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RENIN RELEASE AND AUTOREGULATION OF BLOOD FLOW IN A NEW MODEL OF NON-FILTERING NON-TRANSPORTING KIDNEY

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SUMMARY

1. A recently developed model of a non-filtering, non-transporting dog kidney, obtained by an *in situ* filling of tubules with low-viscosity oil, was applied for studies of renin release and autoregulation of renal blood flow (RBF).

2. Renal blood flow was partially autoregulated after oil blockade of tubules, as indicated by a mean autoregulation index (Semple–de Wardener (1959)) of 0·5. This was comparable to autoregulation of the stop-flow kidney (index 0·6) and contrasted with abolition of autoregulation after hypertonic mannitol loading at stop-flow conditions (index 1·1).

3. The aortic construction at a suprarenal level, which decreased renal perfusion pressure of the oil-blocked kidney $35 \pm$ (S.E. of mean) 6 mmHg, produced an increase in arterial plasma renin activity of $1{\cdot}8 \pm 0{\cdot}1$ ng.ml.$^{-1}$ ($P < 0{\cdot}02$). Renin secretion rate decreased 33 to 70 ng.min^{-1} in three dogs in which renal perfusion pressure was reduced to 60–66 mmHg, but increased 110 ± 41 ng.min^{-1} when pressure reductions were kept within the renal blood flow autoregulation range ($n = 8$, $P < 0{\cdot}025$).

4. These results suggest that signals from the tubular receptor (macula densa) are not necessary for stimulation of renin release or autoregulation of renal blood flow.

INTRODUCTION

Ample evidence has accumulated over the years indicating involvement of two intrarenal receptors in the control of renin secretion: the baroreceptor, responding to changing stretch of the afferent arterioles; and the tubular macula densa receptor, sensing variations in sodium chloride

concentration or transport in the distal nephron (Davis, 1973). The relative importance of the two receptors has not been easy to evaluate.

The difficulty in dissociating between the baroreceptor and macula densa influences in studies of renin secretion has led Blaine, Davis & Witty (1970) to develop a kidney model in which glomerular filtration and fluid movement past the macula densa segment of the renal tubules are abolished. This was accomplished by combining total renal ischaemia for 2 hr with ureteral ligation in the dog. The non-filtering kidney so obtained was capable of releasing renin in response to a reduction of renal perfusion pressure or haemorrhage, suggesting that signals from the macula densa are not essential for stimulation of renin secretion. No systematic study of renal blood flow (RBF) autoregulation in this kidney preparation has yet been published.

Further research employing the model of Blaine *et al.* (1970) has provided new important data favouring the predominant role of the renal baroreceptor mechanism in the control of renin release (Witty, Davis, Johnson & Prewitt, 1971; Gottshall, Davis, Blaine, Mussacchia, Braverman, Freeman & Johnson, 1974). However, the kidney preparation used still remains subject to criticism. As the combination of ureteral and renal artery occlusion results in extensive irreversible necrosis of the kidney parenchyma and formation of tubular casts, the experimental design must be judged highly unphysiological. Furthermore, the evidence for abolition of glomerular filtration, the absence of injected dye in the tubular lumina viewed on the kidney surface, is not entirely convincing. As the authors themselves recognize (Johnson, Davis, Shade & Witty, 1972), filtration could continue in the deeper nephrons, though probably at a markedly reduced rate.

Considering these reservations, it would be important to confirm the results obtained with the Blaine *et al.* (1970) model using some other experimental design for inactivation of the macula densa receptor. This was made possible by development of a new model of non-filtering, non-transporting kidney obtained by filling of the whole renal tubular system, *in situ*, with low-viscosity oil (Sadowski, 1974). This new preparation offers certain advantages over the ischaemic model. During experiments absence of glomerular filtration is indicated by abolition of renal extraction of creatinine, inulin and *p*-aminohippurate. The final verification of successful oil blockage of the kidney is based on the absence of injected indicator (sodium ferrocyanide) in the tubules of both superficial and deep nephrons, as examined by nephron microdissection. More important, introduction of oil does not result in any serious damage of renal tissue, as can be judged by restoration of significant extraction of *p*-aminohippurate after re-opening the ureter and evacuation of oil.

