

"WATER DIURESIS" PRODUCED DURING RECUMBENCY BY THE INTRAVENOUS INFUSION OF ISOTONIC SALINE SOLUTION¹

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(Submitted for publication April 7, 1951; accepted May 28, 1951)

Control of renal excretion of water in man is largely vested in the supra-optico-hypophyseal system. When the tonicity of the blood plasma and extracellular fluid rises, an increased secretion of antidiuretic hormone (ADH) leads to the conservation of water inasmuch as urinary solutes are excreted with a minimum of water. Conversely, when tonicity falls, a diminution of ADH output permits the excretion of a large volume of dilute urine. In both instances homeostasis is served.

Many stimuli, in addition to hypertonicity, increase ADH production, including certain anaesthetic (1) and narcotic drugs (2), barbiturates (3), smoking (4, 5) and nicotine (6, 7), acetylcholine (8), exercise (9), emotion (9), syncope (10), pain (11) and conditioned reflexes (11), as well as the direct electrical (12) or acetylcholine (13) stimulation of nerve cells and fibers connected with the pars nervosa of the pituitary gland. Removal of amounts of blood insufficient to alter blood pressure significantly may nevertheless lead to increased ADH activity (9). There is also suggestive evidence that there may at times be increased ADH activity in patients with cirrhosis of the liver (14, 15).

In contrast to the many factors which may lead to increased antidiuretic activity few other than destructive lesions involving the supra-optico-hypophyseal system and hypotonicity of the plasma and extracellular fluid have been reported to cause a decline in ADH activity. These are hypnotic suggestion (1), alcohol administration (16-18), and exposure to cold (19).

It is the purpose of this communication to present evidence that a rather rapid isotonic expansion of extracellular fluid volume (or some factor associated with such a volume increase) leads to a water diuresis of the type which follows diminished ADH activity.

METHODS

The subjects were three essentially healthy male adults hospitalized for the investigation of minor symptoms for which no organic cause was found and which cleared rapidly. Without previous preparation² they came to the laboratory one to two hours after breakfast, voided, and began the timed collection of urine specimens. When it became apparent that the flow of urine was diminishing, blood was collected without stasis from an antecubital vein after the arm had been immersed in hot water for five minutes to arterialize the blood (20), following which 3,000 ml. of 0.9 per cent solution of sodium chloride in water (Sp. Gr. 1.005 at 15° C.) was infused intravenously at a constant rate of 25 ml./min., the entire infusion requiring two hours. A blood sample was collected from the opposite arm immediately upon the completion of the infusion, and a third at a subsequent time. Urine was voided at intervals during and after the infusion, the subject standing for this purpose.

The volume of packed red blood cells was measured in Wintrobe tubes (21) and hemoglobin photometrically (22) on blood rendered incoagulable by a mixture of ammonium and potassium oxalate. Serum was obtained by centrifugalization of blood collected under oil. Serum total proteins were determined by gradient tube (23); chloride by the method of Sendroy as modified by Van Slyke and Hiller (24); creatinine by the Hare adaptation of Borsook's method (25); and sodium and potassium by means of the Perkin-Elmer or Barclay internal standard flame photometer. Urine specific gravity was determined with a Westphal balance; chloride by the Volhard-Harvey method (26); sodium and potassium by the same

¹ Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

² The unfortunate lack of a truly basal or steady state for the study of water and electrolyte excretion in man has been previously discussed (17). Subjects who have had no fluids after retiring on the preceding night are for the most part somewhat hydropenic on awakening in the morning and hence have enhanced antidiuretic activity.

method as employed for serum; and creatinine by Peter's modification of the Folin procedure (27). Urea and ammonia were determined together by the aeration method of Van Slyke and Cullen (28). The percentage change in plasma volume, $PV_2/PV_1 \times 100$, was calculated from the hemoglobin and hematocrit by the formula:

$$\frac{Hgb_1}{Hgb_2} \times \frac{1 - Hct_2}{1 - Hct_1} \times 100$$

and also from the serum total protein by the formula:

$$\frac{TP_1}{TP_2} \times 100.$$

RESULTS

Renal excretory rates for water and sodium, urinary specific gravity and solute concentrations, together with creatinine U/P ratio and clearance, are shown in Table I. During diuresis urine specimens were usually obtained for analysis every half hour but the results were averaged for intervals of one to two hours except when changes of significance occurred between the shorter periods. Determinations made on venous blood and calculated changes in plasma volume are given in Table II.

