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Research Article

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ABSTRACT The regulation of aldosterone secretion in anephric man was investigated in studies on nephrectomized patients who were being intermittently hemodialyzed while awaiting renal transplantation. The effects of supine and upright posture on the concentration of plasma aldosterone on the 1st day postdialysis and on a 3rd or 4th day postdialysis were compared to the effects of postural variation in normal subjects who were on a low sodium intake and on a high sodium intake. In contrast with the normal subjects who exhibited higher concentrations of plasma aldosterone after 2 hr of upright posture than in the supine position and low concentrations of plasma aldosterone on a high sodium intake, the anephric patients showed less consistent variations in plasma aldosterone due to changes in posture and exhibited higher concentrations of plasma aldosterone on the 3rd or 4th day postdialysis, despite an increase in body weight, than on the 1st day postdialysis.

The increase in the concentration of plasma aldosterone in the anephric patients between the 1st day postdialysis and the 3rd or 4th day postdialysis indicates that aldosterone secretion is not responding primarily, in this situation, to volume-related stimuli. There was a high degree of correlation between the concentration of plasma aldosterone and the corresponding levels of serum potassium concentration, which also rose significantly between the 1st day postdialysis and the 3rd or 4th day postdialysis. Furthermore, when potassium accumulation between dialyses was prevented in three of these patients, the concentration of plasma aldosterone fell to minimally detectable levels. The results of these studies suggest that the primary regulator of aldosterone secretion in the absence of the kidneys is potassium.

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INTRODUCTION

Multiple factors interact in the regulation of aldosterone secretion. Studies on dogs (1–3) and sheep (4) have indicated that renal and anterior pituitary factors act in conjunction to determine the response to a variety of different stimuli and that the role of the renal factors is dominant in situations in which volume-related stimuli are of primary importance. In studies on sodium-depleted dogs and dogs with thoracic caval constriction, Davis, Ayers, and Carpenter observed that aldosterone secretion, which persisted at high levels despite hypophysectomy, was markedly reduced after removal of the kidneys (1). Reduced secretion of aldosterone after bilateral nephrectomy was also observed by Ganong, Biglieri, and Mulrow in studies on dogs that had been maintained on either a low sodium intake or a normal sodium intake (2). Davis, Carpenter, Ayers, Holman, and Bahn demonstrated that the stimulus of acute blood loss does not produce an increase in aldosterone secretion in nephrectomized-hypophysectomized dogs as it does after hypophysectomy alone (3). All of these studies on the effect of nephrectomy on aldosterone secretion, however, involved relatively acute experiments, and none have demonstrated the behavior of aldosterone secretion after bilateral nephrectomy in the chronic stable state. The development of practical and reliable methods for the measurement of plasma aldosterone concentration (5–8) and the ability to maintain anephric patients in excellent condition by intermittent hemo-

dialysis have made studies of the regulation of aldosterone secretion in the absence of the kidneys feasible in man.

In the studies described in this report, bilaterally nephrectomized patients were studied under variable conditions of posture and sodium and potassium accumulation. Plasma samples were assayed for both renin activity and aldosterone concentration, and the results of these studies were compared with data obtained from normal subjects on low and high sodium intake. In addition, plasma corticoid concentrations in the anephric patients were measured to identify the effect of ACTH. Studies were also performed to evaluate further the effect of potassium accumulation or serum potassium concentration on plasma aldosterone in the absence of the kidneys.

METHODS

Studies on normal subjects. 12 normal volunteers, 6 males and 6 females, ranging in age between 23–55 yr, were studied in the Clinical Research Unit of The Johns Hopkins Hospital. All of the subjects were studied at the end of a 5 day period of low sodium intake (less than 17 mEq of sodium per day) and at the end of a 5 day period of high sodium intake (unrestricted diet plus 136–170 mEq of sodium per day). On the morning of the last day of each period, blood samples were collected for determination of plasma renin activity (PRA)[1] and plasma aldosterone concentration while the subjects were still recumbent after sleeping overnight and again after 2 hr of normal ambulation. Blood samples for determination of PRA were collected in iced centrifuge tubes containing EDTA and promptly centrifuged for 15 min at 4°C. The plasma from these samples was then frozen for subsequent analysis. Blood samples for measurements of plasma aldosterone concentration were collected in heparinized glass syringes. Body weight was recorded at the end of each period.

