J. Physiol. (1969), **201**, *pp.* 639–655
With 9 text-figures
Printed in Great Britain

THE EFFECTS OF CHANGES IN HAEMATOCRIT ON THE INTRARENAL DISTRIBUTION OF BLOOD FLOW IN THE DOG'S KIDNEY

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(*Received* 28 *August* 1968)

SUMMARY

1. The effect of changes in the haematocrit of blood perfusing the kidney on its intrarenal distribution was studied in dogs.

2. Two types of preparations were employed. (i) In the isolated perfused kidney evidence is presented that flow in the autoregulating preparation represents predominantly cortical flow while flow in the 'low flow non-autoregulating' kidney reflects medullary flow. (ii) In the intact kidney renal blood flow rate and its intrarenal distribution was studied by the injection of ^{133}Xe into the renal artery and measuring its clearance from the kidney by an external counter.

3. In both types of preparation cortical flow was found to be independent of changes in P.C.V. but medullary flow varied inversely with haematocrit.

4. A change in the haematocrit of the perfusing blood leads to alteration of its viscosity. It was argued that an increase in viscosity must lead to a reduction in the resistance of the cortical afferent arterioles but that medullary afferent arterioles were not able to respond in this manner.

5. These findings demonstrate that changes in total body haematocrit cause a redistribution of blood flow between renal cortex and medulla.

INTRODUCTION

The viscosity of blood is determined largely by its concentration of red cells through which it is related to such factors as bodily hydration, anaemia and polycythemia. The relationship between haematocrit and total renal blood flow (R.B.F.) has been studied extensively (De Wardener, McSwiney & Miles, 1951; Spencer, 1951; Share, 1952; Aperia, Liebow & Roberts, 1968). However, less attention has been focused on the effects

of red cell concentration on the distribution of blood flow between renal cortex and medulla.

Thurau & Kramer (1959), demonstrated that changes in perfusion pressure between 120 and 220 mm Hg, though significantly altering medullary flow, had only a transient effect on flow through the cortex. As medullary flow normally comprises a relatively small fraction of the total R.B.F., its non-autoregulatory performance does not significantly alter total flow, but does, however, modify the flow distribution between cortex and medulla.

The dissimilarity in the flow pattern between cortex and medulla could be attributed to a difference in the resistance offered to flow by the afferent arterioles to these regions in response to the changing perfusion pressure; but the resistance to flow is also determined by the visocity of the perfusing blood. It is therefore probable that changes in viscosity, produced by changes in packed cell volume (P.C.V.), will also effect a re-distribution of renal blood flow. If proved, this theory could provide the basis for a renal homoeostatic mechanism whereby the state of bodily hydration, by changing the intrarenal distribution of blood flow, could alter the ability of the kidney to concentrate urine by modifying the medullary osmotic gradient. Indeed, Thurau, Deetjen & Kramer (1960), have found that the maximal concentration of urine is reduced as the medullary flow is increased.

The experiments described in this paper were conducted to ascertain whether the components of the kidney react to changes in blood viscosity in the same way as they react to changes in pressure. Evidence was sought in two types of preparation, namely, the isolated perfused kidney and the intact kidney of anaesthetized dogs.

METHODS

The isolated perfused kidney. Twenty-two dogs anaesthetized with pentobarbitone were used. The left kidney was exposed through a mid line abdominal incision. The renal artery and vein were carefully dissected. The renal nerves lying between the artery and the vein were identified, dissected and cut. In some experiments the nerves were bathed in a 2% solution of procaine for 15 min before cutting. Tributaries of the renal vein from testicular or ovarian, and occasionally from the suprarenal veins, were divided between ligatures. The renal artery was commonly positioned caudal and posterior to the renal vein. On several occasions more than one artery was found to enter the hilum of the kidney. These were either branches of a short main trunk or two separate vessels arising from the aorta. In cases where cannulation of the main renal artery before its point of division was impossible, or when there were two separate arteries, the largest vessel was selected for the perfusion and all other vessels ligated. This procedure reduced R.B.F. and urine volume proportionately but did not alter the character of the urine produced.

The ureter was cannulated low down in the abdomen so that the tip of the cannula lay some 2–3 in below the renal pelvis. With this approach bleeding from the urinary tract was less common.

The insertion of the perfusion lines into the renal vessels was according to the following sequence: first, the renal artery was ligated close to its origin from the aorta; secondly, in quick succession, the renal vein was held by its anterior surface between three artery forceps, ligated as far centrally as possible, incised between the triangulated forceps and cannulated by a soft polyethylene catheter; lastly, the artery was cannulated and perfusion commenced. The total period of arterial occlusion varied between 5 and 8 min. The period of venous occlusion was very short indeed. The lymphatics surrounding the artery and the vein were cut.

The kidney was perfused with the animal's own heparinized blood from a reservoir. The perfusion pressures used were between 120 and 210 cm blood. It was found necessary to ensure that the free end of the venous outflow line was at a horizontal level with the kidney to prevent siphoning of blood and the collapse of the vein. The blood flow rate was measured by timed collection of outflow at intervals varying between 30 sec and 1 min. The blood was oxygenated by agitation in a large polyethylene flask and returned to the reservoir. The haematocrit was reduced by the addition of saline or plasma and increased by the addition of packed red cells. The range of haematocrit studied was 2–44. Flow was non-pulsatile throughout.

