Direct Measurement of Superficial and Deep Venous Flow in the Cat Kidney

EFFECTS OF EPINEPHRINE, ANGIOTENSIN, MICROSPHERES, AND RENAL NERVE STIMULATION

By Ole I. Nissen and Åge Galskov

ABSTRACT

In an excised cat kidney, the subcapsular veins were clipped near their connections with the renal vein and cut open distal to the clamps. The kidney was then placed in an oil-filled lucite chamber and perfused from a donor cat via tubes entering the chamber through its close-fitting lid. The blood leaking from the cut subcapsular veins was led to one flowmeter; that leaving via the cannulated renal vein (supplied now only by the arcuate vein system) was led to another flowmeter. Catecholamines and stimulation of the renal nerves reduced the arcuate blood flow more than the subcapsular blood flow, the two average reductions being 28% and 20% with epinephrine and 22% and 14% with stimulation of the renal nerves. Angiotensin reduced both flows equally. Microspheres reduced the subcapsular flow more than the arcuate flow, the two average reductions being 42% and 25% of the control flows. This effect was probably caused by trapping of the microspheres in the distal ends of the interlobular arteries beyond the inlets to the afferent arterioles, since these vessels are too narrow to allow free entrance of the microspheres. The preferential effect of epinephrine and nerve stimulation on the deep circulation is thought to be the result of the special structure of the juxtamedullary glomerular units.

KEY WORDS

medullary blood flow
catecholamines
kidney perfusion
Trueta juxtamedullary shunt
juxtamedullary glomeruli
water conservation

In the cat kidney, the veins draining the outer cortex are well separated from those draining the inner cortex and the medulla, because the blood from the outer cortex leaves through subcapsular veins which do not join the arcuate vein system until the hilar region (1, 2) (Fig. 1). In this paper, we will describe how the rates of blood flow leaving the subcapsular and the arcuate veins can be measured directly and simultaneously and show that the vessels in the two drainage areas react differently to certain external stimuli. A short account of the method was published earlier (3).

Methods

Essentially the preparation consists of a kidney removed from one cat and connected to the aorta and caval vein of another cat; two flowmeters record the rates of blood flow leaving the two vein systems.

For each experiment two male cats weighing 3.4–5.5 kg were anesthetized with chloralose (60–80 mg/kg) administered intravenously as a 1% solution in saline. The cats were deprived of food for 10–15 hours before the experiments, but they had free access to water. Tracheal tubes were inserted, and a midabdominal incision was made. In one cat, the kidney donor, the aorta was freed of all side branches for a few centimeters above and below one of the renal arteries; the dissection was performed from the opposite side to disturb the experimental kidney as little as possible.
DIRECT MEASUREMENT OF INTRARENAL BLOOD FLOWS

Left: The two vein systems of the cat kidney. Blood from the superficial cortex passes through the outer cortical and the subcapsular veins. Blood from the deep cortex passes through the inner cortical and the arcuate veins. Blood from the medulla enters the arcuate system through venous vasa recta.

Right: The two vein systems of the dog kidney. The stellate veins correspond to subcapsular veins in cat and drain the superficial cortex. The blood joins the arcuate system through the interlobular veins positioned perpendicularly in the cortex. Otherwise the arcuate vein system drains the same regions as it does in the cat kidney.

