STUDIES OF THE ANTIDIURESIS OF QUIET STANDING: OBSERVATIONS UPON ELECTROLYTE AND ACID–BASE EXCRETION DURING SULFATE DIURESIS[1]

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It is well established that when blood is pooled in the limbs, either by the use of congesting tourniquets or by standing erect and motionless, there is an immediate and marked decrease in urinary flow and in the excretion of sodium and chloride (1, 2). This is usually accompanied by a slight diminution in glomerular filtration rate and by little or no change in the excretion of potassium and ammonium or in urinary pH (2–4). The mechanisms by which sodium excretion is diminished remain unclear, although considerable evidence suggests that the rates of urinary excretion of sodium and other strong electrolytes are interrelated through a process of ionic exchange in the renal tubules (5). It was thought that these relationships might be illuminated by measuring changes in the excretion of K^+ and H^+, when reabsorption of Na^+ was acutely increased but total cation reabsorption limited, by assuming the upright posture during the course of a sodium sulfate diuresis.

METHODS

Experiments were carried out on normal young men, in the morning after a light breakfast. An isotonic solution of sodium sulfate (248 mEq. per L., 296 mOsm. per L.)[2] was infused intravenously at 4 to 5 cc. per min. over a period of six hours in all experiments. Four kinds of experiments were performed. In *Group I* (control) the subject remained supine for the duration of the procedure. In *Group II* he stood upright and motionless during the fifth hour of the infusion. In *Groups III and IV* the latter procedure was repeated while an effort was made to alter renal tubular secretion with a carbonic anhydrase inhibitor (Diamox®) or an organic mercurial (Thiomerin®). On three occasions (*Group III*) subjects ingested 500 mg. of Diamox® at the start of the experiment and 250 mg. at the beginning of the fourth hour. In three subjects (*Group IV*) 1 cc. of Thiomerin® was incorporated in each liter of the infusion and 2 cc. of Thiomerin® were injected intramuscularly at the beginning of the second hour.

Samples of arterialized venous blood and of urine, voided under mineral oil, were collected every half-hour or hour. Serum and urine were analyzed for endogenous creatinine (7), sodium and potassium (8), chloride (9, 10) and carbon dioxide (11). Sulfate was determined by a turbidimetric technique (12) in the earlier experiments and later by a modified colorimetric method using benzidine (13, 14). pH of blood and urine was determined with a Cambridge pH meter. Urine was analyzed for ammonia (15) and in most cases for titratable acidity.

RESULTS

I. *Continuous infusion of sodium sulfate in the supine position (Table I, Figure 1)*

The rates of excretion of sodium and sulfate increased rapidly during the first three hours but continued to rise only very slowly during the fourth, fifth and sixth hours, as equilibrium between the intake and output of sulfate was approached. During the last three hours the clearance of sulfate progressively approached the clearance of endogenous creatinine. Although the excretion of potassium invariably increased from the first to the second hour, this was not true of ammonium, and during the final three hours the excretion of K^+ and NH_4^+ was fairly constant. The excretion of chloride at first increased slightly but then progressively declined to very low levels. The normal diurnal variation in urinary pH was unaltered. Urinary flow and the clearance of endogenous creatinine changed little during the six hours of infusion.

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[2] Seventeen and one-half gm. of Na_2SO_4 (anhydrous) were dissolved in 1,000 cc. of distilled water. This solution has the same freezing point as a solution of NaCl containing 148 mM. per kg., although it contains 248 mEq. per L. of Na_2SO_4. The osmotic coefficient of Na_2SO_4 in this range of concentration is 0.74 (6).

TABLE I

Urinary constituents during the fourth, fifth and sixth hours of a control infusion of isotonic sodium sulfate in supine subjects

