Effect of Hemorrhage and Retransfusion on Intrarenal Distribution of Blood Flow in Dogs

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ABSTRACT Distribution of intrarenal blood flow was studied in 12 dogs anesthetized with Nembutal. Medullary blood flow was estimated by local clearance of hydrogen gas from the outer medulla measured polarographically with needle-shaped platinum electrodes, and by local clearance of ^{85}Kr and mean transit time of ^{32}P-labeled erythrocytes measured with a small semiconductor detector placed in the outer medulla. Cortical blood flow was estimated from cortical red cell transit time and from total renal blood flow measured by electromagnetic flowmeter.

Bleeding to a mean arterial pressure of 50–65 mm Hg in the course of 8–20 min reduced cortical and medullary blood flow on the average to the same extent. In half of the experiments both cortical and medullary blood flow were reduced proportionately less than mean arterial pressure during the first half hour of bleeding. Maintenance of mean arterial pressure at 50–65 mm Hg in all cases led to progressive reduction of both cortical and medullary blood flow, out of proportion to the reduction of arterial pressure. A two step bleeding procedure used in two experiments also led to uniform reduction of renal blood flow. Reinfusion of blood after 2–3 hr of hypotension increased total renal blood flow to an average of 82% and outer medullary hydrogen clearance to an average of 92% of control values. All dogs survived the experiment without evidence of renal failure.

It is concluded that hemorrhagic hypotension in dogs leads to a progressive and fairly uniform rise in renal vascular resistance, without any selective hemodynamic response in the juxtamedullary circulation.

A preliminary report of this work was presented at the Conference on the Microcirculation as related to Shock, Boston University, 30 March 1967.

Received for publication 19 September 1967 and in revised form 26 October 1967.

INTRODUCTION

In man and dog, renal blood flow falls markedly during hemorrhagic hypotension, according to most investigators, more than in proportion to the reduction of arterial pressure (1–4). Several studies also suggest a marked redistribution of intrarenal blood flow during bleeding. Thus, Trueta, Barclay, Daniel, Franklin, and Prichard (5) reported that rapid hemorrhage in rabbits led to almost complete cortical ischemia with "diversion of cortical blood flow" through the juxtamedullary circulation. Their conclusion was based on India ink injections and on angiography, but several later investigators using similar qualitative methods could not confirm their results. Recently, however, Carriere, Thorburn, O'Morchoe, and Barger (6) and Truniger, Rosen, and Oken (7) found by external recording of renal ^{85}Kr or ^{133}Xe clearance in dogs that medullary flow remained unchanged or even increased during bleeding to arterial pressure of 50 mm Hg. On the other hand, Kramer and Deetjen (8) found a greatly prolonged medullary transit time for albumin during hemorrhagic hypotension in dogs and concluded that medullary flow was reduced almost to the same extent as flow through the cortex.

These controversial findings led to the present study in which medullary flow was estimated from

local clearance of hydrogen gas from the outer medulla and also in some experiments by local medullary clearance of ^{85}Kr and transit time for ^{32}P-labeled erythrocytes. These methods, with their different sources of errors, all showed that a marked reduction of medullary blood flow occurred during bleeding, largely in proportion to the fall in total renal blood flow.

METHODS

Experiments were performed on 12 mongrel dogs weighing 16–27 kg. Anesthesia was induced by Nembutal i.v., 25 mg/kg, and maintained by additional doses of 1–2 mg/kg. The dogs had free access to water before the experiments, but no infusions were given during the experiments.

A polyethylene catheter was inserted into the aorta for pressure recording and blood sampling for hematocrit determination. Mean aortic pressure was measured by a Statham transducer (Statham Instruments, Inc., Los Angeles, Calif.) and recorded continuously on a Sanborn recorder (Sanborn Co., Waltham, Mass.). A wide bore cannula connected to a reservoir was tied into the right carotid artery. The right or left kidney was exposed retroperitoneally through a flank incision. The renal artery was dissected free, leaving the renal nerves intact. A polyvinyl tubing with an outer diameter of 0.4 mm was introduced into the renal artery, ad modum Herd and Barger (9), with the tip directed upstream.

Total renal blood flow was measured with a Nycotron electromagnetic flowmeter, type 372 (Nycotron, Oslo, Norway) and recorded on a Sanborn recorder. The 4 mm broad probe was placed oin the renal artery proximal to the renal arterial catheter. The probe size (gap diameter 3–4.5 mm) was chosen so as to provide firm fit without appreciable constriction of the artery. A few pressure measurements at normal renal blood flow revealed a pressure difference of 5–10 mm Hg between aorta and distal renal artery. Zero flow reading was checked at intervals of approximately 1 hr by occluding the renal artery with a snare. Readjustment was rarely necessary. The flow probes were calibrated directly on femoral or carotid arteries of similar size in other experiments.

Local hydrogen concentration in the kidney was measured principally according to Aukland, Bower, and Berliner (10) by needle-shaped platinum electrodes. Hydrogen oxidation current was measured with a six channel polarograph connected to a potentiometer recorder (Model B-64, Rikadenki Kogyo Co., Tokyo, Japan), permitting simultaneous recording from six electrodes (11). We insured minimal oxygen sensitivity by using a polarizing potential of + 0.2 v relative to a KCl-saturated calomel half cell, connected to the animal through a KCl-saturated agar bridge inserted subcutaneously (12). The electrodes used in 10 experiments had a bare pointed tip with a diameter at the base of 0.5–0.8 mm. In two experiments (dogs 11 and 12), the largest diameter was 0.1–0.2 mm. The length of the active platinum surface was 1–1.5 mm in both electrode types.

Three to five electrodes were tentatively inserted into the outer medulla, and the L-shaped shaft was sutured to the capsule (11). The position of each electrode was checked after the experiments by careful dissection of the excised kidney. Of 49 electrode insertions, 15 were excluded for the following reasons: nine were in connective tissue associated with calyces or interlobar or arcuate vessels, three were in the inner medulla, and three in the cortex. (The outer medulla was defined as the 4–5 mm, broad striated zone between the arcuate arteries and the white, homogeneous inner medulla.) These erroneous positions were usually predictable from the desaturation curves, but the decision to exclude electrodes was based only on the anatomical position. Seven accepted electrodes were inserted vertically from the convexity of the kidney, whereas the remaining 27 were inserted tangentially from the medial or lateral side of the organ. The latter way of insertion places the platinum tip parallel to the corticomedullary border, thus eliminating "vertical" electrode movements which might result from swelling or shrinking of the kidney. There was usually no macroscopical bleeding at the electrode site in the outer medulla, but fairly often some bleeding was observed along the electrode shaft in the cortex, and especially at the corticomedullary border.