The present experiments were designed to find out whether this new type of non-filtering, non-transporting kidney preparation can increase renin secretion in response to a reduction of renal perfusion pressure. Moreover, in view of conflicting evidence on the role of fluid delivery rate to, or its composition in, the distal tubular segment for autoregulation of glomerular filtration rate (GFR) and renal blood flow (Guyton, Langston & Navar, 1964; Hierholzer, Mueller-Suur, Gutsche, Butz & Lichtenstein, 1974; Knox, Ott, Cuche, Gasser & Hass, 1974; Morgan, 1971; Schnermann, Wright, Davis, Stackelberg & Grill, 1970; Thurau & Schnermann, 1965), it was also interesting to check whether the oil-blocked kidney would lose or maintain its usual autoregulatory capacity.

METHODS

Mongrel dogs of either sex, weighing 8–24 kg, were fasted overnight but given free access to water. They were anaesthetized with sodium N-methyl-beta-bromallyl-isopropyl barbiturate (Eunarcon; Riedel A.G.), 50 mg.kg^{-1} body weight, supplemented with small I.V. doses as required, or with chloralose given slowly I.V. in the dose 80–100 mg.kg^{-1} body weight as a solution in warm saline.

Preparation of animals for study. Polyethylene catheters were placed in the femoral vein for infusion of creatinine, inulin and *p*-aminohippurate (PAH) solution in saline and in both femoral arteries for blood sampling and recording of aortic blood pressure. The left kidney was exposed from a flank incision, the ureter cannulated and the tip of the arterial catheter, connected with a damped mercury manometer, was positioned in the aorta at the origin of the left renal artery. The pressure so measured was regarded as renal perfusion pressure (RPP). A noose placed around the aorta between the left and right renal artery enabled graded aortic constriction and reduction of left renal perfusion pressure.

After an I.V. injection of heparin, 5 mg.kg^{-1} body weight, the left renal vein was cannulated without interrupting blood flow, the blood effluent was passed through a venous outflow recorder (Sadowski, 1971) and then returned to the dog through a jugular vein cannula. The renal venous blood samples were obtained directly from the shunt. At least 30 min after completion of surgical procedures, a constant rate infusion of a saline solution of creatinine, inulin and PAH was started, preceded by an injection of appropriate priming doses. The volume infusion rate was 0·5 ml. min^{-1} and plasma concentration of the three substances required for measurement of their renal extraction ratios was obtained by adjusting their concentration in the infusate to dog weight.

In four dogs a thin polyethylene catheter connected with a saline manometer was introduced into the renal vein through a side-branch of the shunt and pushed inside the kidney till a sharp increase in pressure indicated a position suitable for measurement of deep venous pressure (DVP).

After completing observations at free urine flow, the left ureteral catheter was connected to a mercury manometer for measurement of ureteral (renal pelvic) pressure.

Autoregulation studies. These were performed in a total of sixteen dogs. Two of them showed initial mean aortic pressure above 160 mmHg; in the others the pressure was raised by occluding both common carotid arteries. The pressure–flow relationships were examined during graded reduction of renal perfusion pressure by

aortic constriction at a suprarenal level. This was done under conditions of: (1) free urine flow; (2) ureteral occlusion, after renal pelvic pressure has stabilized at a maximal level; (3) ureteral occlusion followed by an intravenous loading with mannitol, 5·5 m-mole.kg^{-1} body weight, dissolved in 100–150 ml. isotonic saline and infused during 10 min; and (4) in a non-filtering, non-transporting kidney obtained by filling of the renal tubules with a low-viscosity oil.

The technique of oil blockade of the tubules and methods used for evaluation of its completeness are described in detail in a recent publication (Sadowski, 1974). The essential features can be outlined as follows. A low-viscosity oil (Apiezon B; Shell) warmed to 40° C is forced into the kidney (prepared as described above) through the cannulated ureter until it appears in large amounts in the renal venous effluent. Before re-entering systemic circulation this blood is passed through a separatory funnel where the oil is trapped. A successful oil blockade of the tubules is indicated by abolition of renal extraction of PAH and a failure of injected sodium ferrocyanide to enter the tubules, as examined after experiments by nephron microdissection.

