

URINARY HEMOGLOBIN EXCRETION AND RENAL CIRCULATORY DYNAMICS: A STUDY OF THE EFFECT OF L-NOREPINEPHRINE IN THE DOG^{1, 2}

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The passage of protein molecules across capillary walls is governed by the characteristics of the molecule and the membrane and appears to occur by a process of both filtration and diffusion. From a study of these processes within the isolated, perfused hind limb of the cat (2, 3) and from mathematical considerations and other studies (2, 4) it has been suggested that the transcapillary transport of protein and the degree of molecular sieving of protein molecules across membranes during ultrafiltration may be influenced by concentration gradients of protein between filtrate and filtrand and by the rate of filtration of water through the capillary wall. Moreover, it has been suggested that these processes may be influenced by factors which modify the level of hydrostatic pressure within the capillary (2, 5, 6).

Within the kidney these processes have not been subjected to extensive study. That intraglomerular hydrostatic pressure may modify the rate of filtration of protein molecules has been suggested by experiments in which renin, which presumably elevates intraglomerular pressure, has been shown to accelerate the urinary excretion of plasma proteins (7, 8) and hemoglobin (9). A change in pressure has also been invoked to account, at least in part, for the augmentation of protein clearances following the administration of serum albumin intravenously to patients with renal disease (5).

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Of molecular sieving within the kidney and of the influence of changes in glomerular filtration rate, little is known.

In the present investigation these factors were examined in normal, anesthetized dogs. The rate of urinary excretion and renal clearance of hemoglobin were studied under conditions in which renal hemodynamics and glomerular filtration rate were modified by infusions of the adrenal medullary hormone, l-norepinephrine.

METHOD

A study of the effects of l-norepinephrine was made in 20 female mongrel dogs weighing 7 to 20 kg. All animals were deprived of food, but not water, for 24 hours prior to the test. Anesthesia was induced with sodium pentobarbital, 30 mgm. per kg. intravenously, and was maintained by the administration of 100 mgm. of this drug at intervals throughout the study. An indwelling needle was placed in a femoral artery. Priming and sustaining infusions of creatinine and p-aminohippurate were administered intravenously for measurement of glomerular filtration rate and renal plasma flow, respectively. Along with these substances, solutions of dog hemoglobin were administered intravenously in amounts sufficient to maintain a relatively constant arterial plasma level of hemoglobin of from 212 to 504 mgm. per cent, values well above the renal threshold (10). Priming doses consisted of from one to two grams of hemoglobin in 50 ml. of 5 per cent dextrose and distilled water. The sustaining infusion contained hemoglobin in a concentration of from 430 to 760 mgm. per cent and was made up in 5 per cent dextrose and distilled water. This was administered at a constant rate of from 1 to 2 mgm. of hemoglobin per minute.

After allowing 30 minutes for equilibration of these substances, the urine, collected by urethral catheter, was discarded and the bladder was washed out with distilled water and emptied by manual compression after the introduction of air to facilitate emptying. Three consecutive 10 to 20-minute control clearance periods were then obtained. Following this an infusion of l-norepinephrine (16 μ g. per ml.) was administered intravenously at a rate sufficient to elevate mean arterial blood pressure, measured with a mercury manometer, 20 to 50 mm. Hg. This

TABLE I

*Urinary hemoglobin excretion and renal hemodynamics during the infusion of L-norepinephrine**