possible. In experiments in which the renal nerves were stimulated, the left kidney was always used because it has long and well-defined nerve bundles leading to it. Then the kidney was loosened from its surrounding fat so that its only connections were the artery, the vein, and the ureter. After heparinization of the animal, the ureter was cannulated near the pelvis and, in cases where the nerves were stimulated, a bipolar silver electrode was tied around all visible nerve bundles leading to the kidney. The fibrous capsule was pierced with a sharp knife on both sides of the kidney close to the hilus, and the holes were extended with scissors to windows shaped like half-moons. Cannulas were inserted in the aorta and the caval vein distal to the kidney. Rapid suction with a syringe connected to the aortic cannula removed all air bubbles from the cannula and tube. The aorta and the caval vein were ligated and cut above the renal artery and vein, and the kidney was flushed with isotonic Rheomacrodex- or Macrodex-sodium chloride solution or cat plasma at a pressure of about 1.5 m saline and a temperature of about 10°C. The kidney, including the pieces of aortic and caval vessels with cannulas and tube system, was lifted out of the abdomen. Small pointed silver clamps, normally used in neurosurgery, were pushed through the capsular windows 1–1.5 mm into the renal tissue and clipped around the subcapsular veins near their entrance into the renal veins in the hilus. An artery clamp with grooves milled in the branches was used for applying and closing the clamps. The subcapsular veins were cut open distal to the clamps, of which there were two to four on each side of the kidney. The lymphatics of the renal stalk were incised to avoid lymph stasis. Subsequently the kidney was transferred to an airtight lucite chamber containing blood in the bottom and otherwise filled with paraffin-oil kept at 37–38°C. The arterial, deep venous, ureteral, and electrode connections between the kidney and the surroundings passed through the lid of the chamber. The kidney was partly supported by the funnel-shaped bottom of the chamber and partly hanging from its pedicle; the effective kidney weight was small due to the buoyancy of the oil.

The blood entered the kidney from the aorta of the donor, which had been prepared and heparinized in the meantime, and the venous blood left the chamber along two routes (Fig. 2). From the outer cortex it passed out of the kidney through the incisions in the subcapsular veins and ran along the kidney surface to the bottom of the chamber. Here it left through an opening and was passed through a flowmeter on its way towards the caval vein of the donor animal. The other route, originating in the arcuate system, passed through the renal vein, the small piece of the caval vein, the lid, another flowmeter, and finally joined the other venous stream on its way to the caval vein of the donor animal.

The two flowmeters were identical. Basically they were constructed on the cylinder and stopwatch principle. Two lucite cylinders (13.7 mm i.d., 10 cm high) continuously received the venous blood and were intermittently emptied through tubes at their bases by release of one electronically controlled tube clamp working simultaneously on both outlet tubes. The automatic activation (closure) of the electromagnetic clamp was governed by one of two sensitive pressure transducers (Statham PM 5 TC) connected to the basal parts of the cylinders. Activation occurred at a chosen low blood level in
one of the cylinders. Filling of the cylinders was allowed over a definite time period which was determined by a timing device having step settings between 3 and 20 seconds. The pressures at the base of each cylinder increased when the blood flowed into it, and the pressure increments within the selected time period then served as measures of the two venous outflow rates. The instrument performed about five such measurements each minute. A calibration after each experiment, made by filling the two cylinders with given volumes of blood, showed that the pressure gauges were stable for a month. The pressures were recorded on the photosensitive paper of a mirror galvanometer writer (Ultradelette). The perfusion pressure at the level of the kidney (measured with a Statham transducer connected through a T-tube to the tygon tube leading the arterial blood to the kidney) and the temperatures (detected with thermistors) on the surface of the isolated kidney and in the abdomen of the blood donor were also recorded. The hydrodynamic resistance of the tubes leading the blood back to the caval vein was adjusted by a clamp to give the falling surfaces of the two blood columns time to reach similar heights before the clamp discontinued the outflows from the cylinders. The blood passed through the cylinders by gravity, and accordingly, a fraction of the aortic pressure head was lost for perfusion of the kidney, since the flows into the cylinders had to be positioned 15–20 cm above the level of the abdominal aorta.

