

Mechanism of the Redistribution of Renal Cortical Blood Flow during Hemorrhagic Hypotension in the Dog

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ABSTRACT Studies were performed to define the mechanisms involved in the redistribution of renal cortical blood flow to inner cortical nephrons which occurs during hemorrhagic hypotension in the dog. The radioactive microsphere method was utilized to measure regional blood flow in the renal cortex. Renal nerve stimulation decreased renal blood flow 40% but had no effect on the fractional distribution of cortical blood flow. Pretreatment with phenoxybenzamine, phentolamine, propranolol, or atropine did not alter the redistribution of cortical flow during hemorrhage. A reduction in renal perfusion pressure by aortic constriction caused a qualitatively similar alteration in regional blood flow distribution as occurred during hemorrhage. When perfusion pressure was kept constant in one kidney by aortic constriction followed by hemorrhage, no redistribution occurred in the kidney with a constant perfusion pressure while the contralateral kidney with the normal perfusion pressure before hemorrhage had a marked increase in the fractional distribution of cortical flow to inner cortical nephrons. Additionally, retransfusion had no effect on the fractional distribution of flow in the kidney in which perfusion pressure was maintained at the same level as during hemorrhage while in the contralateral kidney in which pressure increased to normal there was a redistribution of flow to outer cortical nephrons. These studies indicate that the redistribution of renal cortical blood flow which occurs during hemorrhage is not related to changes in adrenergic activity but rather to the intrarenal alterations which attend a diminution in perfusion pressure.

INTRODUCTION

Recent studies from this and other laboratories have demonstrated that hemorrhagic hypotension is associ-

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ated with a marked decrease in the fractional distribution of renal cortical blood flow to outer cortical nephrons (1-3). This alteration in intrarenal hemodynamics may be related to one or more of the following changes known to occur during hemorrhage: (a) increased humoral release of norepinephrine (4), (b) increased humoral release of angiotensin (5), (c) enhanced adrenergic stimulation (6), and (d) diminished renal perfusion pressure. Conflicting results have been obtained in trying to define which of these mechanisms is primarily responsible for the redistribution during hemorrhage. It had previously been shown with the inert gas washout technique that both norepinephrine and angiotensin cause a marked decrease in outer cortical blood flow (7, 8). Since both pressors are markedly increased in hemorrhage (4, 5), it might be construed that the redistribution of cortical blood flow in this model is due to the increased humoral release of either or both agents. In contrast, recent studies from this laboratory using the radioactive microsphere method demonstrated no alteration in regional flow in renal cortex during the administration of either norepinephrine or angiotensin (1). Further conflicting results have been obtained on the effectiveness of alpha adrenergic blockade in altering the pattern of renal cortical flow during hemorrhage. Grandchamp, Veyrat, Rosset, Scherrer, and Truniger (9) found that phenoxybenzamine almost totally reversed the flow distribution during hemorrhage, while Carrière and Daigneault (10), using even higher doses of the alpha blocking agent, found essentially the same pattern of redistribution as occurred during hemorrhage alone. McNay and Abe (11) noted that aortic constriction caused a decrease in the fractional distribution of flow to outer cortical nephrons. What relevance this may have to the findings during hemorrhage is not clear. Therefore, studies were designed to systematically evaluate the possible role of enhanced adrenergic activity and diminished perfusion pressure on the redistribution of

renal cortical blood flow during hemorrhage. In addition, since cholinergic agents such as acetylcholine have been shown to cause a similar pattern of distribution of cortical blood flow as occurs during hemorrhage (12, 13), the effect of cholinergic blockade during hemorrhage was studied. The results of these studies indicate, in contrast to previous data (9), that a diminution in renal perfusion pressure is the primary factor responsible for the redistribution seen in hemorrhagic hypotension.

METHODS

Fasted mongrel dogs (14–25 kg) were anesthetized with pentobarbital (25–30 mg/kg) and given additional doses as needed during the experiment. An endotracheal tube was inserted and the animals were ventilated with a Harvard respirator (Harvard Apparatus Co., Inc., Millis, Mass.). A cannula was inserted in the femoral artery for blood pressure measurement and blood collection. Animals whose control mean arterial blood pressures were less than 100 mm Hg were not utilized. A Goodale-Lubin standard wall catheter was placed in the left ventricle by retrograde threading from either the left common carotid artery or femoral artery. As noted previously, no difference in results were noted with the two methods of placement (1). The left kidney was exposed through a left retroperitoneal flank incision, and in the appropriate studies a 23 gauge hooked needle was placed in the orifice of the left renal artery. Total renal blood flow was measured with an electromagnetic flowmeter (Medicon M-4001, Mediconics International Inc., Waco, Texas). Zero flow base line was determined by a brief occlusion of the renal artery distal to the flow probe. At the conclusion of the experiment, the flow probe was calibrated by *in situ* perfusion.