Renin release studies. Six dogs used in autoregulation experiments and six additional animals, all weighing 18 kg or more, were used for these studies. After completing oil blockade, arterial and renal venous blood samples for plasma renin activity were obtained before and at a time between 1·5 and 12 min after suprarenal aortic constriction which decreased renal perfusion pressure from 119 ± 6 (S.E. of mean) to 84 ± 5 mmHg. Control arterial and renal venous plasma renin activity were determined in nine animals of this group.

While the samples were being withdrawn, the same volume of blood collected slowly earlier during the experiment was re-infused to the dogs. The blood was collected into cooled plastic tubes containing ethylenediaminetetra-acetate (EDTA) and centrifuged immediately in the cold. The plasma was kept frozen till analysis was performed by the method of Boucher, Veyrat, de Champlain & Genest (1964). The plasma renin activities so determined represent nanograms of angiotensin II released by a 10 ml. plasma sample during 3 hr incubation at 37° C. The biological assays were performed in nephrectomized rats treated with pentolinium. Attempts at simultaneous determination of plasma renin by radioimmuno-assay for angiotensin I were abandoned, for even small amounts of oil interfered with the analytical procedure. The renin secretion rate (RSR) was calculated as the product of the renal plasma flow (RPF) and the difference in renin in the plasma of the renal vein and artery ($RSR = RPF(RV - A)_{ren}$) and expressed as ng angiotensin equivalents per minute.

Other methods and calculations. The standard analytical methods for creatinine, inulin and PAH were as described previously (Sadowski, 1974). The extraction ratios of clearance substances (E_{cr}, E_{in}, E_{PAH}) were calculated as $(A_x - RV_x)/A_x$ where A_x and RV_x are concentrations of the respective substances in arterial and renal venous plasma. The arterial haematocrit (Ht) was determined by the capillary method and the renal plasma flow was calculated as RBF.(1·00 − Ht).

Standard statistical methods were used for evaluation of the results. Throughout the paper, standard error (S.E.) of mean or of mean difference is used as an index of data dispersion.

RESULTS

The choice of anaesthetic agent, Eunarcon or chloralose, did not appreciably influence the results of experiments. Under free-flow conditions, renal extraction ratios of exogenous creatinine, inulin and PAH were 0·14 ± 0·01 (S.E. of mean), 0·16 ± 0·01 and 0·74 ± 0·01, respectively. About

15 min after ureteral occlusion, the renal pelvic pressure stabilized at 20–70 mmHg, renal blood flow showed a variable decrease and E_{cr}, E_{in} and E_{PAH} were slightly but significantly reduced. The subsequent infusion of mannitol solution raised ureteral pressure to 50–120 mmHg and produced a variable increase in systemic arterial pressure and in renal blood flow. Simultaneously E_{cr} and E_{in} fell to zero and E_{PAH} decreased to $0{\cdot}49 \pm 0{\cdot}02$. After oil blockade of the tubules, renal blood flow and arterial pressure decreased slightly, the ureteral pressure ranged between 25 and 70 mmHg, and E_{cr} and E_{in} and E_{PAH} became characteristically negative, at $-0{\cdot}04 \pm 0{\cdot}02$, $-0{\cdot}06 \pm 0{\cdot}03$ and $-0{\cdot}26 \pm 0{\cdot}03$, respectively. As discussed in the previous publication (Sadowski, 1974), the negativity of extraction ratios reflects abolition of glomerular filtration and tubular secretion and persistent back-diffusion of clearance substances from renal cells and interstitium to blood.

Re-opening of the ureter and evacuation of the oil was followed by a return of the extraction ratios toward normal values.

Autoregulation studies

The data on autoregulation of the renal blood flow under conditions of free urine flow, stop-flow, stop-flow with superimposed mannitol loading and blockade of the renal tubules with oil, were presented in the form of conventional pressure–flow curves and also analysed using the autoregulation index of Semple & de Wardener (1959). This is calculated by the formula:

$$\text{index} = \frac{RBF_2 - RBF_1}{RBF_1} \Big/ \frac{RPP_2 - RPP_1}{RPP_1}.$$

An index value of one or greater indicates no autoregulation of blood flow, whereas an index of zero indicates maximal autoregulation. The necessity of preserving oil-filled kidneys and kidney fragments for histological and microdissection studies would make accurate weighing of the organ after experiments rather difficult. Therefore renal blood flow values uncorrected for kidney weight are given throughout.

