Relationship between Renin and Intrarenal Hemodynamics in Hemorrhagic Hypotension

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ABSTRACT In order to investigate the possible role of the renin-angiotensin system in the regulation of intrarenal hemodynamics in hemorrhagic hypotension (HH), seven mongrel dogs have been studied under the following conditions: (*a*) Control, (*b*) HH (mean arterial pressure 70 mm Hg), and (*c*) HH + alpha adrenergic blockade by phenoxybenzamine (HH + POB). The following parameters were obtained for the right kidney: Intrarenal distribution of blood flow and local blood flow rates (^{133}Xe washout technique); total renal blood flow (RBF) on the basis of the clearance and extraction ratio of PAH and the arterial hematocrit; plasma renin concentrations in the renal artery and vein by the method of Boucher and his associates; and renin release into the renal circulation.

Alpha adrenergic blockade reverted the typical redistribution of intrarenal blood flow observed under HH. In hemorrhage, arterial and venous renin concentrations increased by a factor of 3.4 and 4.8 respectively. A further small increase was observed during HH + POB with the respective factors increasing to 4.8 and 5.3, as compared with control values. The renin release into the circulation increased by a factor of 1.2 in HH and 4.0 in HH + POB. Whereas in HH there seemed to be a relationship between increased renin concentrations or renin release, and the redistribution of blood flow, no such correlation was found during α-adrenergic blockade. From these observations it is concluded that renin alone is unable to maintain the typical redistribution of RBF seen during hemorrhage. Circumstantial evidence points to a permissive role of the renin-angiotensin system in the pathogenesis of the patchy cortical hypoperfusion caused by sympathoadrenergic mechanisms during hemorrhagic hypotension.

Presented in part at the fourth Annual Meeting of the European Society for Clinical Investigation, Scheveningen 1970.

Received for publication 19 August 1970.

INTRODUCTION

Hemorrhagic hypotension (HH)[1] produces a typical redistribution of renal blood flow (RBF), characterized by a patchy hypoperfusion of the renal cortex, most pronounced in its superficial layers (1, 2). Recently, we have demonstrated that the redistribution of RBF in HH may be totally prevented or corrected by the administration of an alpha adrenergic blocking agent (3). Renal denervation did not prevent these redistribution processes (4). These observations suggest that circulating catecholamines predominately account for the pathogenesis of the patchy cortical hypoperfusion in HH. However, they do not rule out an additional role of the renin—angiotensin system. Several observations, indeed, suggest that renin and angiotensin might be involved in the redistribution of RBF. *First,* there is good evidence that angiotensin increases the renal vasoconstriction in response to sympathoadrenergic stimulation either by facilitating the release of norepinephrine during renal nerve stimulation (5, 6) or by inhibiting norepinephrine uptake into the neuron (7). Vice versa, circulating catecholamines as well as sympathetic nerve stimulation have been shown to increase renin release (8). *Second,* there is a striking analogy between the sites of renin production (9) and the distribution pattern of cortical hypoperfusion in hemorrhage, both processes being accentuated in the most superficial layers of the renal cortex.

In order to define more closely the role of renin and angiotensin in the pathogenesis of the redistribution of renal blood flow in HH, the renal arterial and venous renin concentration and the renin release into the circulation have been studied in dogs, in which a patchy cortical hypoperfusion was induced by bleeding and then

[1] *Abbreviations used in this paper:* HH, hemorrhagic hypotension; RBF, renal blood flow; POB, phenoxybenzamine; CP, component; PAH, para-aminohippuric acid; GFR, glomerular filtration rate; E_{PAH}, the extraction ratio for PAH.

reverted by alpha adrenergic blockade. This model allows the analysis of the relationship between intrarenal hemodynamics, renal excretory function, and renin production at identical perfusion pressure, with and without a redistribution of blood flow. The results indicate that the renin-angiotensin system by itself does not account for the patchy hypoperfusion of the renal cortex in hemorrhage.

METHODS

Experiments were performed in seven mongrel dogs weighing between 21 and 40 kg. The animals were anesthetized with pentobarbital (20-30 mg/kg BW). The right renal artery and vein were catheterized transfemorally by means of an Odman X-ray catheter No. 7, under fluoroscopic control (urographin 76%). The catheter tip was placed 1–5 mm into the renal artery. A coaxial polyethylene tube (PE 20, O.D. 1.09 mm, I.D. 0.38 mm) with a guide wire (O.D. 0.30 mm) was advanced through the Odman catheter (Kifa, Stockholm, Sweden) some 3 cm into the renal artery. The renal vein catheter was kept open by continuous infusion (saline 0.9% + heparin 10 U/ml, infusion rate 0.5 ml/min). The right ureter was catheterized after a flank incision.