Hydrogen was administered as follows. Pure hydrogen gas was first blown into the tracheal tube through a thin catheter at a rate providing an alveolar concentration of about 5%, corresponding to a partial pressure of about 40 mm Hg. A fairly stable current from the electrodes in the outer medulla was usually obtained in the course of 4–6 min, indicating equilibration of this tissue with arterial blood. Inhalation of hydrogen was then stopped and local arterial concentration maintained at a steady level for an additional period of 1–2 min by infusing 5–10 ml of hydrogen-saturated saline into the renal artery (Fig. 1). This procedure provides good equilibration of the outer zone (but not the inner zone) of the medulla, and also nearly instantaneous fall in renal arterial hydrogen concentration when the infusion is stopped. Inhalation of hydrogen did not influence total renal blood flow, whereas the intra-arterial infusion occasionally caused a transitory flow reduction of up to 10%.

The β-activity of ^{32}P and ^{85}Kr was measured with a 3 mm long lithium-drifted silicon crystal enclosed in a stainless steel tube with diameter of 1.5 or 2.0 mm and wall thickness of 0.05 mm (13). The pulses were amplified by a charge-sensitive amplifier (Tennelec, model 100B, Oak Ridge, Tenn.) and recorded on the Rikadenki recorder via a linear amplifier and a rate meter. The setup allowed simultaneous recordings from two detectors. The sensitivity for ^{32}P of the 1.5 mm detector was found to be 120 cps/μc per ml. The sensitivity for ^{85}Kr has not been determined, but is probably about one-third of that for ^{32}P. The 2 mm detector has a somewhat higher sensitivity. In the case of ^{32}P the monitored volume cor-

responds roughly to a sphere with a radius of 3 mm, whereas ^{85}Kr is monitored in a considerably smaller volume.

Two detectors were inserted into the kidney in each of four experiments, one usually tangentially into the middle cortex, and the other to varying depth in the outer medulla.

Erythrocytes were labeled by mixing 2 ml of blood with 0.2–0.5 ml of a citrate–phosphate buffer solution (14), containing 10 mc of phosphate-^{32}P. After incubation at 38°C for 90 min, 60% or more of the radioactivity was incorporated into the red cells. The labeled cells were then washed 3 times in cold saline and finally resuspended in 2 ml of their own plasma. Since phosphate-^{32}P is lost at a rate of about 10%/hr (14), the labeled cells were rewashed every half hour throughout the experiments. For measurement of red cell transit time, 0.3–0.5 ml of labeled blood (about 0.5 mc) was injected as a slug into the renal artery, resulting in 1000–3000 counts recorded by the detectors during a single circulation. Red cell transit time was calculated from the indicator dilution curve as the time when half the number of counts had been recorded, multipled by a factor of 2, which can be shown to be a good approximation of the true mean transit time for red cells through the detected region. A relative measure of regional red cell volume was obtained from the new "background activity" after the labeled cells had been mixed throughout the total blood volume.

Local clearance of ^{85}Kr was measured after 3–8 min intra-arterial infusion of ^{85}Kr dissolved in saline, at a rate of 0.3–1.0 mc/min, producing a counting rate approaching a steady level of 50–100 cps in the cortex and outer medulla.

Experimental procedure. Upon completion of surgery and insertion of the hydrogen electrodes, the kidney was returned to its normal position, the wound temporarily closed, and a period of at least 30 min was allowed for recovery. When β-detectors were inserted, the kidney was left in the wound and covered with a plastic sheet to prevent drying. Heparin, 10,000 U, was given i.v. After two or three control measurements in the course of about 1 hr, bleeding was started. In eight dogs, blood pressure was reduced to 52–65 mm Hg in the course of 8–20 min, and maintained at a constant level for 1.5–3 hr by small adjustments of the reservoir. The initial bleeding volume was 25–40 ml/kg, and an additional 10–20 ml/kg was bled during the remaining part of the hypotensive period. Dog 4 was bled only to 90 mm Hg, and in two experiments (dogs 1 and 10) mean arterial pressure was lowered in two steps, first to 70 and then after about 1 hr to 50 mm Hg. In dog 2, pressure was raised from 50 to 70 mm Hg by partial reinfusion after 45 min. Local flow measurements were carried out at intervals of 20–60 min. Reinfusion of all shed blood was given i.v. in the course of 15–25 min. Gas clearances and transit time measurements were repeated 5–30 min after complete reinfusion of blood. The kidney was then excised and weighed after electrode positions were checked.

RESULTS

Total renal blood flow (RBF), measured continuously throughout 11 experiments, varied between 145 and 407 ml/min in the control periods, corresponding to 2.0–6.9 ml/min per g of kidney weight (average 4.35 ml/min per g). During the initial bleeding, RBF fell approximately in proportion to arterial pressure, but then, in about half of the experiments, showed a transitory rise during the first half hour of reduced pressure. In this period, renal blood flow was reduced less than in proportion to mean arterial pressure, indicating an initial fall in total renal resistance. After the first half-hour of bleeding, flow fell in all experiments, in spite of unchanged aortic pressure, resulting in increased calculated resistance which exceeded control level in all but one experiment (Fig. 5).

Hematocrit showed inconsistent changes during the 1st hr of bleeding, and later fell moderately, usually not more than 0.05.

Urine flow was low in the control period, 0.5 ml/min or less, and fell towards zero during bleeding. Upon reinfusion, urine flow increased transitorily above control level, but did not exceed 1.0 ml/min in any experiment.

After removing the kidney, the wound was closed and the animal allowed to recover from anesthesia. All dogs survived without any evidence of failure of the remaining kidney.