Subject	Hours after start of infusion	Posture	Urine							
			Flow	Na^+	K^+	NH_4^+	pH	Cl^-	SO_4^-	C_{cr}
			cc./min.	*μEq./min.*	*μEq./min.*	*μEq./min.*		*μEq./min.*	*μEq./min.*	*cc./min.*
F. E.	4	Supine	3.61	940	123	24	6.70	67	1,162	128
	5	Supine	3.28	948	122	27	6.19	29	1,185	123
	6	Supine	3.32	1,050	113	26	6.20	34	1,280	130
E. L.	4	Supine	2.02	728	150	42	5.48	32	895	140
	5	Supine	2.02	780	134	42	5.08	21	921	146
	6	Supine	2.05	830	105	38	5.22	18	950	142
M. R.	4	Supine	4.88	895	85	40	5.08	51	1,010	132
	5	Supine	4.92	1,025	74	36	5.42	71	1,120	139
	6	Supine	5.00	1,180	55	35	6.00	105	1,232	140
C. K.	4	Supine	2.62	861	111	23	6.63	58	955	121
	5	Supine	2.21	818	101	28	5.58	22	944	115
	6	Supine	2.42	957	88	34	5.00	15	1,093	126
D. W.	4	Supine	3.92	1,160	121	28	6.65	98	1,304	120
	5	Supine	4.13	1,165	103	25	6.50	76	1,258	113
	6	Supine	3.94	1,230	96	23	6.65	58	1,342	110
Mean	4		3.41	917	118	31	6.11	61	1,065	128
	5		3.31	947	107	31	5.76	44	1,085	127
	6		3.35	1,049	91	31	5.61	46	1,179	127

II. *Effects of motionless standing during the fifth hour of a sodium sulfate infusion (Table II, Figure 2)*

Standing caused a decrease in the excretion of sodium in each of five subjects and produced a urine almost free of chloride, while sulfate excretion remained essentially unchanged. The excretion of both potassium and ammonium, on the other hand, increased in the erect posture and usually diminished when the subject lay down again. There was an abrupt decrease in urinary pH, and values as low as 4.27 (uncorrected for the difference between room and body temperature) were recorded during or shortly after the period of standing. These striking increases in the acidity of the urine were not preceded or accompanied by changes in the pH of arterialized blood or in serum bicarbonate. Endogenous creatinine clearances increased slightly in one subject and fell an average of 11 cc. per min. in four others. Sustained by the continued excretion of sulfate, the flow of urine diminished only slightly during the stimulus of quiet standing.

Experienced subjects reported that while standing erect during sulfate infusions symptoms of faintness, giddiness and nausea appeared earlier and more regularly than during prolonged quiet standing without sulfate. These symptoms were even more pronounced in the experiments of *Groups III and IV,* and always disappeared promptly when the subject lay down.

III. *Effect of a carbonic anhydrase inhibitor (Table III)*

In three men to whom Diamox® had been administered, quiet standing during the fifth hour

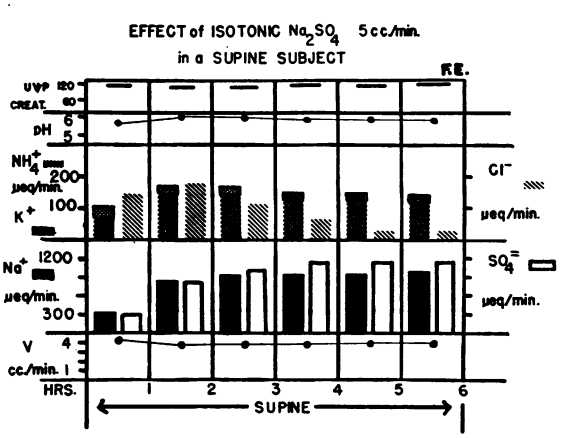

FIGURE 1

TABLE II

Effects of the erect posture upon electrolyte excretion during an infusion of sodium sulfate

Subject	Hours after start of infusion	Posture	Urine							
			Flow	Na^+	K^+	NH_4^+	pH	Cl^-	$SO_4^=$	C_{cr}
			cc./min.	*μEq./min.*	*μEq./min.*	*μEq./min.*		*μEq./min.*	*μEq./min.*	*cc./min.*
F. E.	4	Supine	3.40	843	137	31	5.62	15	1,023	118
	5	Standing	2.47	741	228	38	4.33	4	1,025	112
	6	Supine	2.12	666	180	30	4.83	3	911	101
E. L.	4	Supine	2.41	773	145	44	6.38	69	874	143
	5	Standing	2.04	745	176	56	4.67	18	966	146
	6	Supine	2.09	764	162	49	5.10	9	987	149
M. R.	4	Supine	2.66	1,039	60	40	4.80	33	1,160	125
	5	Standing	2.02	853	84	50	4.27	11	1,023	99
	6	Supine	2.71	989	101	54	4.32	4	1,188	120
C. K.	4	Supine	3.71	1,130	117	18	6.96	151	1,223	147
	5	Standing	2.30	896	127	39	4.85	25	1,131	144
	6	Supine	2.27	994	88	38	4.82	9	1,223	144
D. W.	4	Supine	3.20	1,025	152	27	6.44	33	1,242	111
	5	Standing	2.52	923	188	37	4.85	17	1,250	100
	6	Supine	2.67	1,066	169	33	4.99	15	1,326	112
Mean	4	Supine	3.08	962	122	32	6.04	60	1,104	129
	5	Standing	2.27	832	161	44	4.59	13	1,079	121
	6	Supine	2.37	896	140	41	4.81	8	1,127	125

