Intracortical Distribution of Renal Blood Flow in Hemorrhagic Shock in Dogs

By Alexander Logan, Pedro Jose, Gilbert Eisner, Lawrence Lilienfield, and Lawrence Slotkoff

ABSTRACT

The effect of acute hypotensive hemorrhage on the intracortical distribution of renal blood flow was studied in anesthetized mongrel dogs with radioactive microspheres. In the early stages of shock, when carotid artery manipulation was avoided, outer cortical blood flow fell drastically and juxtamedullary flow was relatively well preserved. Carotid artery cannulation caused a redistribution of blood flow within the kidney even before hemorrhage, presumably by stimulating the carotid sinus reflex. Subsequently, with hemorrhage there was a parallel reduction in outer cortical and juxtamedullary blood flow. 133Xe washout curves agreed with the microsphere findings. It was concluded that when the carotid artery was not disturbed, juxtamedullary blood flow was selectively preserved in the early stages of acute hypotensive hemorrhage.

KEY WORDS microspheres  133xe washout carotid sinus reflex sympathetic nerves redistribution of intrarenal blood flow renal medullary blood flow renal cortical blood flow

The changes in the rate of flow through the juxtamedullary circulation after acute hypotensive hemorrhage are still controversial. In a recent study on the effect of hemorrhage on intrarenal blood flow distribution, Aukland and Wolgast found a parallel reduction in cortical and outer medullary flow even in the early stages of shock (1). Their observations extended those of Kramer, who, by the photoelectric technique, demonstrated a reduction in superficial cortical and inner medullary flow after hemorrhage (2). In contrast Carriere and coworkers, by combining autoradiography with the 85Kr washout technique, found inner cortical and outer medullary flow to be relatively well preserved after stabilization of blood pressure at 50 mm Hg (3). Likewise Truniger et al., using the 133Xe washout method, found a marked increase in the fraction of total renal blood flow passing through the corticomedullary circulation without any significant change in local blood flow rates (4).

In the study of Aukland and Wolgast, the dogs were bled through a large catheter inserted into one carotid artery (1). The effect of this manipulation on intrarenal hemodynamics was not determined in their study, but it is known that bilateral carotid occlusion or renal nerve stimulation will redistribute blood flow within the kidney (5, 6). When pressure in an isolated carotid sinus is reduced, the frequency of renal sympathetic nerve discharge is increased (7). It is therefore possible that in the study of Aukland and Wolgast carotid artery cannulation may have altered intrarenal hemodynamics and obscured the changes caused by subsequent interventions.

The present study was therefore undertaken to determine the effect of acute hypotensive hemorrhage on the intracortical distribution of renal blood flow. In addition, the effect of unilateral carotid artery cannulation on intrarenal hemodynamics was examined before and after hemorrhage. We used the recently validated microsphere method to measure the...
distribution of blood flow within the kidney (8, 9) because it avoids surgical manipulation
of the kidney and its blood vessels and can measure flow through the same regions in the
kidney in different physiological states. Our study demonstrated that carotid artery cannula-
tion changed the intrarenal distribution of blood flow. In addition, it altered the renal
circulatory response to hemorrhage so that outer
cortical and juxtamedullary flow were reduced
in parallel. When carotid artery manipulation
was avoided, our results were very similar
to those of Carriere et al. and Truniger et al. (3,
4).