Studies on anephric patients. Eight bilaterally nephrectomized patients who were being treated by intermittent hemodialysis twice each week while awaiting renal transplantation were studied. The age and sex of these patients, the presenting disorder, and the duration of the anephric state are shown in Table I. Dialyses were performed using Kiil dialyzers and a Milroyal dialysate system (Milton Roy Co., St. Petersburg, Fla.). Each patient was studied on the morning of the day after hemodialysis (1st day postdialysis), and, depending upon the dialysis schedule, either 2 or 3 days later (3rd or 4th day postdialysis) immediately before the next hemodialysis.

First day postdialysis studies. Patients were admitted to the Clinical Research Unit after hemodialysis, and, to minimize reexpansion of body fluid volume, fluid intake was restricted to 100 ml in the interval (usually 16–18 hr) between dialysis and the performance of the studies on the following morning. On the 1st day postdialysis, blood samples for determinations of PRA and plasma aldosterone concentrations were collected while the patients were recumbent before arising in the morning and again 2 hr later after normal ambulation. Additional blood samples were collected for determinations of plasma corticoid concentrations and serum sodium and potassium concentrations, and body weight was recorded. After these studies, the patients were discharged.

3rd- or 4th-day postdialysis studies. Patients were readmitted to the Clinical Research Unit on the evening before the next hemodialysis. On the following morning (3rd or 4th day after the previous dialysis), blood samples for determinations of PRA and plasma aldosterone concentration were collected as before while the patients were still recumbent and 2 hr later after normal ambulation. Additional blood samples were collected for determinations of plasma corticoid concentration and serum sodium and potassium concentrations, and body weight was recorded. The salt intake in the period between hemodialyses was 2–4 g per day.

Comparable studies on a 1st-day postdialysis and on a 3rd or 4th day postdialysis were randomly performed at other times on six of these patients.

Low potassium studies. To determine the effect of potassium accumulation in the period between dialyses on plasma aldosterone, three patients, A. D., E. S., and D. W., were admitted to the Clinical Research Unit after hemodialysis. Potassium intake was restricted to approximately 20 mEq per day and each patient received Kayexalate (sodium polystyrene sulfonate [Winthrop Laboratories, New York]). 25 g administered orally each day. The studies extended over a 7 day period during which each patient was hemodialyzed on the 3rd and seventh day. Blood samples were collected for determinations of PRA, plasma aldosterone concentration, plasma corticoid concentration, and serum sodium and potassium concentrations on the mornings of the 1st, 3rd, 4th, and 7th days. Body weights were recorded daily and potassium balances were obtained on two of these patients, E. S. and D. W. For the balance studies, all of the dialysate from the hemodialysis on the 3rd day was collected and a portion was saved for replicate measurements of potassium concentration. Portions of dialysate before its passage through the dialyzer were collected at 30-min intervals throughout the period of dialysis for subsequent determinations of dialysate potassium concentrations. The potassium lost during dialysis was calculated as the difference between the mean potassium concentration in the dialysate supply, and the potassium concentration in the dialysate collected after its passage through the dialyzer. Additional potassium losses during the 7 day period of the potassium balance studies were determined by stool analysis.

Metabolic clearance rate. The metabolic clearance rate (MCR) of aldosterone in the supine and sitting positions

TABLE I

Age, Sex, Presenting Disorder and Duration of Time Postnephrectomy of Eight Nephrectomized Patients

Patient	Age	Sex	Presenting disorder	Anephric period
	yr			*months*
A. D.	29	F	Chronic pyelonephritis	5
H. G.	23	F	Chronic glomerulonephritis	2
D. J.	15	F	Chronic glomerulonephritis	6
E. S.	35	F	Chronic pyelonephritis	2
J. Br.	52	M	Chronic pyelonephritis	3
J. Ba.	15	M	Chronic glomerulonephritis	4
H. S.	46	M	Polycystic disease	2
D. W.	18	M	Medullary cystic disease	1

[1] *Abbreviations used in this paper:* MCR, metabolic clearance rate; PRA, plasma renin activity.

was determined on a 2nd day postdialysis on three of the patients, A. D., D. J., and E. S., using a method described previously (9).