Radioactive microspheres $15 \pm 5 \mu\text{m}$ in diameter (3M Company, St. Paul, Minn.) were used to measure regional blood flow in different areas of the renal cortex. The nuclides used were ^{86}Sr and ^{141}Ce . Approximately 400,000 microspheres ($15\text{--}20 \mu\text{Ci}$) were given. The appropriate nuclide to be given was suspended in a 1 ml solution of 10% dextran, injected through the left ventricular catheter in approximately 10 s, and then flushed with 5 ml of heparinized saline. The kidneys were removed, sectioned, and counted by methods previously described (12). The cortex was divided into four zones which will be called zones 1–4, going from outer to inner cortex, respectively.

Five series of experimental procedures were performed:

Group I. Renal nerve stimulation studies

In eight studies, the nerves entering the area of the renal artery and vein were dissected free and platinum electrodes were placed on the transected distal portion about 1 cm proximal to the renal artery orifice. The nerves were then stimulated with a Grass stimulator (Grass Instrument Co., Quincy, Mass.) at 6–10 V, 3 msec, 2 mA, and 10 pulses per s. The distribution of blood flow was determined before and 20–30 min after the initiation of renal nerve stimulation.

Group II.

In this group the effect of autonomic blocking drugs on the distribution of intrarenal blood flow during hemorrhagic hypotension were evaluated. The first microsphere injection was given just before drug administration. After the blocking agent had been infused the animal was bled into a

reservoir bottle to a mean blood pressure of 60–70 mm Hg and maintained at this level by adjustment of the height of the bottle. The second microsphere injection was given 30 min after a stable hypotensive pressure had been established. Four groups of animals were studied.

A. Phenoxybenzamine studies. In seven studies, after the control microsphere injection, phenoxybenzamine, 1 mg/kg, was given in the left renal artery over a 20 min period. 15 min after the infusion had been completed, the hemorrhage period was begun.

B. Phentolamine studies. In seven studies, after the control microsphere injection, phentolamine $15 \mu\text{g/kg}$ per min was infused into the left renal artery for the remainder of the study. 30 min after the initiation of the infusion, the hemorrhage period was begun.

In both groups of studies, norepinephrine, $1 \mu\text{g}$, was given in the left renal artery before starting the infusion of the blocking agent and immediately before the bleeding was to begin. Only animals which demonstrated no decrease in renal blood flow during the second injection of norepinephrine were utilized. In addition, in four studies in each group there was no response to the test dose of norepinephrine at the conclusion of the hemorrhage period. Mean arterial pressure decreased 5–10 mm Hg during the infusion of either alpha blocking agent in approximately one-half of the experiments. However, there was no difference in the results of studies in which alpha blockade did or did not alter mean pressure before hemorrhage. In addition, in four studies performed with each of the alpha blocking drugs alone, there was no significant change in the distribution of cortical blood flow with either drug.

C. Propranolol studies. In seven studies, after the initial sphere injection, propranolol 0.4 mg/kg was infused in the left renal artery over a 20 min period. This dose prevented an increase in renal blood flow when isoproterenol $1 \mu\text{g}$ was given in the left renal artery. After the completion of the infusion the hemorrhage period was started.

D. Atropine studies. In six studies, atropine 0.1 mg/kg per min was infused in the left renal artery throughout the experiment. 30 min after the infusion had been started, there was no increase in renal blood flow after the intrarenal injection of $4 \mu\text{g}$ of acetylcholine. After this demonstration of cholinergic blockade, hemorrhage was begun.

There was no change in mean arterial pressure during the intrarenal infusion of either propranolol or atropine. In four additional studies performed with each drug, neither propranolol nor atropine altered regional blood flow.

Group III. Aortic constriction

In six studies left renal arterial pressure was reduced by means of an aortic clamp positioned between the two renal arteries. The degree of constriction was regulated by the pressure change noted from a femoral arterial cannula positioned just distal to the orifice of the left renal artery. Microsphere injections were given before and 30 min after aortic constriction. Special care was taken to prevent constriction of the contralateral renal artery.

Group IV. Hemorrhagic hypotension after aortic constriction

In seven studies, the left renal arterial pressure was reduced to 60–80 mm Hg by means of aortic constriction. The first microsphere injection was given 20–30 min after the initiation of aortic constriction. The aortic clamp was then removed and hemorrhage was induced in the same manner as in the Group II studies and maintained at a

TABLE I
Summary of Renal Nerve Stimulation Studies
n = 8

	Renal blood flow		Per cent distribution to cortical zone								Zonal perfusion rate							
			Zone 1		Zone 2		Zone 3		Zone 4		Zone 1		Zone 2		Zone 3		Zone 4	
	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E
	ml/min						%						ml/min per g					
Mean	181.0	108.0	40.7	42.6	30.9	30.9	19.0	18.2	9.4	8.3	6.1	3.9	5.6	3.4	4.5	2.5	3.1	1.6
SEM	14.8	12.5	1.7	2.6	1.0	1.0	0.6	1.2	1.0	1.1	0.6	0.7	0.5	0.5	0.4	0.3	0.3	0.2
P	<0.005		NS		NS		NS		NS		<0.005		<0.01		<0.005		<0.005	

Abbreviations: C, control period; E, experimental period; n, number of experiments.

pressure similar to that during aortic constriction. The second injection of microspheres was given 30 min after hemorrhage had been initiated.