of a sulfate infusion was accompanied by a decreased excretion of sodium, chloride, bicarbonate and endogenous creatinine. In contrast to the preceding experiments, however, *urinary pH and the excretion of ammonium did not change appreciably.* The excretion of potassium, already at a high level, did not increase further when the subject stood up.

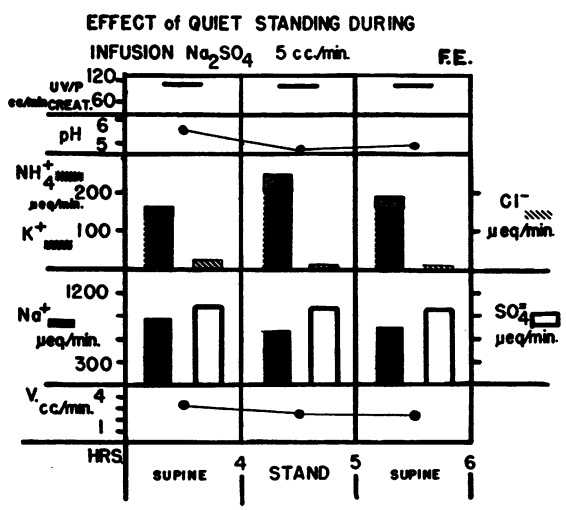

FIGURE 2

IV. *Effect of an organic mercurial (Table IV)*

In three subjects receiving Thiomerin®, the retention of sodium which accompanied motionless standing *was not associated with an increased excretion of potassium.* However, as in *Group II,* urinary pH became more acid and the excretion of ammonium increased.

Infusion of sodium sulfate, which normally diminishes the excretion of chloride (*Group I*), did not prevent the chloruretic effect of mercury in these experiments. Chloride excretion was therefore high throughout the procedure, although it fell in each case during the period of quiet standing.

DISCUSSION

The present experiments demonstrate once again that changing from the supine to the standing posture provides a specific stimulus to the renal tubular reabsorption of the sodium ion. The consequent retention of sodium is not accompanied by an increase in the rates of excretion of potassium and ammonium when quiet standing is superimposed upon a diuresis induced by water ingestion (16, 17), infusion of physiological saline (4, 17),

TABLE III

Modification by Diamox® of the response to quiet standing during an infusion of sodium sulfate

Subject	Hours after start of infusion	Posture	Urine								
			Flow	Na^+	K^+	NH_4^+	pH	HCO_3^-	Cl^-	SO_4^-	C_{cr}
			cc./min.	*μEq./min.*	*μEq./min.*	*μEq./min.*		*μEq./min.*	*μEq./min.*	*μEq./min.*	*cc./min.*
E. L.	4	Supine	6.04	1,165	211	17.1	7.57	360	78	1,010	142
	5	Standing	3.97	1,020	201	17.5	7.50	210	17	1,010	135
	6	Supine	3.98	1,163	184	17.6	7.41	183	20	1,120	148
F. E.	4	Supine	6.20	1,416	224	10.8	7.54	381	125	1,080	110
	5	Standing	2.50	740	227	10.8	7.07	62	20	850	89
	6	Supine	3.29	1,055	200	10.0	7.20	95	10	1,130	99
M. E.	4	Supine	5.50	1,190	221	6.6	7.63	355	134	852	122
	4½	Standing	3.63	970	220	5.2	7.56	262	78	855	122
	5	Standing	2.11	680	174	3.6	7.44	110	33	655	87
	6	Supine	3.33	1,230	211	6.3	7.43	180	30	1,110	148

or infusions of mannitol, sodium bicarbonate or sodium phosphate (4). The fact that urinary outputs of potassium, ammonium and hydrogen ions were simultaneously increased when sodium retention was provoked during the infusion of a non-reabsorbable anion suggests alterations in tubular activity since this cannot be explained by the hypothesis of a lowered rate of glomerular filtration in the presence of unchanged tubular reabsorption. Furthermore, changes in glomerular filtration as indicated by clearances of endogenous creatinine were frequently small or absent in these experiments. However, the data do not permit a final decision as to whether changes in tubular activity might not possibly have been a by-product of lowered glomerular filtration, as Lauson and Thompson demonstrated in dogs whose renal artery was compressed (18).