Medullary hydrogen clearance

Original hydrogen desaturation curves from four electrodes in the middle of the outer medulla are shown in Fig. 1. As evident from the semilogarithmic plot, the washout from the outer medulla does not give ideal monoexponential curves but shows an initial delay and also a slower late component. However, in these experiments only the outer medulla was equilibrated, and the slow component is much less pronounced than when the inner medulla is also completely saturated (15). The fractional rate of removal, $k = 0.693/t_{\frac{1}{2}}$, where $t_{\frac{1}{2}}$ is the half time in minutes, was calculated from the first linear part of the desaturation curve as shown in Fig. 1, and it will for brevity be referred to as outer medullary hydrogen clearance, OM-C_{H_2}. In previous studies it has been found that OM-C_{H_2} varies as a function of the distance from the corticomedullary border, from 0.1 to 0.3 min^{-1} at a depth of 4–5 mm (border to inner

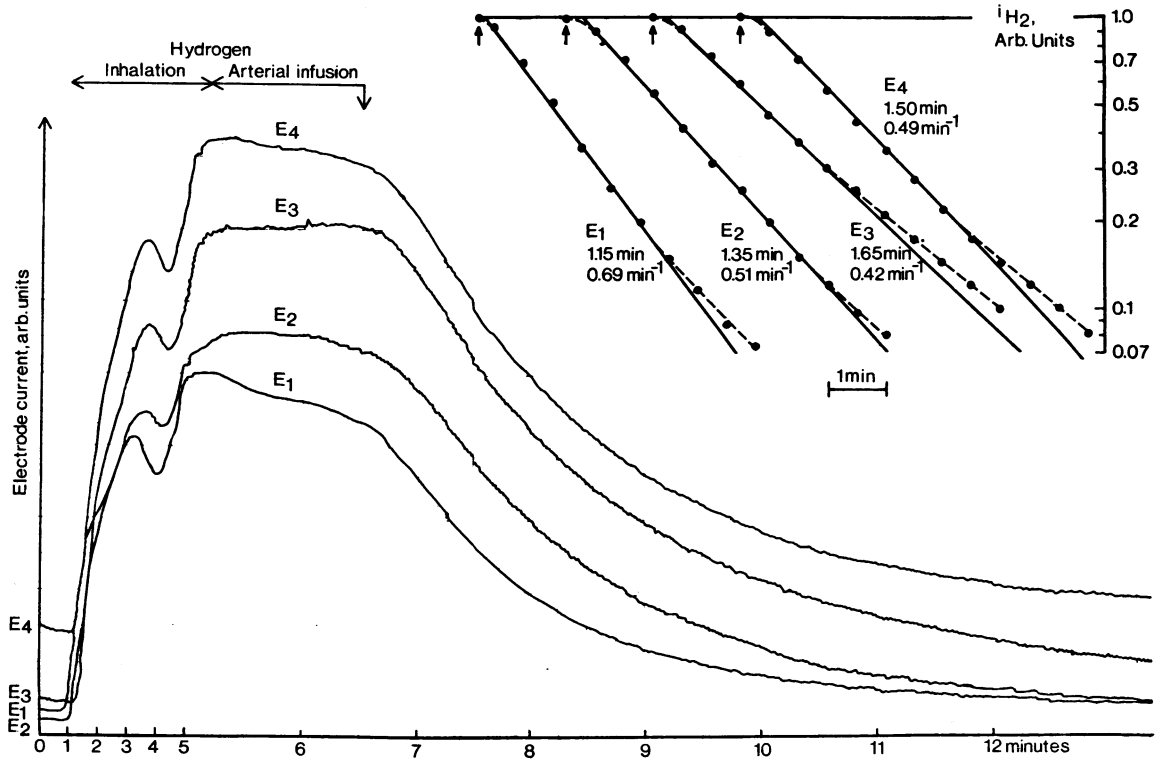

FIGURE 1 Original hydrogen desaturation curves. Four electrodes (E_{1-4}) are in the outer medulla, 2.5–4 mm from corticomedullary border. Waves on curves during saturation are caused by adjustments of hydrogen inhalation. Inset: logarithmic plot of hydrogen current. Stop arterial infusion of H_2 is indicated by arrows. Clearances are calculated from slopes of solid lines.

medulla), to 3.0 min^{-1} or more in the most superficial part of the outer medulla (16). It was therefore necessary to use each electrode site as its own control. Most of the 34 accepted electrode sites in the present study were at a depth of 2–4 mm from the corticomedullary border, giving a mean control clearance of 0.45 min^{-1}. Two or three control measurements before bleeding usually differed by less than 10%, giving a standard deviation of 7.7%, including both methodological errors and spontaneous flow variations.

Generally, OM-C_{H_2} was greatly reduced during hemorrhagic hypotension. Clearance curves from one electrode 2.5 mm from the corticomedullary border (dog 6) are shown as an example in Fig. 2. From a control of 0.66 min^{-1}, the desaturation rate was reduced to less than half as early as 16 min after blood pressure had been lowered to 57 mm Hg and fell progressively throughout the hypotensive period to about one-fourth of control rate. Reinfusion of blood after 2.5 hr of hypotension increased clearance almost to control level. A similar course was observed for total renal blood flow and for clearances from two more electrodes in the outer medulla, as shown in Table I. Calculations made in order to compare different experiments are also shown in Table I. Clearance for each electrode site was calculated in per cent of the average of two control measurements, and the mean of these percentages for two to four electrodes was considered representative for OM-C_{H_2} in each measurement. If we assume clearance to be proportional to blood flow, the ratio $\overline{AP}$/avg. OM-C_{H_2} (Table I, last column), gives a relative measure for vascular resistance in the juxtamedullary circulation, subsequently referred to as "medullary resistance."

Fig. 3 shows another experiment with bleeding to 52 mm Hg in the course of 10 min. OM-C_{H_2} was measured with four 0.1 mm thick electrodes, of which three showed a fall largely in proportion to RBF, whereas the fourth electrode (E_4) showed only moderate reduction of clearance in the first measurement after bleeding. Such ex-

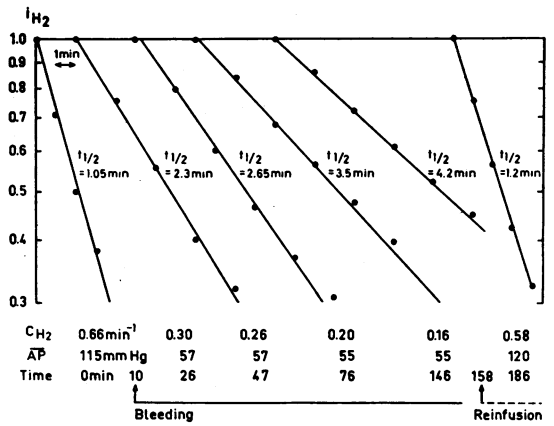

FIGURE 2 Hydrogen clearance curves from one electrode in outer medulla before and during bleeding, and after reinfusion of blood (dog 6). C_{H_2}, hydrogen clearance; $\overline{AP}$, mean arterial pressure.

ceptions to the general finding of an approximately parallel reduction of OM-C_{H_2} and RBF were infrequent, as shown in Fig. 4, where all clearances for each electrode in per cent of control have been compared to RBF, also in per cent of control. Increased clearance was not observed in any measurement, and only two out of 39 measurements in 12 experiments showed unchanged average OM-C_{H_2}, and then only shortly after the initial bleeding.