Group V. Hemorrhage-retransfusion studies

In six studies, the animals were hemorrhaged in the manner described previously. The first injection of microspheres was given 30 min after the initiation of hemorrhage. The animals were then retransfused with their previously shed blood over a period of 20–30 min. As the animal was being retransfused, the left renal artery pressure was kept approximately at the hemorrhage level by aortic constriction. 20 min after the transfusion had been completed and left renal artery pressure had been stabilized at a level similar to that during hemorrhage, the second injection of microspheres was given.

CALCULATIONS

The method of calculating the corrected fractional distribution of renal cortical blood flow per cortical zone (P_z^1) and the absolute flow per zone, zonal perfusion rate, have been described previously (12).

Results are recorded as means \pm SEM. Statistical difference was determined by a paired *t* test.

RESULTS

Renal nerve stimulation. The results of these studies are summarized in Table I and Fig. 1 and are from the stimulated kidney. No sections were taken from the contralateral kidney. Renal blood flow decreased in each study with a mean change from 181 to 108 ml/min ($P < 0.005$) while systemic blood pressure was not significantly altered, indicating a marked increase in renal vascular resistance. However, there was no alteration in the fractional distribution of renal cortical blood flow in any zone during nerve stimulation. The control values of 40.7, 30.9, 19.0, and 9.4% were not significantly different from the experimental values of 42.6, 30.9, 18.2, and 8.3% in zones 1–4. Zonal perfusion rates in each zone decreased in a parallel fashion to the 40% decrease in total renal blood flow.

Autonomic blocking agent studies. The results of these four groups of studies are summarized in Table II and Fig. 2. The data listed is from the left kidney since

total flow was also obtained from this kidney, but similar distributional changes occurred on the contralateral side. In our previous study, a mean value of 30 ml/kg of blood was removed during hemorrhage (1). As would be expected, a smaller amount was removed in both groups of alpha blockade studies to reach the same level of hypotension while 40 ml/kg were removed in the beta blockade experiments. The fall in total renal blood flow during hemorrhage was 51, 42, 51, and 48% in the phenoxybenzamine, phentolamine, propranolol, and atropine groups, respectively, while systemic pressure decreased 54, 51, 52, and 47%, respectively, indicating essentially no change in renal resistance in any of the four groups. In addition, a marked redistribution of renal cortical blood flow occurred during hemorrhage which was qualitatively similar in the four group of studies. The mean absolute per cent decrease in outer cortical zone 1 ranged from 10.6 to 13.3% and was statistically significant in all groups. There was a more variable response in zone 2 with a small mean increase in all groups which were significant at the $P < 0.05$ level only in the phenoxybenzamine and propranolol studies. The increases in the per cent flow to zone 3 of 5.1, 6.4, 7.0, and 4.7% in the four groups were statistically significant. Also, in

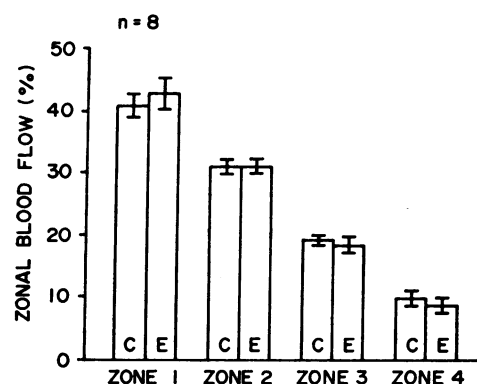


FIGURE 1 Effect of renal nerve stimulation on the fractional distribution of renal cortical blood flow. C, control period; E, experimental period.

