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Effect of Moderate Hemorrhage in Humans on Plasma ADH and Renin (37792)

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(Introduced by E. B. Brown, Jr.)

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In the dog, a loss of at least 10–20% of the estimated blood volume by hemorrhage is usually necessary to cause an increase in the concentration of antidiuretic hormone (ADH) in plasma (1, 2). This observation has been interpreted as indicating that blood volume plays a role in the physiological regulation of ADH release (2, 3). The effect of hemorrhage on plasma ADH in normal man, the subject of the present communication, has not to our knowledge been reported previously, although indirect evidence produced some years ago (4, 5) suggested that effective ADH levels do not change following hemorrhage in humans unless syncope, and hence presumably severe hypotension, is induced as a result of venesection. The present report also describes the effect of hemorrhage on plasma renin activity (PRA).

Materials and Methods. Blood donors at a local community blood center served as experimental subjects. The nature of the study was described to each subject and participation in the project was voluntary. Sixteen men and eight women ranging in age from 19 to 53 (mean, 34) participated in the study. All experiments were conducted between 4:30 and 7:00 PM; earlier in the day each subject had followed his normal daily activities.

The experimental protocol consisted of obtaining blood samples for the determination of ADH and PRA before and after each subject donated one unit of blood. Subjects were seated for at least 10 min before the procedure was begun. The control blood sample (35 ml) was withdrawn by venipuncture, and withdrawal of one unit of blood (450 ml) was then started. Each unit of blood was collected over 5–7 min. Three minutes after the collection ended, a posthemorrhage blood sample (35 ml) was obtained. Each subject had lost 485 ml of blood (control sample plus one unit of blood) before the posthemorrhage sample was taken. Blood volume was estimated to be 65 ml/kg body wt in women and 75 ml/kg body wt in men; these values were chosen after reviewing data compiled from numerous blood volume determinations (6). Before each blood sample was taken, heart rate was determined by palpation of the radial pulse and blood pressure was determined with a sphygmomanometer.

A group of laboratory personnel ranging in age from 20 to 40 served as control subjects. Blood samples were withdrawn in the afternoon after the subject had been seated for at least 10 min; after the first blood sample of 35 ml was withdrawn, the subject remained seated until the second blood sample was withdrawn 10 min later. Blood pressure and heart rate were determined as described above.

An 11–14 ml aliquot of plasma from each blood sample was extracted and concentrated to a final 1.0 ml vol and then assayed for ADH in the ethanol-anesthetized rat as described previously (7, 8). Plasma renin activity was estimated by means of the Schwarz-Mann radioimmunoassay kit which measures the amount of angiotensin I generated by

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plasma. Plasma sodium and potassium concentrations were determined by flame photometry and plasma osmolality by freezing point depression.

Results. The loss of 485 ml of blood represented a mean decrease of 9.9% of estimated blood volume in the 24 subjects. The hemorrhage produced no significant change in either plasma ADH or PRA. Similarly the blood loss produced no significant change in blood pressure, heart rate, or osmolality of the plasma. Small but statistically significant decreases in the plasma concentration of sodium and potassium were evident following hemorrhage. Data from these experiments are summarized in Table I.

A summary of the results from the control subjects appears in Table II. None of the measured variables in these subjects showed statistically significant changes.

Discussion. This study demonstrates that removal of approximately 10% of estimated blood volume in the human causes no significant short-term changes in plasma ADH or PRA. The results with ADH, therefore are comparable with much of the reported work with experimental animals which has shown that 10–20% of blood volume must be removed by hemorrhage before an increase in plasma ADH is detectable (1, 9). A suggestion that ADH responds to smaller blood losses recently came from Claybaugh and Share (10) who reported that loss of as little as 2.6% of blood volume in anesthetized dogs caused an increase in plasma ADH. However, animals in that study had undergone major surgery prior to the experiments, and blood lost during the surgical procedures was not taken into account when estimating the amount of blood removal necessary to produce an increase in ADH titer. Also, plasma concentration of ADH was elevated above physiological levels in the period before the experimental hemorrhage was started. We therefore connot accept the conclusion of Claybaugh and Share that they have demonstrated that ADH release is extremely sensitive to changes in blood volume.

