Intrarenal Distribution of Blood Flow in Dogs during Hemorrhagic Hypotension

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ABSTRACT

Renal medullary blood flow was well maintained for several hours after blood loss which produced hypotension. Renal cortical blood flow was altered by trauma and mild hemorrhage even though blood pressure remained normal; rate of blood flow through the subcapsular, peritubular capillaries decreased to the level of that in the outer medulla. With further hemorrhage and the development of hypotension, rate of blood flow in large cortical areas was reduced to that of the outer medulla. With prolonged hypotension, the rate of blood flow in most of the cortex approached outer medullary rate and a single exponential could describe the flow in this combined area. Small regions of even slower flow rate began to appear in the outer cortex; patches of tissue appeared to be completely ischemic. The progression of cortical ischemia noted in these experiments may provide additional evidence for the pathogenesis of the patchy tubular necrosis noted in hemorrhagic shock.

ADDITIONAL KEY WORDS
renal medulla autoradiography blood loss neural control of kidney
renal cortex blood loss ischemia anesthetized dogs

The progressive changes in distribution of blood flow in the kidney during the course of prolonged hemorrhagic hypotension have not been described in detail. Trueta et al.,1 using radiological methods, reported a marked reduction in cortical blood flow in shock, with the maintenance of normal medullary circulation. However, the views of the Oxford group have not been widely accepted, and Kramer2 was unable to confirm Trueta's findings with a photoelectric technique for estimating distribution of blood flow in the kidney. On the other hand, the decrease in renal extraction of diodrast, first noted by Corcoran and Page3 in hypotensive dogs, and the depression of the transfer maximum of diodrast4 and para-aminohippuric acid5 under such conditions have been interpreted as evidence of redistribution of renal blood flow. By combining autoradiography with the Kr
6 method for measuring the distribution of blood flow in the kidney6 we have been able to quantify and localize the sequential changes in renal circulation produced by hemorrhagic hypotension. Independent validation of the Kr
6 method has recently been reported by Lade-foged and co-workers.7

Methods

Fasted, mongrel dogs (18 to 32 kg) were anesthetized with pentobarbital (25 to 30 mg/kg), and given additional doses as needed during the experiments. The renal artery was exposed through a flank incision with minimal dissection in order to maintain normal innervation; a polyvinyl catheter was introduced into the vessel by a method previously described.8 The stem of a Y-shaped cannula was introduced into a femoral artery; one end was connected to a Statham strain...
Typical $^{85}Kr$ disappearance curve (heavy black line) following injection of the isotope into the renal artery. Graphic representation of the resultant exponentials is shown by thinner lines. The accompanying table represents pertinent data and derived values obtained from such a curve (from Circulation Research 13: 290, 1963).

For the measurement of distribution of blood flow in the kidney, 200 to 400 $\mu$c of $^{85}Kr$ dissolved in 0.2 to 0.5 ml saline (0.85%) were injected rapidly through a double-barreled adapter into the catheter, followed immediately by 0.2 ml of saline. A scintillation probe, with a two-inch sodium iodide crystal three inches from the end of the cylindrical collimator, was placed over the kidney. The output from the probe was led into a scaler and digital printer and the data plotted on semilogarithmic graph paper (fig. 1). The method of graphical analysis of the "decay" curves has been described previously. The blood flow rates in the cortex, outer medulla, inner medulla, and perirenal fat were calculated from the slopes of the component lines (fig. 1). Thus

$$F = \frac{k \times \lambda \times 100}{\rho}$$

(1)

where $F$ is the flow rate in ml/100 g/min, $k$ is the slope of the line, $\lambda$ the partition coefficient for $^{85}Kr$ between tissue and blood, and $\rho$ the specific gravity of the tissue. The percentage of activity going into each region was determined from the zero time intercepts ($A_0$). The relative volume of tissue perfused at each rate ($A_0/k$) was estimated from the intercepts and the flow rate.