**Methods**

**INTRARENAL BLOOD FLOW DISTRIBUTION DURING HEMORRHAGE**

All experiments were performed on fasted adult
mongrel dogs weighing 14–22 kg. The dogs were
anesthetized with pentobarbital sodium (25
mg/kg), and were given heparin. Small (0.5–1.0
ml) periodic venous injections of pentobarbital
sodium maintained the same level of anesthesia.
The left ventricle was catheterized in a retrograde
fashion using a Lehman ventriculography catheter
from either the carotid or brachial artery, and
its position was confirmed by a change in the
pressure tracing. Indicator dilution technique was
used to estimate cardiac output serially. One ml
of indocyanine green (5 mg/ml) was injected
into a right jugular venous catheter and flushed
immediately with 5 ml of saline. Simultaneously,
arterial blood was withdrawn from the femoral
artery catheter and passed through a Gilford
densitometer at a constant rate. The curve
obtained was replotted on semilog paper and
analyzed by the method described by Lilienfield
and Kovach (10). In all dogs, polyethylene
catheters were inserted into the right femoral
artery for blood pressure monitoring with a
Statham pressure transducer connected to a
Sanborn recorder.

Radioactive $^{169}$Yb- and $^{85}$Sr-labeled micro-
spheres with a diameter of 15 ± 5µ were used in
our studies. One µc of the radioisotope was
suspended in approximately 75 ml of dextran to
which 3 drops of Tween 80 were added to
prevent microsphere aggregation. The specific
activity of the resulting suspension was initially
13 µc/ml. The dextran had a specific gravity of
1.073 and the microspheres 1.300. An ultrasonic
probe (Fisher Scientific Company) was used to
place the microspheres into suspension. No
shattering of the microspheres was observed
microscopically. The total radioactivity of the
injection was determined by the following
method. A 0.1-ml sample of the microsphere
suspension was counted in a well scintillation
counter (Nuclear Chicago Model 4216) along
with the pipette used to measure this volume. The
volume of injection drawn from the same
suspension was determined by weighing the
empty and filled syringe on a Sartorius balance
and calculating the volume from the weight
divided by specific gravity. The total activity in
the injection was then calculated. Since this
method to quantify the injection involved count-
ing samples of markedly different geometries, the
following experiment was done to validate the
method. The same volume of the suspension used
in our study (0.4 ml) was drawn into a small
plastic syringe. The syringe was counted 10
inches above the crystal. The contents of the
syringe were then expressed into a test tube. The
empty syringe was then counted 10 inches above
the crystal and again counted in the well of the
same scintillation counter, and the ratio of counts
of the empty syringe in the well to that 10 inches
above the crystal was obtained. The product of
this ratio and the counts of injection in the full
syringe gave the total activity of the injection.
The counts determined by this method agreed
within 2% with the aliquot method. Thus geometry
was eliminated as an important variable in the
quantification of the injection.

Since a large number of spheres adhered to the
sides of the disposable syringe and to a far lesser
to the sides of the injecting catheter, the
total activity delivered to the animal was
determined as follows. After the catheter into
which a known quantity of spheres had been
injected was flushed, the fluid in the catheter was
withdrawn and was placed directly into the
scintillation counter along with the injecting
syringe. The counts obtained were subtracted
from the counts in the original injection to give
the total activity injected into the animal. Since
microspheres tended to settle quickly in the
dextran, they were administered immediately
after mixing.

After all the catheters were in place and blood
pressure stabilized, approximately 8µc of $^{169}$Yb-
labeled microspheres were injected into the left
ventricle over a 10-second interval. The injecting
catheter was flushed with saline. Then the animal
was bled acutely through the femoral artery
catheter to lower the mean arterial pressure to
50–65 mm Hg over 10 minutes. The animal’s
blood pressure was allowed to stabilize at these
hypotensive levels before approximately 8µc
$^{85}$Sr-labeled spheres were administered. There-
after the kidneys were removed, weighed and
decapsulated. The renal cortex (C) was separat-
ed from the medulla with a scalpel and was
divided into an outer two-thirds designated (OC)
and inner one-third (IC). These tissue slices were washed, weighed, and counted in a well scintillation counter. In addition, the remainder of each kidney was counted.