Previously published data have generally been interpreted as indicating that blood volume plays a physiological role in the regulation of ADH secretion (1, 2). Although this interpretation may be correct, it is somewhat disturbing to consider that a decrease in blood volume of 10% in experimental animals often causes no detectable increase in plasma ADH (1, 9; Bond and Goetz, unpublished observations). We now have demonstrated comparable results in humans. In view of these results, it seems that in order to conclude that blood volume does play a physiological role in the regulation of ADH, it is necessary to assume that blood volume normally fluctuates by ± 10% or more. We can find no evidence to indicate that such large variations in blood volume do occur physiologically. Consequently we would suggest that it may be more plausible to consider that an increase in plasma ADH which occurs after sufficient blood loss may represent a pathophysiological (as opposed to physiological) response which is elicited to adapt the circulation to a significant loss of blood.

It has been reported that there is a prog-

TABLE I. Effect of Loss of 485 ml of Blood in 24 Experimental Subjects.[a]

	Control	Posthemorrhage
ADH (μU/ml)	2.1 ± 0.2	1.8 ± 0.2
Renin (ng Angio I/ml/hr)	2.12 ± 0.24	1.86 ± 0.21
Blood pressure (mm Hg) — Systolic	124 ± 3	121 ± 2
— Diastolic	77 ± 2	74 ± 2
Heart rate (bts/min)	77 ± 2	76 ± 2
Sodium (meq/1 plasma)	137.9 ± 0.5	136.8 ± 0.4[b]
Potassium (meq/1 plasma)	4.2 ± 0.1	3.9 ± 0.1[c]
Osmolality (mosm/kg plasma H_2O)	295 ± 2	295 ± 2

[a]Values represent mean ± SE.
[b]Indicates $p < .02$. (Statistics based on Student's t test for paired samples.)
[c]Indicates $p < .001$.

TABLE II. Results from Ten Control Subjects.[a]

	Control 1	Control 2
ADH (μU/ml)	2.8 ± 0.6	2.8 ± 0.8
Renin (ng Angio I/ml/hr)	2.60 ± 0.29	2.57 ± 0.48
Blood pressure (mm Hg) — Systolic	124 ± 3	121 ± 3
— Diastolic	79 ± 2	77 ± 2
Heart rate (bts/min)	78 ± 1	78 ± 3
Sodium (meq/1 plasma)	139.1 ± 0.7	138.5 ± 0.7
Potassium (meq/1 plasma)	3.9 ± 0.1	4.1 ± 0.1
Osmolality (mosm/kg plasma H_2O)	299 ± 4	301 ± 4

[a]Values represent mean ± SE.

ressive increase in the concentration of ADH in blood of human subjects as they change from the supine to the sitting and then to a passive standing position (11), but other investigators have reported that mean plasma ADH concentration measured after 4 hr of ambulation was not different from the control value obtained when subjects were supine (12). Plasma renin activity was increased after 4 hr of ambulation in the latter study (12). We doubt that body position had a significant influence on the results of our study because control subjects, who followed the same general protocol as the blood donors, had constant levels of ADH and renin in plasma.

Our finding that plasma renin activity was not changed significantly by the loss of 485 ml of blood is comparable to the results of Brown *et al.* (13) who demonstrated that removal of 400–500 ml of blood from human subjects caused only small and inconsistent changes in plasma renin. Similarly, Bull *et al.* (14) have demonstrated that a gradually induced average blood volume deficit of over 600 ml was associated with normal levels of renin secretion when sodium balance was normal. Bull *et al.* (14) concluded that intravascular volume *per se* was not of major importance in the control of renin secretion.

The small, but statistically significant, decreases in plasma sodium and potassium following hemorrhage are difficult to interpret. Although the data may be of no biological significance, it is possible that the slight decrease in the plasma cation concentration reflects a movement of interstitial fluid, which has a slightly lower cation concentration because of the Donnan equilibrium, into the vascular compartment following hemorrhage.

Summary. The effect of a moderate hemorrhage on plasma antidiuretic hormone and plasma renin activity was studied in normal human blood donors. An average blood loss of 9.9% of estimated blood volume in 24 subjects caused no significant change in either plasma antidiuretic hormone or plasma renin activity. Systolic and diastolic blood pressure and heart rate also were unchanged by the hemorrhage. It thus appears that the ADH response to hemorrhage in humans is no more sensitive than it is in the dog where often 10–20% of the estimated blood volume must be removed by hemorrhage before an increase in plasma ADH concentration is detectable. In addition, the data confirm previous reports which demonstrated that hemorrhage of this magnitude does not alter plasma renin activity.

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