Role of ADH in the Loss of Renal Concentrating Ability in Primate Hemorrhagic Shock[1] (37230)

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A significant alteration of function of the kidney in hemorrhagic shock is a loss of urinary concentrating ability. This is particularly manifested following retransfusion and restoration of arterial pressure after prolonged hypotension in animals in normal fluid balance (1–4). Free water clearance (C_{H_2O}) may become positive at this time, and U/P_{Osm} decreases to less than unity.

Since the period following retransfusion involves a phase of hypervolemia (restoration of shed blood, plus addition of interstitial fluid to the plasma volume during the preceding period of hypotension), this might serve as a stimulus via the left atrial volume receptors for inhibition of ADH release from the neurohypophysis, and contribute to apparent failure of the concentrating mechanism (5, 6). This possibility was investigated in animals in normal fluid balance by (a) measuring arginine vasopressin plasma concentrations at various times during the experiment, and (b) suprarenal intra-aortic infusion of vasopressin in amounts in excess of those normally required to inhibit water diuresis.

Methods. Experimental observations were from a total of 15 owl monkeys (*Aotes trivirgatus*) of both sexes. Average body weight was 860 g (650–1250). They were anesthesized with 35 mg/kg body weight of pentobarbital sodium administered intraperitoneally, with additional minimal booster doses given when necessary during the course of the experiment. Animals were allowed free access to food and water until the time of the experiment. These consisted of a group of 8 animals (Group A) that was treated with vasopressin in the posttransfusion phase, and a parallel group of 7 untreated animals (Group B).

Details of surgical procedures and the experimental protocol are described in previous reports, as well as chemical procedures (1–3). The latter involved measurement of inulin in plasma and urine for measurement of glomerular filtration rate, PAH for effective plasma flow, sodium, potassium, and osmolality.

Vasopressin (Pitressin, Parke-Davis) was infused for 30 min, beginning 35 min after hypotension and transfusion of blood, at a rate of 6.5 mU/min/kg body weight via a catheter passed up the abdominal aorta from the femoral artery, so that the tip lay just above the axes of the renal arteries. Vasopressin was infused in a minimal volume (0.14 ml/min).

Blood samples for vasopressin analysis were taken during control, at the end of the hypotensive period, soon after transfusion (between urine periods 6 and 7), and 2 hr after vasopressin infusion (3 hr after transfusion), at the termination of the experiment. A radioimmunoassay method was employed for the plasma arginine vasopressin analysis (7).

Results. 1. Hemodynamic changes during hemorrhagic shock in animals in normal fluid balance. Average trends are shown in Fig. 1. The dosage of vasopressin infused in Group A was such that a mild pressor response was observed during periods 8 and 9. C_{PAH} tended to decrease during vasopressin infusion in Group A. Since C_{In} was reduced during hy-

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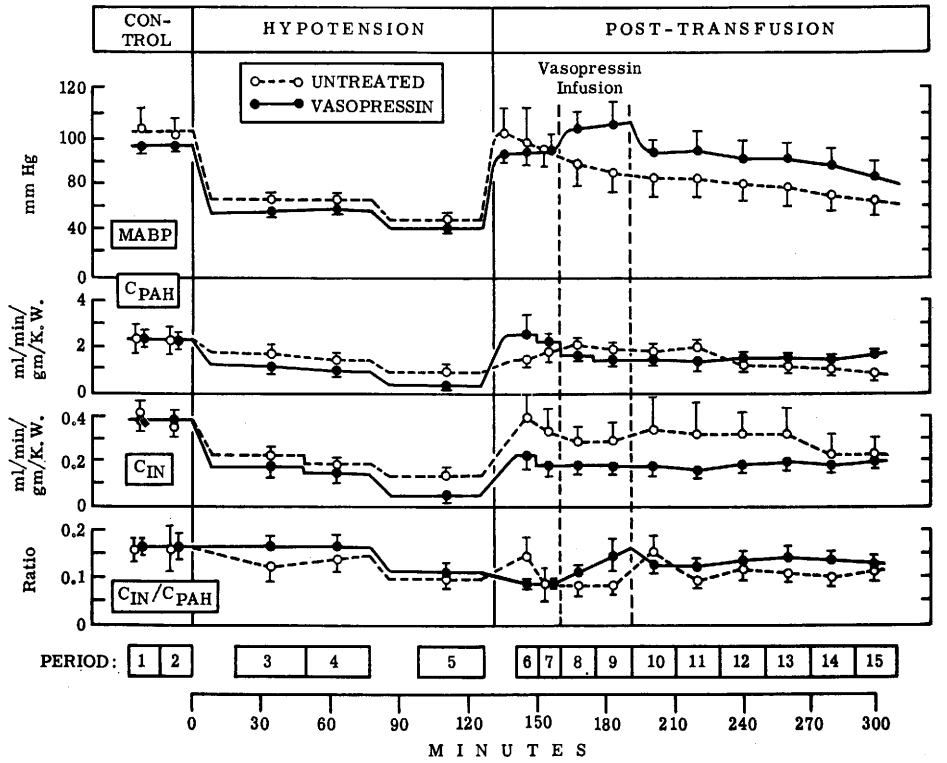