The kidney was perfused alternately with blood of high and low haematocrit. Originally a more automated perfusion circuit was employed but was found to be unsatisfactory because the rotary pump used to raise the blood to the reservoir led to progressive haemolysis, and the bubble oxygenator caused a progressive increase in renal resistance (probably due to micro-emboli). In addition, the readings of blood flow rate by a Shipley Wilson rotameter inserted into the inflow line were found to contain an artifact whose magnitude depended on the haematocrit of the blood used.

The circuit was modified so as to use the animal for oxygenating the blood whenever its condition, following repeated bleedings, permitted it. In these cases the blood that had been used for perfusion was injected into a peripheral vein and an equal quantity recovered from an artery.

The entire circuit was constructed of polyethylene except for 4 cm of glass tubing which was used as the arterial cannula.

The pressure drop between the reservoir and the kidney was measured for bloods of differing haematocrits, and the pressure readings corrected accordingly. Viscosity was measured in an Ostwald viscometer at 37° C and over a 100 mm Hg pressure gradient. Haematocrit was assessed in a Wintrobe tube centrifuged at 3000 rev/min for 30 min.

Carotid occlusion or the intravenous injection of noradrenaline produced marked changes in the animal's blood pressure. The experimental kidney was judged to be functionally isolated if these procedures were not accompanied by changes in the renal blood flow rate. In doubtful cases the dog was bled to death and observation began thereafter.

Intra-renal distribution of blood flow was assessed qualitatively by the injection of 5 ml. solution of methylene blue in water (1 g/100 ml.) into the renal artery just before terminating an experiment; the artery was ligated 2 min after the injection. The kidney was then sliced longitudinally and the surface inspected for appearance of the dye.

A more quantitative investigation of the intrarenal distribution of flow was attempted in eight experiments. Two small Geiger or semiconductor counter probes (3 mm diameter) were used; one was placed between the surface of the kidney and the body wall; the second was threaded up the ureter into the renal pelvis. The probes therefore lay in close proximity to the cortex and the medulla respectively. Red cells (0·1–1·0 ml.) labelled with ^{32}P (50 μc/100 ml. cells) were rapidly injected into the renal artery and the arrival time of the radioactivity into the two regions was recorded.

The intact kidney in the anaesthetized dog. The effect of changes in arterial haematocrit on renal blood flow, and its distribution between cortex and medulla, was studied by the method of Thorburn, Kopald, Herd, Hollenberg, O'Morchoe & Barger (1963), and as modified by

Ladefoged (1966). These authors found that the rate of disappearance from the kidney of a radioactive, inert and lipid soluble gas injected into the renal artery is described by a complex curve containing at least three exponentials. The former workers produced evidence that the slopes of these correspond to the rates of flow in the cortex, outer medulla and inner medulla respectively. Of the equations relating flow rate to the slope of the exponential the following was employed

$$F = \frac{K\lambda_{hct}100}{\sigma},$$

where F is blood flow in ml./min. 100 g tissue, K the slope of the exponential, λ_{hct} the partition coefficient of the gas between tissue and blood corrected for P.C.V. (Ladefoged, 1966) and σ the specific gravity of the tissue, taken as 1.

Dogs anaesthetized with pentobarbitone were used. The left kidney was exposed through an anterior abdominal incision. Greyhounds were preferred because of the ease with which the renal artery could be exposed in this breed by merely displacing the viscera and without need for dissection. The left ureter was cannulated. The tip of a no. 12 gauge needle mounted on the end of a nylon catheter was inserted obliquely into the lumen of the renal artery by a single sharp stab. Normal saline was infused continuously through the catheter at a rate of 1 ml./min to prevent clotting within the needle, thus obviating the use of an anticoagulant. The arterial and ureteric cannulae were led to the outside through stab wounds and the abdomen was closed. 45 min were allowed between completion of the surgery and the first measurements.

For each measurement 200 μc radioactive ^{133}Xe dissolved in 0·2–0·3 ml. saline was rapidly injected through the cannula into the renal artery. The disappearance of radioactivity from the kidney was monitored for 30 min by a collimated counter placed on the flank. The counts over 5 sec intervals were stored in a gamma ray spectrometer used in a multiscaler mode. The information was later retrieved as a digital output and plotted on a semi-logarithmic graph paper. Background activity was taken as the average value of the last twenty 5 sec periods in each measurement. The dose of the radioactivity was selected to give a peak/background ratio of approximately 10 (5 was found to be the minimum value necessary for clear differentiation of the three components).

The plot thus produced was analysed by a method similar to that described by Thorburn *et al.* (1963). The parameters of the exponentials were calculated by the method of least squares (Weatherburn, 1952). In more than 80 % of the measurements the following criteria for defining the various components applied. Component I (cortex) was described by points obtained between 5 and 20 sec: component II (outer medulla) by those between 100 and 300 sec: and component III (inner medulla) by those between 500 and 1500 sec. Occasionally the components were so much faster or slower than usual as to fall outside these ranges, but were still clearly delineated one from another. In a few cases analysis of the curve yielded only two components; such cases were excluded from the present analysis. We could not resolve component IV described by Thorburn *et al.* (1963).

The total body haematocrit was altered by exchange transfusions with dextran in saline, dextran in glucose or packed red cells. These were completed in 20–30 min and were achieved without significant alterations in blood pressure, venous pressure, heart rate or respiration. The results from exchange transfusions which led to any significant alterations in these parameters were excluded. 10–20 min elapsed after each transfusion and before a measurement was made.

RESULTS

Isolated perfused kidney. Each preparation was tested for blood flow rate at a pressure of 110 mm Hg and also for autoregulation in the pressure range between 75 and 155 mm Hg. According to the results the preparations were classified into one of three groups (Fig. 1).

