Influence of Aortic Constriction on the Positive Free-Water Clearance of Primate Hemorrhagic Shock[1] (36430)

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A cardinal manifestation of the shock kidney is a loss of urinary concentrating ability, most commonly observed in dogs (1, 2) and owl monkeys (3, 4) following retransfusion and restoration of arterial blood pressure after prolonged hypotension. Indeed, C_{H_2O} (free-water clearance) may become positive, and U/P_{Osm} decrease to less than unity as a part of the syndrome. Recently, such changes have been observed by Jones and Weil (5) in patients with acute circulatory failure of various etiologies, so that the relevance of the mechanism to human renal pathophysiology is clearly evident.

Although wash-out of the gradient of osmolality of the kidney may largely account for the failure of the concentrating mechanism, the development of positive C_{H_2O} requires another explanation. It is possible that circumstances are created which result in failure of attainment of equilibrium in the distal convolution and collecting duct. A loss of residual sensitivity of the distal nephron to ADH may contribute to the phenomenon.

The present investigation has explored the nature of the derangement of urinary concentrating mechanism by the reduction of solute and water load to the distal segment by experimental reduction in glomerular filtration rate. This was achieved by partial aortic constriction during the phase of positive free-water clearance which is commonly seen in the immediate posttransfusion period in well-hydrated animals.

Methods. Experiments were carried out on a total of 12 male owl monkeys, averaging 830 g body weight (BW). They were anesthetized with 40 mg/kg BW of pentobarbital administered intraperitoneally, with additional minimal booster doses given when necessary during the course of the experiment. Surgical procedures included exposure of the kidneys by flank incision so that the ureters could be catheterized with fine polyethylene tubing for urine collection. A tourniquet was placed around the abdominal aorta just above the renal arteries. Usually data were derived for only one kidney (left). In four animals of the hydrated series, it was possible to place the tourniquet around the aorta between the two renal arteries, so that the upper (right) kidney served as a control for the lower (left) kidney, to which the arterial pressure was reduced. One femoral artery was catheterized for the registration of mean arterial pressure and for blood sampling, and the other artery was catheterized to allow bleeding into an overhanging reservoir. A femoral vein was catheterized for infusion of maintenance solutions.

The general protocol of the experiment was as follows: Following two control periods of 15 min duration each, arterial pressure was reduced to 60 mm Hg for 75 min by hemorrhage into the bleeding reservoir. Two consecutive clearance periods of 30 min duration were taken at this level. Further hemorrhage then reduced the mean arterial blood pressure to 40 mm Hg where it was maintained for a second phase of 45 min duration, before transfusion intra-arterially of the heparinized blood. One 30 minute period was taken at this level of hypotension. The average maximal bleeding volume was 29.4 ml/kg BW (SD 7.7).