Heparin administration. The effect of heparin administration on plasma aldosterone was studied in three patients, A. D., E. S., and D. W. Heparin was administered by constant intravenous infusion on the day before dialysis in the same dosage and over the same duration of time as during hemodialysis (either 80 or 100 mg over a period of 7 hr). Blood samples were collected for measurements of PRA and plasma aldosterone concentration before the infusion was begun, at the end of the infusion, and on the following morning before hemodialysis. Blood samples were obtained for determinations of serum potassium concentration on the day of the infusion and on the following morning.

Analytical methods. Plasma samples for determinations of renin activity were prepared for bioassay by the method of Helmer (10). The angiotensin formed during the incubation (60 min) of the samples was measured by the pressor response of the rat as described by Higgins, Davis, Urquhart, and Olichney (11). Although there is considerable variation in the responsiveness of the rat from one animal to the next and during the course of the day, acceptable preparations consistently exhibit a pressor response to amounts of valine-5-angiotensin II amide as small as 0.5 ng. Smaller quantities (0.2 ng) can be detected by more responsive preparations. Each injected plasma sample is bracketed by injections of the angiotensin II standard and a separate curve is plotted for each measurement of PRA. The volume of dialyzed plasma that is used in the bioassay for lower levels of PRA is 0.1 ml. Using this method, we consider the lower level of sensitivity for PRA in our laboratory to be 500 ng angiotensin II formed/100 ml plasma. Levels between 200 and 500 ng/100 ml can be measured reproducibly in more responsive preparations.

Subsequent to the completion of these studies, a radioimmunoassay for PRA was standardized using the technique described by Haber, Koerner, Page, Kliman, and Purnode[2] (12). It was possible with this method to detect angiotensin I at a concentration of 0.5 ng/ml of plasma with a mean difference of 40% between duplicate samples. At a mean concentration of 1.0 ng angiotensin I/ml of plasma, the mean difference between duplicates was 15%. Thus, this assay should detect PRA capable of generating 0.2 ng angiotensin I/ml per hr when the incubation period is 3 hr. 20 samples of frozen plasma (collected in EDTA and stored in polypropylene tubes at $-10°C$) from seven of the anephric patients were available for further assay by this more sensitive technique.

Plasma aldosterone concentrations were measured using either a double isotope dilution technique (7) or a radioimmunoassay (8). Good agreement was observed using both of these methods to measure plasma aldosterone concentrations in the same samples. A comparison of the data from paired determinations on eight plasma samples yielded a t value of 0.1131, $P > 0.8$. The lower limit of sensitivity for both of these methods is 0.5 ng/100 ml plasma. For statistical purposes, plasma aldosterone concentrations that were lower than this value are arbitrarily reported as 0.5 ng/100 ml plasma.

Plasma corticoid concentrations were determined by a competitive binding radioassay method (13). Potassium concentrations in serum, portions of dialysate and acid digests of homogenized portions of diet and stool, and serum sodium concentrations were determined by an autoanalyzer technique.

[2] Angiotensin-I antibody and other materials for the assay were obtained from Schwarz/Mann Division of Becton-Dickinson & Co., Orangeburg, N. Y.