The renal blood flow responses to graded renal perfusion pressure reduction are graphically presented in Fig. 1. It shows that when mannitol infusion was superimposed on ureteral occlusion, autoregulation of renal blood flow was abolished, as can be concluded from the passive appearance of the respective pressure–flow curve. The slopes for stop-flow without mannitol and for the oil-blocked kidney could be described as intermediate between the typical autoregulatory (free flow) and the typical passive pattern (stop-flow plus mannitol).

However, the data of Fig. 1 alone do not permit any precise evaluation

of the degree of autoregulation impairment under different experimental conditions. In about a third of all experiments, carotid occlusion failed to raise aortic pressure up to 160 or even 140 mmHg, particularly under

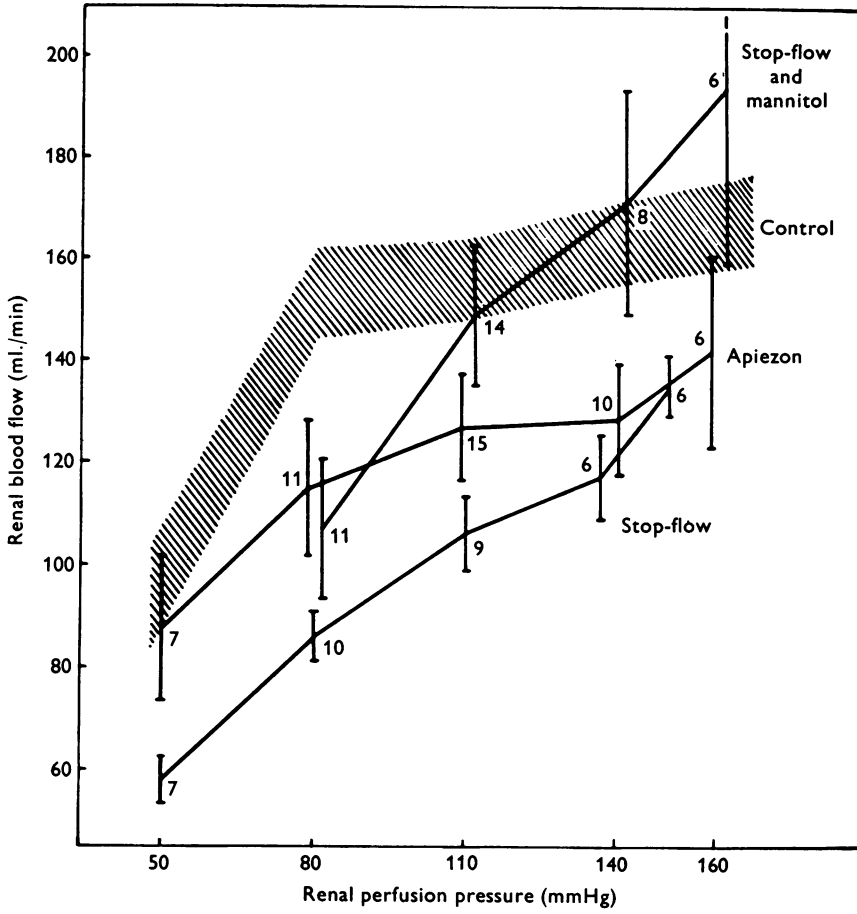

Fig. 1. Pressure–flow curves (mean ± S.E. of mean) obtained under conditions of stop-flow, stop-flow plus mannitol loading and blockade of renal tubules with Apiezon oil, compared to renal blood flow autoregulation of twenty-four normal kidneys (hatched area). The figures denote the number of dogs tested at each pressure step.

stop-flow or oil blockade conditions and autoregulation studies had to be limited to lower pressure range. Sometimes, for technical reasons, not all of the four variants of the pressure–flow test (at free flow, stop-flow, stop-flow plus mannitol and oil blockade) could be performed in one dog. Consequently, the number of observations in individual groups and at

different pressure levels varied. In order to circumvent this difficulty, the efficiency of autoregulation was analysed by a direct paired comparison of autoregulation index (Semple–de Wardener) between different experimental conditions using identical pressure steps in the same dog (Table 1). For instance, a comparison of oil blockade versus control (free-flow) conditions is based on the data of eleven dogs. In each of them autoregulation studies were performed at free flow and at oil blockade using the same pressure reduction within the range of 80–140 mmHg. When two pressure steps were made, mean index values for both experimental conditions were used for calculation of the mean value for the whole group.