After transfusion, 20 mg of protamine sul-

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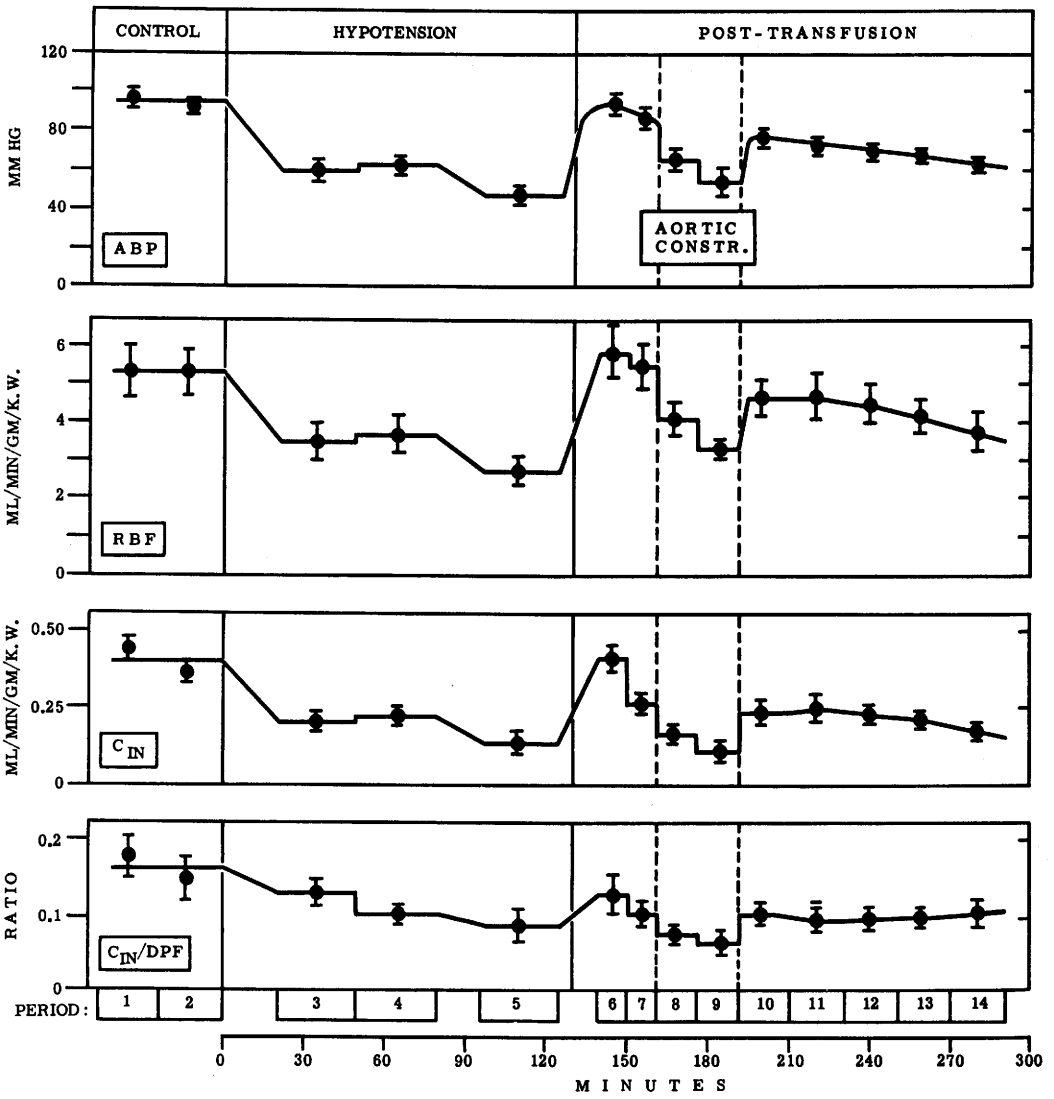

FIG. 1. Hemodynamic alterations in hydrated animals resulting from hemorrhagic hypotension and retransfusion, with effects of graded aortic constriction instituted 35 min posttransfusion (N = 7). Values are given in Figs. 1–5 as mean ± 1 SE. (ABP) arterial blood pressure; (RBF) renal blood flow; (C_{In}) inulin clearance; (DPF) direct plasma flow.

fate were immediately administered to circumvent continued bleeding from surgical sites in the posttransfusion phase. After restoration of blood volume, the observations were continued for a total of 3 hr, at which time the animals were sacrificed. Urine collection was resumed 15 min after transfusion, with two 10 min periods preceding two stages of reduction of arterial pressure, each of 15 min duration. Then the aortic constriction was released, and consecutive 20 min periods were observed until the end of the experiment.