Both 169Yb and 85Sr are gamma-emitting radionuclides. 169Yb has a complex spectrum with most of its energy below 308 keV. 85Sr has an energy peak of 513 keV. Using gamma ray spectrometry, the amount of radioactivity for each isotope in each tissue could be determined (8). The quantity of 169Yb and 85Sr spheres in each tissue slice is a function of tissue blood flow, since they will be distributed in proportion to their share of cardiac output. The ratios of activity (OC/IC, OC/C, and IC/C) for the 169Yb spheres were compared to the same ratios of activity for the 85Sr spheres. Differences represent changes in the proportion of blood flow to each of these regions after hemorrhage. In addition, the amount of radioactivity of each isotope in each tissue slice was divided by the total administered activity of that isotope. This fraction was multiplied by the cardiac output to obtain blood flow to that tissue.

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<td>OC/C</td>
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<tr>
<td>IC/C</td>
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FIGURE 1
Change in outer cortical to inner cortical (OC/IC), outer cortical to cortical (OC/C), inner cortical to cortical (IC/C) ratios before and after hemorrhage in three groups of dogs with femoral, carotid or brachial artery catheter for microsphere administration. The broken line represents mean value.

**RESULTS**

**INTRARENAL DISTRIBUTION OF BLOOD FLOW AFTER HEMORRHAGE**

Acute hypotensive hemorrhage changed the blood flow pattern within the dog kidney as illustrated in Table 1 and Figure 1. In the dogs with the brachial artery catheter, the mean OC/IC of 2.25 before hemorrhage fell to 0.88 after hemorrhage (P < 0.001). The OC/C fell from 1.28 to 0.95 (P < 0.025), and IC/C increased from a mean of 0.53 to 1.40 (P < 0.01). The mean outer cortical flow fell significantly from 6.62 ± 1.02 (SE) ml g⁻¹ min⁻¹...
<table>
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<th>Dog No.</th>
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<th>WK (ml/min)</th>
<th>WK (ml g⁻¹ min⁻¹)</th>
<th>C (ml g⁻¹ min⁻¹)</th>
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<th>IC (ml g⁻¹ min⁻¹)</th>
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<td>86 ± 11.3</td>
<td>8.3 ± 0.7</td>
<td>143 ± 22</td>
<td>3.84 ± 0.41</td>
<td>5.32 ± 0.98</td>
<td>6.62 ± 1.02</td>
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<td>4.4 ± 0.9</td>
<td>35 ± 10</td>
<td>0.92 ± 0.23</td>
<td>2.23 ± 0.60</td>
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<td>P (change from control)</td>
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</table>

\( AP = \) mean arterial pressure; \( CO = \) cardiac output; \( WK = \) whole kidney flow; \( C = \) cortical flow; \( OC = \) outer cortical flow; \( IC = \) inner cortical flow.

\( P < 0.005 \) \( P < 0.05 \) \( P < 0.025 \) \( P > 0.25 \)
to $2.20 \pm 0.65$ ml g$^{-1}$ min$^{-1}$ after hemorrhage ($P < 0.025$). The mean inner cortical flow fell only slightly from $3.14 \pm 0.74$ to $2.60 \pm 0.54$ ml g$^{-1}$ min$^{-1}$ ($P > .25$). Thus acute hypotensive hemorrhage caused a redistribution of intrarenal blood flow characterized by a marked reduction in outer cortical flow with relative preservation of inner cortical blood flow.

**EFFECT OF INJECTION SITE ON INTRARENAL BLOOD FLOW DISTRIBUTION**

Tables 1 and 2 summarize the findings in two groups of dogs: in one the microsphere-injecting catheter was inserted in a brachial artery, and in the other in a carotid artery. The mean arterial pressure, cardiac output, total renal blood flow, and percent of cardiac output per kidney are almost identical before and after hemorrhage in both groups of dogs. Dog 4 (Table 1) had a large hematoma around his right femoral artery as a result of traumatic catheterization. The cardiac index was thus much lower than for the rest of the dogs in that group.