TABLE I

The effect of the intravenous infusion of isotonic saline solution on urine flow, concentration of solutes, creatinine U/P ratio, creatinine clearance, and sodium excretion rate

Subject date	Position	Time	Urine flow	Spec. grav.* (at 15° C.)	Na	Cl	K	Urea +NH ₃ urea†	Creatinine		Na excretion
									U/P ratio	Clearance	
		min.	ml./min.		meq./l.	meq./l.	meq./l.	mM/l.		ml./min.	micro-eq./min.
E. F. 1/12/51	Recumbent	— 60 to 0†	2.25	08	163	168	39	156	58	131	367
	Recumbent	0 to 60(1)	2.08	10	164	183	33	170	67	139	341
	Recumbent	61 to 120	7.08	02	86	88	5	33	13	92	609
	Recumbent	121 to 150	9.08	05	119	120	4	31	12	109	1081
	Recumbent	151 to 240	3.55	08	196	200	18	82	34	121	696
1/9/51	Sitting	— 60 to 0	0.75	20	174	218	79	470	191	143	131
	Sitting	0 to 138(2)	1.70	12	187	238	72	220	82	139	318
	Sitting	139 to 180	1.67	09	176	242	60	219	82	137	294
	Recumbent	181 to 210	3.13	05	138	147	28	118	48	150	432
	Recumbent	211 to 240	5.00	05	90	105	15	73	30	150	450
S. C. 2/6/51	Recumbent	— 60 to 0	2.36	12	93	128	65	204	63	149	219
	Recumbent	0 to 120(3)	3.39	06	82	96	33	114	40	136	278
	Recumbent	121 to 180	8.34	02	64	66	12	47	18	150	534
	Recumbent	181 to 270	4.11	09	173	183	29	103	39	160	711
2/9/51	Sitting	— 60 to 0	1.33	20	84	175	123	403	153	203	112
	Sitting	0 to 145(4)	1.38	15	126	194	92	273	110	152	174
	Sitting	146 to 225	3.63	12	144	189	57	157	66	240	523
	Recumbent	226 to 285	2.30	14	160	197	59	173	73	168	368
	Recumbent	286 to 345	4.94	04	91	101	30	80	30	148	450
E. B. 1/24/51	Recumbent	— 105 to 0	1.24	16	130	146	42	260	101	125	161
	Recumbent	0 to 119(5)	1.65	14	176	202	58	164	67	111	290
	Recumbent	120 to 180	3.00	13	217	238	38	114	42	126	651
	Recumbent	181 to 240	4.35	08	149	161	27	84	30	131	648
	Recumbent	241 to 300	5.17	03	87	101	17	62	24	124	450
	Recumbent	301 to 330	3.67	06	127	130	23	85	33	121	466
1/29/51	Sitting	— 97 to 0	0.93	20	198	241	77	318	146	136	185
	Sitting	0 to 119(6)	1.30	19	192	256	88	209	100	130	250
	Sitting	120 to 197	2.75	12	209	243	56	120	43	118	575
	Sitting	198 to 285	2.75	13	174	198	53	140	42	116	479
	Recumbent	286 to 315	3.66	07	116	132	31	104	36	132	425
	Recumbent	316 to 347	6.56	03	75	77	20	35	17	112	492
	Recumbent	348 to 375	5.00	04	109	113	27	58	25	125	545
	Recumbent	376 to 405	2.67	13	189	198	41	98	40	107	505

* The second and third digits after the decimal are shown.

† Urea and ammonia nitrogen were determined together but are recorded as if all the nitrogen was in the form of urea.

‡ Infusion begun at, and completed at (1) + 10, + 130, (2) + 15, + 135, (3) + 10, + 135, (4) + 19, + 135, (5) + 9, + 135, (6) + 17, + 130 minutes.

TABLE II
The effect of the intravenous infusion of isotonic saline solution on constituents of the blood and on the volume of the plasma