PAH was infused at a rate adequate to give plasma concentrations suitable for calculation of effective plasma flow (EFP), and inulin was given to permit calculation of GFR. Sodium was measured in plasma and urine, as were osmolar constituents. All substances were infused in a small volume (0.12

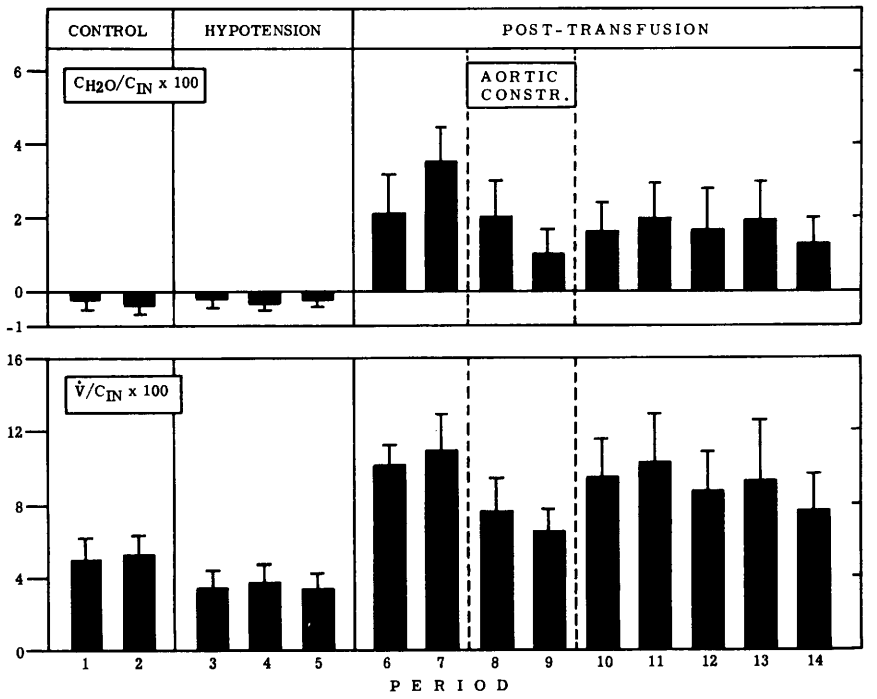

FIG. 2. Alterations in free water clearance (C_{H_2O}) and urine volume ($\dot{V}$) resulting from the hemodynamic changes depicted in Fig. 1. Data are calculated as a fraction of the inulin clearance, and in effect represent percentage of filtrate volume.

ml/min) in order to disturb minimally the base-line volume and electrolyte excretion rates. Renal blood flow was measured with a Carolina Medical Electronics, Inc. electromagnetic flowmeter utilizing a cuff probe around the left renal artery. Pressure and flow were recorded on a Brush polygraph. Blood samples for renal clearance analysis were taken at approximately midpoint of the urine collection periods, with delay time corrections made if plasma concentrations were changing. Usually, reasonable constancy of the plasma levels of the infused substances minimized clearance errors. Urine samples were collected under oil to prevent evaporative losses before analysis.

The animals were divided into two groups. One group of 7 animals was allowed food and water *ad libitum* until the morning of the experiment, and were assumed to be in normal fluid balance. Another group of 5 animals was dehydrated for 24 hr before the hemorrhagic shock procedure.

Chemical procedures. Inulin determinations were made by the anthrone method of Davidson and Sackner (6) and PAH by the method of Smith *et al.* (7). Plasma concentrations were measured from TCA filtrates. Sodium was measured in a Beckman atomic absorption spectrophotometer, and osmolalities by an Advanced Instrument, Inc., osmometer.

Results. I. Hydrated animals. Figure 1 reveals the hemodynamic alterations which result from graded hemorrhagic hypotension in the hydrated animals. After retransfusion, aortic constriction caused the femoral arterial pressure, taken as the pressure supplying the renal arteries, to decrease from 87 to 66 and 55 mm Hg, successively, then immediate restoration to 76 mm upon release. Accompanying the resulting decremental decline in RBF, C_{In} decreased from an average of 0.33 ml/min/g KW (kidney weight) just prior to constriction to 0.170 and 0.114 in successive stages, then returned to 0.24 ml/min/g upon release of the tourniquet.