FIG. 1. Protocol of hemorrhagic shock procedure, showing average ± 1 SE, of hemodynamic trends. Vasopressin was infused at the rate of 6.5 mU/min/kg body weight. (Group A, $n = 8$). Group B, untreated ($n = 7$).

potension and the posttransfusion period compared to the control, the subsequent data are presented as fractional clearances of C_{In}. The C_{In}/C_{PAH} also decreased in both groups during hypotension and remained decreased after transfusion, but tended to increase transiently during vasopressin infusion.

2. Urine volume, free water clearance, sodium and potassium clearance, osmolar clearance, and U/P_{Osm} of animals in normal fluid balance. Figure 2 illustrates in the upper panel the typical trend in C_{H_2O}, namely, negative clearance (Tc_{H_2O}) during the control periods, with a diminishing trend during hypotension, with positive values following retransfusion. A return to isotonicity is evident in both groups at ca. 3 hr posttransfusion.

Urine flow $\dot{V}$ as a fraction of the inulin clearance, decreased during hypotension, then increased markedly above the prehemorrhage values during the immediate posttransfusion phase. Later in this phase, $\dot{V}$ decreased toward prehemorrhage average.

Vasopressin infusion had no significant effect on reducing C_{H_2O}, but $\dot{V}/C_{In} \times 100$ showed a small but statistically significant increase.

The U/P_{Osm} began a downward trend late in hypotension and fell further after transfusion, fortuitously more so in the untreated group. However, infusion of pitressin (Group A) appeared not to change the trend paralleling the untreated group (B) in the posttransfusion period.

The changes in clearance of osmolality, sodium and potassium are shown in Fig. 3. No significant influence of vasopressin on fractional C_{Osm}, C_{Na}, and C_K was observed, although an upward trend in C_{Osm} and C_{Na} was seen during vasopressin infusion; C_K/C_{In} tended to decrease.

3. Plasma vasopressin. Determinations

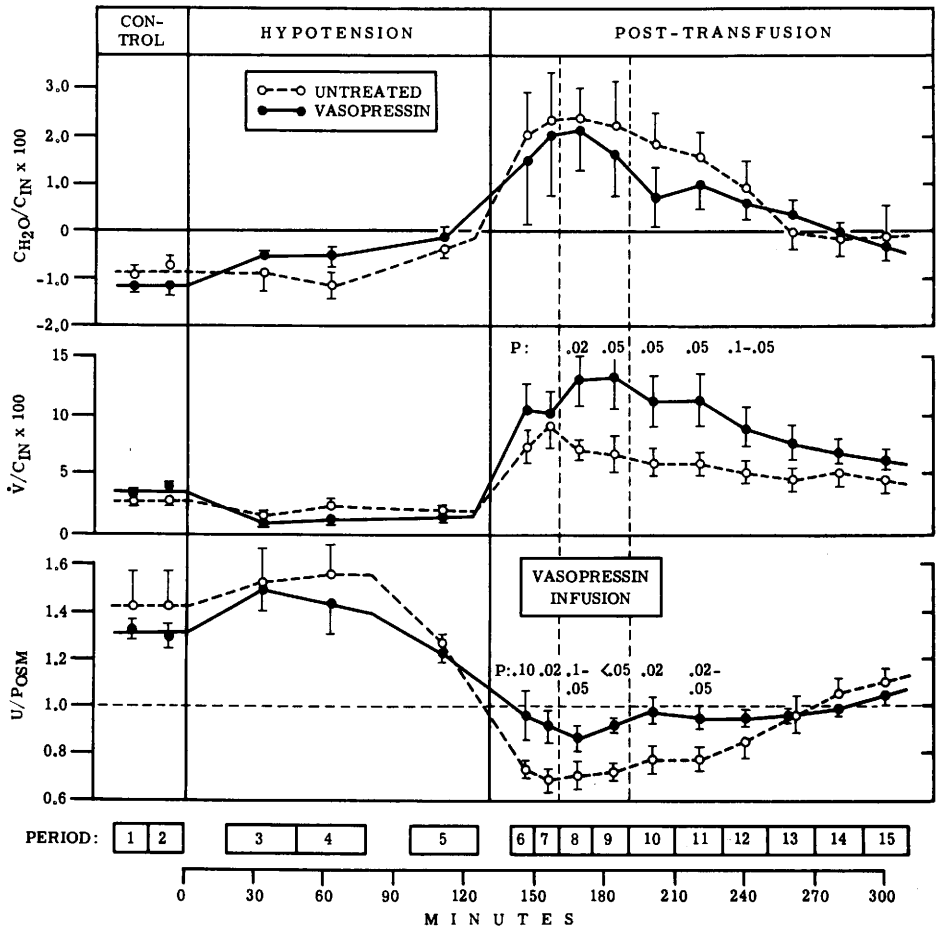

FIG. 2. Showing changes in fractional free water clearance [$(C_{H_2O}/C_{In}) \times 100$], fractional urine volume ($\dot{V}/C_{In} \times 100$), and U/P_{Osm} in Groups A and B (p values calculated by Student's t test).