Subject Date Position	Time	Hemato- crit	Hemoglo- bin	Total serum protein	Serum creatinine	Concentration in extra- cellular H ₂ O			PV ₂ /PV ₁ × 100	
						Na	Cl	K	(from Hct. and Hgb.)	(from T.P.)
	<i>min.</i>	<i>vol. %</i>	<i>gm. %</i>	<i>gm. %</i>	<i>mg./100 ml.</i>	<i>meq./l.</i>	<i>meq./l.</i>	<i>meq./l.</i>	<i>%</i>	<i>%</i>
E. F.	10	48.0	15.2	7.1	0.95	138.4	118.0	4.9	100.0	100.0
1/12/51	135	43.6	14.1	6.1	0.85	145.2	125.7	4.6	116.9	116.4
Recumbent	245	44.6	14.4	6.4	0.88	140.7	124.1	4.8	112.5	110.9
1/9/51	15	47.9	15.2	7.2	0.92	144.3	118.4	5.1	100.0	100.0
Sitting and recumbent	145	43.0	13.4	6.1	0.87	144.8	124.0	5.0	124.3	118.0
S. C.	10	47.0	15.2	6.5	1.06	141.5	118.8	4.4	100.0	100.0
2/6/51	133	43.0	14.0	5.7	0.94	145.0	125.9	4.4	116.8	114.0
Recumbent	223	41.0	13.2	5.7	1.06	143.7	123.2	4.3	128.2	114.0
2/9/51	17	49.1	15.8	7.2	0.91	138.9	116.3	4.7	100.0	100.0
Sitting and recumbent	145	42.0	13.7	5.8	0.87	141.7	121.4	4.9	131.4	124.1
	345	44.0	14.7	6.0	0.94	138.5	121.3	4.1	118.3	120.0
E. B.	9	41.7	13.1	7.0	1.28	147.9	118.9	4.8	100.0	100.0
1/24/51	143	37.3	11.6	6.1	1.13	145.4	124.6	4.4	121.5	114.8
Recumbent	338	38.2	11.9	6.3	1.10	143.8	125.2	4.7	116.7	111.1
1/29/51	15	42.3	12.8	7.0	1.26	144.4	120.1	5.4	100.0	100.0
Sitting and recumbent	135	36.9	11.3	5.9	1.12	146.1	124.8	4.6	123.7	118.6
	350	39.0	12.0	6.3	1.08	143.7	124.0	5.3	112.8	111.1

Infusion was begun immediately after the first blood sample was obtained and concluded just prior to withdrawing the second sample.

E. F. weighed 82 kg., S. C., 91 kg., E. B., 75 kg.

The rate of urine flow together with the value approximating the total electrolyte concentration, $2(\text{Na} + \text{K})$, have been charted in Figures 1-3. In each experiment, during or following the infusion the rate of urine formation rose sharply and the concentration of electrolyte fell below that of

extracellular water as well as below that of the infusion fluid. Specific gravity of the urine as well as the concentration of urea plus ammonia fell concomitantly with the decline in electrolyte concentration. The rate of sodium and chloride excretion rose in each instance during the saline infusion and

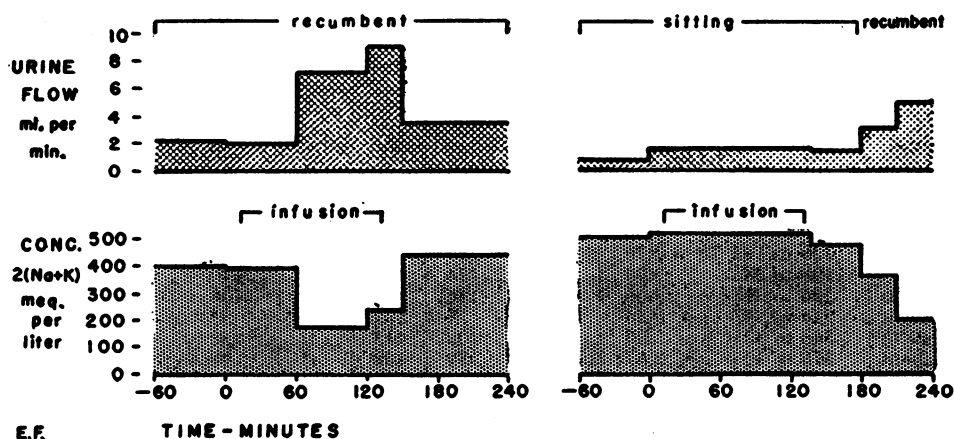


FIG. 1. ELECTROLYTE CONCENTRATION AND FLOW OF URINE IN RELATION TO THE INTRAVENOUS INFUSION OF ISOTONIC SALINE AND TO CHANGE IN POSTURE—PATIENT E. F.