Dog No.	Wt. Kg.	Procedure	B.P. mm. Hg	HR min.	GFR ml./min.	RPF ml./min.	FF	P _{Hgb} mgm. %	U _{Hgb} V mgm./min.	C _{Hgb} ml./min.	$\frac{C_{Hgb}}{C_{cr}}$ %
3	10	Control	114	120	54	112	.482	250	3.04	1.22	2.28
		Infusion	165	72	41	76	.541	305	4.22	1.38	3.42
7	17	Control	94	140	35	70	.501	249	2.30	0.92	2.65
		Infusion	140	180	21	34	.620	348	4.22	1.12	5.71
8	20	Control	104	120	98	207	.471	212	2.11	0.93	0.99
		Infusion	140	120	85	147	.587	223	4.18	1.87	2.18
9	7	Control	85	160	48	87	.552	504	4.58	0.91	2.09
		Infusion	115	140	20	43	.473	501	3.71	0.74	3.71
10	7	Control	110	160	31	135	.230	394	0.72	0.18	0.61
		Infusion	135	128	39	118	.350	470	2.28	0.48	1.26
11	8	Control	85	130	27	131	.203	354	1.90	0.54	2.04
		Infusion	130	100	8	23	.427	403	1.71	0.43	5.69
12	12	Control	95	140	31	92	.339	317	2.18	0.68	2.20
		Infusion	130	128	26	82	.316	379	4.40	1.16	4.46
13	13	Control	120	132	32	117	.276	308	2.35	0.77	2.44
		Infusion	150	—	17	50	.355	391	6.97	1.79	10.36
14	9	Control	100	132	24	76	.320	336	2.66	0.89	3.83
		Infusion	130	168	13	36	.428	397	3.47	0.91	8.22
15	7	Control	90	124	23	53	.435	395	3.12	0.88	3.90
		Infusion	110	160	15	33	.466	410	4.30	1.06	7.68
16	15	Control	90	156	44	111	.406	244	2.71	1.12	2.56
		Infusion	120	160	38	91	.415	283	3.28	1.16	3.70
19	13	Control	105	132	23	56	.434	244	3.62	1.50	6.54
		Infusion	135	120	12	30	.397	310	3.16	1.03	8.83
31	16	Control	100	112	98	209	.473	460	2.07	0.45	0.47
		Infusion	150	100	88	177	.496	523	3.52	0.68	0.77
32	12	Control	100	92	70	108	.648	301	1.69	0.56	0.80
		Infusion	130	140	62	99	.630	405	3.02	0.75	1.21
17	9	Control	98	148	38	106	.358	285	1.94	0.69	1.81
		Infusion	140	120	27	59	.470	321	2.40	0.76	2.91
		Recovery	70	134	32	75	.422	331	2.79	0.85	2.70
18	9	Control	95	148	37	100	.375	273	2.26	0.83	2.22
		Infusion	130	120	18	43	.499	300	2.76	0.92	7.59
		Recovery	90	140	25	63	.416	301	3.19	1.06	4.08
25	9	Control	95	100	62	94	.655	246	3.96	1.65	2.73
		Infusion	140	132	56	90	.615	323	3.62	1.12	2.04
		Recovery	90	98	57	98	.576	331	5.79	1.74	3.02
33	13	Control	110	120	44	117	.396	477	2.67	0.56	1.28
		Infusion	160	100	32	57	.555	598	5.50	0.92	2.91
		Recovery	75	138	41	90	.459	593	4.25	0.71	1.71
34	10	Control	110	84	69	104	.663	345	1.10	0.32	0.47
		Infusion	160	136	59	90	.655	419	2.40	0.57	0.98
		Recovery	75	138	66	142	.471	406	2.01	0.50	0.76
35	12	Control	120	144	32	82	.394	341	1.25	0.38	1.16
		Infusion	160	128	19	35	.553	450	2.83	0.63	3.55
		Recovery	—	—	19	59	.334	441	1.36	0.30	1.74

* All values are averages of three determinations. L-norepinephrine was administered intravenously during infusion periods. Abbreviations are as follows: BP = mean arterial blood pressure; HR = heart rate, beats per minute; GFR = glomerular filtration rate (creatinine clearance); RPF = renal plasma flow (PAH clearance); FF = filtration fraction (GFR/RPF); P_{Hgb} = plasma hemoglobin concentration; U_{Hgb}V = urinary hemoglobin excretion; C_{Hgb} = clearance of hemoglobin; C_{Hgb}/C_{cr} = hemoglobin-creatinine clearance ratio.

required between 4 and 50 μg . of l-norepinephrine per minute. In most animals the amount necessary to maintain arterial pressure at the desired level increased progressively throughout the test. After elevation of the arterial pressure for approximately 15 minutes the urine was discarded and three consecutive 10 to 20-minute clearance periods were obtained during the pressor response to l-norepinephrine. In each of six animals (17, 18, 25, 33, 34, and 35) three recovery periods were obtained immediately following cessation of the infusion of l-norepinephrine.