Measurements of intrarenal hemodynamics, standard clearances and renin determinations were performed successively under the following conditions: Control conditions, hemorrhagic hypotension (HH, arterial pressure 70 mm Hg), and α-adrenergic blockade during sustained HH (HH + POB), with the infusion into the renal artery of phenoxybenzamine (Dibenzyline®, Smith Kline & French Laboratories, Philadelphia, Pa., 10–20 μg/min per kg). 60 min of stabilization time were allowed before any measurements were started in control conditions and in HH; 30 min in HH + POB. Under control conditions and during hemorrhagic hypotension, intrarenal hemodynamics were analyzed once with renin measurements performed 10 min after starting the inert gas washout curve. Under both conditions, clearance values were determined twice. During adrenergic blockade + hemorrhage, measurements were repeated until normalization of the intrarenal distribution of blood flow (Component I [CP I] at least 70% of control values). Renin and clearance values obtained before this point of normalization were rejected. The duration of HH and HH + POB in each experiment is given in Table I.

Hemorrhagic hypotension was induced by bleeding the animals from the left femoral artery into a reservoir placed above the table. By adjusting the position of this reservoir, a mean arterial blood pressure of 70 mm Hg was maintained throughout the periods of HH and HH + POB. The blood volumes shed during hemorrhagic hypotension, as well as the volumes retransfused from the reservoir during HH + POB, are included in Table I. From these values it can be seen that the systemic effect of the α-adrenergic blocking agent varied considerably among the animals. Arterial blood pressure was measured intermittently throughout the experiment (Hg manometry).

POB may prevent a renal cortical vasoconstriction brought about by angiotensin. This possibility was examined in two additional dogs (N and L). Measurements of intrarenal hemodynamics were performed in control conditions and during the infusion into the renal artery of angiotensin (angiotensin-amide, CIBA Pharmaceutical Co., Summit, N. J.), 0.2–0.5 μg/min per kg), with and without α-adrenergic blockade. Again phenoxybenzamine was used as an alpha blocking agent (10 μg/min per kg infused into the renal artery). This dose was sufficient to block the redistribution of intrarenal blood flow during HH as well as that caused by an intrarenal infusion of norepinephrine (2 μg/min per kg).

Intrarenal hemodynamics were analyzed by means of the inert gas washout technique of Thorburn et al. (10), ^{133}Xe being used instead of ^{85}Kr. Radioautographs were developed after the injection of ^{85}Kr into the renal artery. In *normal conditions* the analysis of the washout curve registered after the injection of the radioactive indicator gas into the renal artery resulted in four single exponential components (CP I–CP IV) allowing the calculation of the intrarenal distribution of blood flow and local blood flow rates of the vascular compartments corresponding to each of the components. In normal dogs, CP I has been shown to correspond to the renal cortex, CP II to the outer medulla, CP III to the inner medulla, and CP IV to the perirenal fat (10). The vascular area corresponding to CP I of the washout curve will be called cortex A, as proposed by Carriere et al. (1).

The *plasma renin activity* in the renal artery and vein was determined using Boucher's method (11). For practical reasons the plasma renin *activity* (nanograms of angiotensin/minute per liter of plasma) is expressed as renin *concentration* (units/liter, where 1 U/liter = 1 ng angiotensin/min per liter). The renin release (units/minute) into the renal circulation was calculated by multiplying the renin concentration gradient between the renal vein and artery with the total renal plasma flow. The latter was obtained on the basis of the clearance and extraction ratio for PAH.

PAH and inulin were determined using the methods described by Bratton and Marshall (12) and Schreiner (13). After a priming dose of 4 g of inulin and 0.8 g of PAH 0.9% saline, containing inulin (4–26 g/liter) and PAH (0.5–3.0 g/liter) was infused into the brachial vein at a rate of 1 ml/min. In addition, this sustained infusion contained mannitol (50 g/liter in order to secure a sufficient diuresis), chloramphenicol (1 g/liter) and *d*-aldosterone (2 mg/liter). Aldosterone was added since, in the same experiments, studies on the relationship between the intrarenal distribution of blood flow and sodium excretion were performed. The *statistical analysis* of the data was performed on a CDC 3800 computer (University of Geneva, Switzerland).

