in Five Dogs Receiving 10% Mannitol in 0.3% NaCl**

		Control	AT II, 0.025 μg/kg per min, i.v.	Probability level Control vs. AT II‡
	MABP, *mm Hg*	113 ±7	136 ±10	<0.01
	PNa, *mEq/liter*	137 ±1	139 ±2	NS
	HCT, %	35 ±1	35 ±1	NS
RBF/m², *ml/min*	C	101 ±13§	67 ±11	<0.01
	I	147 ±24	84 ±14	<0.01
GFR/m², *ml/min*	C	20.7 ±2.1	17.9 ±2.1	NS
	I	17.6 ±1.4	17.0 ±1.5	NS
FF	C	0.37 ±0.05	0.43 ±0.07	<0.05
	I	0.22 ±0.04	0.35 ±0.07	<0.05
UV/m², *ml/min*	C	4.6 ±0.8	3.6 ±0.6	<0.05
	I	3.9 ±0.6	3.5 ±0.4	NS
UNa/m², *mEq/liter*	C	22.0 ±7.7	19.9 ±6.6	NS
	I	21.6 ±6.3	18.3 ±5.4	NS
$U_{Na}V/m^2$, *μEq/min*	C	122.3 ±54.4	84.3 ±37.3	<0.05
	I	99.4 ±46.9	72.6 ±32.2	NS
UK/m², *mEq/liter*	C	19.8 ±2.1	18.6 ±1.9	NS
	I	21.6 ±2.6	20.1 ±2.7	NS
U_KV/m^2, *μEq/min*	C	92.0 ±20.1	67.8 ±15.4	<0.05
	I	87.1 ±22.2	72.4 ±17.4	<0.05

* See Table I for explanation of abbreviations.

‡ Significance probability determined by Dunnett's test and paired T test.

§ In two experiments an accessory renal artery was present. Therefore, the RBF is underestimated by the amount of blood flow in the accessory renal artery (estimated 20–40% of total RBF) in these two experiments.

DISCUSSION

Angiotensin II was shown in the present experiments to increase the GFR of an ischemic kidney while having variable effects on the GFR of the contralateral kidney. This differential effect of angiotensin II on GFR during unilateral renal ischemia occurred independently of consistent changes in aortic blood pressure, RBF, sodium excretion, plasma sodium, and hematocrit. The magnitude of the increase in GFR produced by angiotensin II in the ischemic kidney was independent of the dose (within the range of 0.005–0.050 μg/kg per min), the degree of the accompanying pressor response, and altered renal vasoconstrictor activity of angiotensin II (Table I). The present experiments dissociate increments in GFR from simultaneous increases in sodium excretion. Thus, when 5% glucose in water was administered, in spite of a mean increase in GFR of 100% produced by angiotensin II, a coincident increase in sodium excretion did not occur. Furthermore, when a natriuresis oc-

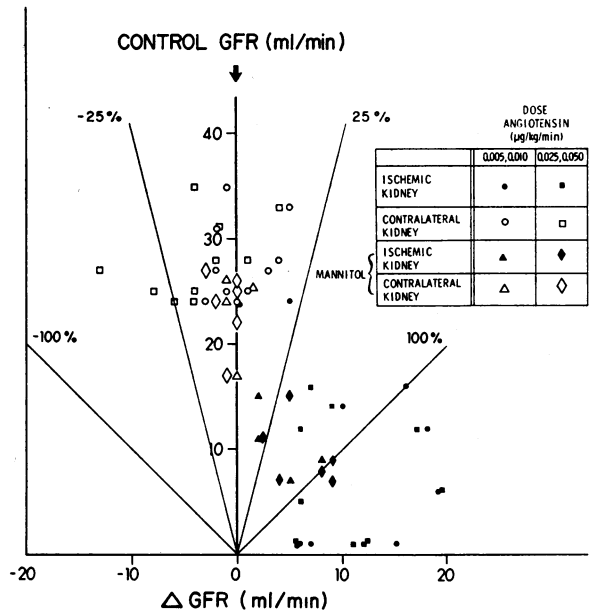

FIGURE 3 Relation between increments in glomerular filtration rate (Δ GFR) and control GFR for all experiments (30 observations in 12 dogs) for the simultaneously determined GFR of ischemic and contralateral kidneys in chloralose-anesthetized dogs. The dose of angiotensin II is expressed in μg/kg per min. Dogs receiving 5% glucose in water are undesignated. Mannitol refers to the dogs receiving 10% mannitol in 0.3% saline.

curred in response to RAC and angiotensin II in the dogs receiving mannitol, the increment of GFR was unrelated to the degree of coincident natriuresis. Lindheimer, Lalone, and Levinsky have dissociated increases in GFR from increases in sodium excretion (11).