The mean cortical blood flow rates in both groups of dogs are almost identical both before and after hemorrhage. The mean flows to the outer and inner cortex however were quite different. Before hemorrhage, the dogs with the carotid artery catheter had a lower mean flow rate to the outer cortex ($5.95 \pm 0.14$ ml g$^{-1}$ min$^{-1}$) and a higher mean inner cortical flow ($4.94 \pm 0.84$ ml g$^{-1}$ min$^{-1}$) compared to those with the brachial artery catheter. With hemorrhage there was a significant reduction in mean flow to both the outer and inner cortex ($2.48 \pm 0.30$ and $1.94 \pm 0.28$ ml g$^{-1}$ min$^{-1}$, respectively; $P < 0.05$), which contrasts with the finding of a relative preservation of inner cortical flow when the microspheres are administered via a brachial artery catheter.

Figure 1 also demonstrates the effect of hemorrhagic shock on intracortical blood flow distribution. The results from a previous study in this laboratory in which the femoral artery was catheterized are included (8). When the femoral or brachial artery was used to administer the microspheres, the OC/IC,
TABLE 3

Effect of Unilateral Carotid Artery Catheterization on Intrarenal Blood Flow Distribution in Normal Anesthetized Dogs

<table>
<thead>
<tr>
<th></th>
<th>OC/IC</th>
<th>OC/C</th>
<th>IC/C</th>
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<tr>
<td>Brachial</td>
<td>2.25</td>
<td>1.28</td>
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<td>Carotid</td>
<td>1.28</td>
<td>1.07</td>
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<tr>
<td><em>P</em> &lt;</td>
<td>0.001</td>
<td>0.02</td>
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</table>

Abbreviations are the same as in Table 1.

OC/C, and IC/C changed significantly after acute hypotensive hemorrhage. The group undergoing carotid artery catheterization (compared to the other two groups) showed a significant difference in all three ratios even before hemorrhage (Table 3). However, the dogs with the carotid artery catheter showed no further significant change in these ratios after hemorrhage (*P* > 0.50). Thus carotid artery catheterization resulted in redistribution of blood flow before hemorrhage in the same direction as the alteration in renal hemodynamics after hemorrhage.

COMPARISON OF THE MICROSPHERE AND ^183^Xe WASHOUT TECHNIQUES

The results of this study are illustrated on Table 4. The mean whole kidney blood flow before hemorrhage was not significantly different using these two techniques. Component I flow of the xenon washout curve of 3.88 ± 0.37 ml g⁻¹ min⁻¹ was comparable to the flow rate of 4.59 ± 0.49 ml g⁻¹ min⁻¹ to the whole cortex measured by microsphere technique. Outer cortical flow of 5.35 ± 0.59 ml g⁻¹ min⁻¹ was significantly greater than component I flow (*P* < 0.05). Component II flow of 1.41 ± 0.10 ml g⁻¹ min⁻¹ was significantly lower (*P* < 0.01) than flow to any portion of the cortex measured by the microsphere method.

After hemorrhage, component I flow did not differ significantly from flow to either the outer or inner cortex. Component II flow was still significantly lower than outer cortical flow (*P* < 0.05), but did not differ significantly from inner cortical flow.

Dog 2 was excluded from the posthemorrhage calculations because the xenon-injecting catheter slipped out of the renal artery after hemorrhage and the second microsphere injection. Bleeding around the renal artery and vasospasm induced by reinsertion of this catheter resulted in low flow rates as measured by the xenon washout method. This case was included because it demonstrated that severe reductions in flow can result in a monoexponential curve to replace the first two components of the xenon washout curve. This phenomenon has been observed by other workers (3, 4, 12).

In accord with the findings of previous investigators (3, 4, 12), the fraction of total radioactivity in component I fell after hemorrhage while that in component II increased. In contrast with these previous results, component I flow fell significantly within 30 minutes after stabilization of the blood pressure at hypotensive levels in three out of four dogs. The only dog (dog 1) with no change in the flow rate to component I in the early stages of shock had a brachial artery catheter for microsphere administration. In the other three dogs the catheter was inserted into the carotid artery.