RESULTS

Intrarenal hemodynamics (Table I, Figs. 1 and 2)

During hemorrhagic hypotension total renal blood flow, as calculated from the clearance and extraction ratio of PAH, decreased from an average of 304 ml/min to 73 ml/min per kidney. It increased again to 191 ml/min under conditions of HH + POB. (When calculated from the initial slope of the washout curve and the kidney weight, the values for RBF were as follows: control conditions 253 ml/min, HH 66 ml/min, and HH + POB 180 ml/min). In HH renal resistance increased to an average of 220% of control conditions and was back to 85% of control in HH + POB.

The values for glomerular filtration rate (GFR) averaged 38 ml/min in control conditions, 6 ml/min in HH, and 22 ml/min in HH + POB.

TABLE I

Clearance Values and Intrarenal Hemodynamics under Control Conditions, in Hemorrhagic Hypotension (HH) and HH + α-Adrenergic Blockade (HH + POB)

		Dog No.								
		1	2	3	4	5	6	7	Mean	P*
1. Clearance values										
RBF, *ml/min*‡	Control	404	256	365	238	176	262	427	304	P_1 < *0.001*
	HH	34	37	68	196	54	74	49	73	P_2 *0.005*
	HH + POB	155	146	188	241	95	199	316	191	P_3 *0.027*
GFR, *ml/min*‡	Control	27	37	30	45	18	43	72	38	P_1 < *0.001*
	HH	3	4	1	10	6	13	5	6	P_2 *0.009*
	HH + POB	22	14	6	31	13	25	46	22	P_3 0.070
Filtration fract. (C_{IN}/C_{PAH})	Control	0.23	0.34	0.29	0.43	0.29	0.36	0.36	0.32	P_1 0.110
	HH	0.25	0.31	0.25	0.11	0.26	0.35	0.31	0.26	P_2 0.292
	HH + POB	0.38	0.26	0.25	0.29	0.33	0.28	0.31	0.30	P_3 0.355
E_{PAH}‡	Control	0.60	0.76	0.54	0.87	0.64	0.85	0.86	0.73	P_1 0.737
	HH	0.68	0.71	0.22	0.90	0.73	0.86	0.78	0.69	P_2 1.000
	HH + POB	0.71	0.75	0.27	0.86	0.69	0.80	0.80	0.69	P_3 0.712
2. Intrarenal hemodynamics										
(*a*) Percentage of total RBF supplied to compartment										
I	Control	73	76	84	61	80	91	70	76	P_1 < *0.001*
	HH	0	14	0	0	19	52	31	16	P_2 < *0.001*
	HH + POB	52	68	73	70	70	75	65	67	P_3 0.083
II	Control	22	18	22	29	14	4	17	16	P_1 *0.003*
	HH	86	69	11	90	71	40	47	59	P_2 *0.009*
	HH + POB	42	26	22	20	22	20	23	25	P_3 0.118
III	Control	3	3	2	8	3	3	5	4	P_1 0.197
	HH	8	6	52	7	4	5	8	12	P_2 0.232
	HH + POB	4	4	4	8	4	3	5	4	P_3 0.481
IV	Control	2	3	2	2	3	2	8	3	P_1 0.097
	HH	6	11	37	3	6	3	14	11	P_2 0.087
	HH + POB	2	2	1	2	4	2	7	3	P_3 0.805
(*b*) local blood flow rates in compartment										
I, *ml/min per 100 g*	Control	429	466	597	416	495	500	643	506	P_1 0.618
	HH	—	650	—	—	300	263	(1126)	584	P_2 0.240
	HH + POB	458	422	457	234	208	409	520	386	P_3 0.051
II, *ml/min per 100 g*	Control	104	99	51	110	73	81	117	90	P_1 0.410
	HH	39	148	229	106	73	95	93	111	P_2 0.565
	HH + POB	128	142	96	80	40	90	98	96	P_3 0.722
3. Arterial BP, *mm Hg*	Control	140	125	135	115	110	140	140	129	—
	HH	70	70	70	70	70	70	70	70	—
	HH + POB	70	70	70	70	70	70	70	70	—
4. Duration of *min*	HH	70	80	110	80	75	60	85	80	—
	HH + POB	100	45	42	55	115	40	80	68	—
5. Max. shed blood volume in HH, *ml*		900	1300	1340	1660	660	890	1770	1217	—
6. Max. reinfused blood vol. in HH + POB, *ml*		180	450	900	620	360	40	1050	514	—
7. Art. hematocrit %	Control	52	45	48	50	44	46	46	47	P_1 0.950
	HH	49	47	53	51	39	42	51	47	P_2 0.468
	HH + POB	46	49	52	48	38	44	41	45	P_3 0.399
8. Body weight, *kg*		23	34	25	36	21	31	40	30	—

* Differences between control and HH (P_1), HH and HH + POB (P_2), and control and HH + POB (P_3). Student's *t* test.
‡ RBF, renal blood flow; GFR, glomerular filtration rate; E_{PAH}, PAH extraction ratio.