TABLE II
Summary of Autonomic Blocking Agent Studies in Hemorrhagic Hypotension

Blocking agent	Blood pressure		Blood removed	Renal blood flow		Per cent distribution to cortical zone								Zonal perfusion rate							
	C	E		C	E	Zone 1		Zone 2		Zone 3		Zone 4		Zone 1		Zone 2		Zone 3		Zone 4	
						C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E
mm Hg		ml/kg	ml/min		%								ml/min per g								
Phenoxy-benzamine, N = 7																					
Mean	147.7	66.4	17.6	176.4	87.1	46.0	35.4	30.9	33.6	17.0	22.1	6.1	8.9	6.6	2.5	5.5	2.9	4.0	2.6	2.0	1.5
SEM	6.0	1.0	2.0	14.3	10.2	1.6	1.1	0.4	0.7	1.1	1.0	0.4	0.5	0.3	0.3	0.5	0.3	0.6	0.4	0.2	0.2
P	<0.001			<0.001		<0.005		<0.05		<0.005		<0.005		<0.001		<0.001		<0.025		<0.025	
Phentolamine, n = 7																					
Mean	134.0	65.6	18.3	178.6	104.3	42.7	29.4	32.5	33.9	18.0	24.4	6.8	12.3	7.4	2.9	6.9	4.2	4.9	3.9	2.7	2.8
SEM	8.6	1.4	2.3	13.4	9.2	2.4	1.6	1.8	0.6	0.6	1.0	0.4	1.2	0.8	0.3	0.7	0.3	0.3	0.2	0.2	0.3
P	<0.001			<0.001		<0.005		<0.05		<0.005		<0.005		<0.001		<0.001		<0.025		<0.026	
Propranolol, n = 7																					
Mean	138.3	65.7	40.3	181.4	87.9	45.9	33.4	33.0	35.4	16.0	23.0	5.1	8.2	7.2	2.6	6.2	3.3	3.9	2.7	1.8	1.4
SEM	5.2	0.7	4.0	9.0	8.1	1.8	1.0	1.1	0.8	1.0	1.1	0.5	0.6	0.5	0.3	0.3	0.3	0.2	0.2	0.2	0.2
P	<0.001			<0.001		<0.001		<0.05		<0.005		<0.01		<0.001		<0.001		<0.005		NS	
Atropine, n = 5																					
Mean	132.6	69.6	27.0	149.0	77.0	46.4	34.8	30.2	34.0	17.0	21.6	6.4	9.6	6.3	2.4	5.0	3.0	3.7	2.5	2.0	1.6
SEM	6.0	1.6	5.4	8.7	4.4	3.4	0.6	1.5	1.3	1.6	1.2	0.4	0.8	0.9	0.2	0.3	0.3	0.4	0.4	0.1	0.1
P	<0.001			<0.001		<0.05		NS		<0.05		<0.001		<0.05		<0.005		<0.05		NS	

Abbreviations: *n*, number of experiments; C, control period; E, experimental period.

inner cortical zone 4, there was a statistically significant mean increase in the fractional distribution of flow in all four groups of studies. Zonal perfusion rate decreased in all groups in zones 1-3, while in zone 4 there was a significant fall only in the phenoxy-benzamine studies. When the data from all 26 studies were combined, zonal perfusion rate was found to decrease 61, 43, 29, and 15% in zones 1-4, respectively, while total flow decreased 46%. The fall in zone 1 was significantly greater than the decrease in total blood flow ($P < 0.001$) while the change in zones three and four were significantly less than the fall in total flow ($P < 0.001$ for both). There-

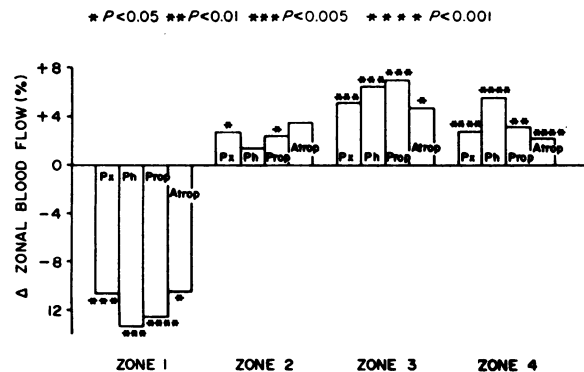


FIGURE 2 Effect of autonomic blocking agents on the fractional distribution of cortical blood flow during hemorrhage. The data presented is the absolute per cent change in zonal blood flow. Px, phenoxybenzamine; Ph, phentolamine; Prop, propranolol; Atrop, atropine.

fore, this data demonstrates a qualitatively similar change in the fractional distribution of renal cortical blood flow as was found during hemorrhage alone (1) and indicates that neither alpha, beta, nor cholinergic blockade has a significant effect on this alteration in regional blood flow.

Aortic constriction studies. The results of these six studies are summarized in Table III and Fig. 3. Renal artery pressure was decreased from 137 to 70 mm Hg, in association with a decrease in total renal blood flow from 180 to 140 ml/min. Therefore, blood flow was decreased by 22% in association with a 49% fall in pressure indicating a decrease in renal resistance and partial autoregulation. In addition, in each study there was a decrease in the fractional distribution of flow in outer cortical zone 1 and a concomitant increase in inner cortical zones 3 and 4. The changes in zones 1 and 4 were significant at the $P < 0.025$ level and at the $P < 0.005$ level in zone 3. In contrast, there was no significant change in the contralateral nonconstricted kidney. Zonal perfusion rate decreased 41% in zone 1 ($P < 0.025$) and 24% in zone 2 ($P < 0.005$) while there was no significant change in either inner cortical zones 3 and 4 during a reduction in renal perfusion pressure.