Urinary and plasma concentrations of hemoglobin were determined by the method of Evelyn and Malloy (11). Creatinine concentrations in urine and plasma were assayed by the method of Bonsnes and Tausky (12) and PAH levels were determined by the method of Smith, Finkelstein, Aliminoso, Crawford, and Graber (13). Hemoglobin-saline solutions were prepared according to the method of Amberson, Jacobs, Hisey, and Monke (14). Solutions of hemoglobin prepared in this manner were dialyzed against normal saline at 8°C for 48 hours. After filtration through a Seitz filter the solution was stored in

a sterile container at 8°C for periods not exceeding two weeks.

RESULTS

The results of the effects of l-norepinephrine on renal hemodynamics and hemoglobin excretion are presented in Table I and in Figures 1 to 6. An illustrative experiment is presented in Figure 1 (dog 33).

Systemic circulatory response

During the infusion of l-norepinephrine the arterial blood pressure increased from 20 to 50 mm. Hg, with a mean change of 38 mm. Hg. Considerable variation was encountered in the pressor response to l-norepinephrine. Some animals required as much as 50 μg . per minute to maintain the pressure within this range whereas others re-

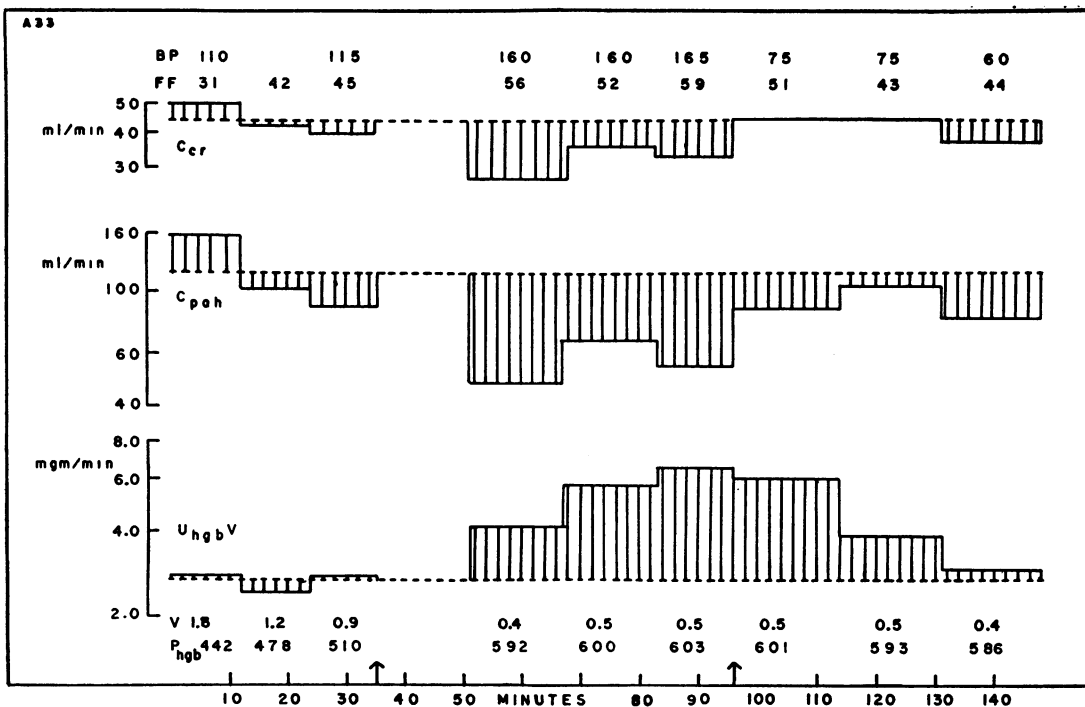


FIG. 1. THE EFFECT OF L-NOREPINEPHRINE ON RENAL FUNCTION AND URINARY HEMOGLOBIN EXCRETION (DOG 33)

Glomerular filtration rate (C_{cr} -creatinine clearance), renal plasma flow (C_{PAH}), urinary hemoglobin excretion (U_{HgbV}) and mean arterial blood pressure (BP) were determined before, during and following the administration of l-norepinephrine. The drug was given intravenously during the time noted between the arrows. The urine obtained during the first 15 minutes after beginning infusion was discarded because of intrarenal delay. Urinary hemoglobin excretion increased in association with a rise in arterial pressure and plasma hemoglobin concentration (P_{Hgb} , at bottom) and a fall in glomerular filtration rate and renal plasma flow. The filtration fraction increased. Urine flow (V) diminished. After the infusion was discontinued all values returned towards control levels.