TABLE 1. Analysis of the index of renal blood flow (RBF) autoregulation (see Methods) measured at four different experimental conditions. The data are derived from paired comparison of index values, each pair consisting of tests with identical renal perfusion pressure reductions at two experimental situations in the same dog

RBF autoregulation index (Semple–de Wardener)			n	P value*
Control	*vs.*	Stop-flow		
$0{\cdot}13 \pm 0{\cdot}06$		$0{\cdot}52 \pm 0{\cdot}08$	9	$<0{\cdot}01$
Control	*vs.*	Stop-flow, mannitol		
$0{\cdot}21 \pm 0{\cdot}05$		$1{\cdot}05 \pm 0{\cdot}06$	12	$<0{\cdot}001$
Control	*vs.*	Oil block		
$0{\cdot}14 \pm 0{\cdot}05$		$0{\cdot}50 \pm 0{\cdot}06$	11	$<0{\cdot}001$
Stop-flow	*vs.*	Oil block		
$0{\cdot}64 \pm 0{\cdot}06$		$0{\cdot}50 \pm 0{\cdot}06$	8	$<0{\cdot}3$
Oil block	*vs.*	Re-opening of ureter		
$0{\cdot}64 \pm 0{\cdot}08$		$0{\cdot}28 \pm 0{\cdot}08$	8	$<0{\cdot}001$

* Assessed by paired Student's t test.

The results of this analysis (Table 1) confirmed disappearance of autoregulation with stop-flow and superimposed mannitol infusion, as well as maintained, though impaired, autoregulation after ureteral occlusion without mannitol and in oil-blocked kidneys. After re-opening the ureter and evacuation of oil autoregulation improved significantly.

Fig. 2 shows that during stop-flow and oil blockade greater impairment of autoregulation (higher index) was associated with higher values of ureteral pressure and presumably also of renal interstitial pressure. In four dogs the latter was estimated indirectly by measuring deep venous pressure. These data, presented in Table 2, show that deep venous pressure changed in a manner similar to that in ureteral pressure. It increased after ureteral occlusion, attained highest level after mannitol loading of the stop-flow kidney and then decreased slightly after oil blockade. Both ureteral and deep venous pressures of the stop-flow and of the oil-blocked

kidney decreased distinctly with decreasing renal perfusion pressure, which implies important parallel changes in intrarenal venous resistance,

Simultaneous measurements of renal perfusion pressure, renal blood flow and deep venous pressure enabled calculation of intrarenal resistance values (corrected to exclude the contribution of the intrarenal venous segment) as (RPP − DVP)/RBF. Fig. 3 shows that the resistances so calculated decreased uniformly after reduction of renal perfusion pressure by suprarenal aortic constriction.