After heparinization, the anesthetized animals were allowed to bleed freely into the pressure reservoir until blood pressure began to decrease, and then more slowly until blood pressure fell to 50 mm Hg. In most animals the blood pressure was lowered to 50 mm Hg in 15 to 30 minutes, with a loss of 20 to 40% of blood volume. The reservoir was then adjusted intermittently to maintain the pressure at 50 mm Hg throughout the remainder of the experiment. During this period, in which blood pressure was stable at 50 mm Hg, the animals lost an additional 15 to 20% of the initial blood volume.

In all animals control $^{85}Kr$ curves were obtained before hemorrhage, and were then repeated one or more times during hypotension. The measurement of the distribution of renal blood flow by the $^{85}Kr$ method took approximately one hour during which time it was necessary for flow and distribution to remain relatively stable. Since preliminary experiments indicated that rapid fluctuations in renal blood flow distribution occurred as blood pressure fell, the posthemorrhage $^{85}Kr$ curves were not started until pressure was steady at 50 mm Hg.

At the end of the experiment, for anatomical localization of each component of the $^{85}Kr$ curve, the kidneys were removed for autoradiographs at predetermined times after the injection of the same amount of $^{85}Kr$ into the renal artery. The renal pedicle was ligated, the kidney extirpated, and frozen immediately in acetone and dry ice.
mixture. Autoradiographs were then prepared as previously described. The duration of exposure was determined by the amount of activity remaining in the kidney. In some of the experiments, 5 ml of a suspension of carbon black particles (200 Å) were infused into the renal artery for 15 seconds prior to removal of the kidney to obtain independent evidence for alterations in circulatory pattern. In three dogs total renal blood flow was obtained by renal venous cannulation and direct measurement of the outflow for comparison with the Kr* determinations; venous outflow was not interrupted during cannulation through the inferior vena cava.

Results

Control data from 12 experiments are summarized in table 1, showing the blood flow rates for cortex, outer medulla, inner medulla, and hilar fat, with the percentage of the Kr* initially distributed to each of these areas. In these dogs the mean of the control cortical blood flow rates was 481 ml/100 g/min, with 85% of the radioactivity going to this region; outer medullary flow averaged 111 ml/100 g/min, with 12% of the activity; inner medullary flow was 18 ml/100 g/min, with 3% of the Kr*.* These values are in agreement with those previously reported for unanesthetized animals. Furthermore, repeated determinations made during control experiments with prolonged anesthesia (pentobarbital) showed little variation with time in animals in good condition. Control autoradiographs made from sections of such kidneys removed immediately after KT* injection showed uniform distribution of activity in the cortex (fig. 2).

Within 30 minutes of the lowering of blood pressure to 50 mm Hg, the Kr* disappearance curves were markedly altered (table 1), with further progressive changes as hypotension was prolonged. The alterations in the curves induced by hemorrhagic hypotension are illustrated in figure 3 (exp. 3, table 1) in which the original data (for 0 to 8 minutes) are indicated by the closed circles (normotensive) and crosses (hypotensive). Although the reduced “washout” of Kr* and hence total blood flow during hypotension is apparent from the original data, the derived flow rates for the cortical components (slopes of solid and broken line) are essentially the same in the normotensive and hypotensive states. However, the amount of activity entering the first, rapid component during hypotension was grossly reduced, suggesting that the volume of cortex (A'/k') perfused at the rapid rate was diminished from control values. Much of the Kr* was now entering regions of the cortex perfused at a rate so close to that of the outer medulla that only a single slope was found for these two areas by graphical or computer analysis. Thus, with hypotension, blood flow through the cortex was no longer described by a single exponential. In table 1 and figure 11, the region of the cortex with the more rapid flow rate is designated as cortex A, while the area with flow rate similar to that of the outer medulla is labelled cortex B. Further evidence for this redistribu-