Angiotensin II increased the GFR of the ischemic kidney independently of simultaneous changes in MABP and RBF. In two experiments, increases of GFR of 7 and 8 ml/min occurred (> 100% of control GFR) within the ischemic kidney in response to a subpressor dose of angiotensin II (0.005 μg/kg per min). Furthermore, increments in GFR were not correlated with the magnitude of the accompanying pressor response to angiotensin II. While only increases in GFR occurred in the ischemic kidney in response to the lower doses of angiotensin II, variable changes in blood flow occurred. In response to the higher doses of angiotensin II (0.025 and 0.050 μg/kg per min), in spite of large reductions in RBF, increases in the GFR of the ischemic kidney occurred which were similar to those produced by the lower dose (Tables I and II).

The afferent and efferent glomerular arterioles are the major vascular resistance sites in the renal vascular tree, since the greatest dissipations of hydrostatic pressure occur: *a*) between the renal arteries and the glomerular capillaries (afferent arteriolar resistance site), and *b*) between the glomerular capillaries and peritubular capillaries (efferent arteriolar resistance site) (12). The contribution of the preglomerular arteriole to the regulation of GFR is conspicuous when renal perfusion pressure is markedly increased by hypertension (13). To maintain a constant GFR, a degree of independence of the glomerular arterioles would be required in their response to conditions having such disparate effects on intrarenal hemodynamics as essential hypertension, renal arterial stenosis, and hypovolemia.

The determinants of the dominant site of vasoconstrictor action (pre- or postglomerular) of angiotensin II remain to be defined. A preferential effect of angiotensin II on either pre- or postglomerular arteriolar resistance may be modulated by the sympathetic nervous system in which fibers invest the juxtaglomerular apparatus and the vascular pole of the glomerulus (14). The interaction of renal adrenergic nerves and angiotensin II was considered to be a determinant of the renal vascular and natriuretic effects of angiotensin II (8, 15).

Thurau proposed a dominant preglomerular action of angiotensin to adjust the tubular sodium load to the tubular reabsorptive capacity for sodium (2). However, this hypothesis fails to account for the increased release of renin which occurs immediately on reducing renal arterial pressure, at which time a reduced sodium load has the same effect as Thurau proposed for an increased sodium load (2, 16). The major effect of angiotensin II when infused intravenously is presumably registered on the postglomerular arteriole since filtration fraction consistently increased (17). A dominant postglomerular action of endogenous angiotensin was suggested on the basis of failure to maintain GFR when the efferent glomerular arteriolar tone was reduced. Thus, dogs, having a high titer of antirenin, were shown to have a reduced capacity to adjust to decreased postglomerular resistance as reflected in a reduced GFR (1).

The increase in GFR of the ischemic kidney, and its relative constancy in the contralateral kidney, is consistent with an increase primarily in postglomerular arteriolar tone, in view of the large reductions in RBF produced by angiotensin II at doses of 0.025 and 0.050 μg/kg per min. This consideration does not exclude a simultaneous lesser increase or even reduction in afferent glomerular arteriolar tone. The alternate hypothesis of primary dilation of the afferent arteriole (and accompanying constriction of the efferent arteriole) by angiotensin II within the ischemic kidney challenges a large body of work demonstrating that a vasoconstrictor action, presumably of physiologic significance, is a fundamental property of this polypeptide (18). Attenuation of the vasoconstrictor action of angiotensin II during renal ischemia was described, but a direct renal vasodilator action has not been demonstrated (6). The suggested locus of action of angiotensin II under these experi-

mental conditions does not exclude a dominant preglomerular action under other conditions. Physiologically, the vascular activity of angiotensin is partially defined by the site of its activation, i.e., somewhere between the points of release of renin from the afferent arteriole and the vascular tree downstream. Ng and Vane have shown that the major conversion of angiotensin I to II required passage through the pulmonary circulation (19). The implications of this important observation relative to dominant intrarenal sites of action and differences in the effects of the two angiotensins remain to be determined.