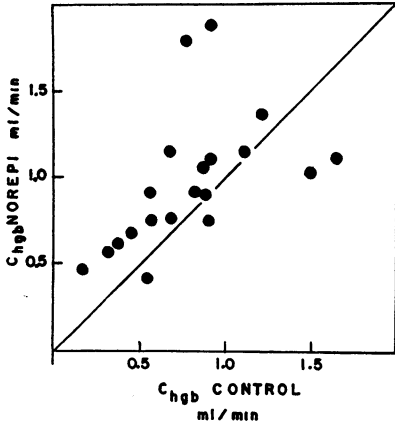


FIG. 2. THE EFFECT OF L-NOREPINEPHRINE ON THE RENAL CLEARANCE OF HEMOGLOBIN

The averaged values for the clearance of hemoglobin during the control periods are plotted against the clearances of this protein during the pressor response to l-norepinephrine. The clearance of hemoglobin increased in 14 studies, decreased in 4, and remained unchanged in 2.

quired as little as 4 μ g. per minute. After the infusion was discontinued the blood pressure returned promptly to control levels or below. Two dogs (17 and 33) became hypotensive at this time (Table I). In most animals the cardiac rate decreased 20 to 30 beats per minute during infusion of l-norepinephrine; in others, a tachycardia with

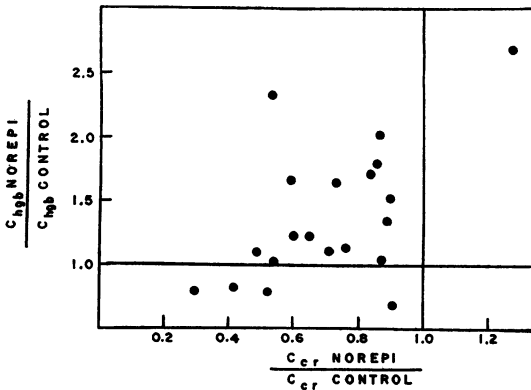


FIG. 3. THE RELATIONSHIP BETWEEN THE CHANGES IN THE CLEARANCE OF HEMOGLOBIN AND THE CLEARANCE OF CREATININE DURING THE PRESSOR RESPONSE TO L-NOREPINEPHRINE

The ratio of the infusion to the control values of the clearance of hemoglobin is plotted against the changes in the creatinine clearance. The clearance of hemoglobin tended to increase during the infusion of l-norepinephrine except in those instances when the reduction in the creatinine clearance exceeded 50 per cent of control values.

varying degrees of irregularity of cardiac rhythm was observed.

Renal hemodynamics

During control observations prior to the infusion of l-norepinephrine the mean renal plasma flow for the entire group of 20 animals was 100 ml. per 10 kg. body weight per minute, a value less than that reported (15) for normal dogs under basal conditions—135 ml. per 10 kg. body weight per minute. The mean renal filtration fraction (GFR/RPF) was 0.43, a value higher than that reported (15) for normal animals — 0.32. These differences may be attributed to the administration

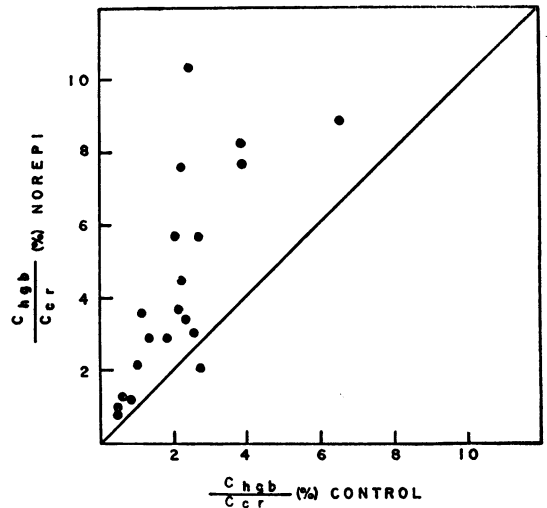


FIG. 4. THE EFFECT OF L-NOREPINEPHRINE ON THE HEMOGLOBIN-CREATININE CLEARANCE RATIO

The control values of the hemoglobin-creatinine ratios (C_{Hgb}/C_{Cr}) are plotted against these ratios obtained during the infusion of l-norepinephrine. The hemoglobin clearance increased relative to the creatinine clearance in all studies but one.

of hemoglobin, which elicits intrarenal vasoconstriction (16). The mean glomerular filtration rate was 41 ml. per 10 kg. body weight per minute, a figure not significantly different from normal values (15).