(i) In five preparations the blood flow rate at 110 mm Hg, was about 300 ml./min.100 g and remained substantially unchanged when perfusion pressure was varied between 110 and 155 mm Hg (Fig. 1*A*). These are referred to as 'normal autoregulating kidneys'.

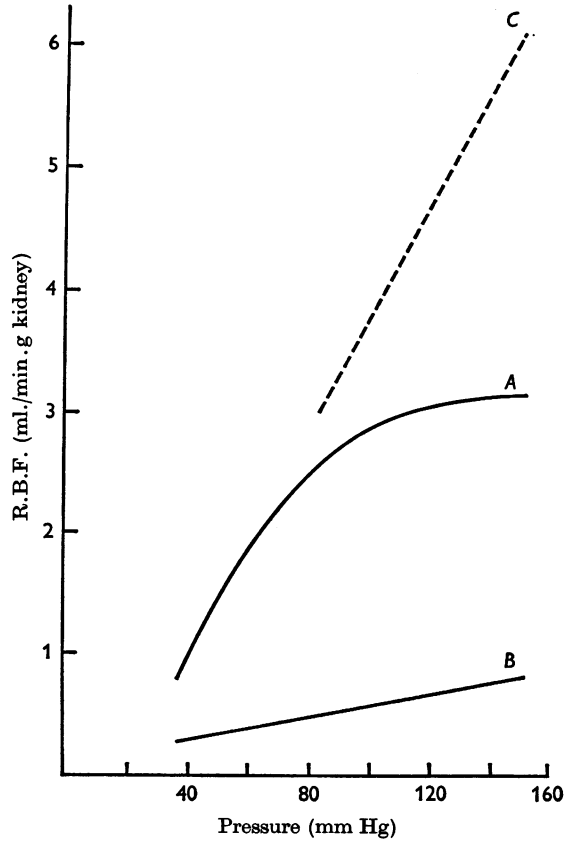

Fig. 1. Composite diagram of the three types of flow–pressure relationship found with isolated perfused kidney. *A*, 'normal autoregulating kidney'; *B*, 'low flow non-autoregulating kidney'; *C*, 'high' flow non-autoregulating kidney.' Note that the ordinate of this figure expresses flow in ml./min.g kidney.

(ii) In fourteen preparations the blood flow rate at 110 mm Hg was less than 100 ml./min.100 g and averaged 50 ml./min.100 g; flow was dependent on perfusion pressure in the range 75 and 155 mm Hg (Fig. 1*B*). Such preparations are referred to as 'low flow non-autoregulating kidneys', or 'medullary kidneys'.

(iii) In three preparations the blood flow rate at 110 mm Hg was above 300 ml./min.100 g but the flow was dependent on perfusion pressure throughout the range of pressures employed (Fig. 1*C*). These kidneys are

referred to as 'high flow non-autoregulating kidneys' and were not investigated in detail.

It was found that whilst venous occlusion for any period of time during preparation favoured the production of 'low flow non-autoregulating kidneys', extreme care during the dissection of the vessels, limiting the period of venous occlusion to a few seconds, application of procaine to the nerves before severing them and the establishment of a moderate mannitol diuresis were prerequisites for the production of 'normal autoregulating kidneys'. The ability to autoregulate tended to be lost within 2–3 hr and, once lost, was never regained. Autoregulation was succeeded by a low or high flow non-autoregulating response. Injection of papaverine into 'autoregulating kidneys' produced a high flow but autoregulation was lost. 'Low flow non-autoregulating kidneys' could occasionally, but not always, be converted into 'high flow non-autoregulating kidneys' by injection of papaverine.

Methylene blue injected into the renal artery before terminating the experiment stained all the regions of the kidney in the 'autoregulating' and 'high flow non-autoregulating kidneys' but only the medullary region of the 'low flow non-autoregulating kidney'.

All kidneys produced urine. The volume varied between 0·01–2·3 ml./min. It was isotonic with 'non-autoregulating kidneys' but was sometimes hypertonic with 'autoregulating' kidneys.

The results of typical experiments appear in Figs. 2 and 3. Figure 2 represents results from an 'autoregulating kidney.' In Fig. 2*A* blood flow rate is plotted against perfusion pressure and the graph shows that as the perfusion pressure increased from 75 to 100 mm Hg, flow rose from 58 to 95 ml./min. However, in the autoregulating range raising the pressure from 100 to 135 mm Hg caused hardly any change in flow. In Fig. 2*B* renal blood flow rate is plotted against P.C.V. of the perfusing blood at a constant pressure of 110 mm Hg. Changes in P.C.V. between 2 and 31 are seen not to alter flow rate. Autoregulation had occurred when blood flow was measured 1 min after changing the haematocrit.

Characteristic results from a 'low flow non-autoregulating kidney' are depicted in Fig. 3. There is a complete dependence of flow rate on perfusion pressure and on blood viscosity. 'High flow non-autoregulating kidneys' also responded in this manner.

Figure 4 reproduces Mingograf records of radioactivity recorded by cortical and medullary probes following the injection of a dose of radioactively labelled red blood cells into the renal artery. The top record (Fig. 4*A*) was obtained during perfusion with a blood having a P.C.V. of 20 and the lower record (Fig. 4*B*) during perfusion with a 7% suspension of red blood cells in saline. The arrival time is taken as the time between injection

and the appearance of the peak. Dilution of the perfusing blood shortens the arrival time as recorded by the medullary probe. In contrast the cortical probe shows little difference between the arrival time in the two conditions.