The function of the perfused kidney was judged from the clearance of creatinine and the extraction fraction of para-aminobenzoate (PAH). These substances were infused continuously into one of the jugular veins in an isotonic sodium chloride solution at 0.4 ml/min. In addition, cat blood was infused through the vein to replace blood losses. One or two clearance measurements lasting 10 minutes each were made for each kidney after free outflow from the pelvis was ascertained by quick recollection of 0.5 ml of saline injected into the ureter. Arterial and superficial and deep venous blood samples for determination of creatinine concentrations and PAH extractions were taken 2 minutes before the middle of the collection period, and the urine was collected from a tube connected to the ureter through the lid. In a few experiments designed for calculation of the arterial inflows to the two venous drainage areas (see below), blood from the three sites was collected continuously and simultaneously over several minutes (both during control and experimental periods) to obtain as representative and comparable samples as possible. Since the sampling of venous blood took place upstream from the flowmeters, the samplings were interrupted occasionally to allow accurate flow measurements. The renal arterial blood samples were taken far downstream from the site of the hormone solution infusion to allow complete mixing of blood and hormone-saline solution.

The hormones were dissolved in an isotonic solution of sodium chloride and infused into the renal arterial blood at a constant speed between 0.05 and 1.0 ml/min. The doses were as follows: epinephrine 0.25–2.50 μg/min, norepinephrine...
DIRECT MEASUREMENT OF INTRARENAL BLOOD FLOWS

1.0–2.0 μg/min, and angiotensin (Hypertensin, Ciba) 0.025–1.0 μg/min. At each dose level, it generally took 5–10 minutes to obtain new constant blood flows. These were compared with those from the preceding control period. Sometimes two experimental runs at different dose levels were made in succession. Blind infusions of saline were given at the same rate during the control periods as during the experimental ones. The stabilization of the flows during nerve stimulation or after injection of microspheres took about the same time as with hormone infusion.

The "carbonized" microspheres (Nuclear Products) were used in four sizes (diameters: 15 ± 5 μm, 25 ± 5 μm, 35 ± 5 μm, and 50 ± 10 μm) and were suspended in saline with 1 drop Tween 80/10 ml to keep them from aggregating. The injection of the microspheres into newly made suspensions were always treated with ultrasound for a few minutes to break up the aggregates. The injection of the microspheres into the kidney was decapsulated and weighed. After this the kidney was decapsulated and weighed.

The nerves were stimulated with rectangular 1-msec current pulses from an electronic stimulator (Disa Ministim) at a frequency between 1 and 5 impulses/sec.

The rates of inflow of arterial blood and of outflow of venous blood from a drainage area are generally not identical, since the amount of fluid lost from the blood through glomerular ultrafiltration may differ from that regained by tubular reabsorption (4). Calculation of the inflow rate of blood from the outflow rate can be carried out if the hematocrit (Hct) of the venous blood from the drainage area and the protein concentrations in arterial plasma (Cp art) and in drainage plasma (Cp vcn) are known. The calculations are based on the following assumptions.

We assume that during steady state the same volume of red blood cells (rbc) enters and leaves the drainage area per unit of time,

\[ Q_{\text{rbc art}} = Q_{\text{rbc vcn}}, \]

and that the same amount of protein enters and leaves the area per unit of time,

\[ Q_{\text{pi art}} \times C_{\text{p art}} = Q_{\text{pl vcn}} \times C_{\text{p vcn}} \]

\[ Q_{\text{pl art}} = (C_{\text{p vcn}}/C_{\text{p art}}) (Q_{\text{pl vcn}}), \]

where \( Q_{\text{pl art}} \) and \( Q_{\text{pl vcn}} \) are in- and outflow rates of plasma. The rate of flow of blood entering the area,

\[ Q_{\text{h art}} = Q_{\text{rbc art}} + Q_{\text{pl art}}, \]

is then calculated by combining with Eqs. 1 and 2:

\[ Q_{\text{h art}} = Q_{\text{rbc vcn}} + (C_{\text{p vcn}}/C_{\text{p art}}) (Q_{\text{pl vcn}}) = Q_{\text{rbc vcn}} \times \text{Hct} + (C_{\text{p vcn}}/C_{\text{p art}}) (1 - \text{Hct}) (Q_{\text{pl vcn}}) = Q_{\text{h vcn}} \times \text{Hct} + (C_{\text{p vcn}}/C_{\text{p art}}) (1 - \text{Hct}), \]

\[ \text{RBF} = \text{renal blood flow; } C_{\text{cr}} = \text{clearance of creatinine; PAH = para-aminohippurate; } S = \text{superficial or subcapsular; } D = \text{deep or areuate.} \]