were made in five animals of Group A. The results appear in Table I. In all cases, about 2 hr of hypotension caused marked increments of plasma vasopressin (av increase, 12.9×). Importantly, although decreasing upon restoration of lost blood, the values remained considerably elevated at this time in all animals (av of experimental/control was 2.0; range, 1.24–3.7). Thus, the possibility that hypervolemia at this time might suppress ADH release was not supported.

It was calculated that blood volume was increased about 14% in the immediate post-transfusion phase (based on a decrease in hematocrit ratio from control average of 46.6 to 41.0% in period 6).

Moreover, terminal plasma vasopressin levels averaged 10.6 times the starting control values in Group A. These elevated values were due to residual circulating vasopressin after infusion during periods 8 and 9, possibly augmented by the stimulus of hypotension which later ensued in normovolemic shock.

Discussion. The above observations confirm the conclusion that the positive free water clearance observed under the given experimental conditions reflect a type of ADH resistant loss of urinary concentrating ability which is revealed after prolonged hypotension in the normally hydrated owl monkey. Such changes have also been observed in patients with acute circulatory failure of various etiologies (8), so that the relevance of

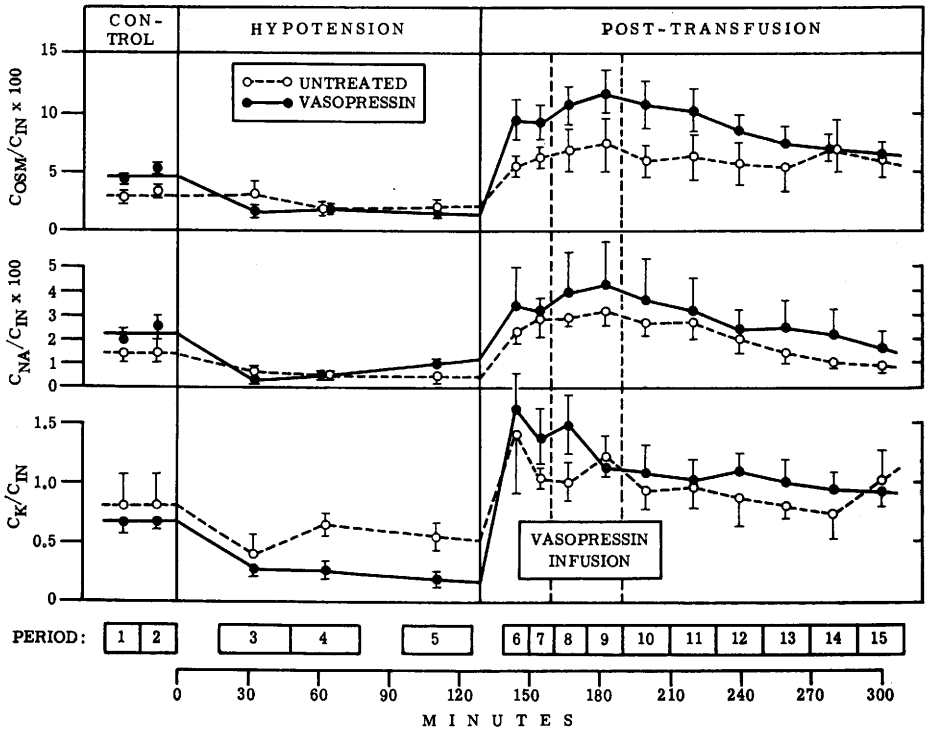

FIG. 3. Showing fractional osmolar and electrolyte clearances (Groups A and B).

the mechanism to human renal pathophysiology is clearly evident.

The mechanism of the kidney's loss of ability to concentrate the urine, with resultant dilute urine (isotonic or hypotonic) of relatively large volume (after restoration of blood volume) we believe is the result of wash-out of the gradient of osmolality (1), upon which is superimposed loss of residual sensitivity to ADH action. This results in failure of attainment of equilibrium (isotonicity) in the distal nephron so that positive free water clearance results. A recent study in the monkey (3) has supported the notion of a loss of sensitivity and failure of equilibrium attainment. In this study it was demonstrated that experimental reduction in GFR, and hence reduction of solute and water load to the distal nephron, during the phase of (+) C_{H_2O} resulted in reduction of C_{H_2O} toward 0, and increase of U/P_{Osm} from < 1.0 to 1.0.