Figure 5 shows the results of an experiment using this technique in a 'low flow non-autoregulating kidney'. The cortical probe shows no peak at any time whereas the medullary probe shows peaks at varying distances

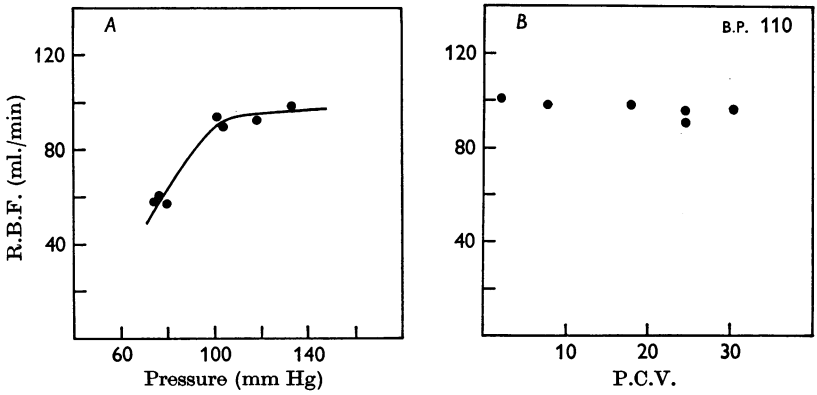

Fig. 2. Results from an isolated perfused kidney experiment on a 'normal autoregulating kidney'. *A* demonstrates autoregulation of R.B.F. to change in perfusion pressure within the range 95–140 mm Hg. *B* shows that the flow remains unaltered as the P.C.V. of the perfusion fluid is altered between 2 and 31; perfusion pressure was kept constant at 110 mm Hg. Total kidney weight was 102 g, but two branches of the renal artery were ligated during preparation which must have reduced the perfused renal mass.

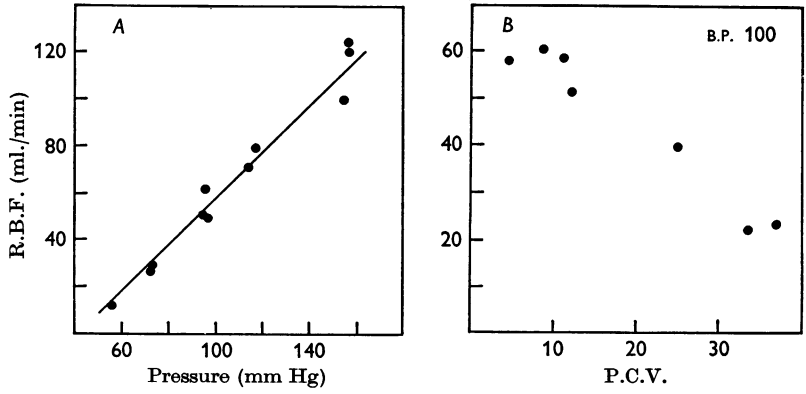

Fig. 3. Results from an isolated perfused kidney experiment on a 'low flow, non-autoregulating' kidney. *A* demonstrates that flow varies with pressure over the range tested. *B* shows that flow also varies with change in P.C.V. over the range tested.

The kidney weighed 89 g and was perfused through a single renal artery. Injection of methylene blue in this artery at the end of the experiment stained the medulla uniformly but failed to stain the cortex.

with different haematocrits. The arrival time bears a close relationship to the P.C.V. of the perfusing blood.

Intact kidneys in the anaesthetized dog. The results of a typical experiment appear in Fig. 6. Change of arterial haematocrit between 30 and 60

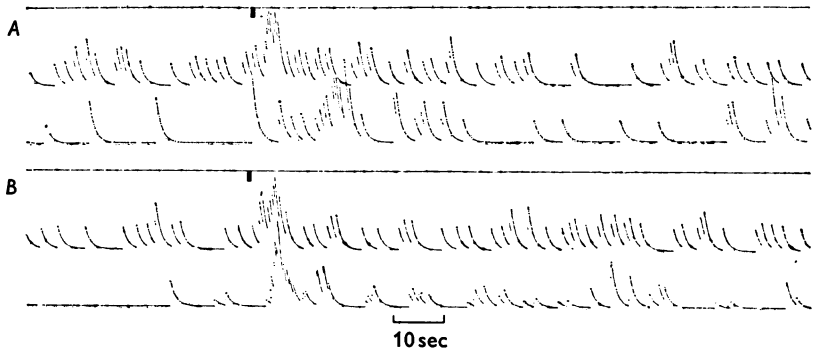

Fig. 4. Records showing the arrival time of ^{32}P labelled red blood cells in an isolated perfused kidney of the 'normal, autoregulating' type. The top tracing in each record is from the 'cortical' counter and the bottom tracing from the 'medullary' counter. The first vertical line in each tracing marks the injection of radioactivity into the renal artery.

The top record (*A*) was obtained while the kidney was being perfused with blood having a P.C.V. of 20. The lower record (*B*) was obtained while the kidney was being perfused with a 7 % suspension of red blood cells in saline.

The time scale is shown on the horizontal axis.