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<th>Blood donor wt (kg)</th>
<th>Kidney wt (g)</th>
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<th>(Total RBF)/Kidney wt (ml/min g⁻¹)</th>
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TABLE 2

Inflow and Outflow Determinations

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where $Q_k$, $v_b$ is the outflow rate of blood from the area.

Creatinine was analyzed according to Peters's (5) modification of Jaffe's reaction. The color was read at 530 nm. PAH was analyzed by the technique of Smith et al. (6). In both these analyses, the protein was removed from plasma by addition of ZnSO$_4$ in H$_2$SO$_4$ and NaOH. The hematocrits were tested in duplicates on well-mixed samples, and the plasma protein concentrations were determined by means of a biuret reaction (7).

Results

The results reported were obtained in experiments on 12 kidneys from 12 adult male cats. Individual functional data for the kidneys are given in Table 1; the average value for kidney weight was 21 g, total renal blood flow (superficial plus deep) 68 ml/min, total renal blood flow/g kidney weight 3.4 ml/min g$^{-1}$, clearance of creatinine 7.1 ml/min, and time of kidney ischemia during preparation 16 min. The clearance rates were measured about 0.75 hours after initiation of the perfusion; the blood flows are average values of all the control periods. The total blood flows decreased about 25% during 3-5 hours of perfusion in eight experiments, stayed stable in three, and increased 10% in one. The extraction fractions of PAH (arterial minus venous divided by arterial plasma concentration) averaged 0.85 in the superficial venous plasma and 0.61 in the deep venous plasma (in the last three experiments presented in Table 1, the extractions were not measured). The arterial plasma concentrations of PAH were around 0.02 mg/ml and never exceeded 0.03 mg/ml. The urine flows averaged 0.4 ml/min (range 0.03 to 0.85).

The ratio between the deep and the superficial venous control outflows varied from kidney to kidney. The range was 0.65 to 1.30, and the average value of all the experiments was 1.0. There was a tendency in nine of the experiments towards a drop of the ratio with time. The average fall in these experiments was 0.2 during 3-5 hours of perfusion. In the remaining three experiments, the flow ratio was reasonably stable. Typical examples of the courses of the flow ratios may
The effect of stimulation of the renal nerves with 1-5 stimuli/sec (1 msec, 15 v) in three kidneys. In one kidney, the nerves were stimulated twice, in the two other kidneys eight times each. The paradoxical response was from one of the latter experiments.

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Plugging of the vessels with microspheres (diameters 15–50 μm) produced results opposite to those from nerve stimulation and catecholamine infusion (Fig. 6, Table 2). The subcapsular flow decreased more than the arcuate flow. The reduction of the outer flow averaged 42% while that of the inner flow averaged 25%. With the 15 μm spheres, injection of a total of 6.5 mg did not affect the flows in one kidney (data not included in Fig. 6), but reduced them in another. The perfusion pressure averaged 130 mm Hg and was not altered by the injections.

Statistical calculations showed that the effects on the two flows were clearly different ($P < 0.001$) for epinephrine, nerve stimulation, and microsphere injection, but not for angiotensin ($P > 0.05$).