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*As Thorburn et al. have noted, the counter-current exchange in the vasa recta introduces some error in the calculation of the nutrient flow in the inner medulla; for this reason it may be more appropriate to designate the estimated “washout” rate in this region as effective flow. However, since the movement of Kr* in the medulla may serve as a model for that of water, O₂, and CO₂, the physiological importance of this method of measuring “capillary flow” is apparent.
Summary of 12 Experiments Showing Blood Flow Rates (ml/100 g/min) and Initial Distribution of Kr<sup>85</sup> in Re Cortex, Outer Medulla, Inner Medulla and Perirenal Fat Before and After the Production of Hemorrhagic Hypotension (50 mm Hg)

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*Time: minutes after blood pressure stabilized at 50 mm Hg.*

†Renal vein cannulated. Average blood flows during Kr<sup>85</sup> curves in exp. 10 were 200 ml/min and 55 ml/min (kidney weight 55 g); exp. 11, the flows were 375 and 30 (kidney weight 69 g); and exp. 12, 220, 35, and 45 ml/min (kidney weight 63 g).
### Renal Blood Flow in Hypotension

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*Data from Circulation Research, Vol. XIX, July 1966*
Comparison of the first eight minutes of the $Kr^{85}$ disappearance curves following injection of isotope into renal artery of dog 3 (table 1) during normotensive state and 60 minutes after hemorrhage. Note that the rapid cortical component (hypotensive) is indicated by cortex A in table 1, while combined slow cortical and outer medullary component corresponds to cortex B and outer medulla.

The progressive changes in renal blood flow distribution are indicated in table 1. After 30 minutes of hypotension the percentage of activity entering the cortical region with the more rapid flow rate was reduced to 65% (cortex A) from the control average of 85% (exp. 2, 5, 7), although the flow rate was significantly decreased only in exp. 7. Outer and inner medullary flow rate was unchanged. After 60 minutes of hypotension the percentage of $Kr^{85}$ entering cortex A was further reduced, and in three dogs was less than 10%; in exp. 12 no fast component was observed, and flow rate in the entire cortex and outer medulla was described by a single exponential. Outer medullary flow was still unaltered from control values in five dogs. Inner medullary flow rate was also unchanged. In the dogs maintained in the hypotensive state for 90 minutes or longer, cortical flow rate decreased, and in two of the animals (exp. 11, 12) no rapid component was detected. Outer medullary flow rate was in the normal range in three dogs (exp. 2, 6, 9), but was reduced markedly in the two animals in which the renal vein was catheterized; perhaps the elevated renal venous

![Image of diagram showing radioactive decay curves]
pressure may have accelerated the deterioration of renal function. Inner medullary flow rate was also decreased at this time.

Autoradiographs prepared from kidneys removed after varying periods of hypotension, and at selected times after the injection of Kr*4 confirmed the data on flow rates and distribution of renal blood flow noted above. Although the severity of renal changes produced by a given period of hypotension varied from animal to animal, the sequence of alterations was essentially the same. In preliminary experiments we noted that trauma and blood loss during the operative procedure were associated frequently with a reduced percentage of activity entering the cortex, while flow rate (cortex A) and blood pressure were relatively unchanged. Autoradiographs prepared from such kidneys removed immediately after Kr*4 injection demonstrated a narrow, subcapsular band of decreased density (fig. 4), indicating that blood flow rate in this portion of the cortex was reduced after relatively minor trauma and hemorrhage. Histological examination of kidney sections made after intravenous infusion of carbon black particles revealed that this narrow rim contained a distinct band of tubules and peritubular capillaries (fig. 5). Such unsuccessful experiments, in which the control Kr*4 curves suggested subcapsular ischemia, were terminated, and the data are not included in table 1.