In dog 1, the first measurement 12 min after lowering $\overline{AP}$ from 140 to 70 mm Hg showed clearances of 100, 82, and 108% of control for three electrodes respectively. Half an hour later, clearances were reduced to 70, 57, and 71%. RBF was not measured in this experiment. In dog 5, the first measurement with two electrodes 10 min after reduction of $\overline{AP}$ from 110 to 52 mm Hg gave OM-C_{H_2} of 108 and 102% of control, whereas RBF had fallen to 63%. In the next measurement, 22 min later, clearances were 57 and 72%, and RBF was 52% of control.

All remaining measurements showed markedly reduced average OM-C_{H_2} during bleeding, as shown in Fig. 8.

The time course of flow reduction is evident from Table II, including eight experiments where arterial pressure was reduced in one step to 52–65 mm Hg and maintained at this level for at least 90 min. Only the measurements closest to each half hourly interval are shown. In spite of considerable individual variations, there is a clear trend towards relatively rapid fall in RBF and outer medullary hydrogen clearance in the 1st hr of hypotension and only moderate reduction during the next hour. The average reduction of RBF and OM-C_{H_2} did not differ significantly.

In about half of the experiments, "medullary resistance" fell during the initial stage of bleeding,

TABLE I

Effect of Bleeding and Retransfusion on Renal Blood Flow, Outer Medullary Hydrogen Clearance, and Calculated Resistances in Dog 6

Time	$\overline{AP}$*	RBF		R	OM-C_{H_2} Electrode 1		Electrode 2		Electrode 3		Avg.	$\overline{AP}$ Avg. OM-C_{H_2}
	mm Hg	*ml/min*	*%*	*PRU*	*min*$^{-1}$	*%*	*min*$^{-1}$	*%*	*min*$^{-1}$	*%*	*%*	
12:00	120	255		0.47	0.64		0.77		0.48			
			100			100		100		100	100	1.18
12:16	115	240		0.43	0.66		0.71		0.51			
12:26–12:36 bleeding to $\overline{AP}$ 57 mm Hg												
12:42	57	132	54	0.43	0.30	46	0.36	49	0.35	70	55	1.04
13:03	57	108	44	0.53	0.26	40	0.18	24	0.19	38	37	1.68
13:32	55	88	36	0.63	0.20	31	0.14	19	0.13	26	25	2.20
14:10	55	88	36	0.63	0.19	29	0.13	18	0.12	24	24	2.30
14:42	55	80	32	0.69	0.16	25	0.10	14	0.12	24	21	2.62
14:54–15:15 reinfusion of 1000 ml of blood												
15:22	120	184	75	0.65	0.58	89	0.47	64	0.49	98	84	1.45

$\overline{AP}$, mean arterial pressure; RBF, total renal blood flow; R, total renal resistance in peripheral resistance units (PRU); OM-C_{H_2}, outer medullary hydrogen clearance.

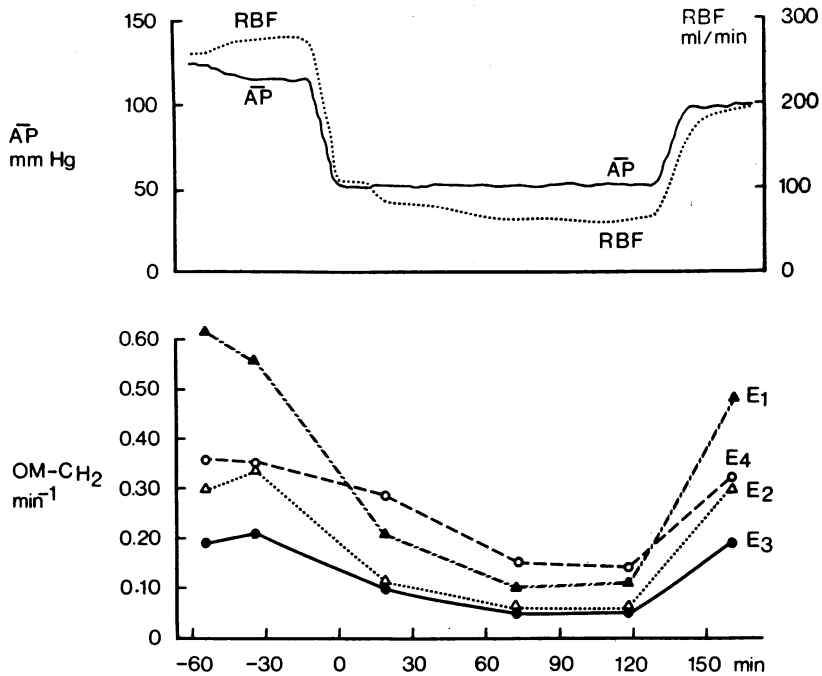

FIGURE 3 Mean arterial pressure ($\overline{AP}$), total renal blood flow (RBF), and outer medullary hydrogen clearance ($OM\text{-}C_{H_2}$) measured simultaneously with four "microelectrodes" in outer medulla in dog 12.

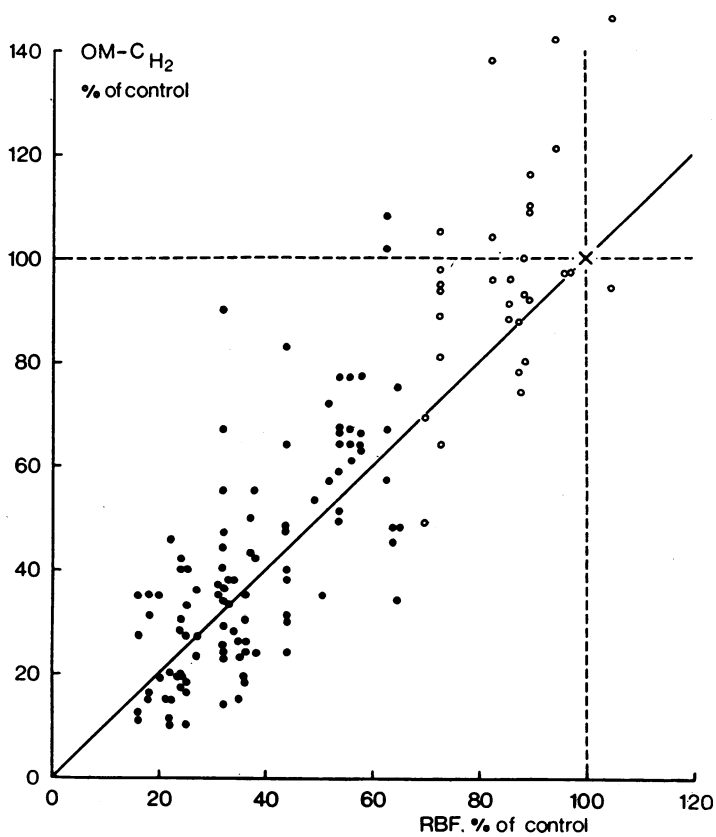

FIGURE 4 Hydrogen clearances from all electrodes during bleeding (closed circles) and after retransfusion (open circles) in per cent of control, compared to total renal blood flow.