For the last three kidneys considered in Table 1, the rates of arterial inflow to the two drainage areas were calculated according to Eq. 3. Inflow rates, outflow rates, flow ratios (arcuate to subcapsular), hematocrits, and fractional protein concentrations, together with experimental flows calculated in percent of the control flows may all be read from Table 2. Epinephrine was tested seven times, angiotensin only four, because in one experiment the flows returned to control values (escaped) in spite of continued infusion of the hormone. This phenomenon was also sometimes observed in the experiments in which the arterial inflow was not determined. The microspheres were injected only three times because of an accident at the end of one experiment. The nerves were not prepared for stimulation in these rather demanding experiments. The responses are also presented in Figures 3, 4, and 6. In six of seven tests with epinephrine, the relative fall (deep to superficial) was found to be the largest when blood inflows were considered, i.e., the points in Figure 3 moved farther away from the line of equal percent reductions in flow. This result was expected: the finding of a fractional plasma protein concentration in subcapsular blood larger than one (1, 4) (Table 2) was interpreted as the result of subtraction of a volume of protein-free water from the blood by glomerular ultrafiltration which was larger...
Illustration of the procedure used to ensure that only a minimal difference exists between the pressures in the renal and the subcapsular veins. The rigid cannula inserted into the renal (or caval) vein is shown entering the chamber through the lid. In two subcapsular veins, cuts and clamping sites are indicated. By placing the outlet of the tube leading the arcuate blood into the flowmeter cylinder at a level somewhat below (2–3 cm) the outlet of the tube through which the subcapsular blood entered the other flowmeter, flapping (indicated by narrowing at b) was produced in the renal vein just below the tip of the cannula. Since the wall of the vein is unable to carry a pressure gradient in the collapsed state, the alteration between collapse and partial opening, occurring at a frequency of about 2/sec, means that at this level essentially the same pressure must exist inside the renal vein (at a) and in the surrounding oil (at b). Using this pressure as reference and neglecting the small frictional pressure drop in the renal vein below the flapping site, the pressure in the renal vein at the hilus must be about 1 cm of blood and the pressure in the subcapsular veins at the level of the wide cuts must be about 1 cm of oil.

In the fractional protein concentrations all other things being equal, because a larger fraction of the plasma water perfusing the drainage area is handled by the nephrons. This will lead to movement of the data points when going from outflow to inflow in the direction observed in the experiments (Fig. 3).

Discussion

In interpreting the results obtained in the present study there are two major problems demanding consideration: (1) Can the two venous outflows recorded simultaneously be assumed to represent unmixed venous outflows from well-defined superficial and deep parts of the kidney? (2) Do the kidneys used than that regained by the blood through tubular reabsorption (opposite for the deep drainage area). It is well known that epinephrine in smaller doses (and increased tone in the renal nerves) reduces the renal blood flow but leaves the filtration rate relatively unchanged (8–10), and therefore the filtration fraction increases. Now, when this occurs, the inequality between the rates of ultrafiltration and reabsorption should show up even more
in the experiments, exposed to about 15 minutes of ischemia as they have been, correspond to denervated kidneys in situ with respect to function and response to stimuli?

With regard to the first question, the morphology of the renal veins in the cat indicates that the venous blood leaves along two fairly well-separated routes (11, 12). These studies, and unpublished observations on polyvinylchloride casts of the veins show that the border line between the two venous drainage areas is in the middle of the cortex, since the outer and inner cortical veins are of similar lengths. Interdigitation between the vein systems was not observed.

Interlobular veins, which, in the dog, are wide enough to lead all blood from the stellate veins into the arcuate veins (13) (Fig. 1), are rare and rudimentary in the cat (11, 12, and unpublished observations on polyvinylchloride casts). In the cat they would seem to be capable of allowing only minute flows between the subcapsular and arcuate veins (unless considerable pressure differences existed between these). Peritubular capillaries form a continuous plexus throughout the cortex and constitute a connection between the two systems.