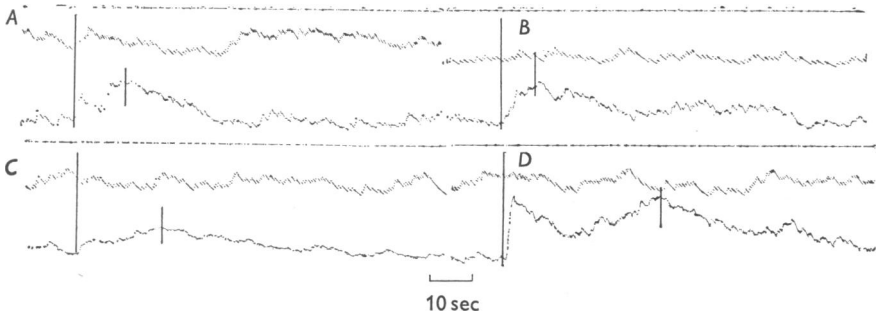

Fig. 5. Records showing the arrival time of ^{32}P labelled red blood cells in an isolated perfused kidney of the 'low flow, non-autoregulating' type. The top tracing in each record is from the 'cortical' counter, and the bottom tracing from the 'medullary' counter. The first vertical line in each tracing marks the injection of radioactivity into the renal artery, and the second the position of the integrated peak.

The P.C.V. of the perfusing fluid was as follows: *A* 17, *B* 10, *C* 22 and *D* 38. The time scale is shown on the horizontal axis. The records are in chronological order.

Note that there are no demonstrable peaks of radioactivity from the cortical counter but peaks are clearly visible from the medullary counter. In two cases additional early peaks are visible from the medullary counter, which are probably due to radioactivity passing the counter as it enters the kidney.

did not change blood flow in the cortex but inner and outer medullary flow rates decreased with increasing P.C.V. Immediately after an exchange transfusion of dextran, both cortical and medullary flow rates increased. Thereafter it took an average of 20 min, but occasionally as much as 80 min, for cortical flow rates to return to their original values. Medullary flow rates, however, increased further. This is shown in Fig. 7. Figure 8 is an

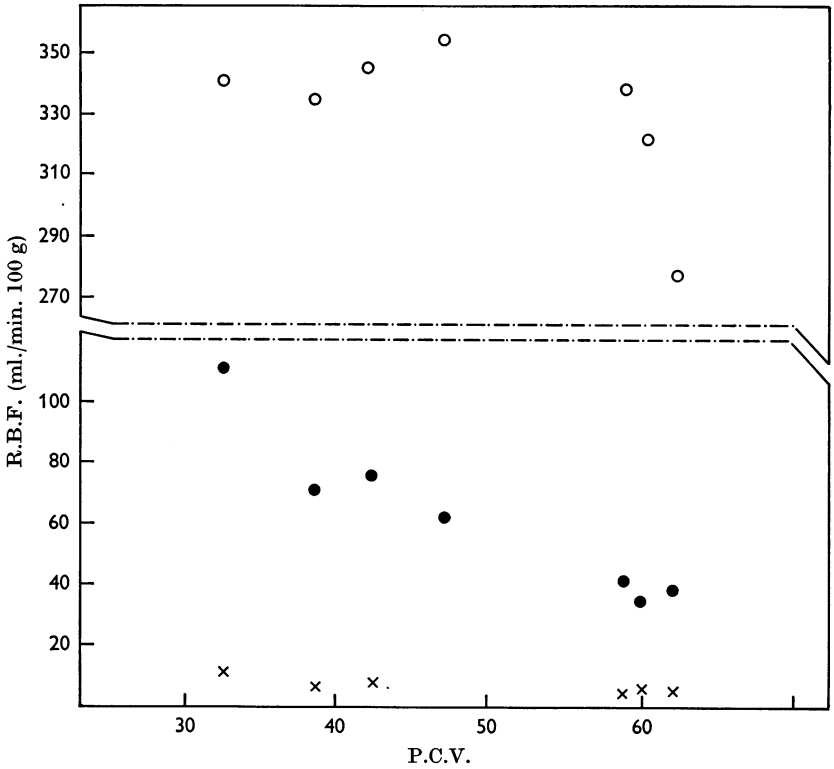

Fig. 6. Results obtained from a typical experiment in an anaesthetized dog. The renal blood flow rates were measured by the clearance of ^{133}Xe. Open circles represent cortical flow rate, filled circles outer medullary flow rate and crosses inner medullary flow rate. Note that whereas the cortical flow rate remained unaltered between a P.C.V. of 30 and 60, medullary flow increased with decreasing P.C.V.; this change in flow rates is more marked in the case of the outer medulla than of the inner medulla. Measurements were made after a steady state had been reached, within 30–60 min following a change in haematocrit.

electromagnetic flow meter record of total renal blood flow showing changes which are compatible with the above findings. Flow increases by 23 % in 10 min but returns to 9 % above original in 35 min. The same temporal relationship pertained when red blood cells were transfused to increase the haematocrit.

The pooled results of eighteen exchange transfusions in twelve animals are presented in Fig. 9. All measurements were made after sufficient time had been allowed for the cortical flow to readjust. It can be seen that although cortical flow is little altered by changes in P.C.V., outer medullary flow varied in the manner described in every case.