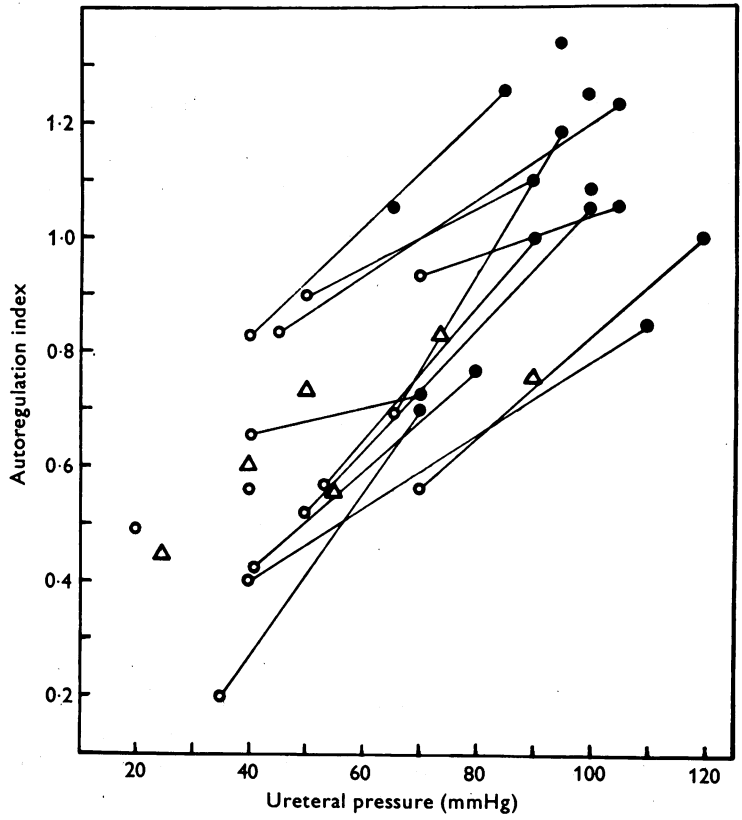

Fig. 2. Correlation of ureteral pressure and renal blood flow autoregulation index (see Methods) during stop-flow (○), stop-flow and superimposed mannitol infusion (●) and oil blockade of renal tubules (△). Symbols ○——● indicate the data obtained in any one dog.

Renin release studies

The data on renal perfusion pressure, renal plasma flow and parameters of renin release as influenced by suprarenal aortic constriction are summarized in Table 3 which also includes the values obtained during free

urine flow. These, however, cannot be easily compared with the oil-blockade data, for the two experimental conditions were separated by a period of stop-flow and mannitol loading. Plasma renin activities were not measured at that time so as to avoid the withdrawal of excessive volume of blood during experiments.

TABLE 2. Deep venous pressure measured in four kidneys at four different experimental conditions

	Deep venous pressure (mmHg)			
Dog	Control (free flow)	Stop-flow	Stop-flow, mannitol	Oil blockade
1	20	30	85	41
2	13	28	63	64
3	23	41	55	44
4	20	23	47	46
Mean	19	31	63	49

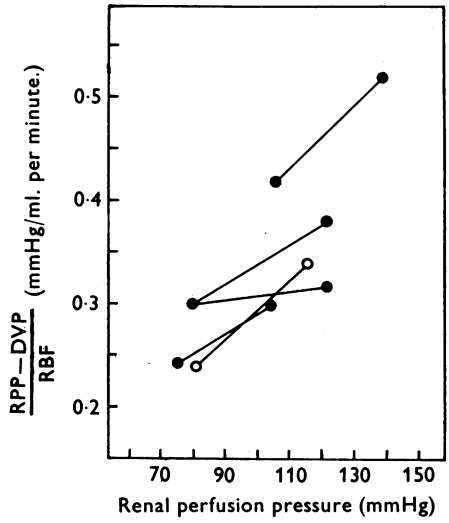

Fig. 3. Changes in intrarenal non-venous resistance (RPP − DVP)/RBF, in response to a reduction of renal perfusion pressure (RPP) in one control (open circles) and three oil-blocked kidneys (filled circles). DVP = deep venous pressure, RBF = renal blood flow.

When renal perfusion pressure of the oil-blocked kidney was reduced by a mean of 35 mmHg, renal plasma flow fell distinctly and A_{ren} and R_{ren} showed a significant increase. The changes in $(RV-A)_{ren}$ and renin secretion rate were highly variable and not significant. This was

partly due to unusually high values noted before aortic constriction in one of twelve dogs (see footnote to Table 3). However, even when this aberrant result (a decrease in renin secretion rate of 397 ng.min^{-1} in

TABLE 3. Effect of aortic constriction at a suprarenal level on renal plasma flow (RPF) and on parameters describing renin release by the oil-blocked kidney. Control data for nine normal kidneys are included (mean ± S.E. of mean)

		Oil blockade (n = 12)		
	Control (n = 9) (before block)	Before constriction	After constriction	P value
RPP (mmHg)	124 ± 5	119 ± 6	84 ± 5	—
RPF (ml. min^{-1})	98 ± 7	105 ± 9	81 ± 7	—
A_{ren} (ng.ml^{-1})	2·5 ± 0·2	5·2 ± 0·2	7·0 ± 0·2	= 0·02
RV_{ren} (ng.ml.$^{-1}$)	3·0 ± 0·3	5·9 ± 0·4	8·1 ± 0·4	< 0·01
$(RV-A)_{ren}$ (ng.ml.)	0·5 ± 0·2	0·7 ± 0·5*	1·1 ± 0·4	< 0·3
RSR (ng.min^{-1})	28 ± 20	62 ± 54*	89 ± 45	< 0·4