Discussion

Recent studies have validated the use of radioactive microspheres to measure intracortical distribution of renal blood flow (8, 9). They have not previously been used to study the changes in intrarenal hemodynamics during acute hypotensive hemorrhage. However, considerable evidence has now accumulated to validate their use even in shock. In shock no arteriovenous shunts within the kidney have been demonstrated (13), and thus virtually all spheres entering the kidney are completely trapped in glomerular tufts or afferent arterioles (8, 9). Changes in renal perfusion pressure of 140 to 40 mm Hg per sec did not alter the intrarenal distribution of spheres, suggesting that there is no significant axial migration of microspheres within the kidney over a wide range of perfusion pressures (9). Finally, in this study flows measured both before and after hemorrhage by microsphere method correlated well with those measured by the ^183^Xe washout method. However, this comparison of flow rates must be made with
TABLE 4
Comparison of the Microsphere and $^{133}$Xe Washout Techniques for Determination of Renal Blood Flow

<table>
<thead>
<tr>
<th>Dog</th>
<th>AP (mm Hg)</th>
<th>CO (ml/kg)</th>
<th>% CO (per kidney)</th>
<th>WK Spheres</th>
<th>WC</th>
<th>OC</th>
<th>IC</th>
<th>WK Xenon</th>
<th>Co I (ml g$^{-1}$ min$^{-1}$)</th>
<th>Co II (%) total radioactivity</th>
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<td>1</td>
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Before Hemorrhage

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<th>Dog</th>
<th>AP (mm Hg)</th>
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<th>% CO (per kidney)</th>
<th>WK Spheres</th>
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<td>0.9</td>
<td>0.11</td>
<td>0.48</td>
<td>0.68</td>
<td>0.52</td>
<td>0.33</td>
<td>0.60</td>
<td>0.28</td>
</tr>
</tbody>
</table>

After Hemorrhage

Co I and Co II = components I and II. Other abbreviations are the same as in Table 1.
LOGAN, JOSE, EISNER, LILIENTHFIELD, SLOTKOFF

some reservations since tissue volumes are not exactly the same. The xenon washout method measures flow through a dynamic kidney volume, whereas the microsphere method expresses flow rates in ml per unit drained kidney volume.

In the normal anesthetized dog, flow to the whole cortex as measured by microspheres correlated well with component I flow. Outer cortical flow was significantly higher than component I flow, and inner cortical (juxtamedullary) flow was significantly higher than component II flow. Since it has been shown by autoradiography that component I represents the entire cortex, and component II, the outer medulla (3), these two methods appear to measure flow through similar regions within the kidney. Blood flow to the inner cortex would be significantly higher than outer medullary flow (component II flow) since a portion of its flow supplies the juxtamedullary peritubular capillary system rather than entering the vasa recta in the outer medulla (14).

The anatomical location of the various components of the $^{133}$Xe washout curve changes after hemorrhage (3). Component I, the rapid component, becomes localized to the deeper portion of the cortex and component II represents flow through the outer medulla as well as portions of the outer cortex. Occasionally, as seen in one of our posthemorrhage xenon washout curves, a fast component can no longer be identified, and a single exponential defines the flow rate in the entire cortex and outer medulla. In our study, flow to the whole cortex as well as to the outer and inner cortex as measured by the microsphere method were very similar. In addition, component I flow was no longer significantly different from flow to either the outer or inner cortex. Furthermore, component II flow was not significantly less than inner cortical flow. These results support the findings of Carriere et al. that the volume of cortex perfused at a rapid rate is markedly diminished and that much of the cortex is perfused at a slower rate (3). The small areas in the cortex with the rapid flow rates as defined by $^{133}$Xe method could not be identified by the microsphere technique. This is probably the result of inclusion in the tissue slices of regions with high and low flow rates, and the resultant flow in any tissue slice represents an average of all these different flow rates. The microsphere technique, unlike the $^{133}$Xe method, has the advantage of being able to measure flow through the same regions of the cortex in different physiological states. This is particularly important in light of recent evidence indicating functional differences between superficial cortical nephrons arising in the outer two thirds of the cortex and juxtamedullary nephrons occupying the inner third of the cortex (15-18).