The *intrarenal distribution of blood flow* during HH and HH + POB showed changes comparable to those described previously (3). In hemorrhage the fraction of total RBF supplied to the cortex A (first component of the xenon—washout curve) decreased from 76 to 16%, corresponding to the appearance of a patchy hypoperfusion of the superficial layers of the cortex (1–3, Fig. 1 A). During adrenergic blockade and sustained hy-

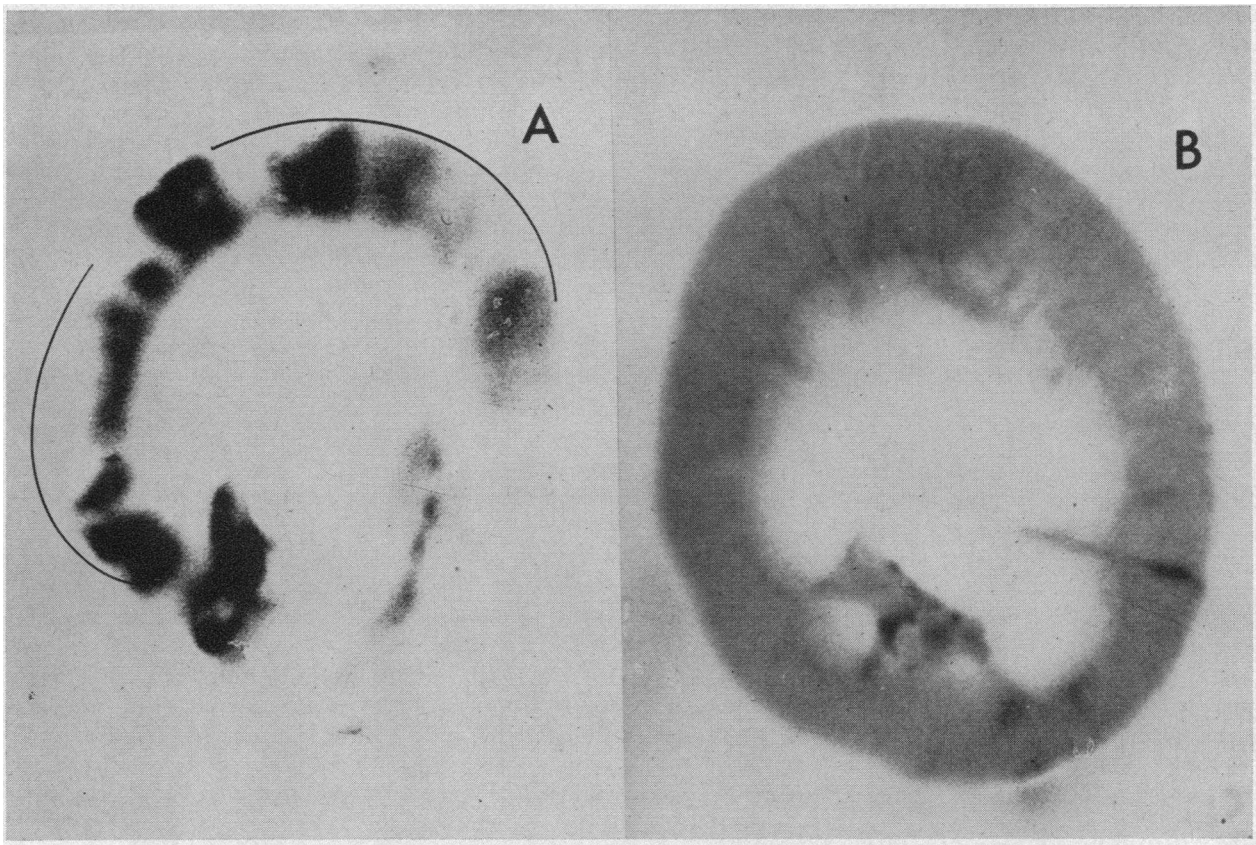

FIGURE 1 ^{85}Kr radioautographs of two dog kidneys in hemorrhagic hypotension (A) and hemorrhagic hypotension plus phenoxybenzamine (B). The patchy cortical hypoperfusion of HH is reversed by α-blockade. (Contour delineates position of the renal capsule).

potension this fraction rose again to 68% indicating the normalization of the distribution of renal blood flow and the disappearance of the patchy hypoperfusion of the cortex as shown by autoradiography (Fig. 1 B).