In the in situ cat kidney, the pressure in the large subcapsular veins is, within the accuracy of measurement, identical to that in the renal veins. This has been observed several times by puncturing subcapsular veins with a thin steel cannula (which did not obstruct the lumen) connected to a pressure transducer and comparing the pressure with that in the renal veins (unpublished observations). To reestablish the equality of the pressures in the cut subcapsular veins and the renal vein in the isolated perfused kidney, a special arrangement was employed which is shown in Figure 7. Under these experimental conditions, a fast infusion of blood deep into the arcuate veins only appeared as an increase in the deep flow recording (Fig. 8). Correspondingly, a fast infusion of blood into the oil from outside never showed up in the deep flow recording but only in the superficial recording. We take this as an indication that capillary connections, rudimentary interlobular veins, or leaks where the silver clamps injured the tissue constitute communications between the two venous drainage areas that are too small to carry blood flows of sufficient magnitude to invalidate the method.

Furthermore, at normal flows, a pressure in the renal vein of as much as 30–40 cm blood above chamber pressure was needed to force the flow of blood, normally carried away along the arcuate and the renal veins of the preparation, into the oil through such communications. (This was tested several times by lifting the tube connected to the renal vein to a vertical position and noting the level reached by the blood in the tube.) Combined with the fact that our experimental conditions were such that virtually no pressure difference existed between the renal vein and the subcapsular veins, this observation is a further indication that under the experimental conditions only very small blood flows could pass through communications between the two drainage areas.

The possibility that blood could pass from the arcuate veins to the subcapsular veins through interlobular veins was also tested in the in situ kidney. After a control period with sampling of arterial and superficial venous blood (1) which yielded an extraction fraction of PAH of 0.95 in the subcapsular blood, the site of infusion of the sustaining dose of PAH (concentration about 3 mg/ml) was altered from the jugular vein to the arcuate veins of the experimental kidney; a catheter had been inserted beforehand into these veins. Again blood was sampled from the same subcapsular vein and from an artery; the extraction fraction was still 0.95 (and the arterial plasma concentration unchanged). After the experiment, it was confirmed that the tip of the catheter in the arcuate veins was lying right beneath the V-shaped drainage area of the punctured subcapsular vein. Since admixture of even slight amounts of the strong sustaining solution of PAH to the subcapsular blood samples would have decreased the measured extraction fraction appreciably, we conclude that passage of blood from the arcuate veins
to the superficial veins does not occur. Finally, it should be mentioned that the pattern of the osmolalities and the concentrations of different ions in the arcuate, subcapsular, and arterial plasma fits well into the anatomical picture of the drainage routes presented here—e.g., the arcuate plasma is hypertonic to arterial plasma, corresponding to the drainage of medullary blood into the arcuate veins, etc. (2).

The kidneys were submerged in warm oil and were thus well protected against cold, drying, and squeezing. They were perfused with blood from another cat, and during the transfer to the chamber oxygen consumption was kept low by flushing with dextran-saline solution at 10°C. Still, however, the ischemic stress on the kidneys during the preparation manifested itself in a reduced capacity for PAH extraction. The extraction fractions for the superficial and deep venous blood were 0.85 and 0.61, respectively, as compared to 0.95 and 0.82 in previous experiments on kidneys in situ (14). This is in accordance with previous reports (15) that impairment of PAH transport capacity is a consequence of kidney ischemia. The ischemic trauma was not substantial, however. The fact that the extraction fractions were still of considerable magnitude shows that the tubular cells were able to transport PAH uphill from plasma to the tubular fluid. The vessels always reacted strongly to the stimuli. The magnitude of the clearance rates of creatinine showed that the displaced kidneys were able to ultrafilter (average 7.1 ml/min, one kidney) and, more importantly, to reabsorb fluids at the same rates as untouched organs in anesthetized or unanesthetized cats (16, 17).

These findings indicate that the functional state of the kidneys was not materially reduced by the procedure and that the preparation gives essentially separate venous outflows from two areas, the outer part of the cortex and the deep part of the cortex together with the medulla. The two flows were of similar magnitude, a fact which is consonant with the presence of a considerable amount of cortical tissue in addition to the medullary tissue in the deep area; the medullary blood flow is probably only 10–20% of the total blood flow (18).