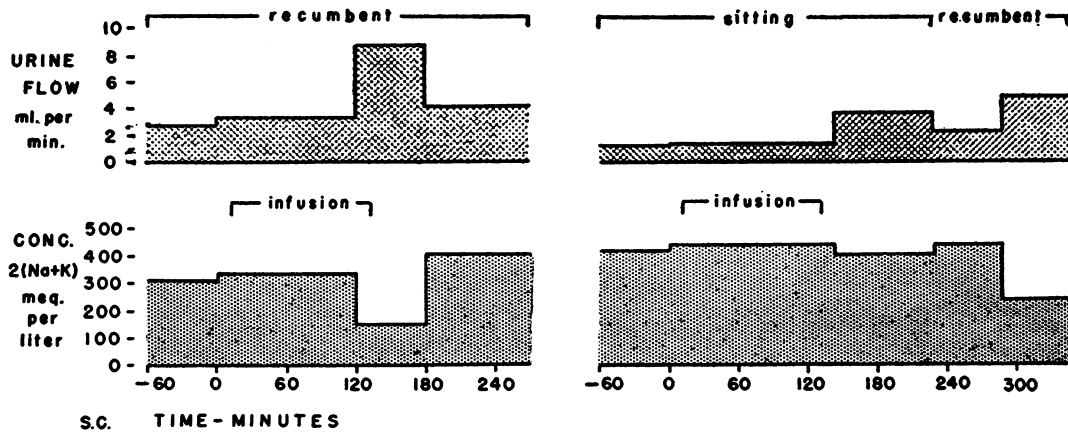


FIG. 2. PATIENT S. C.

Legend as in Figure 1.

continued well above the fore-period level throughout the entire post-infusion period. At the time that the urine was most hypotonic, the excretion rate of sodium and chloride averaged 2.6 times as great as in the fore-period.

It will be noted that in each instance with the subject sitting the urine flow was less and the electrolyte concentration greater during the fore-period than during recumbency. The creatinine U/P ratios were correspondingly higher with the subjects sitting. In the case of E. F., whose creatinine U/P ratio in the fore-period was 58 while recumbent, the most hypotonic urine was secreted during the second hour of the infusion and in S. C., tonicity was lowest during the first hour after the infusion. In the third subject, E. B., whose creatinine U/P ratio was considerably higher during the fore-period, and who was disturbed by the intravenous infusion (becoming pale and faint when

the needle was inserted) the most hypotonic urine was not obtained until two hours after the completion of the infusion. In contrast, with the same subjects sitting, hypotonic urine was not elaborated during even longer periods of time, but was secreted one-half to one hour after recumbency was assumed.

The variation in endogenous creatinine clearance in some experiments may be explained in part by incomplete bladder emptying at low rates of urine flow. Although a rather consistent trend to lower clearance values may be noted in the periods during or just after the intravenous infusion, the significance of this is uncertain. Since, in these observations, concentration of urinary solutes was the variable under study and not their rate of output, and since the change under consideration was a fall of tonicity of the urine, collection and timing errors could only serve to delay the recognition of

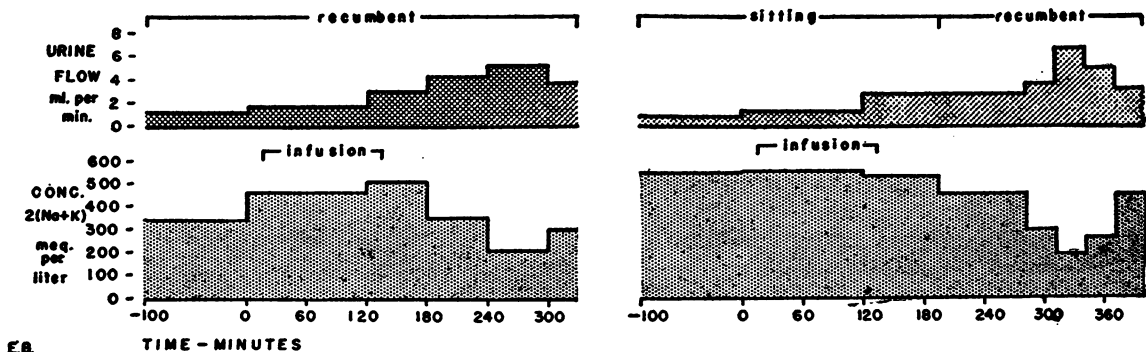


FIG. 3. PATIENT E. B.

Legend as in Figure 1.

such a fall in tonicity or decrease its apparent magnitude. Although more accuracy could have been achieved by means of an indwelling catheter, the presence of such a foreign body in the urethra for a period of many hours would not be conducive to minimum emotional stimulation of the supra-optico-hypophyseal system.