The influence of these changes on urine

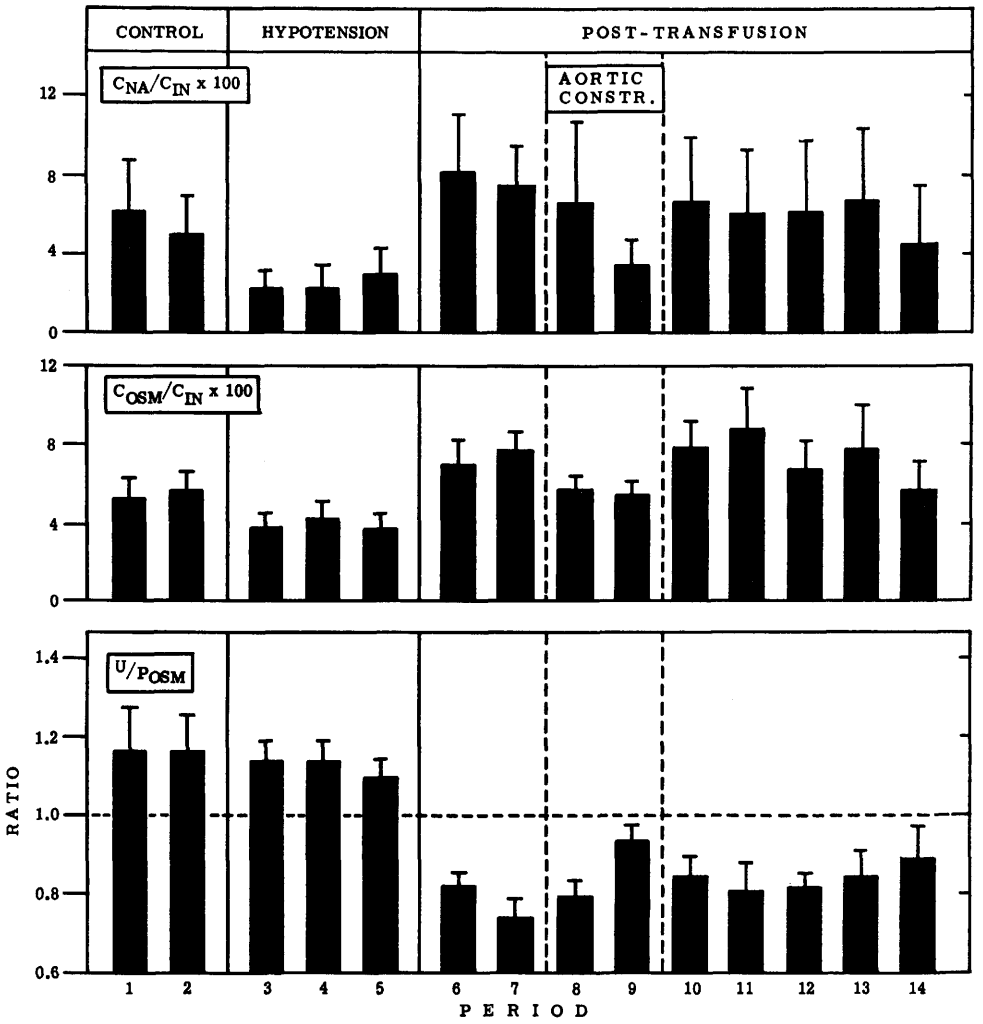

FIG. 3. Changes in C_{Na}, C_{Osm}, and U/P_{Osm} corresponding to alterations shown in Figs. 1 and 2.

volume and free water clearance is shown in Fig. 2. In order to bring out any underlying influence on the functional parameters, the values here and in Fig. 3 are expressed as a fraction of the inulin clearance, *e.g.*, $C_{H_2O}/C_{In} \times 100$.