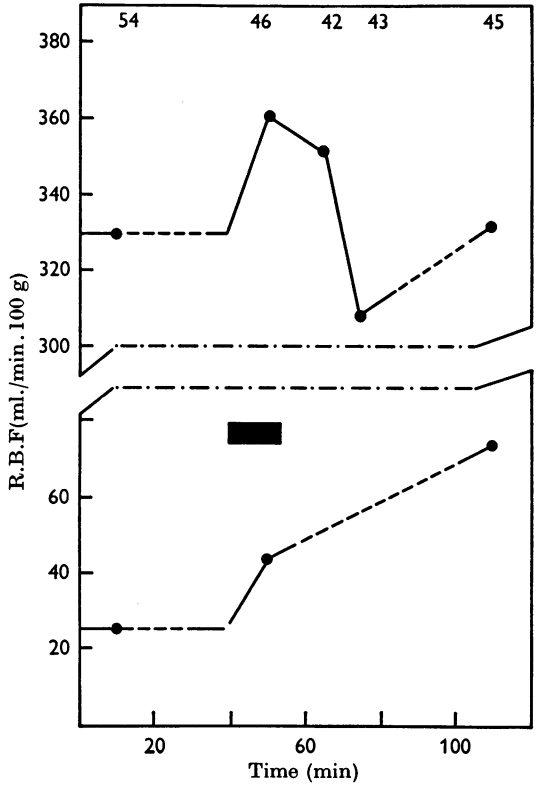

Fig. 7. Graph to show the time sequence of changes in cortical (upper) and outer medullary blood (lower) flow rates measured by the ^{133}Xe clearance method following an exchange transfusion with 500 ml. dextran in saline. Figures at the top are the P.C.V. at the time of measurements. The filled rectangle represents the duration of the exchange transfusion. Before the measurements included in this graph were taken, cortical flow rates were measured 7 times over 150 min; the mean value was 323 ± 9 ml./100 g tissue per min; the mean P.C.V. over this period was 58 ± 1. Note that both cortical and outer medullary flow rates increased during exchange transfusion but whereas the cortical flow rate returned to normal by 45 min the medullary flow rate increased further.

Table 1 demonstrates that inner medullary flow changes in a parallel direction to that of the outer medulla in thirteen out of eighteen experiments. The difference in the behaviour of the cortical and outer medullary flow is reflected in a change in their ratio.

DISCUSSION

Critique of methods employed. The estimation of renal cortical and medullary blood flow rates by the arrival time of radioactive red blood cells has become possible since the development of small, sensitive Geiger and semi-conductor counters. Such a method was employed by Thurau & Deetjen (cited by Kramer, 1959). We have used this technique, with

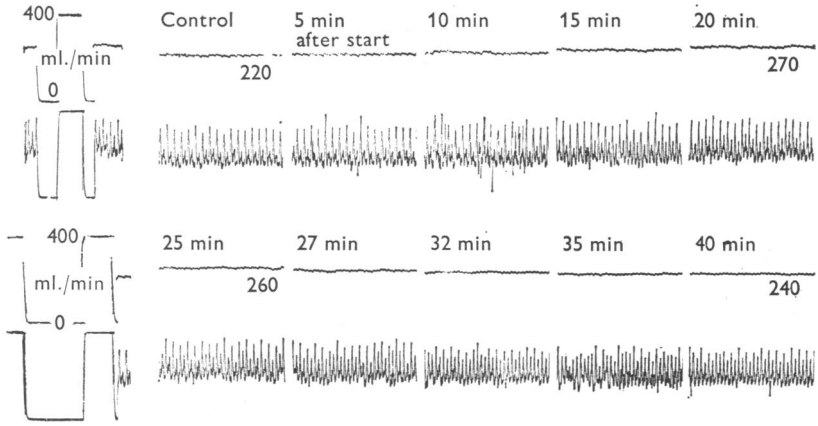

Fig. 8. Electromagnetic flow meter record of total R.B.F., to the left kidney in an anaesthetized dog, during and after an exchange transfusion with 500 ml. dextran in saline. The top line in each record is the integrated flow rate, the bottom record the instant flow rate. The time of the observation after the start of the exchanged is shown on the left-hand corner in each slip. The first record was obtained immediately before the exchange which lasted 12 min. Note that the total R.B.F. increased from 220–230 within 5 min of the start of the exchange transfusion, reached a maximum of 270 at 20 min, and stabilized at 270 ml. by 35 min.

The P.C.V. was 53 before exchange transfusion and fell to 42 after it was complete.

The calibration of the flow meter is given on the left-hand side of each row of records.

Geiger or semi-conductor probes, in a number of experiments with both intact kidneys in anaesthetized dogs and isolated perfused kidneys. However, only twice were we successful in obtaining records of radioactivity from the medullary probe which were discernible from the background. This may be due to the difficulty of positioning the probe in the calyces adjacent to the perfused tissue without collapsing the thin-walled vessels of the medulla. It is probable that in the two successful cases the tip of the probe came to rest lightly in the apex of a calyx and sensed radioactivity from a radial rather than a planar environment. The fact that the β emissions from the ^{32}P we used to label red blood cells could be detected across only 3 mm of tissue must also contribute to the difficulty. Varying the volume or concentration of the labelled cells did not modify the results.

The details of the technique of measuring divided renal blood flow using the disappearance curve of radioactive inert gas have been critically investigated since first described by Thorburn *et al.* (1963). Ladefoged (1966) has proved that recirculation of xenon is negligible and does not affect the calculations, that a single injection of the gas yields similar results to those obtained following a longer infusion, that three components only are to be expected if measurements are made with ^{133}Xe over 30 min