TABLE II

Renal Blood Flow and Outer Medullary H_2 Clearance in Per cent of Control during Bleeding and after Reinfusion of Blood

Dog No.	$\overline{AP}$	30 min*		60 min*		90 min*		≷ 120 min*		After reinfusion‡	
		RBF	OM	RBF	OM	RBF	OM	RBF	OM	RBF	OM
	mm Hg										
3	65	44	47	38	40	22	27			88	79
5	52	52	65	37	47	31	36			106	120
6	55	44	34	36	27	36	24	32	21	73	84
7	63	32	44			25	33	27	29	89	91
8	57	34	33	20	27	20	24			70	59
9	57	35	21	25	15			22	12	83	113
11	52	50	44	18	25	16	24	16	19	97	97
12	52	32	54	24	27			24	27	73	95
Mean	57	40	44	28	30	25	28	24	22	84	92

$\overline{AP}$, mean arterial pressure during bleeding; RBF, total renal blood flow, % of control; OM, outer medullary H_2 clearance, % of control, average of 1–4 electrodes.

* Time after $\overline{AP}$ had been reduced to desired level.

‡ Measured 5–30 min after complete reinfusion.

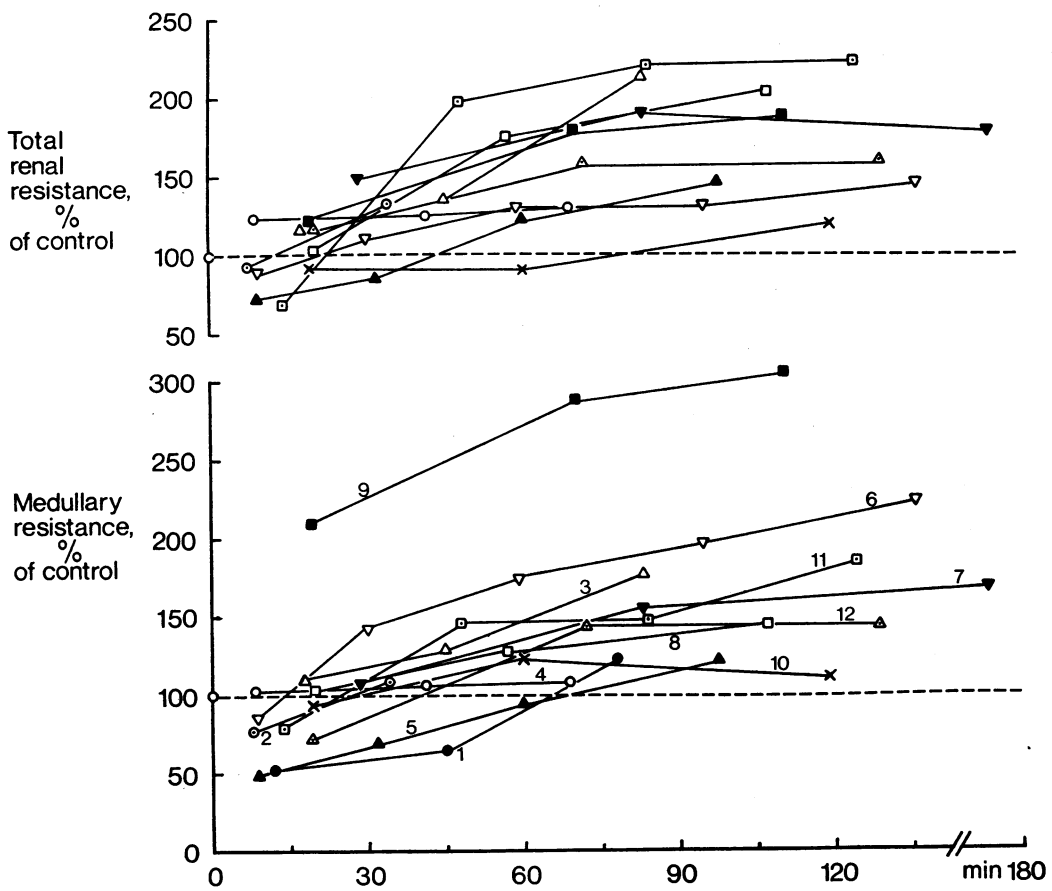

FIGURE 5 Total renal resistance and outer medullary resistance calculated from hydrogen desaturation during bleeding, in per cent of control. Numerals on curves indicate dog numbers.

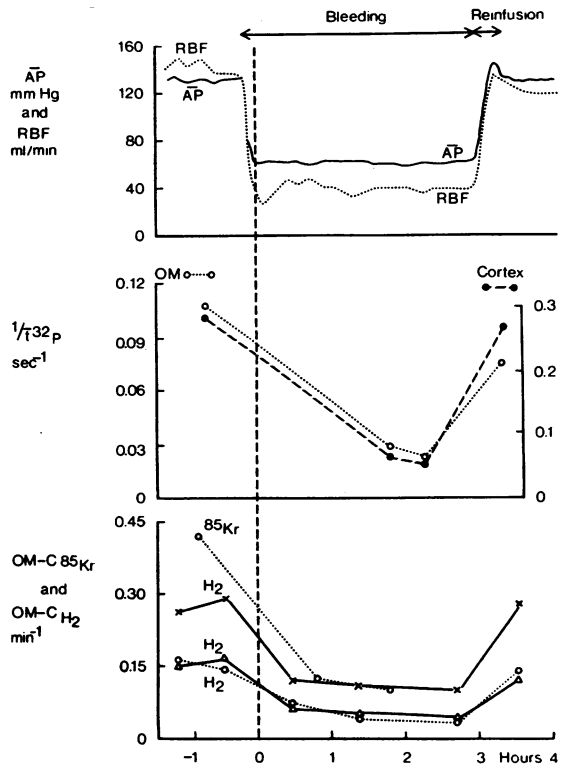

FIGURE 6 Effect of bleeding and retransfusion on renal blood flow, reciprocal of mean red cell transit time ($1/\bar{t}^{32}P$) in cortex and medulla, and outer medullary clearances for ^{85}Kr and H_2 (three electrodes) in dog 7.

in some cases more than total renal resistance. This was the case in dog 6 (Fig. 2 and Table I) and is also evident from Fig. 5, which shows percentile changes in resistance in all 12 experiments. (In dog 1 only medullary resistance is shown, since RBF was not measured.)