Free-water clearance was slightly negative during the control and hypotension, but became typically positive following transfusion. Aortic constriction caused $C_{H_2O}/C_{In} \times 100$ to decrease in steps from 3.48 to 1.99 and 1.06; the last value was a significant reduction ($p = .05$).

Fractional urine volume ($\dot{V}/C_{In} \times 100$), which was significantly above control (periods 6 and 7 following transfusion), also declined in a similar manner during aortic constriction. Both functions tended to be restored upon release of the partial aortic compression.

Figure 3 presents the findings with regard to $C_{Na}/C_{In} \times 100$, $C_{Osm}/C_{In} \times 100$, and U/P_{Osm}. A typical finding, previously reported (3, 4), was the enhanced sodium clearance observed posttransfusion. The osmolar clearance showed a similar increase. Aortic constriction caused $C_{Na}/C_{In} \times 100$ to decrease from 7.55 to 3.29 during the second stage of aortic constriction. The $C_{Osm}/C_{In} \times 100$ showed a similar, but less

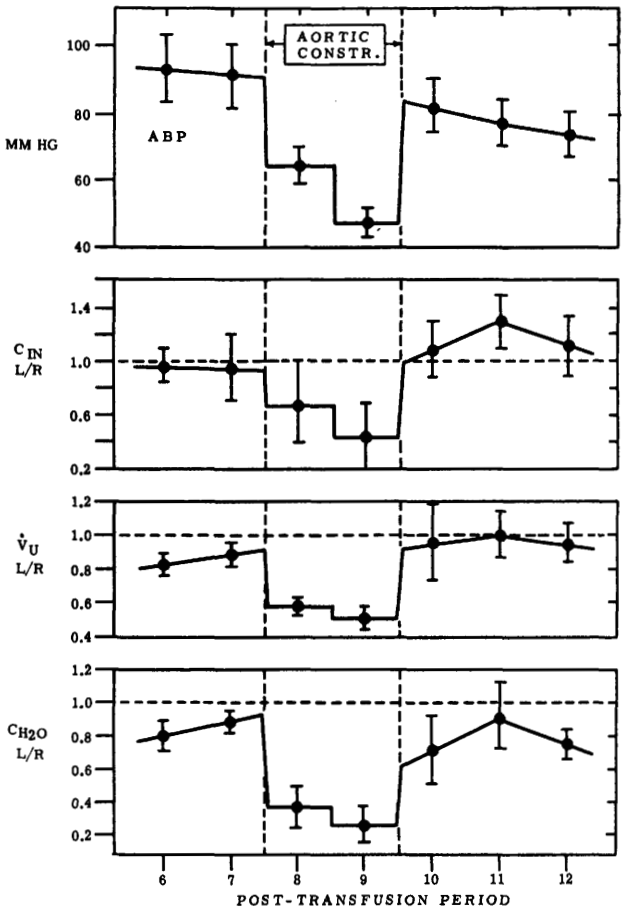

FIG. 4. Changes in urine volume, $\dot{V}_U$, and C_{H_2O} resulting from graded reduction of C_{In}, with results expressed as a ratio of left kidney (below constriction) to right kidney (above constriction). Results shown here are only for the posttransfusion periods ($N = 4$).

marked trend (7.60 to 5.45).

Of interest is the effect of aortic constriction on U/P_{Osm}. This ratio had declined typically below unity in the posttransfusion phase (3, 4). Reduction of renal perfusion pressure and the related decrement in GFR caused this parameter to increase from 0.74 just prior to constriction to 0.93 during the second stage. The latter value was not significantly different from the ratio 1.0, indicative of isotonic urine.