An increased activity of the sympathetic nervous system, produced by stimulating the renal nerves or simulated by infusing epinephrine or norepinephrine, invariably reduced the deep circulation disproportionately (Figs. 3 and 4). The most likely explanation for this pattern of intrarenal response appears to be one of the following: (1) The sensitivity of the afferent or efferent arterioles or both to epinephrine and nerve activity is graded topographically, in the sense that these vessels respond by constriction increasingly more, the deeper they lie in the cortex. (2) The flows through all cortical glomeruli are equally affected by nerve activity and epinephrine, while the medullary circulation, originating from the juxtamedullary glomeruli, is affected to a considerably higher degree. A number of special structural features related to the medullary circulation would seem to favor the latter interpretation. First, juxtamedullary glomeruli possess afferent and efferent vessels which are wide and contain considerable amounts of smooth muscle in their walls; smooth muscle cells are also present in the arteriole rectae of the outer medulla (19–21). Cortical efferents are mainly narrow endothelial tubes. Second, filling defects are described in the juxtamedullary efferent arterioles of ink- and Neoprene latex-injected specimens, which are interpreted as the result of a sphincterlike action (12). Third, authors (22–25) now agree on the existence of thoroughfare channels (continuous vessels) in the juxtamedullary glomeruli. Such channels could allow relatively large variations in the flows through the medulla with only small changes in the pressure drop across the juxtamedullary glomerular unit. Nerve fibers follow the afferent arterioles, the thoroughfare channels, the efferent arterioles, and the upper parts of the arteriole rectae (25, 26).

During infusion of epinephrine and stimulation of the renal nerves, Aukland (27) observed a fall in the local clearance of hydrogen in the outer medulla which was of a
similar fractional magnitude as the fall in the total renal blood flow, measured with an electromagnetic flowmeter. He took this as an indication that medullary blood flow varies proportionately to cortical blood flow. It may be questioned whether alterations in the hydrogen washout rate from the outer medulla specifically indicate alterations in the medullary blood flow rate, since this area is also traversed by tubular fluid in the loops of Henle at rates which may be similar in magnitude to the normal vasa recta flow. His failure to observe a disproportionately large fall in hydrogen clearance appears to be compatible with a strong reduction in vasa recta flow, during which the hydrogen washout becomes mainly dependent on a maintained flow through the loops of Henle.

The present results are also in disagreement with the findings obtained by extrarenal recording of the $^{85}$Kr clearance from the kidney (28, 29). Each curve was graphically resolved into four components: the fast component presumably was caused by the washout effect of the blood flow through the outer cortex, while the slower components were thought to be of deeper origin. The authors found selective reductions in the outer cortical flows with angiotensin infusions and stimulation of the renal nerves in unanesthetized and anesthetized dogs with an exposed kidney. The results and interpretations of these measurements may be incorrect due to the occurrence of countercurrent exchange and tubular washout.

The intrarenal distribution of radioactive microspheres (5-50 μm $^{131}$I-macroaggregates of albumin or 18, 27, and 36 μm plastic spheres) injected into the left ventricle has been used to quantify flow to the different kidney areas (30, 31). The basic principle of this method, that such nonyielding particles are distributed according to flow in the branching vascular system, may fail to hold for various reasons. Some of these have to do with the diameters of the particles compared with that of the branch. If the particle is larger than the inlets to the branches, it will follow the main stream. If the particle is only a little smaller than the diameter of the inlet, it is probable that the statistical chance that it will enter the branch is smaller than the chance of entrance of plasma constituents. If more than one particle is simultaneously heading towards the same branch, mutual collisions may also reduce the statistical chance for their entrance into the branch. Second, the phenomenon of axial streaming of particles is more pronounced the bigger the particles (32). According to Saffman (32), the rate of radial displacement of a particle towards the axis should be proportional to the particle diameter to the fourth power. Thus particles as large as 15-50μm may stick to the central stream and have less chance to reach an opening of a side branch.