During infusion of l-norepinephrine renal plasma flow (RPF, Table I) decreased in all dogs but one (dog 25). The mean renal plasma flow at this time was 63 per cent of control values, with a range of 16 to 96 per cent of control levels. Glomerular filtration rate (GFR, Table I) diminished more than 10 per cent in 17 dogs (range of

change, 11 to 70 per cent), remained unchanged in two (dogs 25 and 31) and increased in one (dog 10). For the entire group the mean value of GFR during the infusion of l-norepinephrine was 71 per cent of control levels. There was no correlation between the magnitude of blood pressure elevation and the degree of change in GFR. The correlation between the rate of infusion of l-norepinephrine and the change in GFR was significant ($r = -.446$; $p < .05 > .01$). The filtration fraction (FF, Table I) increased in 11 dogs, decreased in 4 and remained unchanged in 5. On cessation of infusion of l-norepinephrine RPF, GFR, and FF returned towards control values (recovery period, Table I).

Urinary hemoglobin excretion ($U_{Hgb}V$, Table I, Figure 1) increased during the pressor response to l-norepinephrine in 17 studies, decreased in 2 (dogs 9 and 11) and remained unchanged in one (dog 25). The mean excretory rate at this time was 166 per cent of control values with a range of 81 to 316 per cent. These changes in excretion were usually but not invariably accompanied by an increase in the concentration of hemoglobin in plasma. In 17 animals the plasma level of hemoglobin increased 10 to 40 per cent (mean change, 20 per cent); in three (dogs 8, 9 and 25) the plasma level did not change. The rise in plasma concentration may be attributed to the hemocon-

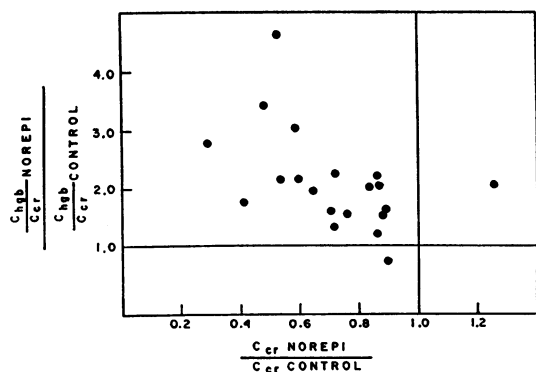


FIG. 5. THE RELATIONSHIP BETWEEN THE CLEARANCE OF CREATININE AND THE HEMOGLOBIN-CREATININE CLEARANCE RATIO DURING THE PRESSOR RESPONSE TO L-NOREPINEPHRINE

The ratio of the infusion to the control values of the hemoglobin-creatinine clearance ratios (C_{Hgb}/C_{Cr}) is plotted against the ratio of the infusion to control values of the clearance of creatinine (C_{Cr}). As C_{Cr} diminished, the clearance of hemoglobin increased relative to creatinine. In one study C_{Hgb}/C_{Cr} increased as C_{Cr} rose.

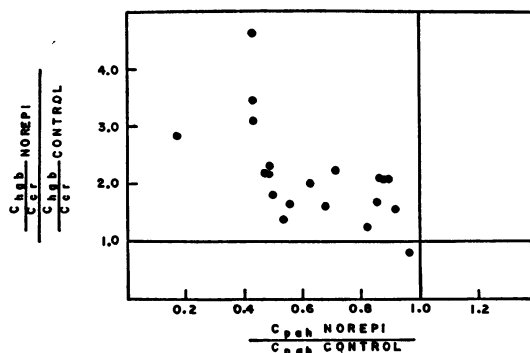


FIG. 6. THE RELATIONSHIP BETWEEN THE CLEARANCE OF PAH AND THE HEMOGLOBIN-CREATININE CLEARANCE RATIO DURING THE PRESSOR RESPONSE TO L-NOREPINEPHRINE

The ratio of the infusion to the control values of the hemoglobin-creatinine clearance ratios (C_{Hgb}/C_{Cr}) is plotted against the ratio of the infusion to the control values of the PAH clearance. As the clearance of PAH diminished, the clearance of hemoglobin increased relative to creatinine.

centrating effects of l-norepinephrine (17, 18) and, in some instances, to a greater rate of administration than of excretion of hemoglobin.