RESULTS

Studies on normal subjects. Plasma renin activity and plasma aldosterone concentrations in 12 normal subjects who were studied while recumbent before arising in the morning and after 2 hr of ambulation during periods of low sodium intake and high sodium intake are shown in Table II. Values of PRA (ng angiotensin II formed/100 ml of plasma) that are lower than 500 ng/100 ml, although below the usual level of sensitivity of the bioassay procedure, denote a pressor response in more sensitive preparations and are included in the data for comparative purposes. ND denotes the absence of a pressor response, i.e., PRA lower than 200 or 500 ng/100 ml which could not be quantified further. During the period of low sodium intake, the mean PRA was 1025, SEM ±187 ng/100 ml, in the supine position, and increased significantly ($P < 0.005$)[3] to 1610, SEM ±200 ng/100 ml, after 2 hr of ambulation. Plasma aldosterone, during the low sodium intake, was similarly increased from a mean concentration of 16.7, SEM ±2.7 ng/100 ml, in the supine position, to 32.6, SEM ±6.1 ng/100 ml, after 2 hr of ambulation ($P < 0.005$).

During the high sodium intake, no PRA could be detected by the insensitive bioassay in seven of the subjects for whom the data are available (PRA < 500 ng/100 ml). The range of PRA detected in the supine position was 500–700 ng/100 ml (three subjects), and after 2 hr of ambulation, the range of PRA detected was 510–830 ng/100 ml (two subjects). Plasma aldosterone levels during the period of high sodium intake, were significantly lower than the comparable levels in the studies performed during a low sodium intake in both the supine position ($P < 0.001$) and after 2 hr of ambulation ($P < 0.001$). However, despite the suppression of plasma aldosterone levels during the high sodium intake, the mean concentration of plasma aldosterone after 2 hr of ambulation, 4.5, SEM ±1.0 ng/100 ml, was significantly higher ($P < 0.005$) than the mean concentration in the supine position, 1.6, SEM ±0.3 ng/100 ml.

All of the subjects gained weight during the period of high sodium intake; the difference in body weight ranging from 0.5 to 2.75 kg with a mean increase in body weight of 1.66, SEM ±0.24 kg.

Studies on anephric patients. Plasma renin activity and plasma aldosterone concentrations in the supine position before arising in the morning and in the upright position after 2 hr of ambulation on the 1st day postdialysis and on the 3rd or 4th day postdialysis are

[3] The P values were calculated using a t test for paired variates.

TABLE II

PRA and Plasma Aldosterone Concentration in Normal Subjects on High and Low Sodium Intake

Subject no.	Sex	Low sodium				High sodium			
		PRA*		Plasma aldosterone		PRA*		Plasma aldosterone	
		Supine	Upright	Supine	Upright	Supine	Upright	Supine	Upright
				ng/100 ml				*ng/100 ml*	
1	F	990	2150	25.0	40.0	600	—	1.1	8.9
2	F	1260	—	32.5	81.6	ND	ND	3.3	13.2
3	F	1050	1080	—	30.0	500	ND	1.7	5.0
4	F	840	1175	14.0	27.6	ND	ND	0.5	3.0
5	F	—	940	—	—	700	830	0.5	3.8
6	F	500	—	16.5	40.6	ND	ND	0.9	2.1
7	M	1100	2300	—	—	—	—	1.3	3.0
8	M	430	1025	20.3	30.1	ND	ND	1.2	3.0
9	M	2100	2130	10.7	18.0	ND	ND	2.4	3.5
10	M	—	2000	15.3	20.0	ND	ND	2.9	3.6
11	M	1780	2400	6.7	13.9	ND	510	2.3	2.7
12	M	200	895	9.4	23.8	ND	ND	1.2	1.7
Mean		1025	1610	16.7	32.6			1.6	4.5
±SEM		±187	±200	±2.7	±6.1			±0.3	±1.0

* ng angiotensin II formed /100 ml plasma in the renin bioassay. ND, none detectable, i.e., less than 200–500 ng/100 ml (see Analytical Methods).

shown in Tables III and IV. Serum sodium and potassium concentrations and body weights are also shown in these tables. Plasma renin activity or plasma "renin-like" activity was detected by the bioassay in low concentration in one of these patients, D. J., a 15-yr old female. No PRA could be detected by the bioassay technique in the other seven patients on either the 1st day postdialysis or the 3rd or 4th day postdialysis. When stored plasma samples from seven of these patients were subsequently assayed by the radioimmunoassay, PRA could be detected in only one additional patient, H. S., a 46 yr old male. A low level of PRA (< 20 ng angiotensin I generated/100 ml plasma per hr) was detected by this method after 2 hr of ambulation on the