Autoradiographs prepared from kidneys removed after completion of the first Kr*4 curve during hypotension showed a patchy distribution of cortical blood flow with the earlier changes most prominent in the outer portions of the cortex (fig. 6). Since the kidney (fig. 6) was removed immediately after the Kr*4 injection, and before any appreciable "washout" had occurred, the dark areas rep-
Histological sections of kidneys removed 15 seconds after intrarenal artery infusion of carbon particles illustrating the uniform cortical distribution of carbon in the normotensive dog (A) and the alterations produced by hemorrhagic hypotension (B). The cortical ischemia appears to be most pronounced in the outer region (arrow).

Histological sections made from kidneys injected with carbon particles (fig. 7) also demonstrate these outer cortical areas of ischemia. With still more prolonged hypotension, autoradiographs demonstrate wedge-shaped areas of decreased density (and hence reduced blood flow) which extended across the entire cortex (fig. 8). Thus, the autoradiographs offer visual evidence for a progressive decrease and redistribution of cortical blood flow. Further proof for the uneven distribution was provided by autoradiographs of kidneys removed some minutes after Kr85 injection. Figure 9A illustrates the uniform and rapid disappearance of the radioactivity from the renal cortex of a normotensive dog two minutes after intrarenal injection of Kr85, with activity remaining only in the outer medulla and fat. In contrast, in a kidney removed after prolonged hypotension and two minutes after injection of Kr85 (fig. 9B and C) most of the cortex has a density approximately the same as that of the outer medulla; the darker areas indicate that some small regions of the cortex may have even slower rates of flow. Figure 10, an autoradiograph prepared

 Autoradiographs prepared from different areas of same kidney removed immediately following Kr85 injection. The animal had been hypotensive for seven hours. Areas of reduced blood flow extend across the entire cortex.
RENAL BLOOD FLOW IN HYPOTENSION

FIGURE 9
Autoradiographs of kidneys removed two minutes after Kr⁸⁵ injection. A: Kidney from normal animal illustrating the uniform "washout" of the cortex, with activity remaining in the outer medulla, veins and fat. The dots outlining the cortex have been drawn by hand. B and C: Kidney from hypotensive dog demonstrating the similarity of rates of blood flow for most of the cortex and the outer medulla. The darker areas may represent regions with slower flow rates, or regions in which flow rate was rapid at time of injection but relatively ischemic thereafter.

FIGURE 10
Autoradiograph of kidney from hypotensive animal removed four minutes after intrarenal injection of Kr⁸⁵ showing some areas of cortex cleared of activity, while other regions have a density similar to that of outer medulla.

from a kidney removed four minutes after Kr⁸⁵ injection, also demonstrates a large area of the cortex perfused at a rate similar to that of the outer medulla. Autoradiographs of kidneys from normal dogs had previously enabled us to relate each exponential of the Kr⁸⁵ disappearance curve to a specific anatomical region of the kidney, e.g., component I and cortex, component II and outer medulla, component III and inner medulla (fig. 1).

In the hypotensive animal such a discrete relationship frequently is not present; each component may no longer correspond to a circumscribed anatomical region but merely describes an average flow rate for portions of the kidney which may include, for example, areas of both outer cortex and outer medulla.

In the normal animal the volume of kidney perfused at each rate can be estimated from the weight of the cortex, outer medulla, and inner medulla, or from autoradiographs made from serial sections of the entire kidney. However, following hemorrhage, with increasing vasomotion and variability of flow rate in a given region from moment to moment, and ischemia of progressively larger regions of the cortex, these methods are no longer valid. An approximation of the relative volumes \( \left( A_0/k \right) \) of tissue perfused at each average rate can still be made. Since the total radioactivity in each region \( \left( A_0 \right) \) is determined by the flow rate \( \left( k \right) \) and the volume of tissue \( \left( A_0 = k \times V \right) \), the fraction \( \left( f \right) \) of the total pool represented by a single
component may be obtained by dividing the value for its relative volume by the sum of the relative volumes for all components. Thus,

$$f = \frac{A'_n}{\sum A'_n/k'}$$

Since we have demonstrated that the inner medulla contains little radioactivity for the first several minutes after Kr$^{88}$ injection, the relative volumes of component I and II may be compared directly at zero time. For example, in exp. 1 (table 1), the relative volumes during the control period may be determined as follows:

$$\frac{A'_n}{k'} = \frac{88}{620} = 0.14 \text{ and } \frac{A''_n}{k''} = \frac{108}{108} = 1.00$$