In contrast with these clearcut changes in intrarenal distribution of blood flow, the extraction ratio for PAH (E_{PAH}) did not change significantly during HH and HH + POB as compared with control conditions. Thus no relationship was found in these experiments between E_{PAH} and the intrarenal distribution of blood flow.

In normotensive dogs, α-adrenergic blockade did not prevent nor reverse the typical redistribution of intrarenal blood flow brought about by angiotensin. Our observations in dogs L and N are in good agreement with our preliminary observations in the rat (rats 9 and 11): in spite of an alpha adrenergic blockade sufficient to prevent and reverse the renal cortical vasoconstriction of HH as well as that of exogenous norepinephrine, angiotensin caused a redistribution of intrarenal blood flow characterized by a progressive hypoperfusion of the renal cortex (Table III).

Renin measurements (Table II, Fig. 2)

In *control conditions* the renin concentration in the renal vein averaged 101 U/liter, in the renal artery 80 U/liter. The concentration gradient between the renal vein and artery was 21 U/liter, single values being positive in four dogs, and zero or negative in three animals. For the method of Boucher, used in these experiments a statistical evaluation proposed by Hosie et al. (14) showed that for single paired values arteriovenous concentration differences greater than 20% of the arterial concentration are significant. The three negative values found in control conditions (as well as two values in HH + POB) are below this critical level. The renin release into the circulation was 4.3 U/min on the average.

In *hemorrhagic hypotension* the renin concentration in the renal vein and artery increased significantly to 486 U/liter and to 273 U/liter respectively. In contrast, due to the reduction in RBF, the renin release into the circulation increased to 5.3 U/min only. This increase

is not statistically significant (the significance of the differences between control conditions, HH and HH + POB for the various parameters is included in Tables I and II).

Under *alpha adrenergic blockade + sustained arterial hypotension* the renin concentrations in the renal vein and artery showed a small, statistically *not* significant increase to 534 U/liter and 374 U/liter respectively, in spite of adrenergic blockade and normalization of the intrarenal distribution of blood flow. In HH + POB the renin release into the circulation via the renal vein increased to 16.6 U/min on the average. Again this increase is not quite statistically significant ($P = 0.073$).

DISCUSSION

The analysis of the relationship between renin and renal hemodynamics has to consider two facets of renin, namely (*a*) the renin concentrations reaching the kidney (as well as other vascular beds) by way of the arterial blood flow and (*b*) the renin production within the kidney. In the present experiments the latter was estimated on the basis of the venous-arterial renin concentration difference and the renal plasma flow, thus measuring the amount of renin released into the renal circulation without taking into account the release into the interstitium and the lymphatics.

Hemorrhagic hypotension causes a patchy hypoperfusion of the renal cortex, demonstrated by a decrease in the fraction of blood flow supplied to the vascular compartment corresponding to CP I of the inert gas washout curve (cortex A) (references 1 and 2, Figs. 1 and 2). At the same time arterial renin concentrations in our experiments rose from 80 to 273 U/liter, while the renin release into the circulation increased insignificantly from 4.3 to 5.3 U/min. Thus, during HH, no correlation seems to exist between the arterial renin concentration and renin release. This apparent lack of correlation is possibly accounted for by an increased renin release via the lymphatics, by an extrarenal source of renin (15), or by a decreased inactivation of renin. On the other hand, our experiments seem to indicate a positive relationship between increased arterial renin concentrations and the patchy cortical hypoperfusion of HH, but no correlation between the intrarenal hemodynamics and the renin release into the circulation.

Alpha adrenergic blockade totally corrects the redistribution of RBF in HH (reference 3, Table I, Figs. 1 and 2); in spite of a sustained arterial hypotension the renal cortex is perfused homogeneously and without patchy areas of hypoperfusion. Thus, the comparison of HH and HH + POB allows the analysis (at identical perfusion pressures) of the relationship between the variations in intrarenal distribution of blood flow and those of renin concentration and renin production. In these experiments the arterial renin concentration did not change significantly at the transition from HH to HH + POB. The increase in renin release from 5.3 to 17.2 U/min is not quite statistically significant. Since under conditions of HH + POB the arterial renin concentration and the renin release did not change significantly, in spite of a normalization of the intrarenal distribution of blood flow, it would seem that there is no relationship between renin and the patchy cortical hypoperfusion.