TABLE III

Data from Anephric Patients Studied on the 1st-Day Postdialysis

Patients	PRA*		Plasma aldosterone		Serum Na	Serum K	Body weight
	Supine	Upright	Supine	Upright			
			ng/100 ml		*mEq/liter*	*mEq/liter*	*kg*
A. D.	ND‡	ND	0.5	0.5	137	3.0	44.9
H. G.	ND‡	ND‡	—	0.7	129	4.0	36.6
D. J.	ND	ND	0.6	0.6	135	3.5	40.9
E. S.	ND‡	ND‡	1.0	1.3	136	4.9	63.4
J. Br.	—	—	—	1.2	136	2.3	52.4
J. Ba.	ND‡	ND‡	—	21.2	132	5.4	52.9
H. S.	ND‡	ND§	0.8	0.5	135	4.4	68.3
D. W.	ND	ND	2.8	2.7	134	5.0	39.7
Mean			1.1	3.6	134.3	4.1	
±SEM			±0.4	±2.5	±0.9	±0.4	

* ng angiotensin II formed /100 ml plasma in the renin bioassay. ND, none detectable, i.e., less than 200–500 ng/100 ml.

‡ PRA also undetectable by radioimmunoassay.

§PRA detected by radioimmunoassay, but <20 ng angiotensin I generated/100 ml per hr.

TABLE IV

Data from Anephric Patients Studied on the Third or Fourth Day Postdialysis

Patients	PRA*		Plasma aldosterone		Serum Na	Serum K	Body weight
	Supine	Upright	Supine	Upright			
			ng/100 ml		*mEq/liter*	*mEq/liter*	*kg*
A. D.	ND	ND	17.2	—	137	5.0	45.4
H. G.	ND‡	ND‡	0.5	1.0	132	4.8	37.1
D. J.	300	ND‡	6.6	10.9	135	6.3	41.7
E. S.	ND‡	ND‡	3.9	3.9	135	4.9	63.8
J. Br.	—	—	—	2.7	136	5.2	53.1
J. Ba.	ND‡	ND‡	41.4	60.2	136	7.8	55.7
H. S.	ND§	ND§	—	1.1	145	5.2	69.8
D. W.	ND‡	ND‡	10.4	8.3	135	5.8	40.9
Mean			13.3	12.6	136.4	5.6	
±SEM			±6.1	±8.0	±1.3	±0.4	

* ng angiotensin II formed /100 ml plasma in the renin bioassay. ND, none detectable, i.e., less than 200–500 ng/100 ml.

‡ PRA also undetectable by radioimmunoassay.

§ PRA detected by radioimmunoassay (450 ng angiotensin I generated/100 ml plasma per hr supine and 120 ng/100 ml plasma per hr upright).

1st day postdialysis, and on the 4th day postdialysis, the concentration of angiotensin I generated was 450 ng/100 ml plasma per hr in the supine position and 120 ng/100 ml plasma per hr after 2 hr of ambulation. Thus, although this patient's plasma contained measurable PRA on the 4th day postdialysis, the level was not increased after 2 hr of upright posture.

With one notable exception, patient J. Ba., the anephric patients exhibited low concentrations of plasma aldosterone in both the supine position and after 2 hr of ambulation (Table III). The means of the plasma aldosterone concentrations in the supine position, 1.1, SEM ±0.4 ng/100 ml, and after 2 hr of ambulation, 3.6, SEM ±2.5 ng/100 ml, were not significantly different ($P > 0.4$), and, if one excludes the data from patient J. Ba., the range of concentrations of plasma aldosterone, 0.5–2.8 ng/100 ml in the supine position and 0.5–2.7 ng/100 ml after 2 hr of ambulation, were nearly identical. Analyzing the paired data separately (n = five pairs of observations) further illustrates the similarity between the low concentrations of plasma aldosterone in the supine position and the concentrations detected after 2 hr of ambulation ($P > 0.8$). These low concentrations of plasma aldosterone on the 1st day postdialysis are in marked contrast with the data from the group of normal subjects on a low sodium intake.