The possibility existed that the maneuver of aortic constriction might affect carotid sinus receptors, in turn influencing the release of ADH (8–10). Thus, mean arterial and pulse pressure might be increased by aortic constriction. In accordance with Share's theory (9, 10) this might tend to inhibit ADH release. The technique of selective reduction of renal arterial perfusion pressure to one kidney (the left), while using the opposite kidney as a control, offered a means of revealing specific alterations when expressing the experimental results as a ratio, L/R. This would tend to minimize the influence of nonspecific systemic effects, anticipated to operate equally on both kidneys. The results of four successful experiments are shown in Figs. 4 and 5. The data are presented for only the posttransfusion phase in these figures.

Note in Fig. 4 that with reductions (L/R ratios) of C_{In} to 0.69 and 0.43, $\dot{V}$ and C_{H_2O} declined in a highly significant man-

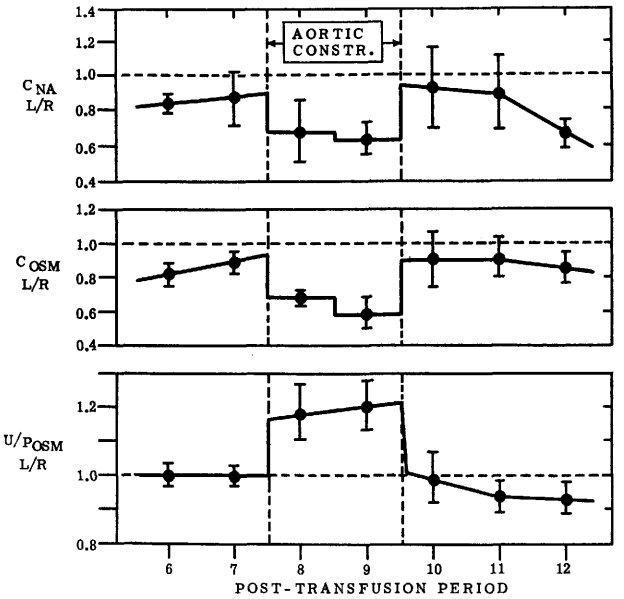

FIG. 5. Influence of aortic constriction on C_{Na}, C_{Osm}, and U/P_{Osm} in the four experiments shown in Fig. 4.

ner ($p = < .01$) from the preconstriction values. Likewise (Fig. 5), C_{Na} and C_{Osm}, L/R, decreased significantly, C_{Na} to an average ratio of 0.64 in the second period of reduced aortic pressure ($p = < .02$) while C_{Osm} was highly significantly reduced in both stages ($p = < .01$).

The ratio U/P_{Osm} increased by an average of 20% in the kidneys to which arterial pressure and GFR had been reduced, as compared to the opposite control kidneys.

II. Dehydrated animals. Hemodynamic changes are presented in Table I. The reduction in GFR by about 60% with aortic constriction caused during the second stage of constriction a sharp decline in negative free-water clearance (Tc_{H_2O}) and C_{Na} to *ca.* 22% of the immediate preconstriction value. As with the hydrated group, influences underlying the immediate effect of reduction in GFR are looked for in Table II by expressing these functions as percentage of filtration rate.

Table II reveals several important differences between the dehydrated and hydrated groups. Urine volume, as the ratio $\dot{V}/C_{In} \times 100$, was less during the control periods, and was lower than the hydrated animals throughout most of the remainder of the phases of hypotension and posttransfusion. Free-water clearance had a greater negative value, when expressed as $C_{H_2O}/C_{In} \times 100$, during the control, and remained negative throughout the experiment. Moreover, aortic constriction did not appear to alter these values significantly.

Likewise, $C_{Na}/C_{In} \times 100$ and $C_{Osm}/C_{In} \times 100$, were significantly less throughout, particularly C_{Na}. Aortic constriction did not particularly influence the C_{Osm} ratio, although $C_{Na}/C_{In} \times 100$ was somewhat reduced (2.76 to 1.81) with aortic constriction. However, this alteration was not significant.

The ratio U/P_{Osm} was significantly decreased below the initial control value during the posttransfusion phase, but values were never below 1.0. The experimental reduction of aortic pressure did not detectably change this ratio.