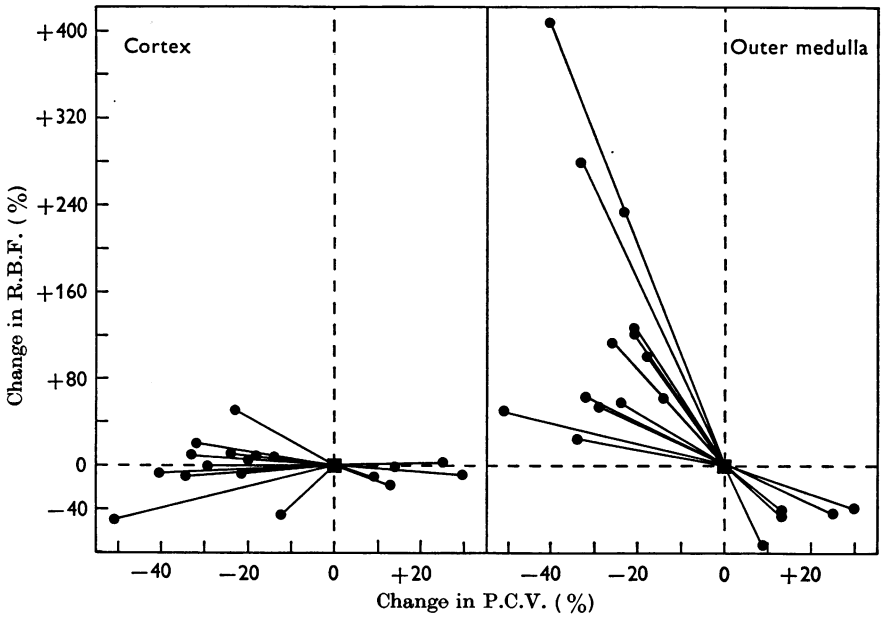

Fig. 9. Composite graph of the results of seventeen exchange transfusion in twelve dogs. The blood flow rate is expressed as the percentage of the value before transfusion and is plotted against the percentage change in P.C.V. The left-hand graph depicts changes in cortical flow and the right-hand one changes in medullary flow. This graph was constructed from the data presented in Table 1.

(Ladefoged, 1966), and that the figures produced for total renal blood flow agree closely with those obtained by the electromagnetic flowmeter (Ladefoged, Pedersen, Doutheil, Deetjen & Selkurt, 1965). However, Aukland & Berliner (1964) have stated that the rate of uptake or removal of inert gases cannot be used as an indicator for medullary blood flow. This conclusion was drawn because these authors found that up to two thirds of the hydrogen gas used in that investigation was cleared from a region of the kidney, equivalent to our component III, by the urine. However, their data show that only insignificant quantities of hydrogen are removed by the urine from the medullary region corresponding to our component II. In our experiments using xenon, an amount equivalent to only 4% of

the total supplied to component III or 1 % of that supplied to component II appeared in the urine during established diuresis (Table 2). The extreme diffusibility of hydrogen compared with xenon may have been one of the properties which could account for their different behaviour. Moreover,

TABLE 1. The effect of exchange transfusion on the distribution of renal blood flow in the intact kidney of the anaesthetized dog

	Before exchange transfusion					After exchange transfusion				
Expt. no.	P.C.V.	C	O.M.	I.M.	C/O.M.	P.C.V.	C	O.M.	I.M.	C/O.M.
		(ml./min. 100 g)					(ml./min. 100 g)			
3	58	390	55	8·5	7·09	44	434	87	8·6	4·99
6	62	344	38	7·0	9·05	37	323	193	18·5	1·67
7	60	318	33	7·9	9·64	47	344	73	6·9	4·71
7	47	342	71	6·9	4·82	33	340	111	11·3	3·06
8	64	273	57	8·7	4·79	42	341	93	8·2	3·66
10	43	441	66	8·4	6·68	21	220	99	11·6	2·22
11	68	101	33	8·4	3·06	52	153	112	7·5	1·37
12	64	392	57	7·7	6·88	42	347	71	9·1	4·89
13	63	277	31	6·2	8·7	41	264	58	9·4	4·6
16	63	347	41	7·5	8·46	50	365	93	13·4	3·92
17	53	329	29	7·8	11·34	45	360	58	8·0	6·21
26	54	333	26	10·9	12·80	46	360	43	12·0	8·37
BS	63	351	58	10·5	6·05	42	387	220	20·9	1·76
6	40	339	102	16·3	3·32	52	308	62	11·4	4·97
7	32	340	111	11·3	3·06	40	353	62	6·6	5·69
13	38	350	78	11·0	4·49	43	288	43	12·7	6·70
13	43	288	43	12·7	6·70	49	286	24	19·2	11·92
16	53	465	49	1·0	9·49	58	417	13	5·0	32·10

The group of figures on the left-hand side are those for cortical (C), outer medullary (O.M.) and inner medullary (I.M.) blood flow rates in ml./min. 100 g before exchange transfusion; those on the right-hand side are the values after exchange transfusion. The last column on each side (C/O.M.) presents the ratio of cortical to outer medullary flow rates.

TABLE 2. Calculation of the distribution of radioactivity between the three components of the kidney following the injection of ^{133}Xe into the renal artery, and measurement of radioactivity excreted in the urine during the subsequent 24 min. Urine flow was 2·6 ml./min

Total activity injected = 32,600 counts/sec

Distributed
- 27,000 counts/sec in cortex
- 4,400 counts/sec in outer medulla
- 1,200 counts/sec in inner medulla

Activity excreted in 24 min = 52 counts/sec
- 17 counts in first 4 min
- 31 counts in second 4 min
- 3·5 counts in third 4 min
- 0·5 count in fourth 4 min
- 0·1 count in fifth 4 min
- 0·1 count in sixth 4 min

the olive oil–water solubility ratio at 37° C of xenon is 6·5 times that of hydrogen (Lawrence, Loomis, Tobias & Turpin, 1946). The greater relative lipid solubility of xenon will favour its removal in a fluid containing cells. We therefore consider that the critical conclusions of Aukland & Berliner

(1964) do not apply to the method we have used to measure cortical and outer medullary blood flow rates. Nevertheless, because of uncertainty in the interpretation of data derived from component III, further discussion is limited to consideration of cortical and outer medullary flow rates alone.