Most studies have shown that in the anesthetized dog renal blood flow is reduced even in the early stages of acute hemorrhagic shock (19-21). Our results are consistent with these findings. However, Kaihara et al., using microspheres of 50 $\mu$m in diameter, found an inconsistent reduction in total renal blood flow in the early stages of shock (22). The only major difference in their protocol from our study was the microsphere diameter. They used microspheres 50 $\mu$m in diameter and ours were 15 $\mu$m. The importance of this factor in explaining the different results is unknown. However, Phibbs et al. have shown that microspheres 50 $\mu$m in diameter tended to have an axial distribution in the rabbit femoral artery (23).

Although most investigators agree that flow to the outer cortex is reduced after acute hypotensive hemorrhage (1-4, 12), the changes in medullary flow are still controversial. Kramer, using the photoelectric technique, found inner medullary flow to be markedly reduced during hypotension in approximately the same proportion as superficial cortical blood flow (2). He did not however measure inner cortical or outer medullary flow. Using radioactive $^{85}$Kr washout curves, Carriere et al. found outer medullary blood flow to be relatively unchanged after stabilization of blood pressure at 50 mm Hg, whereas outer cortical flow fell drastically (3, 12). These findings were
confirmed using $^{133}$Xe washout curves (4). Furthermore, our study also demonstrated a similar change in intrarenal hemodynamics in shock when carotid artery manipulation was avoided. Our results, although agreeing with the washout studies, did not agree with the findings of Aukland and Wolgast (1). They found no selective preservation of juxtamedullary flow, and concluded that there was a parallel reduction of cortical and medullary blood flow in shock. In their study, a wide-bore cannula was inserted into the right carotid artery. Our study demonstrated that this manipulation may have influenced their results. When we catheterized a carotid artery to administer microspheres, blood flow within the kidney was redistributed. With hemorrhage, there was a parallel reduction in outer cortical and juxtamedullary flow, as found by Aukland and Wolgast (1). These findings contrast sharply with the selective preservation of juxtamedullary flow in shock when carotid artery manipulation was avoided. There is some indirect evidence to suggest that carotid artery cannulation might increase renal sympathetic nerve activity. Pressure reduction in an isolated carotid sinus will increase the frequency of renal sympathetic nerve discharge (7), which in turn would redistribute blood flow within the kidney (5).

Our $^{133}$Xe studies also revealed that carotid artery manipulation altered the renal vascular response to hemorrhage. Carriere et al. showed that component I flow rate was essentially the same in the normotensive and hypotensive states, although the size of this compartment during hypotension was markedly reduced (3, 12). In contrast, in our study component I flow was markedly reduced in the first 30 minutes after hemorrhage in every dog with a carotid artery catheter. The only dog with no change in flow rate to component I in this period had a brachial artery catheter for microsphere administration. Thus the results using the $^{133}$Xe washout method support our microsphere findings.

In conclusion, this study demonstrates that juxtamedullary blood flow is relatively well preserved in the early stages of shock. This could account for the observed loss of concentrating ability of the kidney in shock (21). In addition, redistribution of cortical blood flow as a governing mechanism for salt balance has recently been emphasized (5, 16-18). Thus the selective preservation of juxtamedullary blood flow and, presumably, glomerular filtration rate in nephrons with a high resorptive capacity for sodium and water would serve to restore homeostasis in hemorrhagic states.

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