Measurements were also made 10–30 min after complete reinfusion of blood in 11 experiments. Both $OM\text{-}C_{H_2}$ and RBF increased considerably, with some tendency to better restoration or even overshoot of $OM\text{-}C_{H_2}$ (Figs. 4 and 8, open circles).

Medullary ^{85}Kr clearance

Outer medullary ^{85}Kr clearance ($OM\text{-}C^{85}Kr$) was measured in three experiments, in one with two detectors simultaneously. The recordings were not as smooth as the hydrogen desaturation curves because of the relatively low counting rate and a time constant adjusted to 2 or 5 sec, but usually presented no major interpretation problem. The desaturation curves, showing the same characteristics as the hydrogen curves, were analyzed in the same way, and gave clearances of the same magnitude as those of hydrogen.

Outer medullary ^{85}Kr clearance was markedly reduced compared to control during hemorrhagic hypotension, as shown in Fig. 6 and Table III. Except for one measurement with one detector (dog 10), $OM\text{-}C^{85}Kr$ was reduced more than in proportion to $\bar{AP}$ and showed good correlation to RBF, as evident from Fig. 8, where clearances are shown in per cent of control. (In dog 10, clearances are shown as mean of two detectors.) Figs. 6 and 8 also demonstrate the good agreement between $OM\text{-}C^{85}Kr$ and $OM\text{-}C_{H_2}$ during bleeding. $OM\text{-}C^{85}Kr$ was measured after reinfusion of blood in only one experiment, because of high background activity produced by repeated injections of ^{32}P, and in this case showed some overshoot compared to control (Table III).

Red cell transit time

Cortex. Mean transit time for ^{32}P-labeled erythrocytes through the cortex ($Co\text{-}\bar{t}^{32}P$) was measured in three experiments. Control values varied between 3.5 and 1.4 sec; the latter figure was observed in dog 8, a dog with exceptionally high total renal blood flow (Table III). During bleeding, $Co\text{-}\bar{t}^{32}P$ was markedly prolonged in all

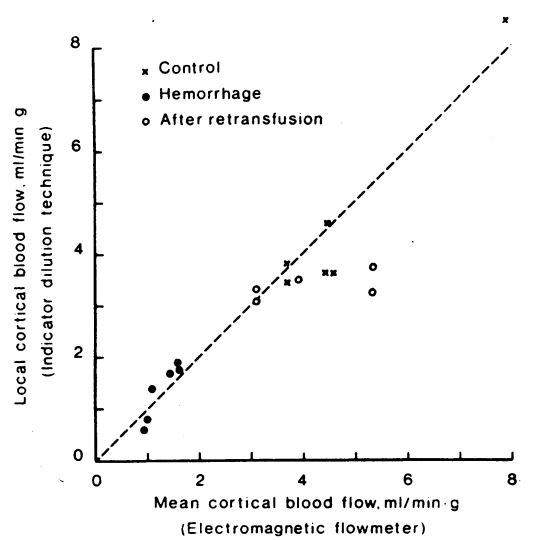

FIGURE 7 Comparison of cortical blood flow estimated by electromagnetic flowmeter and from cortical red cell transit time. Calculations are explained in text.

TABLE III

Local Clearance of ^{85}Kr and Red Cell Transit Time during Hemorrhagic Hypotension and after Retransfusion

Dog No.	Time*	$\overline{AP}$	RBF	OM-$C_{^{85}Kr}$		$\bar{t}_{^{32}P}$ OM		$\bar{t}_{^{32}P}$ Cortex
	min	*mm Hg*	*ml/min*	*min*$^{-1}$		*sec*		
7	−30	135	152	0.42		9.2		3.5
	50	63	48	0.12				
	110	60	38	0.10		36		14.2
	140	62	36			46		21.2
	200	135	128			13.3		3.7
8	−70	155	384	0.55				
	−40	155	410	0.53		4.0		1.4
	40	60	96	0.11				
	80	57	72			21		7.2
	120	57	76	0.08		23		7.0
	190	140	280			15		3.4
9	−40	130	320			6.2		3.2
	−20	135	320			10.5		2.9
	20	57	108			18.2		6.6
	70	57	76			27.4		8.2
	150	115	264			10.6		3.4
10	−30	120	144	0.53‡	0.49‡	13.6‡	12.4‡	
	30	70	94	0.36	0.21	20.8	23.6	
	60	70	92	0.33	0.23			
	140	50	44	0.13	0.11			
	160	50	40			30.8	30.8	
	200	105	140	0.63	0.60			
	230	105	132	0.63	0.51	13.2	12.8	

$\overline{AP}$, mean arterial pressure; RBF, total renal blood flow; OM-$C_{^{85}Kr}$ outer medullary ^{85}Kr clearance; $\bar{t}_{^{32}P}$, mean transit time for ^{32}P-labeled erythrocytes.

* Zero time, arterial pressure lowered to desired level.

‡ Both detectors in outer medulla.

experiments, whereas local cortical blood volume showed small and inconsistent changes. The reciprocal of mean red cell transit time, $1/Co\text{-}\bar{t}_{^{32}P}$, which can accordingly be used as a relative measure of local cortical blood flow, fell on the average approximately in proportion to RBF (Fig. 6). Retransfusion of blood practically normalized $1/Co\text{-}\bar{t}_{^{32}P}$ in two experiments, whereas return to only 42% of control was observed in dog 8.

In accordance with previous observations,[1] the absolute estimate of regional cortical red cell volume varied considerably, presumably because of bleeding around the detector. An average cortical red cell volume of 8% (17–20) was therefore used for calculating regional cortical flow in ml/min·g, according to the formula $8/Co\text{-}\bar{t}_{^{32}P} \times$ Hct. An estimate of average cortical blood flow may also be obtained from RBF, if we assume that all blood passes through the cortex, and estimate cortical weight as 70% of total kidney weight. No correction was made for possible shrinking or swelling of the kidney during the experiment. A comparison of cortical blood flow obtained by the two methods is shown in Fig. 7, which includes four measurements during control and retransfusion in addition to those given in Table III. If we consider the several assumptions made in this comparison, the agreement is satisfactory.