Aortic constriction-hemorrhage studies. The results of these seven studies are summarized in Table IV and Fig. 4. In these studies left renal perfusion pressure was diminished from 143 to 72 mm Hg in the control period. This resulted in a 25% fall in total renal blood flow from 198 to 148 ml/min ($P < 0.001$). The constriction was

TABLE III
Summary of Aortic Constriction Studies

Kidney	Perfusion pressure		Renal blood flow		Per cent distribution to cortical zone							
					Zone 1		Zone 2		Zone 3		Zone 4	
	C	E	C	E	C	E	C	E	C	E	C	E
	mm Hg		ml/min		%							
Right (<i>n</i> = 6)												
Mean	137	137	—	—	41.7	43.0	33.3	34.5	18.3	17.2	6.7	5.3
SEM	6	6	—	—	1.4	1.0	1.0	1.0	0.8	1.4	0.5	0.2
<i>P</i>	NS		—		NS		NS		NS		NS	
Left (<i>n</i> = 6)												
Mean	137	70	180	140	43.5	33.5	32.3	33.7	18.0	22.2	6.2	9.0
SEM	6	6	10	9	1.8	2.0	1.6	1.2	0.6	1.3	0.3	0.7
<i>P</i>	<0.001		<0.001		<0.025		NS		<0.005		<0.025	

Abbreviations: C, control period; E, experimental period; *n*, number of experiments.

removed and the animal was hemorrhaged to a mean pressure of 68 mm Hg which was not significantly different from the constriction value. During hemorrhage blood flow fell further to 109 ml/min which was significantly different from the constriction value ($P < 0.001$). However, in contrast to the previous findings during hemorrhage, there was no significant alteration in the fractional distribution of flow in any zone in the experimental kidney. In four studies, the contralateral non-constricted kidney was studied and demonstrated the same pattern of distributional changes as was found in hemorrhage. It is also of note that the per cent flow in outer cortical zone 1 in the experimental kidney during aortic constriction was consistently lower than that of the contralateral control kidney and that reciprocal changes were present in the inner cortical zones. Although fractional flow was unchanged during hemorrhage in the previously constricted kidney, the further fall in total renal blood flow was associated with a significant fall in zonal perfusion rate from 4.2 to 2.8, 5.0 to 3.5, 4.3 to 3.0, and 2.4 to 1.7 ml/min per g in zones 1–4, respectively ($P < 0.001$ in each).

Hemorrhage-retransfusion studies. A summary of these studies is given in Table V and Fig. 5. During hemorrhage blood pressure decreased from 141 to 68 mm Hg ($P < 0.001$) while blood flow decreased from 171 to 90 ml/min ($P < 0.001$). The animals were then retransfused and left renal artery pressure was kept at approximately the same mean pressure as during hemorrhage by aortic constriction. During retransfusion systemic pressure increased to 143 mm Hg while left renal artery pressure was maintained at 68 mm Hg. Renal blood flow increased to 129 ml/min which was significant at the $P < 0.001$ level when compared with the flow during hemorrhage. However, there was no change in the fractional distribution of flow in the left kidney

with a constant perfusion pressure. In contrast, in the contralateral kidney, retransfusion was associated with an increase in the fractional distribution of flow in outer cortical zone 1 from 33 to 45% ($P < 0.005$) and significant decreases from 23 to 17% in zone 3 ($P < 0.001$) and from 10 to 7% in zone 4 ($P < 0.001$). Although fractional distribution in the left kidney was unchanged, the increase in blood flow during retransfusion and aortic constriction was associated with a concomitant increase in zonal perfusion rate from 2.4 to 3.5 ($P < 0.001$), 2.7 to 4.1 ($P < 0.001$), 2.4 to 3.3 ($P < 0.005$), and 1.3 to 1.6 ml/min per g ($P < 0.01$) in zones 1–4, respectively.

DISCUSSION

In the present study, the radioactive microsphere method has been utilized to further evaluate the mechanisms responsible for the redistribution of renal cortical blood flow during hemorrhagic hypotension. This method has been extensively evaluated in this (12) and other laboratories (11, 14, 15) and felt to be a marker of glomerular

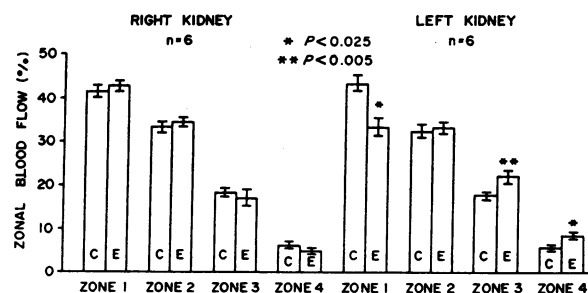


FIGURE 3 Effect of aortic constriction on the fractional distribution of renal cortical blood flow. Perfusion pressure was diminished in the left kidney. C, control period; E, experimental period.