Discussion. The current investigation demonstrates that the phase of positive free-water clearance, following transfusion after hypotension, with $U/P_{Osm} < 1$, is partially reversible by the expedient of reducing GFR and accompanying this, reduction of the so-

TABLE I. Effect of Hemorrhage and Aortic Constriction during Posttransfusion Phase on Hemodynamics in Dehydrated Animals ($N = 5$).[a]

Period:	Control[b] 1 and 2	Hypotension 3	4	5	Posttransfusion 6	7	Aortic constriction 8	9	10	11	12	13	14
1. MABP (mm Hg)													
Av	102	58	62	41	94	92	65	48	82	77	74	72	66
SE	5	1	3	2	10	10	6	4	8	7	7	9	9
p		***	***	***			***	***	**	**	***	***	***
2. C_{In} (ml/min/g KW)													
Av	0.33	0.16	0.17	0.06	0.20	0.19	0.15	0.08	0.12	0.15	0.11	0.11	0.09
SE	0.04	0.03	0.03	0.03	0.06	0.06	0.05	0.03	0.05	0.06	0.05	0.04	0.04
p		**	**	***	*	*	**	***	***	**	***	***	***
3. C_{PAH} (ml/min/g KW)													
Av	2.47	1.55	1.63	0.81	2.29	2.52	1.64	0.76	1.93	1.49	1.33	1.14	1.04
SE	0.23	0.26	0.31	0.27	0.49	0.96	0.38	0.11	0.73	1.39	0.63	0.41	0.40
p		**	**	***			*	***			**	***	***
4. C_{In}/C_{PAH}													
Av	0.14	0.12	0.10	0.08	0.11	0.10	0.10	0.06	0.09	0.11	0.08	0.10	0.10
SE	0.02	0.02	0.01	0.01	0.02	0.02	0.02	0.01	0.02	0.05	0.03	0.04	0.04
p								**					

[a] Significance is calculated for consecutive periods compared to the control average (periods 1 and 2). p: 0.10–.05 (*) .05–.01 (**) $< .01$ (***) (Significance was calculated by Student's t test.) KW = kidney weight.

[b] Average of 2 consecutive periods.

TABLE II. Effect of Hemorrhage and Aortic Constriction on Renal Function in Dehydrated Animals.[a]

Period:	Control[b] 1 and 2	Hypotension 3	4	5	Posttransfusion 6	7	Aortic constriction 8	9	10	11	12	13	14
1. $\dot{V}/C_{In} \times 100$													
Av	3.80	3.11	3.46	7.40	6.90	6.45	5.53	6.23	7.04	7.91	8.79	8.17	8.20
SE	0.48	0.63	0.65	2.51	1.63	1.39	1.10	1.42	1.70	2.17	2.61	2.02	2.00
p				*	**	**		**	**	**	**	**	**
2. $C_{H_2O}/C_{In} \times 100$													
Av	—1.29	—0.87	—0.91	—1.03	—0.79	—0.98	—1.08	—0.96	—0.62	—0.63	—0.76	—0.48	—0.61
SE	0.24	0.22	0.35	0.25	0.25	0.45	0.42	0.62	0.17	0.22	0.34	0.29	0.27
p									**				
3. $C_{Na}/C_{In} \times 100$													
Av	1.54	1.30	0.77	0.98	2.40	2.76	1.81	1.96	2.43	2.26	2.73	2.62	2.53
SE	0.21	0.33	0.20	0.71	0.94	0.70	0.52	0.41	0.52	0.69	0.62	0.66	0.58
p			**			**			*		**	*	*
4. $C_{Osm}/C_{In} \times 100$													
Av	5.08	3.88	4.30	6.42	7.65	7.37	6.40	7.40	7.65	8.31	9.41	8.88	9.20
SE	0.66	0.93	0.73	2.46	1.65	1.63	1.26	2.00	1.78	2.34	2.66	2.27	2.21
p											**	**	**
5. U/P_{Osm}													
Av	1.34	1.28	1.30	1.14	1.15	1.16	1.17	1.15	1.11	1.07	1.09	1.09	1.10
SE	0.06	0.06	0.09	0.02	0.10	0.14	0.09	0.10	0.06	0.11	0.10	0.20	0.18
p				***	**	*	**	**	***	**	***	**	**