A natriuresis occurred in the dogs receiving mannitol as an initial response of the contralateral kidney to RAC and in the ischemic kidney in response to angiotensin II (Table II). The natriuresis produced by angiotensin II did not require for its demonstration a pressor response, blunting of its renal vasoconstrictor action, or altered filtration fraction, for similar changes in these parameters occurred irrespective of simultaneous changes in sodium excretion. While an increased blood pressure may have facilitated the demonstration of a natriuresis in response to angiotensin II, it could not have contributed to the natriuresis of the contralateral kidney induced initially by RAC since the latter was not accompanied by a pressor response. The two interventions producing natriuresis, RAC and angiotensin II in the dogs receiving mannitol, were each associated with reductions in RBF. Furthermore, blunting of the renal vasoconstrictor effect of angiotensin II by mannitol which has been reported did not occur (20). In the dogs receiving the lower doses of angiotensin II, the frequent occurrence of increased blood flow to the ischemic kidney did not result in natriuresis (Table I). An increased filtered load of sodium did not account for the natriuresis produced by angiotensin II since the greater concentration of plasma sodium of the group receiving mannitol was more than offset by their diminished GFR. Mannitol was reported to reduce GFR by increasing proximal intratubular pressure (21).

Changes in plasma sodium may have been a determinant of the failure of angiotensin II to produce natriuresis in the dogs receiving glucose (Table I). This factor could not account for the natriuresis in the dogs receiving mannitol since plasma sodium remained constant throughout the experiments. The role of altered plasma sodium concentrations in modifying sodium excretion is uncertain. An inverse relationship was reported between plasma concentration of sodium and its reabsorption (22, 23). However, Martino and Earley considered the effect of the sodium ion on tubular transport to be related rather to accompanying intratubular volume effects (24).

The natriuretic effect of angiotensin II in the rat was reported to be dependent upon expansion of the extracellular space (25) and abolished in the presence of diuresis invoked by water loading (26). Expansion of the extracellular space, though it may have been contributory, was not a major determinant of the natriuresis produced by RAC and angiotensin II. Thus, in the dogs, not demonstrating a natriuresis to angiotensin II, expansion of the extracellular space was probable, for plasma sodium showed a progressive reduction in the face of an antidiuresis (Table I). If this factor were a determinant of the natriuresis produced by angiotensin II in the dogs receiving mannitol, it was later nullified, for release of the RAC resulted in a restoration of the antinatriuretic action of angiotensin II (Table III).

The effects of mannitol in revealing a natriuresis in response to RAC and angiotensin II may have operated through its effect on proximal tubular reabsorption of sodium (27) which then allowed the demonstration of a natriuresis to either administered angiotensin II or endogenous angiotensin by increasing delivery of sodium to the distal nephron. Angiotensin also may have an effect on proximal tubular reabsorption of sodium (4, 28). Thus, Earley and Friedler reported a natriuresis in response to angiotensin II during induction of renal vasodilation by acetylcholine and bradykinin (28). They suggested that the natriuresis resulted from facilitated transmission during vasodilation of the pressor effect of angiotensin II to the postglomerular capillaries, thereby secondarily influencing proximal tubular reabsorption of sodium. A distal tubular action (though not exclusive) of angiotensin II was proposed by several investigators (29–31). A proximal tubular action of angiotensin II, while not necessary for this consideration, if it occurred, would have facilitated the effects of mannitol. However, this hypothesis neither explains the antinatriuresis produced by angiotensin II (postconstriction) in these same experiments, nor does it encompass the effects of RAC on the initial natriuresis from the contralateral kidney (before giving angiotensin II) unless the effects of increased circulating levels of endogenous angiotensin produced this effect on the contralateral kidney (Tables II and III). Renin release and presumably formation of angiotensin are known to occur rapidly after induction of renal ischemia (32).

We must conclude that the induction of RAC has modified the response to mannitol and angiotensin by introducing (eliminating) a factor(s) which awaits definition. Unilateral RAC in rats was reported to alter the natriuretic response to angiotensin II in the contralateral kidney, if hypertension was induced, and in the clipped kidney, if hypertension did not develop (33, 34). The present experiments cannot exclude intrarenal hemodynamic or extrarenal humoral factors acting in concert with or independently of angiotensin to produce natriuresis during renal ischemia in dogs receiving 10% mannitol in 0.3% saline (35).

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