DISCUSSION

In each of the six experiments described above, during or following the infusion of 3 liters of an 0.9 per cent solution of NaCl, the urine volume rose sharply and the concentration of both Na and Cl fell to *below* their respective concentrations in the extracellular water as well as *below* their concentrations in the infusion solution, while the urinary specific gravity measured at 15° C. fell to or below 1.005 in the sitting and 1.003 in the recumbency studies. The concentration of urea plus ammonia concomitantly fell to less than one-fourth of the pre-infusion concentration in each instance. This excretion of water in excess of solutes is characteristic of the diuresis which follows the ingestion of water, of alcohol (17), of exposure to cold (19), and damage to the supra-optico-hypophyseal system (1). It may be inhibited in these instances by the administration of pitressin. In the experiments reported above the duration of the diuresis was limited, presumably because of stimulation of the supra-optico-hypophyseal mechanism by the increasing tonicity of the plasma and extracellular fluid which must of necessity have occurred since during the diuresis water was excreted in excess of solutes.

Murphy has observed that subjects receiving 20–30 ml./kg. of 0.85 per cent NaCl intravenously in 25–40 minutes have an initial water diuresis which he suggested was “related to dilution of circulating pitressin and related renal tubular effects” (29). In view of the fact that such dilution in our experiments should have been maximal at the conclusion of the infusion but diuresis did not occur in the sitting subjects until they assumed the recumbent position, sometimes several hours later, this hypothesis receives no support.

Welt and Orloff (30) have found that the intravenous administration of 4–6 per cent albumin in normal salt solution leads, in semi-recumbent subjects, to a water diuresis of as great or greater

magnitude than that encountered in the studies reported here. Thus their observations indicate that it is not the dilution of the plasma proteins which is involved in the response. It is of interest that when, as a control for the albumin in saline experiments, they administered 2,500 ml. of saline alone intravenously there was no clear-cut water diuresis, although during the first hour of the infusion the urinary concentration of sodium chloride fell to 100 meq./l., and rose only to 145 meq./l. during the second hour. The difference between these findings and those reported here may be due to the fact that their subject received no fluids for 12–14 hours before the infusion and that he was semi-recumbent on a couch rather than flat on a bed.

Since the water diuresis produced by 4 per cent albumin in saline could be inhibited by adding 200 milli-units of posterior pituitary hormone to the infusion, Welt and Orloff suggested that the diuresis was produced by suppression of posterior pituitary activity.

Our observations, demonstrating that the isotonic expansion of extracellular fluid volume (both intra- and extravascular) was ineffective under the conditions of study in producing a water diuresis in the sitting subject, but did so during recumbency, suggest that the receptors for expanded volume (or an associated factor) may have their locus in the cephalad portion of the body. Since the supra-optico-hypophyseal system is believed to be largely involved in the control of water excretion and since it is so located, it may be suggested that the receptor cells, known to respond to changes in osmotic pressure, may also respond to hydrostatic pressure.

The failure of Lewis and associates (31) to secure consistent changes in the rate of urine flow by compression of the neck with an inflated blood pressure cuff, a maneuver which presumably increased the intracranial pressure, may well have been due to the antidiuretic effect of the considerable discomfort produced by the procedure.

The fact that an isotonic expansion of extracellular volume of some magnitude did not initiate a water diuresis in the sitting position is of interest in connection with the observation recorded for the fore-period here which has been repeatedly made in other studies (32–37) that the normally hy-

drated subject has an increased water diuresis upon lying down, with a decrease in urinary electrolyte concentration. This water diuresis, presumably due to decreased ADH action, differs from the comparable increase in urine volume encountered in the water-loaded subject, in whom ADH activity is presumably already minimal and whose excretion and *concentration* of electrolyte both rise upon assuming the recumbent position (37). The enhanced excretion of both water and electrolyte which occurs in edematous states associated with both heart and liver disease when the patient assumes a more recumbent position (38) may well be due in part to the redistribution of the already isotonicity expanded extracellular volume.

CONCLUSIONS

1. Antidiuretic activity, ordinarily diminished by hypotonicity of the extracellular fluid, may also be diminished in the recumbent subject by isotonic expansion of the extracellular fluid volume.

2. The fact that an equal expansion of extracellular volume in the sitting subject does not significantly diminish antidiuretic activity, although there is an equal or greater expansion of both plasma and extracellular volume, suggests that the distribution as well as the magnitude of the expanded extracellular volume is of importance.

ACKNOWLEDGMENTS

The technical assistance of Mrs. Eleanor Harkins and Miss Miriam Halpin is gratefully acknowledged.

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Since this manuscript was submitted for publication, G. Blomhert has published a doctoral thesis (*Over de zogenaamde waterdiurese*, Scheltema & Holkema, Amsterdam, 1951) in which he describes the production of a "water-diuresis" in recumbent subjects receiving isotonic saline either by mouth or by vein.