The percentage volume of component I is thus

$$\frac{A'_n}{A'_n + A''_n} = \frac{0.14}{0.26} = 0.62, \text{ or } 62\%$$

The percentage volume of component II is

$$\frac{0.10}{0.26} = 0.38, \text{ or } 38\%$$

After sixty minutes of hypotension, the ratio is

$$\frac{A'_n}{k'} = \frac{8}{418} = 0.02, \text{ and } \frac{A''_n}{k''} = \frac{83}{130} = 0.64$$

$$\frac{0.02}{0.02 + 0.64} = 0.03, \text{ or } 3\%$$

Component I has thus decreased from 62% of the total volume to 3%.

From the estimate of the relative volumes of component I and II, the flow rates (ml/100 g/min) and the kidney weight, total flow (ml/min) can be estimated and compared with that directly measured by renal venous outflow. For example, in exp. 10 (table 1) the average renal venous outflow during the second Kr$^{88}$ curve was 55 ml/min, the kidney weighed 55 g when removed. The flow rate for essentially the entire cortex and outer medulla was 106 ml/100 g/min. Thus total flow estimated from the Kr$^{88}$ "washout" was 0.55 X 106 = 58 ml/min. For the other two experiments in which venous outflow was measured during hypotension, the calculated and measured flows were 33 and 30 ml/min, 50 and 35, 50 and 45. Because of the experimental design, the weight of the kidney during the control flow measurements was not determined. If we assume that kidney weight decreased 20% during hypotension, and use 70 g as control kidney weight in exp. 10 (table 1), excellent agreement between measured and calculated flow is observed.

$$\frac{A'_n}{k'} = \frac{88}{361} = 0.24, \frac{A''_n}{k''} = \frac{9}{87} = 0.10,$$

$$\frac{0.24}{0.34} = 0.71, \text{ or } 71\%, \frac{0.10}{0.34} = 0.29, \text{ or } 29\%$$

$$71\% \times 361 = 256$$

$$29\% \times 87 = 25$$

$$\frac{281 \text{ ml/100 g/min}}{197 \text{ ml/min}} = 0.24$$

The measured outflow was 200 ml/min. Close agreement was also observed in the control flow in exp. 12; however, the calculated and observed values differed by 25% in exp. 11.

**Discussion**

Renal medullary blood flow is relatively unchanged by hemorrhagic hypotension for several hours after stabilization of blood pressure at 50 mm Hg (fig. 11). In contrast, the pattern of blood flow in the cortex is altered progressively, with reduction in flow rate observed first in the subcapsular, peritubular capillaries (fig. 11b), and then in the outer third of the cortex (fig. 11c), while the perfusion rate of the rest of the cortex is essentially unchanged (cortex A). Thus, with hypotension, vascular resistance in the medullary region and inner cortex is reduced by approximately 50%, for flow rate is well maintained at approximately half the blood pressure. Since perfusion rate in the outer cortex decreases to that of the outer medulla (from approximately 500 to 125 ml/100 g/min) re-
RENAL BLOOD FLOW IN HYPOTENSION

Diagrams of progressive changes in cortical blood flow induced by hemorrhagic hypotension. Relative flow rates are indicated by the density of the areas: cross-hatched, ~500 ml/100 g/min; unbroken lines, ~150 ml/100 g/min; broken lines, ~20 ml/100 g/min; and blank region, essentially no flow. The portion of the cortex with normal flow rate is designated cortex A, while the area with flow rate similar to outer medullary rate is labelled cortex B. (a) Normal distribution of flow rates. (b) Blood flow pattern with trauma and mild hemorrhage. Although the animal is normotensive, blood flow rate through the subcapsular peritubular capillaries is decreased to the level of outer medullary flow. (c) Blood flow in early hypotension. The blood flow rate in large areas of the outer cortex is reduced to outer medullary rate. (d) Blood flow distribution in late hypotension. The rate of blood flow in most of the cortex approaches that of the outer medulla. Small regions of slower flow begin to appear in the outer cortex, while some patches of tissue appear to be completely ischemic.