In view of current theories of urinary acidification which postulate an inverse relationship between the rates of secretion of potassium and hydrogen ions (19), it is of interest that increases in the production of ammonium and marked falls in urinary pH were promoted acutely by quiet standing with a simultaneous increase in the excretion of potassium. Moreover, abrupt and intense acidification of the urine was produced without systemic acidosis. Analogous findings have been reported by Lauson and Thompson in dogs (18), by Schwartz, Jenson, and Relman in human subjects depleted of sodium or given adrenal steroids (20), and by other investigators who have given large loads of non-reabsorbable anions to patients with a tendency to retain sodium (21, 22).

The increased excretion of potassium and acid during the period of quiet standing must have been

TABLE IV

Modification by mercury of the response to quiet standing during an infusion of sodium sulfate

Subject	Hours after start of infusion	Posture	Urine									
			Flow	Na^+	K^+	NH_4^+	Titr. acidity	pH	Cl^-	SO_4^-	HCO_3^-	C_{cr}
			cc./min.	*μEq./min.*	*μEq./min.*	*μEq./min.*	*μEq./min.*		*μEq./min.*	*μEq./min.*	*μEq./min.*	*cc./min.*
C. K.	4	Supine	4.22	1,238	60	22	1.6	6.68	365	865	33	92
	5	Standing	3.84	1,080	64	32	9.5	5.40	305	864	0	77
	6	Supine	10.0	2,215	61	28	2.4	6.23	1,030	1,125	34	93
E. L.	4	Supine	6.50	2,240	137	41	1.0	6.75	1,422	985		92
	5	Standing	6.40	1,315	132	48	12.5	5.94	530	950		91
	6	Supine	6.40	1,974	178	38	1.0	6.70	947	1,150		112
F. E.	4	Supine	5.52	1,140	143	19	3.0	6.93	249	780	54	120
	5	Standing	2.02	520	140	32	10.0	4.72	31	475	0	67
	6	Supine	8.35	1,540	163	30	8.8	5.66	745	980	0	108

secondary either to diminished tubular reabsorption or to increased tubular secretion of these substances. The results of the studies with Diamox® and mercury might be considered to favor the latter view. The dose of Diamox® administered would be expected to inhibit tubular secretion of H^+ and to accelerate to a maximum the secretion of K^+ (19). Under these circumstances the stimulus of quiet standing was ineffective in changing the rates of excretion of either of these ions, although sodium was retained. Administration of mercury, which inhibits renal tubular secretion of K^+ in dogs (23), blocked the increase in K^+ excretion which usually accompanied motionless standing, but did not prevent a rise in ammonium excretion and fall in urinary pH. The possibility cannot be excluded that increased amounts of chloride and bicarbonate in the tubular urine contributed to and modified these results by permitting the reabsorption of Na^+ with a reabsorbable anion. The data are compatible, however, with the theory that the renal retention of sodium produced acutely by quiet standing is caused in part by increased tubular reabsorption of sodium from urine through a mechanism of ionic exchange with tubular cells for both potassium and hydrogen ions. This process, not ordinarily apparent, is unmasked during a sulfate diuresis by the obligatory excretion in the urine of a large number of negative sulfate ions which require neutralization.

SUMMARY

1. Quiet standing during the course of a sodium sulfate diuresis produced the following changes:

a. An abrupt decrease in the renal excretion of sodium and chloride.

b. Little change in urine flow, creatinine clearance, or the excretion of sulfate.

c. An increase in the excretion of potassium and ammonium and a fall in urinary pH.

2. Administration of Diamox® prior to quiet standing prevented the increase in excretion of potassium and acid during quiet standing.

3. Administration of Thiomerin® prior to quiet standing blocked the increase in potassium excretion but did not prevent the formation of a more acid urine with an increase in the excretion of ammonium.

4. The results suggest that under these circumstances both potassium and hydrogen ions may participate simultaneously in the reabsorption of sodium by the renal tubules through an active process of ionic exchange.