TABLE IV
Summary of Aortic Constriction-Hemorrhagic Hypotension Studies

Kidney	Perfusion pressure			Renal blood flow			Per cent distribution to cortical zone							
							Zone 1		Zone 2		Zone 3		Zone 4	
	C	E ₁	E ₂	C	E ₁	E ₂	E ₁	E ₂	E ₁	E ₂	E ₁	E ₂	E ₁	E ₂
	<i>mm Hg</i>			<i>ml/min</i>			<i>%</i>							
Right (<i>n</i> = 4)														
Mean	147	147	67	—			45.0	33.5	32.5	35.0	17.0	21.5	5.5	8.5
SEM	7	7	3				2.7	1.9	2.2	0.4	0.4	0.5	0.5	1.3
<i>P</i>	<0.001*						<0.025		<0.05		<0.001		<0.05	
Left (<i>n</i> = 7)														
Mean	143	72	67	198	148	104	34.4	33.6	34.3	34.6	22.4	22.7	8.9	9.1
SEM	5	3	3	12	10	8	1.0	0.6	0.9	0.6	0.5	0.3	0.4	0.3
<i>P</i>	<0.001† NS*			<0.001† <0.001*			NS		NS		NS		NS	

Abbreviations: C, control period; E₁, aortic constriction period; E₂, hemorrhagic hypotension period; *n*, number of experiments.

* E₁ vs. E₂.

† Control vs. E₁.

perfusion rate. The main concern with this technique has related to the possible significance of axial streaming of the microspheres. Katz, Blantz, Rector, and Seldin (14) found that 30- μ m spheres had a greater concentration in outer cortical nephrons than the 15 μ m size, although no definite differences could be ascertained between 7 and 15 μ m beads. In contrast, McNay and Abe (11) found that the distribution of cortical blood flow was quite similar with microspheres of different size and density. We have shown in two models with similar alterations in the velocity of renal blood flow quite different effects on cortical flow distribution (1). Also, acetylcholine, an agent known to increase the velocity of flow through the kidney (16), caused a redistribution of renal cortical blood flow to inner cortical nephrons (12). Both of these findings are evidence against axial streaming being a predominant determinant of the distribution of the radioactive microspheres. Recently, Wallin, Rector, and Seldin (17) have described a method to measure cortical plasma flow utilizing radioactive antiglomerular basement membrane antibody (AGBM). Although in

three studies in the dog these authors noted a greater flow rate in the superficial cortex with the microsphere method than with the AGBM technique, this same group also found a similar alteration in the distribution of cortical flow during saline diuresis in the dog with the two methods (18). Although alterations in flow velocity may have some rheologic effect on the microspheres, the data obtained to date would suggest that the radioactive microsphere method is a valid index of the distributional changes which occur in a given experimental model.

The results of the present study using this technique indicate that the redistribution of renal cortical blood flow which occurs during hemorrhage is not functionally related to alterations in adrenergic or cholinergic activity. As is shown in Fig. 1 and Table I, renal nerve stimulation diminished total renal blood flow 40% but had no effect on cortical blood flow distribution. As we have recently reported, a similar effect occurs during the intrarenal infusion of subpressor doses of norepinephrine (1). These results suggest that both alpha adrenergic receptors and nerve fibers are evenly distributed throughout the vasculature of the renal cortex. However, this data seems to be at variance with previous results obtained during nerve stimulation (19). Pomeranz, Birtch, and Barger (19) using the krypton 85 washout method, noted that renal nerve stimulation induced either by bilateral carotid ligation or splanchnic nerve stimulation in anesthetized dogs decreased outer cortical flow and increased inner cortical and medullary flow. Although it is possible that the apparent differences in these two studies may be related to the magnitude of renal nerve stimulation, the decrease in renal blood flow of 33% in the splanchnic stimulation studies of Pomeranz et al. (19) is quite similar to the 40% fall found in the present studies. It is more likely that these apparently divergent

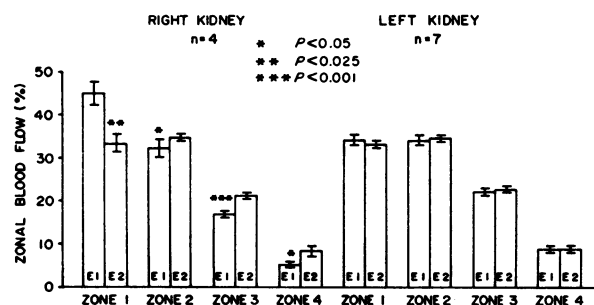


FIGURE 4 Summary of aortic constriction-hemorrhage studies. Perfusion pressure was kept constant in the left kidney. See text for description of periods E₁ and E₂.