In the majority of cases we have measured both P.C.V. and viscosity, but in some only one or the other was estimated. In the discussion of results changes in P.C.V. are referred to as changes in viscosity. This we believe is justifiable. The relationship between the two has been established by numerous authors using different methods (Dreizen, 1962; Virgilio, Long, Mundth & McClenathan, 1964). The viscosity of blood decreases as the haematocrit is reduced. Dextran behaves in the same way as other diluents (Schrier, McDonald, Marshall & Lauler, 1968). In investigating this point we have found that the graph relating P.C.V. and viscosity is of the same shape whether the haemodilution is achieved by dextran, plasma or saline but that at any given P.C.V. the viscosity with dextran is higher than that obtained with saline or plasma.

Results. Results from the two types of preparations used show that blood flow through the medullary region is viscosity dependent whereas flow through the cortex is so regulated as to be independent of changes in viscosity. The range of P.C.V. studied was 30–60 in the intact animal and 2–44 in the isolated perfused kidney. A rise in P.C.V. of blood leading to a rise in its viscosity increases the ratio of cortical to medullary blood flow rates and a reduction in P.C.V. decreases it. This response is similar to that reported by Thurau & Kramer in 1959 for changes in the intrarenal distribution of blood in face of changes in perfusion pressure.

It is widely held that the afferent arteriole to the cortex is a resistance vessel and the prime regulator of blood flow to the region; changes in the afferent arteriolar resistance in response to pressure changes are the basis of autoregulation of blood flow to the kidney. Our results indicate that following an increase in blood viscosity this resistance falls, whereas following a decrease in blood viscosity it rises. The blood flow to the cortex thus remains unchanged despite changes in blood viscosity. The medullary circulation appears to be incapable of this adjustment.

The manner in which this regulation is achieved and the reasons why it does not occur in the juxtamedullary nephrons are not known. However, of the current hypotheses to explain autoregulation to pressure changes, the one by Thurau (1964) is particularly well suited to explain our results. Thurau maintains that afferent arteriolar diameter is regulated by changes in the local renin release through the juxtaglomerular apparatus in response to changes in the sodium load delivered into the distal tubule. We could postulate that a reduction in viscosity increases R.B.F., G.F.R.

and the sodium load delivered into the distal tubule, that this invokes local renin release, afferent arteriolar constriction and thus an adjustment of the R.B.F. However, an alteration in the resistance of the afferent arteriole could not by itself provide for simultaneous autoregulation of R.B.F. and G.F.R. to changes in viscosity. For as the haematocrit increases, the effective renal plasma flow (E.R.P.F.) must fall if the R.B.F. remains unchanged. This leads to a smaller quantity of plasma being presented to the glomerular capillaries for filtration. However, Nashat & Portal (1967) have shown that in the dog a rise in arterial haematocrit is accompanied by a rise in the filtration fraction and argued that this was due to a passive increase in efferent arteriolar resistance as a result of increased viscosity. This elevation in the outflow pressure of the glomerular capillaries leads to a greater proportion of the E.R.P.F. appearing as filtrate. Simultaneous autoregulation of the R.B.F. and G.F.R. in the renal cortex to changes in the viscosity of the perfusing blood therefore involves an alteration in the afferent arteriolar resistance in conjunction with a passive increase in the resistance to flow in the efferent arteriole.

The failure of the medullary nephrons to autoregulate could be explained by the findings of Brown, Davies, Lever, Parker & Robertson (1965), who found that in the rabbit's kidney renin content of nephrons decreased from a high level in the outer cortex to a low one in the inner cortex and that no renin could be extracted from the juxtamedullary nephrons. This finding has recently been confirmed in the dog kidney (Ueda, 1968). Further discussion on this subject is hampered by the present uncertainty concerning the precise relationship between juxtamedullary nephrons and the vessels supplying the medulla (Ljunqvist, 1964; Fourman, Kennedy & Moffat, 1967).

The injection of methylene blue into the renal artery of 'low flow, non-autoregulating' kidneys left the cortex unstained. However, in each of the 'autoregulating' kidneys cortical staining was clearly evident. These observations suggest that the major contribution to the measured total R.B.F. of the 'low flow, non-autoregulating' kidneys emanates from medullary blood flow. As blood flow to this region is not autoregulated, this provides an explanation for the failure of autoregulation of the total R.B.F. in this type of kidney. Procedures stimulating the renal nerves during preparation tended to produce 'low flow, non-autoregulating' kidneys. But it is evident that other factors must also be involved because of the frequent production of such kidneys some time after isolation and perfusion. Their characteristics bear many resemblances to those of kidneys in the 'shocked' state (Selkurt, 1962).

In contrast, the 'high flow, non-autoregulating' kidney has the characteristics of a vascular bed fully dilated and incapable of active response.

Strong evidence for this conclusion is the ability of papaverine to convert any isolated perfused kidney into one of this class.

A number of authors have demonstrated that medullary circulation is altered under a variety of conditions, some of which are accompanied by changes in blood viscosity. For example, both saline infusion (Earley & Friedler, 1965), and bodily hydration (Fourman, 1964), which must lower haematocrit, are accompanied by a rise in medullary blood flow rate.

The dependence of the medullary osmotic gradient on medullary blood flow, and the probability that changes in blood viscosity reflect changes in the state of bodily hydration, could lead to interesting speculation on the renal effect of such viscosity changes. A more detailed discussion of this topic must await information on the influence of blood viscosity on the characteristics of the urine produced.

The electromagnetic flowmeter used in producing Fig. 8 was kindly lent to us by Messrs Sierex Ltd., Wembley, Middlesex.

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