Sympathoadrenergic stimulation has been shown to increase plasma renin activity (8). Therefore, a decrease in renin concentrations and renin release could be expected during alpha adrenergic blockade. The discrepancy between the actual and the expected findings may be due to either one of the following mechanisms. First, it could be argued that increased arterial renin

TABLE II

Renin Values in Control Conditions during Hemorrhagic Hypotension (HH) and HH + Alpha Adrenergic Blockade (HH + POB)

		Dog No.									
	Condition	1	2	3	4	5	6	7	Mean		P*
Arterial renin concentration, *U/liter*	Control	69	108	125	54	112	53	45	80	P_1	*0.003*
	HH	277	360	517	138	222	121	280	273	P_2	0.366
	HH + POB	427	890	427	177	190	223	288	374	P_3	*0.009*
Venous renin concentration, *U/liter*	Control	116	144	194	54	97	44	61	101	P_1	*0.002*
	HH	804	736	528	219	250	199	670	486	P_2	0.797
	HH + POB	836	1307	374	227	177	379	439	534	P_3	*0.015*
V-A concentration difference, *U/liter*	Control	47	36	69	0	−15	−9	16	20	P_1	*0.034*
	HH	527	376	11	81	28	78	390	213	P_2	0.624
	HH + POB	409	417	−53	50	−17	156	151	159	P_3	0.082
Renin release into renal circulation, *U/min*	Control	9.0	5.0	12.9	0	0	0	3.6	4.3	P_1	0.682
	HH	8.9	7.1	0.3	7.7	0.9	3.3	9.3	5.3	P_2	0.073
	HH + POB	33.9	30.8	0	6.2	0	17 3	28.0	16.6	P_3	0.059

* Differences between control and HH (P_1), HH and HH + POB (P_2), and control and HH + POB (P_3). Student's *t* test.

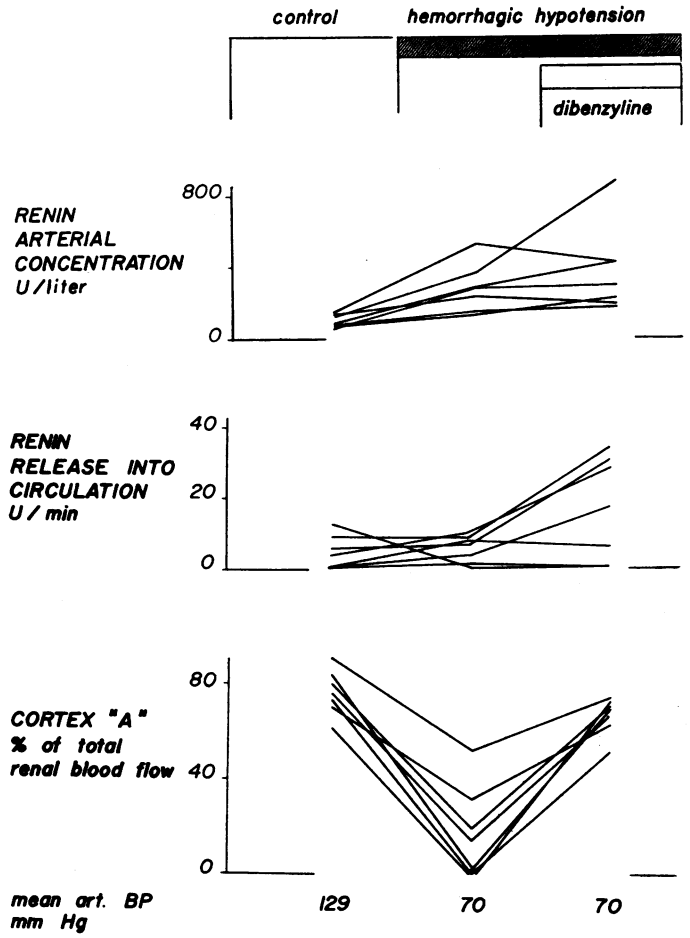

FIGURE 2 Arterial renin concentrations, renin release into the renal circulation, and percentage of renal blood flow supplied to CP I (cortex A) in control conditions, during hemorrhagic hypotension and during α-adrenergic blockade with sustained arterial hypotension.

concentrations and the increased renin release during HH + POB reflect a washout of renin due to an increased renal plasma flow. Second, and more likely, the sustained arterial hypotension acts as a continuous powerful stimulus for renin production. Since sympathetic stimulation (via the renal nerves or by circulating catecholamines) produces outer cortical vasoconstriction similar to that seen in HH (3, 16), the renin production in both conditions could be due to a decreased pressure in some areas of the renal cortex.