TABLE V
Summary of Hemorrhagic Hypotension-Retransfusion Studies

Kidney	Perfusion pressure			Renal blood flow			Per cent distribution to cortical zone							
							Zone 1		Zone 2		Zone 3		Zone 4	
	C	E ₁	E ₂	C	E ₁	E ₂	E ₁	E ₂	E ₁	E ₂	E ₁	E ₂	E ₁	E ₂
	<i>mm Hg</i>			<i>ml/min</i>			<i>%</i>							
Right (<i>n</i> = 5)														
Mean	141	68	143	—			33.0	44.8	33.8	31.4	23.0	17.0	10.2	6.8
SEM	4	2	4				1.6	1.1	1.2	1.5	0.4	0.5	0.9	0.7
<i>P</i>	<0.001*		<0.001†				<0.005		NS		<0.001		<0.001	
Left (<i>n</i> = 6)														
Mean	141	68	68	171	90	129	35.7	36.0	33.7	34.7	22.0	21.8	8.6	7.5
SEM	4	2	2	11	7	10	1.1	1.2	0.8	1.0	0.5	0.7	0.5	0.4
<i>P</i>	<0.001*		NS†	<0.001*		<0.001†	NS		NS		NS		NS	

Abbreviations: C, control period, E₁, hemorrhage period, E₂, retransfusion period; *n*, number of experiments.

* Control vs. E₁.

† E₁ vs. E₂.

findings are due to theoretical and semantic differences between the two methods utilized. The outer cortical component of the inert gas washout method (C₁), is approximately equivalent to zones 1-3 of the sphere method. Therefore, the fall in C₁ during nerve stimulation is quite compatible with the marked fall in total flow in zones 1-3 obtained in the present study (Table I). In contrast, the results obtained with the two methods for inner cortical flow are seemingly contradictory. However, the relationship between inner cortical zone 4 flow of the sphere method and outer medullary flow (C₂) of the gas technique is less clear. Slotkoff, Logan, Jose, D'Avella, and Eisner (15) could not correlate C₂ flow with any specific anatomical area of the cortex and questioned the validity of the use of this component in analyzing regional blood flow in the kidney. In addition, since the sphere method measures glomerular blood flow while the inert gas technique is an index of peritubular capillary flow, it is possible because of the anatomical arrangement of the postglomerular circulation of juxta-medullary nephrons (20) that the flow patterns which each method measures may not be altered in a parallel fashion. In any case, using a direct index of glomerular perfusion rate, we find that renal nerve stimulation of a magnitude which decreased total renal flow 40% was associated with a parallel decrease in blood flow in all four cortical zones, a finding quite contrary to the alteration in intrarenal blood flow which occurs during hemorrhage.

As is shown in Table II and Fig. 2, neither phenoxybenzamine nor phentolamine blocked the redistribution of renal cortical blood flow during hemorrhage. Previous evaluation of these agents during hemorrhage has yielded conflicting results (9, 10). Carrière and Daigault (10) noted no effect of phenoxybenzamine on regional distribution or total blood flow during hemorrhage

while Grandchamp et al. (9), found a reversal of the distributional pattern during hemorrhage after the administration of the same agents. These disparate results are especially surprising since both studies utilized the inert gas method to measure regional blood flow. Although the reasons for these differences are not clear, we can only conclude from our microsphere data, which is in agreement with the work of Carrière et al. (10), that alpha blockade does not alter the redistribution of renal cortical blood flow which occurs in this model of hemorrhage. A similar failure to alter the distributional pattern during hemorrhage was found during beta and cholinergic blockade. Also, neither norepinephrine (1) nor renal nerve stimulation mimics the effect of hemorrhage. We, therefore, have no evidence that an alteration in the adrenergic or cholinergic nervous system is the primary factor involved in the distributional changes which occur during hemorrhage.

McNay and Abe (11) have previously demonstrated that aortic constriction decreases the fractional distribution of renal cortical blood flow to outer cortical nephrons and conversely increases the per cent flow to the

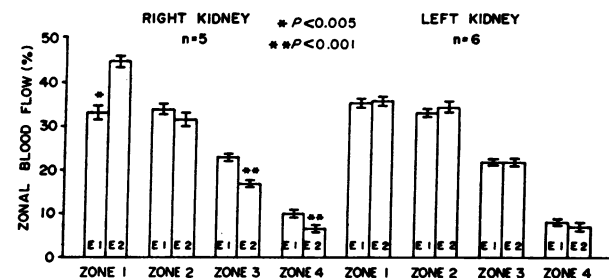


FIGURE 5 Summary of hemorrhage-retransfusion studies. Perfusion pressure was kept constant in the left kidney. See text for description of periods E₁ and E₂.

inner cortex. The present results confirm and extend these findings. Since it is possible that the effect of a unilateral decrease in renal perfusion pressure could be bilateral if it was related to the release of some humoral substance such as a prostaglandin (21), we also evaluated the contralateral nonconstricted kidney. As is shown in Table III and Fig. 3, there was no effect in the normal kidney while a marked redistribution occurred in each study in the kidney with a diminished perfusion pressure. This would suggest that the redistribution in this model is due to a local intrarenal event and independent of the release of some humoral substance. In addition, it should be noted that the redistribution which occurred during aortic constriction was quite similar to the pattern during hemorrhage.