Medulla. Outer medullary mean transit time for ^{32}P-labeled erythrocytes ($OM\text{-}\bar{t}_{^{32}P}$) was measured in four experiments. Eight measurements were performed during the hypotensive period and four after reinfusion of blood, each measurement obtained as a mean of one to three single determinations. The reciprocal of mean transit time ($1/OM\text{-}\bar{t}_{^{32}P}$) was used as a relative measure of outer medullary blood flow, assuming regional

[1] Wolgast, M. Data to be published.

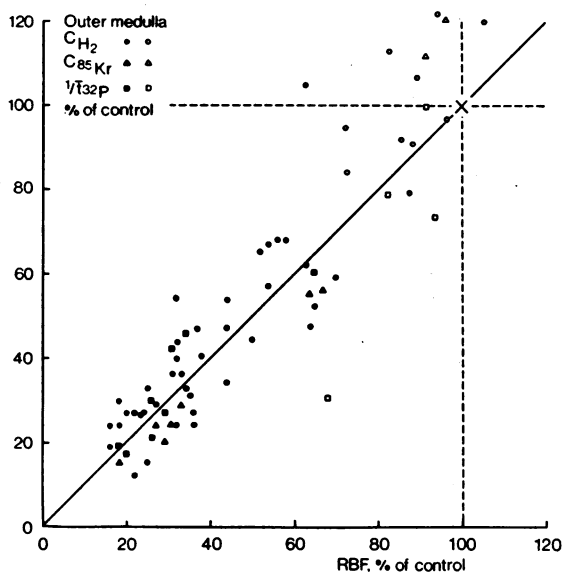

FIGURE 8 Average outer medullary gas clearances and reciprocal of mean red cell transit times in per cent of control during bleeding (closed symbols) and after reinfusion of blood (open symbols), related to total renal blood flow.

blood volume to be constant. In two experiments, outer medullary red cell volume increased moderately during the initial stage of hemorrhagic hypotension but returned close to control in the course of 10–20 min. During reinfusion, possible changes of regional blood volume were beyond control, because of the hazard in estimating the activity of the reinfused blood, making the blood flow estimates in this period more uncertain. Local bleeding around the detectors was much less conspicuous in the outer medulla than in the cortex, in accordance with consistent estimates of outer medullary red cell volume to about 8%,[2] which agrees well with data obtained with other methods (18, 20).

OM-$\bar{t}_{^{32}P}$ increased considerably in all measurements during hemorrhagic hypotension (Table III). Apart from the first measurement with one detector in dog 10, 1/OM-$\bar{t}_{^{32}P}$ fell more than in proportion to arterial pressure, but largely in proportion to the reduction of RBF and outer medullary gas clearances, as is evident from Table III and Figs. 6 and 8. Reinfusion of blood restored 1/OM-$\bar{t}_{^{32}P}$ almost to control in two experiments but to only 30% of control in dog 8, in which postreinfusion OM-C_{H_2} was also lower than in any other experiment, i.e. 59% of control, and RBF only 70% of control.

DISCUSSION

The present experiments showed an average reduction of outer medullary clearance of H_2 and ^{85}Kr and of 1/OM-$\bar{t}_{^{32}P}$ in proportion to the fall in RBF during bleeding, indicating a parallel reduction of medullary and cortical blood flow. The validity of this conclusion will be discussed.

Since the cortex constitutes about 70% of kidney volume, and probably receives a considerably larger fraction of blood flow (21, 22), major changes in RBF will mainly reflect changes in cortical flow. (Since nearly all blood entering the medulla has passed through the juxtamedullary glomeruli in the cortex, it might be more appropriate to discuss flow through cortical vs. juxtamedullary types of glomeruli; since the latter type has been estimated as 15–18% of the total number of glomeruli (23, 24), it is likely that RBF mainly reflects flow through the cortical type of glomeruli.)

In previous experiments, it has been shown that the removal rate of hydrogen gas from the area sampled by a platinum electrode in the outer medulla is practically uninfluenced by small changes in urine flow, and that diffusion of hydrogen from medulla to cortex is of little importance (15, 16). By exclusion, therefore, OM-C_{H_2} must be a function of blood flow in the area around the electrode. The fact that representative clearances are obtained in myocardium (10, 12, 25), brain (26), pancreas,[3] and in the renal cortex at low blood flow (10) suggests that local measurements in the outer medulla also give clearances which are representative for the whole region. Cortical clearance was not recorded, because it has been found that measurements in the renal cortex at normal flow often give multiexponential curves, which cannot be interpreted in terms of absolute blood flow (10). This phenomenon was assumed to be due to frequent occurrence of bleeding around the electrode in the fragile cortical parenchyma. Although theoretically an uncirculated layer of uniform thickness around the electrode does not change the slope of the recorded desaturation curve (27), it seems likely that a diffusion

[2] Wolgast, M. Data to be published.

[3] Aune, S., and L. Semb. Personal communication.

layer of uneven thickness could prevent correct recording of the very rapid desaturation in the cortex (3–5 min^{-1}).

The possibility of a change in vasomotor activity in the area around the detectors should also be considered. Because smooth muscle cells are mainly confined to the cortical part of the juxtamedullary vessels (28), most platinum electrodes were inserted laterally to avoid disturbance of the part of the cortex sending vasa recta to the monitored area. However, the same response to bleeding was observed with vertical and lateral insertions. It also seems unlikely that local vasomotor disturbances should give as reproducible results as those obtained in the present experiments. The observation of good autoregulation of outer medullary hydrogen clearance also suggests an intact vasomotor regulation of the local circulation (16). Furthermore, the reduction of electrode diameter to 0.1 mm did not alter the observed response to hemorrhagic hypotension, which was also nearly identical with that observed for ^{85}Kr, recorded with considerably larger detectors, but with a greater sampling volume.

The validity of the local gas clearances in the outer medulla is further supported by the good agreement with red cell transit time, which was shown to give absolute flow in the cortex close to values expected from total blood flow and kidney weight (Fig. 7). It therefore seems justifiable to conclude that the local measurements of gas clearance are representative for the undisturbed outer medulla. The volume monitored for both hydrogen and ^{85}Kr is such that clearance from vasa recta bundles and the intermingled tissue is averaged, but because of the smaller volume occupied by the vascular bundles the clearances will mainly reflect washout from the parenchyma.