In dogs, a hemorrhage of 14–26 ml/kg has been observed to produce an increase in arterial angiotensin of 0.10–0.33 ng/ml (17). Scornik and Paladini (18) reported an increase of 2.43 ng/ml with a hemorrhage of 17–58 ml/kg. In our experiments similar arterial angiotensin concentrations could be expected during hemorrhage (31–53 ml/kg) and even higher values during HH + POB, where arterial renin concentrations and renin release showed a further increase. On the other hand, the intraarterial infusion of angiotensin (0.06–0.25 μg/min) in normotensive dogs has been shown to cause a redistribution of RBF comparable to that observed in HH (19). Calculated for a renal plasma flow of 150 ml/min per kidney, these infusion rates would increase the arterial angiotensin concentrations by 0.4–1.8 ng/ml. In the present experiments, a similar increase in arterial angiotensin concentration during HH + POB did not maintain the typical patchy cortical hypoperfusion of HH. Therefore, there appears to be a decreased responsiveness of the renal vasculature to angiotensin during HH + POB. Various mechanisms could account for this phenomenon. *First,* angiotensin in some vascular beds seems to act by a direct stimulation of the vascular smooth muscle as well as by adrenergic factors (20, 21).

Phenoxybenzamine could interfere with both components of action, either by virtue of its α-blocking action or by blocking the direct effect of angiotensin. Our observations concerning the effect of angiotensin on the intrarenal distribution of blood flow under conditions of α-adrenergic blockade (Table III) suggest that neither mechanism can account for the lack in responsiveness to angiotensin in HH + POB. In normotensive dogs and rats, angiotensin infusions into the renal artery caused a typical redistribution of RBF despite POB having been given in amounts sufficient to block the renal cortical vasoconstriction of HH as well as that of exogenous norepinephrine. These data are in agreement with previous observations concerning total RBF (21): alpha adrenergic blockade by phentolamine did not block the renal vascular response to angiotensin II. Although these findings do not rule out an interference of alpha blockade with the vasoconstrictor action of angiotensin, they do indicate that such an interference in a normotensive animal does not prevent the renal cortical vasoconstriction brought about by angiotensin. *Second,* the decreased responsiveness of the renal vasculature to angiotensin under conditions of HH + POB could be related to the hypotensive state itself. Conditions characterized by a stimulation of the renin-angiotensin system due to hypovolemia are, indeed, generally associated with a diminished pressor responsiveness (25). Since tachyphylaxis seems to develop with high doses of renin and angiotensin only (22), the decrease in responsiveness to angiotensin in our experiments is more likely due to the relaxation of the arterial wall in hypotension and/or to some unknown factors. These mechanisms may explain why, under conditions of HH + POB, in contrast to the normotensive state, angiotensin alone is unable to produce or maintain a redistribution of RBF.

So far, the present experiments indicate that the sympathoadrenergic system is mainly responsible for the pathogenesis of the patchy cortical hypoperfusion of HH while there is no evidence for a significant contribution of the renin-angiotensin system. However, the striking analogy between the pattern of the cortical vasoconstriction and the sites of renin production, as shown by Brown and coworkers (9), remains to be considered

TABLE III

Effect of Phenoxybenzamine (POB) on the Redistribution of Intrarenal Blood Flow Caused by Norepinephrine (NE) and Angiotensin (ANGIO)

	Percentage of total RBF supplied to CP			Local blood flow rate in CP	
	I	II	III + IV	I	II
				ml/min per 100 g	
Dog N					
Control	70	25	5	193	60
NE (2μg/min, kg)	22	60	18	186	93
NE (2 μg/min, kg) + POB (10 μg/min, kg)	59	29	12	417	125
ANGIO (0.5 μg/min, kg) + POB (10 μg/min, kg)	21	69	10	450	78
Dog L					
Control	87	9	4	542	93
ANGIO (0.4 μg/min, kg)	75	21	4	429	110
ANGIO (0.4 μg/min, kg) + POB (10 μg/min, kg)	66	27	7	614	150
Rat 9					
Control	83	12	5	673	112
ANGIO (0.2 μg/min, kg)	77	10	13	441	104
ANGIO (0.2 μg/min, kg) + POB (30 μg/min, kg)	68	18	14	415	71
Rat 11					
Control	81	11	8	609	53
ANGIO (0.2 μg/min, kg)	65	22	13	461	92
ANGIO (0.2 μg/min, kg) + POB (10 μg/min, kg)	42	43	15	369	168