Two further groups of studies were then performed to evaluate the effect of hemorrhage in a kidney with a constant perfusion pressure. In the first group shown in Table IV and Fig. 4, the perfusion pressure was lowered in the control period by aortic constriction. The constriction was then removed and the animal was hemorrhaged to approximately the same pressure as during aortic constriction. No redistribution occurred during hemorrhage in the experimental kidney while the usual pattern occurred in the nonconstricted kidney. In a second group of studies, the dogs were hemorrhaged and then retransfused with renal perfusion pressure in one kidney kept constant by aortic constriction. Again, there was no redistribution in the kidney with constant perfusion pressure while the kidney with the increased perfusion pressure during retransfusion had a redistribution of renal cortical blood flow to outer cortical nephrons.

This data suggests that the redistribution of renal cortical blood flow which occurs in this model of hemorrhage is related in some manner to the local intrarenal events which attend a diminution in perfusion pressure. It is well known that a decrease in renal perfusion pressure will lead to a decrease in renal resistance and tend to maintain renal blood flow constant (autoregulation). Although autoregulation was not perfect in these hypotensive dogs during aortic constriction at a mean pressure of 70 mm Hg, renal blood flow was decreased only approximately 22% while perfusion pressure decreased 49%, indicating a decrease in renal resistance. During hemorrhage, perfusion pressure and blood flow fell in a parallel fashion, 52 and 48%, respectively, and renal resistance was essentially unchanged (Table II). Previous investigators have also shown no change or even a slight decrease in renal resistance in the first 30 min after the induction of hemorrhagic hypotension (22, 23). This constancy of renal resistance may be due to the combination of persistent autoregulatory mechanisms counterbalanced by the release of vasoconstrictor substances either systemically or locally. Stein, Ferris, Huprich,

Smith, and Osgood (12, 24), McNay and Abe (13), and Bay, Stein, Rector, Osgood, and Ferris (25) have demonstrated that the administration of acetylcholine, bradykinin, furosemide, and ethacrynic acid as well as elevation of ureteral pressure are all associated with a similar pattern of redistribution as occurred during hemorrhage. The common denominator of these models is a decrease in renal resistance. In the context of the present data, the decrease in renal perfusion pressure would cause renal vasodilatation and the pattern of cortical distribution noted with this hemodynamic alteration. However, autoregulation would be set at a lower level or even obviated at any given perfusion pressure because of the release of norepinephrine and angiotensin and/or enhanced sympathetic nerve stimulation, all factors which increase renal resistance but have no effect on cortical blood flow distribution. Supportive evidence for this hypothesis is shown in the data in Table IV. When compared to the aortic constriction values, hemorrhage decreased total renal blood flow further to 104 ml/min, with no change in the fractional distribution of flow. Therefore, hemorrhage increases renal resistance but has no effect on the distribution of cortical blood flow in a kidney previously vasodilated by aortic constriction.

Although a definite mechanism has not been established, there are at least two possible explanations for the alterations in resistance at different levels of the renal cortical vasculature which occurs when total renal resistance is decreased. First, since renin is predominantly located in outer cortical nephrons (26) it is possible that renal vasodilatation may, in some manner, stimulate the local release of renin and lead to a preferential decrease in the distribution of flow to outer cortical nephrons. If it can be assumed that renal venous renin release is a reasonable marker of the local concentration of this enzyme, then renin should be increased in all of the models of renal vasodilatation if this hypothesis were correct. However, renin release is decreased during saline loading (27) and is unchanged during the administration of acetylcholine (28), both models of renal vasodilatation which we have shown to have a similar pattern of distribution of cortical blood flow as occurs during hemorrhage (12 and unpublished observations). Although both of these models may be exceptional or not adequately reflect local changes in the concentration of renin, these findings would make this hypothesis less attractive.

Second, the distributional pattern during renal vasodilatation may be due to intrinsic differences in the myogenic tone of the vasculature of different groups of cortical nephrons. We have found that absolute flow in outer cortical zone 1 remained constant in the various models of (decreased renal resistance associated with no change in renal perfusion pressure) (12, 24, 25). In addition, in

the present aortic constriction studies, as renal perfusion pressure was decreased 49% absolute flow in zone 1 decreased 41% while there was no change in total flow in inner cortical zones 3 and 4. These results suggest that resistance in outer cortical nephrons is relatively fixed and that flow is altered primarily as a function of perfusion pressure. In contrast, resistance in the more inner cortical nephrons is markedly decreased by maneuvers which decrease total renal resistance either at a constant or diminished perfusion pressure. This would indicate, in contrast to previous data (29), that the inner cortical nephrons are primarily responsible for the kidney's capacity to maintain flow constant at varying perfusion pressures.

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