The renal clearance of hemoglobin (C_{Hgb} , Table I) showed similar directional changes (Figure 2). However, since the concentration of hemoglobin in plasma increased in most studies, the percentage change in hemoglobin clearance was less than that of hemoglobin excretion. C_{Hgb} increased in 14 animals, decreased in 4 (dogs 9, 11, 19 and 25) and remained unchanged in 2 (dogs 14 and 16). This variability may be attributed in part to the magnitude of the reduction in the volume of glomerular filtrate, since the clearance of hemoglobin tended to fall when GFR was reduced more than 50 per cent (Figure 3). The mean C_{Hgb} during the infusion of l-norepinephrine was 137 per cent of control values with a range of 69 to 267 per cent.

On cessation of the infusion, the excretion and clearance of hemoglobin returned towards control values in three studies (dogs 33, 34 and 35) and increased in three (dogs 17, 18 and 25). The increase in dog 25 was spurious since this animal developed gross hematuria during the recovery periods.

The hemoglobin-creatinine clearance ratio (C_{Hgb}/C_{Cr} , Table I) increased in every study but one (dog 25) (Figure 4). The mean value during the

administration of l-norepinephrine was 211 per cent of control levels with a range of 75 to 463 per cent. The correlation between the changes in this ratio and GFR was of borderline significance ($r = -0.436$; $p < .10 > .05$) (Figure 5).⁵ The correlation between the changes in $C_{\text{Hgb}}/C_{\text{Cr}}$ and RPF was significant ($r = -0.590$; $p < .01$) (Figure 6). On cessation of the infusion of l-norepinephrine the hemoglobin-creatinine clearance ratio returned towards control levels in all animals except dog 25, which developed gross hematuria.

DISCUSSION

Hemoglobin molecules circulating in plasma are excreted in the urine at a rate which is determined by the rate of transport of these molecules across the glomerular membrane and by the capacity of the renal tubular cells to abstract this protein from glomerular filtrate during the process of urine formation. The present study suggests that either one or both of these processes concerned in hemoglobin excretion may be modified during the pressor response to l-norepinephrine. The increase in urinary excretion and in the renal clearance of hemoglobin elicited by the infusion of l-norepinephrine may be attributed to either an increase in transglomerular transport of hemoglobin or to a decrease in tubular reabsorption, or to both. Although the precise mechanism of this excretory response was not established, the magnitude of the changes suggests that alterations in tubular reabsorption alone were not responsible. In dogs 12, 13, and 33 the increment in hemoglobin excretion exceeded 2.0 mgm. per minute (by 2.2, 4.62, and 2.83 mgm. per minute, respectively), the approximate maximal rate of tubular reabsorption of hemoglobin in dogs the size of those employed in the present study (10). Hence, the augmented hemoglobin excretion may be attributed, at least in part, to a more rapid rate of transfer of hemoglobin molecules into glomerular filtrate. Whether changes in tubular reabsorption also occurred is not known.

The mechanism of this alteration in transglomerular transport is not clear. Since the concen-

⁵ When the one study (dog 10) in which the creatinine clearance increased is omitted from these calculations, the correlation between GFR and $C_{\text{Hgb}}/C_{\text{Cr}}$ is significant ($r = -0.539$; $p < .02 > .01$).

tration of hemoglobin in glomerular filtrate rises in a linear manner as plasma hemoglobin concentration increases (10, 19), the increment in plasma concentration usually elicited in the present study by the infusion of l-norepinephrine undoubtedly contributed to this increase in transport in most studies. However, the increase in plasma level was inconstant (dogs 8 and 9) and was insufficient in most instances to account for the magnitude of the increment in the clearance of hemoglobin and in the hemoglobin-creatinine clearance ratio.⁶ Hence other factors appear to have been operative as well to augment the glomerular transport of this protein.

That alterations in glomerular filtration rate may have initiated these changes in transport must

⁶ This view can be illustrated by theoretical calculations of the change in the clearance of hemoglobin and in the hemoglobin-creatinine clearance ratio to be expected by a 20 per cent increase in the plasma hemoglobin concentration, the average increment observed in the present study during the infusion of l-norepinephrine.