Although all the patients gained weight (1.05, SEM ±0.84 kg) between dialyses, implying retention of sodium and water, plasma aldosterone concentrations on the 3rd or 4th day postdialysis (Table IV) were higher than the levels on the 1st day postdialysis. As before, the mean concentrations in the supine position, 13.3, SEM ±6.1 ng/100 ml, and after 2 hr of ambulation, 12.6 SEM ±8.0 ng/100 ml, were not significantly different ($P > 0.9$). However, three of the five patients from whom paired data were obtained, exhibited higher concentrations of plasma aldosterone after 2 hr of ambulation than in the supine position.

Patient J. Ba., whose repeat studies were performed on a 3rd day postdialysis and whose serum potassium concentration, despite the short interval between dialyses, was 7.8 mEq/liter, again exhibited higher concentrations of plasma aldosterone than did the other patients who were studied. Excluding these values, the mean concentrations of plasma aldosterone on the 3rd or 4th day postdialysis were 7.7, SEM ±2.9 ng/100 ml in the supine position, and 4.7, SEM ±1.7 ng/100 ml after 2 hr of ambulation ($P > 0.4$).

There was no change in serum sodium between the 1st day postdialysis and the 3rd or 4th day postdialysis. Serum potassium, on the other hand, increased from a mean level of 4.1, SEM ±0.4 mEq/liter on the 1st-day postdialysis to 5.6, SEM ±0.4 mEq/liter on the 3rd or 4th day postdialysis ($P < 0.01$). The highest serum potassium concentrations on both the 1st day postdialysis and the 3rd or 4th day postdialysis were those of patient J. Ba.

Correlation between serum potassium and plasma aldosterone concentrations. To determine the correlation between serum potassium concentrations and plasma aldosterone levels in the anephric patients, additional studies on six of these patients were performed at random on a 1st day postdialysis and on a 3rd or 4th day postdialysis. Postambulatory levels of plasma aldosterone

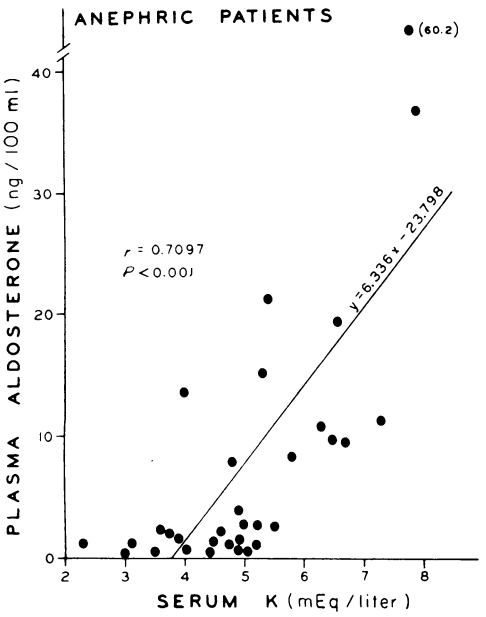

FIGURE 1 Correlation between postambulatory concentration of plasma aldosterone and corresponding serum potassium concentrations (n = 32).

and serum potassium concentrations from each of these studies and the paired studies discussed previously are shown in Table V. Averaging the data from each of these patients and using these averages to determine the means (n = 8), it can be seen that plasma aldosterone ($P < 0.02$) and serum potassium concentrations ($P < 0.01$) both increased significantly between the 1st day postdialysis and the 3rd or 4th day postdialysis.