It has been deduced that because of the medullary countercurrent exchange system, gas clearance from the medulla should be a power function of blood flow, and not linearly related to flow rate (29, 30). The good agreement between changes in red cell transit time and gas clearances in this study suggests that the power of medullary flow appearing in the theoretical formulas is not very far from one, in other words, that clearances are fairly proportional to blood flow.

The present experiments thus indicate that during hemorrhagic hypotension in dogs, medullary and cortical blood flow are reduced on an average to the same extent. This conclusion agrees well with Kramer and Deetjen (8), who reported that medullary blood flow was reduced almost to the same extent as cortical flow in three dogs investigated with inner medullary transit time of albumin-bound dye.

A different conclusion was reached by Carriere et al. (6) from ^{85}Kr clearance curves recorded externally over the kidney by a γ-scintillation counter. The second component of the decomposed curve, assumed to represent clearance of ^{85}Kr from the outer medulla, on the average showed a rise during the 1st hr of bleeding to 50 mm Hg, indicating an absolute rise in medullary blood flow, whereas the present experiments showed a decrease to about one-third of control (Table II). They also found that blood flow in the major part of the cortex was reduced to the same level as outer medullary flow, and was therefore also represented by component II in the clearance curve. This conclusion was based on radioautograms obtained 2–4 min after injection of ^{85}Kr, showing similar gas concentrations in cortex and outer medulla. However, this observation may just as well be interpreted to show parallel reduction of cortical and medullary clearances. Assuming, for instance, a 5 : 1 ratio between cortical and outer medullary gas clearances, both normally and during bleeding, the initial gas concentration immediately after a bolus injection will be 5 times higher in cortex than in outer medulla. Because of the more rapid cortical clearance, the concentration curves will cross, as readily demonstrated in a semilogarithmic plot. Thus, with a cortical clearance rate of 5 min^{-1} (blood flow 500 ml/min·100 g) and outer medullary clearance of 1 min^{-1}, cortical and medullary concentrations will be equal after 24 sec, in good agreement with the observation of Thorburn, Kopald, Herd, Hollenberg, O'Morchoe, and Barger (31). With reduction of cortical and medullary blood flow to 20% of control, cortex and outer medulla will have identical concentrations after 2 min, and with flow reduction to 10%, identical concentrations will be obtained after 4 min. This is exactly the pattern described by Carriere et al. (6).

Truniger et al. (7), using external counting of ^{133}Xe, observed curves similar to those obtained by Carriere et al. (6), but favored the interpretation

that most of the cortex became completely ischemic during bleeding, whereas flow was unchanged in the "corticomedullary zone" and medulla. The analytical difficulties inherent in the external counting technique are also apparent from the fact that the clearance curves are analyzed in various ways (three or four components) in different laboratories (32). It may therefore be questioned whether the second component really represents outer medullary clearance, especially if, during bleeding, this component includes 90% of the cortex or more, as assumed by Carriere et al. (6). Furthermore, the decisive requirement of a steady state with respect to flow in all compartments for at least 1 hr (6) is obviously not satisfied within the 1st hr of bleeding in spite of constant arterial pressure, leading to completely unpredictable errors in the curve analysis.

Selkurt and Elpers (4) suggested that a reduction of *p*-amino-hippurate (PAH) extraction in the late bleeding period might be due to redistribution of blood flow from cortex to medulla. However, the evidence for complete cortical extraction of PAH and no extraction from juxtamedullary blood seems inconclusive under normal conditions (33), and is even more doubtful during the oliguria induced by bleeding.

Of the large number of injection studies (India ink, dyes) following Trueta's report (5) of medullary diversion of cortical flow in rabbits, some confirmed and others rejected this hypothesis. A detailed discussion of this literature seems unwarranted because of the qualitative nature and the pitfalls of these methods (34), but it may be noted that most investigators, including Trueta's collaborators (35), were usually unsuccessful in producing "medullary diversion" in dogs. Instead, they pointed out the frequent occurrence of patchy or segmental cortical ischemia in this species. This pattern, which is compatible with studies of tubular transfer maxima (36), has recently been supported by radioautography which showed uneven initial distribution of ^{85}Kr in the cortex during hemorrhage, with ischemia most pronounced in the superficial part of the cortex (6, 7). The present data on local cortical ^{32}P transit time do not support this view, but the small number of observations does not permit any definite conclusion.

In all dogs, outer medullary blood flow and RBF decreased during bleeding, but a transitory fall in calculated resistance was observed in about half of the experiments (Fig. 6). Since hematocrit showed small and inconsistent changes, this pattern suggests an initial dilation of the renal resistance vessels, as previously described by Jirka, Ganz, Fencl, Cort, and Trávniček (37). Absence of renal vasoconstriction during early bleeding has also been reported by other investigators (4, 38, 39). As proposed by Haddy, Scott, and Molnar (39), the initial vasodilation might be caused by local autoregulative mechanisms, which have been shown to include both the cortical and the juxtamedullary circulation (16). In the further course of bleeding, vascular resistance rose progressively, as also found by previous investigators (2–4, 38, 39). This rise could be due to increasing renal sympathetic activity and (or) increasing plasma concentrations of catecholamines (40) or angiotensin (41) during bleeding, since it has been shown that all these factors cause a roughly parallel increase of medullary and cortical resistance (11). A selective cortical ischemia with maintained medullary flow would, on the other hand, demand a reduction of juxtamedullary resistance, since vasoconstriction in the outer cortex cannot contribute significantly to maintenance of perfusion pressure of the juxtamedullary glomeruli (42). The present experiments provided no evidence for such a difference in response between deep and superficial arterioles.

The fairly homogeneous reduction of renal blood flow observed during hemorrhagic hypotension would not be expected to produce deleterious cortical hypoxia, in the first place because tubular functions and renal oxygen consumption are well maintained at low arterial oxygen saturation (43), and in the second place because the renal oxygen requirement falls markedly with reduction of glomerular filtration rate and tubular salt reabsorption (44, 45). This conclusion agrees well with the finding of Munck, Lassen, Deetjen, and Kramer (46), that both cortical and renal venous oxygen saturation remained relatively high even during severe hemorrhagic hypotension, and is further supported by the survival of all dogs in the present series without evidence of renal failure. The fact that uncomplicated hemorhagic shock in man practically never leads to acute anuric renal failure (47) suggests a vascular response in the

human kidney similar to that observed here in dogs.

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