(a) Assuming the following values: plasma hemoglobin concentration, 3.0 mgm. per ml.; creatinine clearance, 40 ml. per minute; glomerular permeability to hemoglobin, 5 per cent of the creatinine clearance (18); and T_{Hgb} , 2.0 mgm. per minute:

$$\begin{aligned}\text{Filtered Hgb} &= 3.0 \times 40 \times .05 \\ &= 6.00 \text{ mgm./min.}\end{aligned}$$

$$\text{Reabsorbed Hgb} = 2.00 \text{ mgm./min.}$$

$$\text{Excreted Hgb} = 4.00 \text{ mgm./min.}$$

$$C_{\text{Hgb}} = \frac{4.00}{3.00} = 1.33 \text{ ml./min.}$$

$$C_{\text{Hgb}}/C_{\text{Cr}} = \frac{1.33}{40} = .033$$

(b) Assuming a 20 per cent increase in P_{Hgb} and no change in glomerular permeability or tubular reabsorption:

$$\begin{aligned}\text{Filtered Hgb} &= (3.0 + 0.6) \times 40 \times .05 \\ &= 7.20 \text{ mgm./min.}\end{aligned}$$

$$\text{Reabsorbed Hgb} = 2.00 \text{ mgm./min.}$$

$$\text{Excreted Hgb} = 5.20 \text{ mgm./min.}$$

$$C_{\text{Hgb}} = \frac{5.20}{3.60} = 1.44 \text{ ml./min.}$$

$$C_{\text{Hgb}}/C_{\text{Cr}} = \frac{1.44}{40} = 0.36$$

$$\text{Per cent change in } C_{\text{Hgb}} = 8 \text{ per cent.}$$

$$\text{Per cent in } C_{\text{Hgb}}/C_{\text{Cr}} = 9 \text{ per cent.}$$

These changes are less than those determined experimentally (average experimental change in C_{Hgb} , 37 per cent and in $C_{\text{Hgb}}/C_{\text{Cr}}$, 111 per cent). Hence an increase in plasma hemoglobin concentration of 20 per cent cannot alone account for the observed alterations.

be considered in view of the relationship between protein transport and filtration rate as formulated in the theory of molecular sieving. According to this theory, the concentration of protein in capillary filtrates increases as the rate of formation of filtrate diminishes, owing to differences in the diffusion characteristics of protein and water (creatinine) molecules (2-4). Although GFR characteristically fell in the present study, the role of this reduction is obscure. That the excretory response to l-norepinephrine may have been *modified* by changes in GFR is evident in Figure 3, which shows that the typical increase in hemoglobin clearance was abolished by marked decrements of GFR.⁷ But whether adjustments of GFR *initiated* the excretory response to l-norepinephrine in accordance with the concept of molecular sieving is not clear. In one study (dog 10) the clearance of hemoglobin increased (both in absolute terms and relative to creatinine) in association with an increase rather than a decrease in GFR. Moreover, the relationship between filtration rate and protein transport is uncertain owing to doubt concerning the mechanism of the reduction of GFR in the dog during the vasoconstrictive response to l-norepinephrine. If, as has been suggested (20), filtration diminishes as a result of selective cessation of glomerular activity in a portion of the nephron population, the theory of molecular sieving as outlined cannot account for the changes in hemoglobin clearance elicited in the present study. Since, under these circumstances, filtration would be unaltered in those nephrons contributing to urine formation, the relationship between the transglomerular transport of hemoglobin and creatinine would not change in these nephrons and the hemoglobin-creatinine clearance ratio would remain constant. If, however, GFR decreases by a generalized, partial reduction of filtration in active nephrons, or if variable alterations of filtration rate in residual, active glomeruli occur during nephron exclusion, the transport of hemoglobin across the glomerular membrane of functioning

⁷ The decrease in the clearance of hemoglobin under these circumstances may be attributed to the marked reduction in the volume of glomerular filtrate. Since the clearance of hemoglobin increased relative to creatinine in these instances, the factors tending to augment the transglomerular transfer of hemoglobin appear to have been operative in these as in the other studies.

nephrons might increase relative to creatinine in accordance with the theory of molecular sieving and the clearance of hemoglobin would rise relative to creatinine. Until, however, the precise mechanism of the reduction of GFR is established, the role of these changes in filtration rate cannot be evaluated.