Walker and Oliver noted local fluctuations of blood flow in the superficial peritubular capillaries in exposed mammalian kidneys, with "brief cycles of contraction and relaxation." Similarly, Gottschalk (personal communication) has observed that trauma to kidneys prepared for micropuncture studies produced circumscribed areas of ischemia, with normal flow in adjacent areas; hemorrhage in such a preparation may lead to generalized vasoconstriction of these superficial vessels, as noted also in the present studies. With prolongation of hypotension, the volume of cortex perfused at or close to the normal cortical rate (cortex A) progressively decreased, and autoradiographs demonstrated the patchy pattern of blood flow of the outer cortex as noted previously by Trueta et al., by Insull et al. and by others in comparable experiments. However, in none of the kidneys observed in the present study was evidence found for the complete exclusion of blood from the cortex, or for the opening of non-nutrient shunts. The pattern of ischemia noted in the present experiments is in agreement with the observations of Oliver et al. in their studies of acute renal failure. They wrote that "the patchy cortical ischemia which produces the tubular lesions is quite a different pattern than what might be suggested by the simple statement that cortical renal blood flow is reduced. As we have suggested, perhaps over-all renal blood flow..."
flow is not greatly reduced and yet the patchy distribution of blood to nephrons may still result in tubular dysfunction and eventual structural damage." The marked ischemia of the outer cortex may have additional physiological significance because Brown et al.10 have shown that the renin content of the outer glomeruli is many fold higher than that of the juxtamedullary glomeruli.

The mechanism responsible for the progressive cortical vasoconstriction is still to be elucidated. Preliminary experiments in this laboratory suggest that reduction of renal artery pressure does not alter distribution of blood flow. Patterns of renal cortical blood flow distribution similar to those observed in hemorrhagic hypotension have been described with stimulation of renal nerves16 or cerebral cortex.17 The reported observations that nerve fibers are found mainly in the renal cortex18 lend support to the suggestion that the vasoconstriction is neurogenic in this region. However, other agents may play a role, and experiments in this laboratory have shown that intrarenal infusions of norepinephrine, epinephrine, and angiotensin produce a similar pattern of progressive cortical ischemia, starting in the outer cortex, but sparing the medullary circulation. The paucity of nerve fibers in the medulla may account for the lack of vasoconstriction during hypotension, but does not afford an explanation for the decreased resistance in the medulla. The maintenance of medullary blood flow rate during hypotension may be, in part, the result of the decrease in hematocrit during hemorrhage, and the reduction of viscosity which may help to decrease resistance in the long vasa recta. It is conceivable also that the reduction of cortical blood flow may lessen the pressure drop (ΔP) in the arcuate arteries so that the pressure in the juxtamedullary glomeruli may be relatively well maintained. However, microscopic examination of injected specimens suggests that vasodilatation is present in the medullary vessels; this dilatation may be produced by the local release of metabolites or medullin20, 21 which has been shown to reverse the pressor effects of norepinephrine.22 The maintenance of medullary blood flow at a blood pressure insufficient for glomerular filtration may explain the loss of medullary hypertonicity noted by Boylan and Asshauer23 and Selkurt and Elpers24 in hypotension. In addition, the observation that Kr51 "washout" from the inner medulla was unchanged, when urine flow ceased, is further evidence that urinary loss of Kr51 in the antidiuretic state is not significant, and does not modify the Kr51 decay curve.

References


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