The tendency for C_{H_2O} to return to zero (isotonic urine) during the 3 hr of posttrans-

TABLE I. Plasma Vasopressin in Hemorrhagic Shock (pg/ml).[a]

Expt	Control	2 hr Hypotension		25 min Postransfusion		2 hr Post-vasopressin	
	Concn	Concn	E/C	Concn	E/C	Concn	E/C
1	4.1	85.2	20.80	5.1	1.24	27.5	6.71
2	8.3	25.7	3.10	30.9	3.70	66.3	8.00
3	9.9	30.3	3.06	20.1	2.03	—	—
4	49.0	1200.0	24.50	73.4	1.50	948.0	19.35
5	72.8	948.0	13.02	125.8	1.73	608.0	8.35
Av			12.90		2.04		10.60

[a] Each value is the average for paired determinations. E/C = experimental/control.

fusion, irrespective of whether or not vasopressin is infused, may, in fact, be a manifestation of the above phenomenon. Thus, continued reduction of GFR in the posttransfusion period as shock developed would cause reduced solute and water load to the concentrating segment. The smaller load, probably coupled with a slower movement of tubular urine, would lead to concentration of solutes to a U/P_{Osm} of 1.0 by an ADH insensitive mechanism.

Fractional clearances of Na, Osm, and K were characteristically elevated following the period of hypotension and transfusion. Possible reasons for the enhanced C_{Na}, C_{Osm}, and C_K have been discussed previously (1). These parameters also tended to decrease during the 3-hr posttransfusion phase as all functions deteriorated.

In the animals given vasopressin, a small increase in $\dot{V}$ actually occurred at the time of infusion of the agent. This was accompanied by a tendency for fractional C_{Osm} and C_{Na} to increase. It is believed that at the dosage given, vasopressin had a slight natriuretic effect, to account for the increase in C_{Osm}, and in turn, $\dot{V}$ (9). Potassium clearance, however, actually decreased at this time, hence was noncontributory to the enhanced C_{Osm}.

The mechanism of the loss of sensitivity of the concentrating segment of the nephron to ADH can only be speculative at this time. An avenue to pursue in search of an answer is suggested by the work of Orloff and Handler (10). They believe that vasopressin, operating at the Ca^{2+} sensitive basal surface of the cell, enhances the production of cyclic AMP (3′,5′-AMP) from ATP, by promoting adenyl (adenylate) cyclase activity. Cyclic-AMP is viewed as an intracellular mediator affecting "pores" for H_2O uptake in the apical surface of the cell. Supportive evidence for the concept comes from the findings of Chase and Aurbach (11), Grantham and Burg (12), and Senft *et al.* (13). How the stagnant anoxia of hemorrhagic shock affects this mechanism remains even more speculative. Anoxia *per se* could deleteriously influence the system in a manner comparable to DNP, N_2 environment, iodoacetic acid and azide poisoning (10). Some degree of hypoxia is likely to occur under our conditions of experimental hypotension (14).

An interesting alternative mechanism has been outlined by Fisher (15). His experimental findings indicated that catecholamines inhibit the action of vasopressin in the sequence of events outlined above. This was also demonstrated by Handler, Bensinger and Orloff (16). Catecholamines are exceedingly high in the blood during hypotension (17, 18), and may remain at elevated levels in the posttransfusion phase of normovolemic shock.

Finally, prostaglandins have been shown to enter the renal circulation from medullary sites under stress conditions comparable to those created in hemorrhagic shock (nerve stimulation, renal ischema) (19, 20). Low concentrations of prostaglandins have been observed to inhibit the hydro-osmotic effect of vasopressin in the toad bladder (21, 22). In the kidney, they promote (+) free water clearance and increased sodium excretion (23).

Summary. Positive free water clearance (C_{H_2O}), signifying production of hypotonic urine, is produced in the normally hydrated owl monkey after prolonged hypotension when hemorrhaged blood is transfused, and U/P_{Osm} less than unity is typically seen. Assay of plasma vasopressin showed marked increases after 2 hr of hypotension. After transfusion, concentrations still averaged twice the control value, demonstrating that the loss of concentrating ability of the collecting duct at this time was not due to inadequate ADH production and release. Moreover, when vasopressin was infused intra-arterially posttransfusion in amounts far in excess of those needed to inhibit water diuresis (6.5 mU/min/kg), no significant effects were observed on positive free water clearance, nor did experimentally reduced U/P_{Osm} improve significantly during infusion. Thus, prolonged hypotension had resulted in a type of vasopressin (ADH) resistant failure of the concentrating segment of the nephron.

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