Accordingly, while the distribution of radioactive particles (injected into the left heart) in various whole organs undoubtedly permits the determination of the distribution of the blood flow to them, caution should be exerted on trying to determine the flow distribution within an organ by this method. In the kidney, it was observed (30, 31) that much activity accumulated in the outer layers of the cortex and less in the juxtamedullary cortex. Also, counted as activity per glomerulus, the figures were larger for the outer half of the cortex (31). In our opinion, a probable explanation is that many of the particles bypassed the proximal afferent arterioles for reasons mentioned above and followed the interlobular arteries until they became lodged distally in these vessels or in their terminal branches. The inner diameters of afferent arterioles are 18 μm in dog (31)—13 μm in man (19)—i.e., smaller than, or on a par with, the diameter of the microspheres, a fact which is consonant with the finding that most of the spheres of 27 μm in diameter or larger were found in preglomerular vessels and not in the glomeruli (31). Since the microspheres most likely plug the vessels in which they become lodged, the present observation of a disproportionately large decrease in the outer cortical flow after microsphere injection may have a similar explanation.
The results presented in this paper may be of interest in two respects. One concerns the effect of the medullary blood flow on the concentrating mechanism in the renal medulla. It has long been thought that a reduction of medullary blood flow may favor the reabsorption of water in the collecting tubules, because fewer sodium ions and fewer anions would be removed from the medullary interstices by the blood flow (33–35). The demonstration here of an extraordinary sensitivity of the deep renal flow to catecholamines and to stimulation of the renal nerves makes it likely that a preferential reduction in the blood flow to the medulla (and possibly to the juxtamedullary cortex) produced by these stimuli plays a role in the conservation of water under conditions where the blood volume is reduced due to dehydration, blood loss, etc. Relatively low medullary blood flows in concentrating dehydrated animals compared to those in hydrated animals were indeed reported in the pioneer work of Thurau et al. (36) in which the time course of the passage of dye through the vasa recta was used to assess the flow. Later on Harsing and Pelley (18) and Balint et al. (37) presented data on the distribution of 86Rb in the renal tissue 1 minute after a fast intravenous injection of this ion which indicated that dehydration lowers the plasma flow in the medulla and in the juxtamedullary cortex; the decreases in the middle and outer cortical flows were relatively smaller. Hydration of cats with saline produces a rather selective fall in the filtration fraction of arterial plasma passing into the deep drainage area (38). All these data agree very well with our present findings that alterations of sympathetic nerve activity and administration of epinephrine predominantly cause changes in the medullary and juxtamedullary circulation.

Our findings may also have some bearings on the interpretation of the Trueta phenomenon—a fall in cortical flow with maintained (or possibly increased) medullary flow in response to crush lesions and shock (39). Increased activity in the sympathetic nervous system can hardly explain this observation because various authors (40–43) failed to reproduce the Trueta juxtamedullary shunt pattern by infusion of epinephrine or stimulation of the renal nerves. Our present finding that these stimuli do not selectively reduce the outer cortical flow is also in disagreement with such a mechanism. Some investigators believe that under shock and crush conditions aggregations of erythrocytes or thrombocytes may damage the microcirculation by plugging the vessels (44–46); this theory has also been offered as an explanation of the Trueta shunt pattern (47). This view receives some support from our finding that the outer cortical flow actually is reduced to a comparatively larger degree by the microspheres. Much of the confusion (48) as to the interpretation of the findings of Trueta et al. (39) may then be explained by the difficulty of reproducing the state in which aggregated blood cells (or fibrin) clog the microcirculation of the kidney in experimental animals.

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References


Direct Measurement of Superficial and Deep Venous Flow in the Cat Kidney: EFFECTS OF EPINEPHRINE, ANGIOTENSIN, MICROSPHERES, AND RENAL NERVE STIMULATION

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