* These mean values are strongly influenced by extremely high difference in renin in the plasma of the renal vein and artery ($(RV-A)_{ren}$) and renin secretion rate (RSR) noted in one dog: 5·0 ng.ml.$^{-1}$ and 525 ng.min^{-1}, respectively. When this animal is disregarded (n = 11), mean $(RV-A)_{ren}$ of the oil-blocked kidney would increase considerably from control of 0·3 ± 0·5 to 1·0 ± 0·5 ng.ml.$^{-1}$ after constriction (P = 0·05) and mean renin secretion rate would increase from 20 ± 36 to 86 ± 49 ng.min^{-1} (P < 0·1). RPP = renal perfusion pressure.

TABLE 4. Changes in renin secretion rate (ΔRSR) of the oil-blocked kidney as related to the reduction of renal perfusion pressure. When three studies (1–3) performed at lowest pressure range are not considered, the mean increase in renin secretion rate for the remaining dogs becomes significant

	Renal perfusion pressure (mmHg)			
Dog	Before constriction	After constriction	ΔRSR (ng.min^{-1})	
1	90	60	−44	
2	93	66	−70	
3	95	63	−33	
4	154	100	+51	
5	102	72	+112	
6	140	110	+287	
7	127	104	−5	
8	122	84	+88	
9	112	80	+287	
10	123	80	+3	
11	127	86	+60	
4–11	126 ± 7	89·5 ± 5	+110 ± 41	P < 0·025

contrast to an increase in A_{ren} of 5·0 ng.ml.$^{-1}$) is excluded from the series, individual renin secretion rate changes given in Table 4 are remarkably non-homogeneous. Notably, decreases in renin secretion rate were observed in three dogs in which initially low aortic pressures (90–95 mmHg) were reduced by aortic constriction markedly below the autoregulation range (60–66 mmHg). For the remaining eight dogs the mean increase in renin secretion rate of 110·4 ng.min^{-1} was statistically significant ($P < 0.025$).

DISCUSSION

Autoregulation studies

Analysis of pressure–flow curves and of the Semple–de Wardener index of autoregulation showed a marked impairment of renal vascular autoregulatory capacity after ureteral occlusion and its total abolition when occlusion was followed by mannitol loading. The progressive disappearance of autoregulation with increasing ureteral pressure, as noted in the present study, confirms many previous observations (Gilmore, 1964; Kiil, Kjekshus & Løyning, 1969; Navar & Baer, 1970; Rothe, Nash & Thompson, 1971).

Since ureteral pressure was elevated also in the oil-blocked kidney, impairment of autoregulation observed in this model is not surprising. Unfortunately, the fact that ureteral pressure elevation *per se* can explain the defect of autoregulation after oil blockade makes it difficult to evaluate any specific effect due to exclusion of the macula densa receptor. At best, autoregulatory capacity of the oil-blocked kidney can be compared with that of the stop-flow kidney (without mannitol loading) showing a comparable increase in ureteral pressure. Such a comparison revealed a quite similar degree of autoregulation defect under these two conditions. Thus, nothing in the present study suggests that inactivation of the tubular receptor by oil blockade contributed to the impairment of autoregulation of renal blood flow.

The question may be raised whether maintained partial autoregulation of the oil-blocked kidney has much in common with vascular adjustments to perfusion pressure changes exhibited by the normal organ. An elevation of intrarenal venous pressure (deep venous pressure) in this model shows that, unlike the normal kidney, the contribution of the venous segment to the overall renal vascular resistance here was quite significant. It is known that ureteral, intrarenal venous and presumably also interstitial pressures of the stop-flow kidney are highly responsive to variations in renal arterial pressure, changing distinctly in the same direction (Navar, 1970; Waugh, 1964). Since the same was also observed for the oil-blocked kidney, a reduction of intrarenal venous pressure and resistance in response

to a decrease in renal arterial pressure could explain partial autoregulation of the renal blood flow. It should be emphasized, however, that this mechanism plays only an insignificant role under physiological conditions when changes in preglomerular (arteriolar) resistance predominate.