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REFERENCES

1. Epstein, F. H., Goodyer, A. V. N., Lawrason, F. D., and Relman, A. S., Studies of the antidiuresis of quiet standing: The importance of changes in plasma volume and glomerular filtration rate. J. Clin. Invest., 1951, **30**, 63.
2. Wilkins, R. W., Tinsley, C. M., Culbertson, J. W., Burrows, B. A., Judson, W. E., and Burnett, C. H., The effects of venous congestion of the limbs upon renal clearances and the excretion of water and salt. I. Studies in normal subjects and in hypertensive patients before and after splanchnicectomy. J. Clin. Invest., 1953, **32**, 1101.
3. Farber, S. J., Becker, W. H., and Eichna, L. W., Electrolyte and water excretions and renal hemodynamics during induced congestion of the superior and inferior vena cava of man. J. Clin. Invest., 1953, **32**, 1145.
4. Goodyer, A. V. N., and Seldin, D. W., The effects of quiet standing on solute diuresis. J. Clin. Invest., 1953, **32**, 242.
5. Berliner, R. W., Renal excretion of water, sodium, chloride, potassium, calcium and magnesium. Am. J. Med., 1950, **9**, 541.
6. Lifson, N., and Visscher, M. B., Osmosis in living systems *in* Medical Physics, Glasser, Otto, Ed., Chicago, Yearbook Publishers, 1944, vol. 1, p. 876.
7. Hare, R. S., Endogenous creatinine in serum and urine. Proc. Soc. Exper. Biol. & Med., 1950, **74**, 148.
8. Hald, P. M., The flame photometer for the measurement of sodium and potassium in biological materials. J. Biol. Chem., 1947, **167**, 499.
9. Hald, P. M. *in* Peters, J. P., and Van Slyke, D. D., Quantitative Clinical Chemistry, Vol. II, Methods, Baltimore, Williams and Wilkins, 1932, p. 838.
10. Harvey, S. C., The quantitative determination of the chlorids in the urine. Arch. Int. Med., 1910, **6**, 12.
11. Van Slyke, D. D., and Neill, J. M. *in* Peters, J. P., and Van Slyke, D. D., Quantitative Clinical Chemistry, Vol. II, Methods, Baltimore, Williams and Wilkins, 1932, p. 285.
12. Nalefski, L. A., and Takano, F., A photonephelometric method for the determination of sulfates in biologic fluids. J. Lab. & Clin. Med., 1950, **36**, 468.

13. Letonoff, T. V., and Reinhold, J. G., A colorimetric method for the determination of inorganic sulfate in serum and urine. J. Biol. Chem., 1936, **114**, 147.
14. Kleeman, C. R., Taborsky, E., and Epstein, F. H., An improved method for the determination of inorganic sulfate. To be published.
15. Conway, E. J., Microdiffusion Analysis and Volumetric Error. London, Crosby Lockwood and Son, Ltd., 1947.
16. Pearce, M. L., and Simmons, D. H., Effects of water diuresis and postural and Pitressin antidiuresis on urine composition. Federation Proc., 1954, **13**, 109.
17. Epstein, F. H., and Kleeman, C. R., Unpublished studies.
18. Lauson, H. D., and Thompson, D. D., Effects of decrease in glomerular filtration rate on cation excretion during loading with nonreabsorbable anions. Federation Proc., 1953, **12**, 83.
19. Berliner, R. W., Kennedy, T. J., Jr., and Orloff, J., Relationship between acidification of the urine and potassium metabolism. Effect of carbonic anhydrase inhibition on potassium excretion. Am. J. Med., 1951, **11**, 274.
20. Schwartz, W. B., Jenson, R. L., and Relman, A. S., Acidification of the urine and increased ammonium excretion without change in acid-base equilibrium: sodium reabsorption as a stimulus to the acidifying process. J. Clin. Invest., 1955, **34**, 673.
21. Ingbar, S. H., Kass, E. H., Burnett, C. H., Relman, A. S., Burrows, B. A., and Sisson, J. H., The effects of ACTH and cortisone on the renal tubular transport of uric acid, phosphorus, and electrolytes in patients with normal renal and adrenal function. J. Lab. & Clin. Med., 1951, **38**, 533.
22. Metcoff, J., James, J. A., Gordillo, G., and Antonowicz, I., Renal electrolyte transport in normal and nephrotic children. Effects of simultaneous infusion of carbonic anhydrase inhibitor and nonreabsorbable anion. J. Lab. & Clin. Med., 1955, **46**, 333.
23. Mudge, G. H., Ames, A., III, Foulks, J., and Gilman, A., Effect of drugs on renal secretion of potassium in the dog. Am. J. Physiol., 1950, **161**, 151.