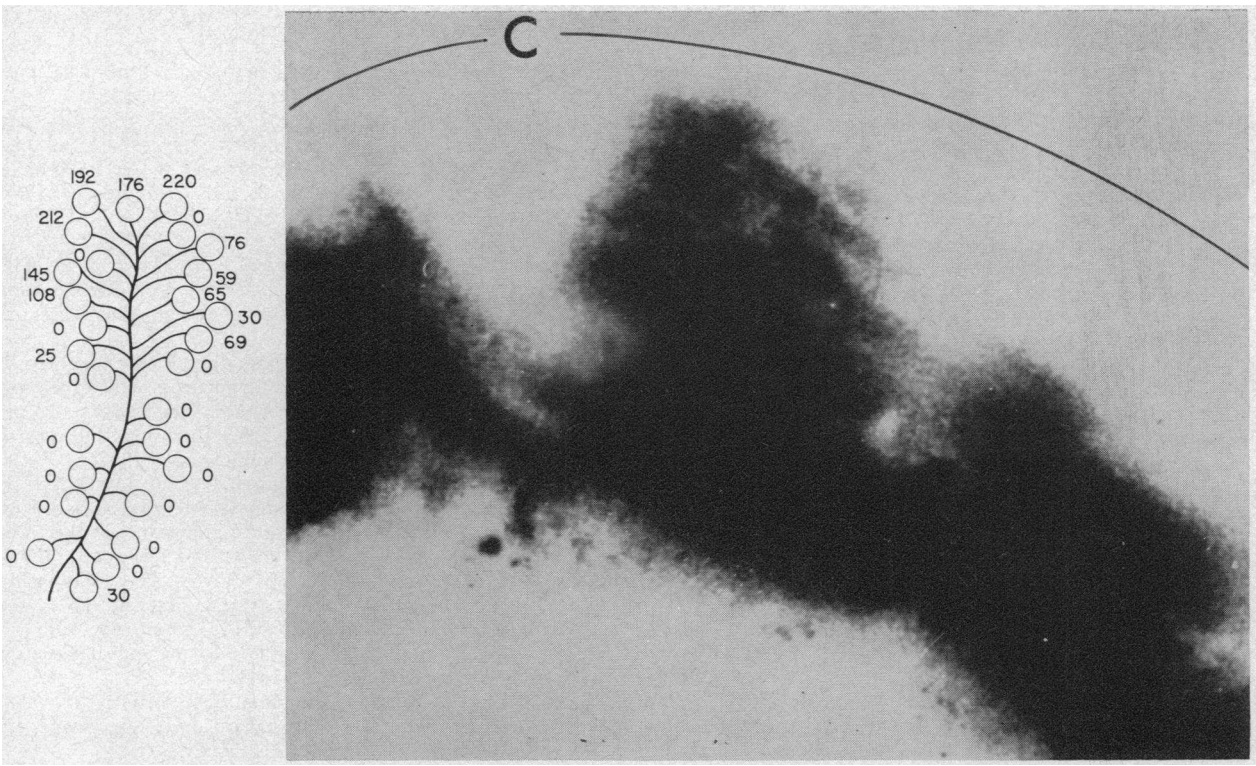

FIGURE 3 Normal distribution of renin in the rabbit renal cortex (9) (left) *versus* distribution of hypoperfused areas (white subcapsular zones) in the renal cortex of a dog in hemorrhagic hypotension (right; ^{85}Kr radioautography, enlarged section from the renal cortex). The renin content of individual glomeruli dissected from a single interlobular artery is highest in the superficial cortical layers where vasoconstriction and hypoperfusion is most accentuated during HH. (C = contour of the renal capsule.)

(Fig. 3). If this analogy is more than pure coincidence, it might be explained on the basis of the model of vascular smooth muscle organization proposed by Pals and Fulton (23). It is postulated that each smooth muscle cell, consisting of a contractile element and a series elastic component, would have one alpha adrenergic receptor and one angiotensin receptor. Only the simultaneous action of both agonists (norepinephrine and angiotensin) would result in a strong contraction of the smooth muscle cells. In contrast, stimulation of only one receptor would result in an ineffective contraction, part of the contractile effort being spent in eliminating the series elastic component. Arterial hypotension would favor this mechanism by further folding the elastic elements. Thus, the higher content in renin and, presumably, in angiotensin (24) of the superficial layers of the cortex would potentiate the vasoconstrictive action of norepinephrine resulting in a preferential hypoperfusion of these segments.

ACKNOWLEDGMENTS

It is a pleasure to acknowledge the skillful assistance of Miss Busslinger and Mr. E. Roth. We are indebted to Dr. H. Strebel for his help and advice in the preparation of the dogs.

This work was supported by Grant Numbers 3.201.69 and 3.167.69 of the Swiss National Funds for the Advancement of Science.

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