[a] Clearance data and urine volume are expressed as a ratio to $C_{In} \times 100$. Significance: p: .10–.05 (*) .05–.01 (**) < .01 (***).

[b] Average of 2 consecutive periods.

lute and water load to the nephron. The initial increase in C_{H_2O} during this phase probably resulted from enhanced delivery of sodium and other solutes to the distal segment (diluting segment in the ascending limb of Henle, and the concentrating segments of distal convolution and collecting duct). Under these circumstances, equilibrium between the urine in the collecting duct and the papillary osmolal concentration failed to occur. The precise reason for the depressed sodium reabsorption triggered by the prolonged hypotension is not known; stagnant anoxia of the nephrons and/or altered mineralocorticoid hormonal levels, or other humoral factors may be concerned. The indication is strong that the concentrating segments have, in addition, lost their sensitivity to ADH, to account for the dilute urine.

With aortic constriction, positive C_{H_2O} decreased, and U/P_{Osm} approached unity. A smaller load of Na, Cl, and other osmotic constituents entered the distal segment from the proximal convolution. When a smaller volume of only slightly diluted urine was delivered to the concentrating mechanism, which was now operating essentially without dependence on ADH or insensitivity to it, the segment was nevertheless able to remove enough water to render the urine isotonic to plasma.

The mechanism is analogous to that described by Berliner and Davidson (11) and Del Greco and De Wardener (12) in unanesthetized dogs undergoing water diuresis. Renal arterial clamping in these investigations was able to produce in some instances urine slightly hypertonic to plasma. With the anticipated wash-out of the kidney's gradient of osmolality in the present investigation, urine osmolality no higher than that of the plasma can be expected in the monkeys under the experimental conditions imposed.

The differences in response between the hydrated and dehydrated series to aortic constriction can be speculated upon. With anticipated higher levels of circulating ADH, and a steeper gradient of renal osmolality as reflected in the higher U/P_{Osm} throughout, there would be a lesser tendency for wash-out of the gradient to occur in the posttransfusion stage. As a consequence, although Tc_{H_2O} was reduced in direct proportion to GFR with aortic constriction, it remained negative in the limited series of experiments reported here.

The model used here may represent an animal that is particularly sensitive to the experimental procedure used. Thus, even in the 24 hr dehydrated animals of the present series, the highest U/P osmolal ratio observed was 1.73, and in a larger series, a ratio as high as 3.0 occurred only once.

However, what is particularly germane to the present problem is that when dilute urine was observed, the situation was altered in the direction of an isotonic urine by experimentally reducing GFR. When the resulting reduced volume was delivered to the final concentrating segment, removal of only a small portion of the residual volume was necessary for the elaboration of a urine of higher solute concentration, approaching that of plasma, so that U/P_{Osm} close to 1.0 resulted.

Summary. Positive free-water clearance, signifying production of hypotonic urine, is commonly observed in well-hydrated owl monkeys following transfusion of shed blood after prolonged hemorrhagic hypotension. This investigation has examined the nature of this derangement of the urinary concentrating mechanism by experimental reduction of glomerular filtration rate by partial aortic constriction during this phase of experimental shock, and in turn, diminution of solute and water load to the nephron. When the resulting reduced volume was delivered to the final concentrating segment, removal of only a small portion of the residual volume was necessary for the elaboration of a urine of higher solute concentration, approaching that of plasma, so that U/P_{Osm} which was well below 1.0 immediately after transfusion was restored close to unity.

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