Studies of the effects of plasma volume expansion on proteinuria (5) and of the effect of renin on the excretion of hemoglobin and plasma proteins in rabbits and rats (7-9) have suggested that the transport of protein molecules across the glomerular membrane may be conditioned by the level of intracapillary hydrostatic pressure. Renin, which has hemodynamic effects in the kidney similar to those elicited by l-norepinephrine, is thought to elevate intraglomerular pressure by vasomotor adjustments of the efferent and afferent arterioles (8). This rise in pressure, it has been suggested (8), accelerates the filtration and/or diffusion of protein across the glomerular membrane by mechanisms which are not clear, but which may be related to stretching of the glomerular membrane (5). Whether l-norepinephrine acts in a similar manner is not known. A rise in intraglomerular pressure would be expected to elevate glomerular filtration rate relative to renal plasma flow (an increase in the renal filtration fraction), a functional pattern which is elicited by both renin and l-norepinephrine. But whether this relationship between filtration rate and plasma flow actually reflects adjustments of intraglomerular pressure is not clear (15). Moreover, if nephron exclusion occurs during the administration of l-norepinephrine, a variable and uncertain relation between flow and filtration may exist in active and inactive nephrons and hemodynamic interpretation of the filtration fraction would be impossible. Hence the changes in protein transport elicited in the present study cannot be evaluated in terms of adjustments of intraglomerular pressure. Whether the level of hydrostatic pressure genuinely influences protein transport has not been unequivocally established. The precise role of this factor in the kidney and other sites remains to be determined.

That hemodynamic adjustments within the kidney may have altered the transport of hemoglobin across the glomerular membrane independently of alterations in glomerular filtration rate and intraglomerular pressure is possible. The relationship

illustrated in Figure 6 indicates that as renal plasma flow diminished the clearance of hemoglobin increased relative to creatinine. Whether this correlation indicates a causal relationship between renal plasma flow and transglomerular hemoglobin transport is, however, not clearly established. Moreover, the mechanism by which changes in renal plasma flow might condition hemoglobin transport is obscure. An increased rate of transglomerular transport might occur under these conditions as a result of a reduction in the rate and velocity of blood flow through the glomerulus. If these changes in glomerular blood flow accompany a reduction in renal blood flow, the contact between hemoglobin molecules and the glomerular capillary wall may be prolonged, thus allowing more time for the diffusion of these molecules into glomerular filtrate.

This view may explain in part the relatively high values recorded for the glomerular permeability to hemoglobin in both man and dog, since the administration of this protein intravenously is attended by intrarenal vasoconstriction and a reduction of renal blood flow (16). Moreover, the higher values for glomerular permeability elicited when the rate of intravenous administration is increased (19) may be attributable to a greater reduction of blood flow through, and an increased rate of diffusion of hemoglobin from, the glomerulus under these conditions.

SUMMARY

The administration of pressor doses of 1-norepinephrine to anesthetized dogs elicited abrupt alterations in the urinary excretion and renal clearance of hemoglobin. When renal vasoconstriction was moderate, the clearance of hemoglobin increased; when renal vasoconstriction was intense and glomerular filtration rate diminished sharply, hemoglobin clearance decreased or remained unchanged, presumably since less filtrate was available for excretion under these conditions. Since the clearance of hemoglobin increased relative to filtration in all studies but one, regardless of the intensity of the vasoconstrictive adjustments, and since this change could not be attributed to a decrease in tubular reabsorption of hemoglobin alone, the administration of 1-norepinephrine apparently

elicited an acceleration in the transglomerular capillary transport of hemoglobin molecules.

The mechanism of this change in transport was not determined. An increase in plasma hemoglobin concentration usually occurred and contributed to, but was not alone responsible for, the increase in transglomerular hemoglobin transport. The possibility that alterations in renal blood flow played a role was considered. The way in which a reduction in flow might have acted was not established, but it was suggested that if the rate and velocity of glomerular blood flow diminished as renal blood flow decreased, the contact between hemoglobin molecules and the glomerular membrane may have been prolonged, thus allowing more time for the diffusion of those molecules into glomerular filtrate. Although adjustments of glomerular filtration rate and intraglomerular hydrostatic pressure may have contributed to the observed changes in hemoglobin transport, the role of these adjustments could not be evaluated in the present study.

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