Furthermore, it will be noticed that despite an increase in intrarenal venous pressure (and resistance), renal blood flow of the oil-blocked kidney was not significantly reduced. This indicates a decrease in the resistance within some other renal vascular segment, e.g. dilatation of afferent arterioles. According to Navar (1970), after total ureteral occlusion preglomerular resistance approaches a minimal value. If, by analogy, afferent arterioles were maximally dilated in the oil-blocked kidney, no further adjustment of preglomerular resistance would occur after perfusion pressure reduction and the observed partial autoregulatory response would depend solely on a decrease in intrarenal venous resistance.

Direct evidence against such interpretation comes from four experiments in which simultaneous measurement of renal blood flow, renal perfusion pressure and deep venous pressure provided the data for calculation of renal vascular resistance with exclusion of intrarenal venous component. This value, corresponding largely to preglomerular resistance, was shown to change in parallel with changes in renal perfusion pressure. Thus, as a whole, the present studies suggest that preglomerular vessels retain some ability to autoregulate renal blood flow in absence of signals from the macula densa receptor.

Renin release studies

The changes in various parameters describing renin release in response to perfusion pressure reduction of the experimental (left) kidney do not permit any straightforward interpretation. Theoretically, significant elevation of arterial plasma renin acivity in the absence of significant changes in renin secretion rate of the left kidney could be explained by increased renin release by the contralateral kidney. This does not seem likely for constriction of the aorta between the origins of the left and right renal artery decreased, exclusively, the left renal perfusion pressure. Indeed, when during preliminary testing the tip of the catheter used for measurement of aortic pressure was inadvertently positioned above the noose, a slight increase in aortic pressure was measured during aortic constriction. This means that while left renal perfusion pressure was lowered, right renal perfusion pressure increased slightly which, if anything, would tend to suppress renin release by the right kidney.

An alternative explanation might relate to the time of blood sampling which, in the present series, was performed at a moment ranging between 1·5 and 13 min after the start of aortic constriction. If the increase in

renin secretion rate of the oil-blocked kidney were a transient phenomenon, possibly demonstrable only within first minutes of renal perfusion pressure reduction, later sampling could disclose only an elevation of arterial plasma renin activity. Gutman, Tagawa, Hober & Barger (1973) observed very rapid increases in renal vein plasma renin activity after renal artery constriction in the dog. However, no obvious correlation was seen in the present series between the time of sampling and change in RSR and, in view of a limited number of observations, this possibility can be neither confirmed nor disproved.

The discrepancy between increasing arterial plasma renin activity and unchanged renin secretion rate of the oil-blocked kidney could also be due to methodological reasons. As discussed recently by Eide, Løyning & Kiil (1973), the method of Boucher *et al.* (1964) may underestimate high renin activity, particularly in the dog plasma where substrate concentration is low. This methodological shortcoming would affect mostly the highest (i.e. renal venous) renin activities, which would result in underestimation of renin secretion rate. As the presence of Apiezon oil in blood samples interfered with the radioimmuno-assay for angiotensin I, the results obtained with Boucher's method could not be verified.

Aside from the above considerations, attention should be given to a high variability of renin secretion rate changes after aortic constriction. When the single experiment with an extremely high, pre-constriction renin secretion rate value is excluded from the series, the renin secretion data fall into two distinct groups. In three dogs in which initially low renal perfusion pressure was reduced by aortic constriction definitely below the autoregulation range (60–66 mmHg), renin secretion rate fell distinctly. Decreases or stable renin secretion rates with renal perfusion pressure reductions below 70–80 mmHg were also reported by Imbs, Velly, Fontaine & Schwartz (1970) and Eide *et al.* (1973). For the remaining eight dogs of our series the mean increase in renin secretion rate which followed pressure reduction from 126 ± 7 to 90 ± 5 mmHg was statistically significant.

Thus, in accordance with the data derived from studies with the non-filtering kidney model of Blaine *et al.* (1970), the present results further support the view that renal renin release can occur in absence of signals from the macula densa segment of the renal tubule.

Since in our experiments renal nerves of the experimental kidney remained intact, the possible contribution of changing sympathetic input to the observed alterations of renin secretion cannot be here evaluated.

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