When the various concentrations of plasma aldosterone on the 1st day postdialysis and the 3rd or 4th day postdialysis (postambulatory levels, n = 32) were related to the corresponding levels of serum potassium concentration as shown in Fig. 1, a highly significant correlation was apparent ($r = 0.7097$, $P < 0.001$). A significant correlation between a smaller number of plasma aldosterone concentrations in the supine position (n = 15) and serum potassium concentrations ($r = 0.7679$, $P < 0.001$) was also demonstrable as shown in Fig. 2.

Correlation between plasma aldosterone levels and plasma corticoid concentrations. Also shown for comparison in Table V, are plasma corticoid concentrations (postambulatory levels) on the 1st day postdialysis and the 3rd or 4th day postdialysis. In contrast with the changes in plasma aldosterone there were no significant increases in plasma corticoid concentrations ($P > 0.4$).

Low potassium studies. The effect of potassium balance or serum potassium concentration on plasma aldosterone in the anephric patients was investigated further during longer study periods of very low potassium intake and Kayexalate administration. Potassium balance data, including measured potassium losses in the feces and during dialysis are shown for two of these patients, E. S. and D. W., in Table VI. Although fecal potassium losses were not measured in the studies on patient A. D., all the patients received the same constant diet and the same dosage of Kayexalate, and in the absence of an increase in serum potassium concentration, the data from this patient should be comparable to the data from the other two patients. The cumulative potassium balances at the end of the study periods were + 26.4 mEq and − 13 mEq for patients E. S. and D. W., respectively. Thus, both potassium accumulation and potassium depletion were avoided.

Table VII shows the level of plasma aldosterone, serum potassium concentrations, and plasma corticoid concentrations before the beginning of the low potassium diet and Kayexalate administration, and on the 1st, 3rd, 4th, and 7th days of the studies on all three of the patients. Serum potassium concentrations remained consistently normal both pre- and postdialysis throughout the subsequent study period of severely restricted potassium intake and Kayexalate administration. Plasma aldosterone concentrations, instead of increasing between dialyses as previously observed, fell to the minimal levels detectable by the radioimmunoassay. This change was not accompanied by a similar reduction of plasma corticoid concentrations which were stable throughout.

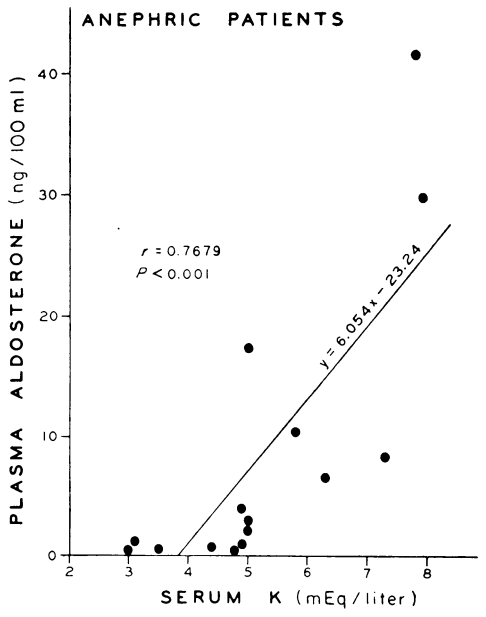

FIGURE 2 Correlation between plasma aldosterone concentrations in the supine position and corresponding serum potassium concentrations (n = 15).

TABLE V

Plasma Aldosterone, Serum Potassium Concentrations and Plasma Corticoid Concentrations in Anephric Patients

Patient	1st day postdialysis			3rd or 4th day postdialysis		
	Plasma aldosterone	Serum K	Plasma corticoids	Plasma aldosterone	Serum K	Plasma corticoids
	ng/100 ml	*mEq/liter*	*μg/100 ml*	*ng/100 ml*	*mEq/liter*	*μg/100 ml*
A. D.	1.3	3.1	9.3	2.6	5.5	—
	0.5	3.0	9.0	9.6	6.7	13.5
	2.1	4.6	13.0	15.3	5.3	13.1
H. G.	0.7	4.0	19.0	1.0	4.8	13.2
	2.1	3.7	19.3	9.7	6.5	10.0
				1.3	4.5	—
				1.5	3.9	11.7
D. J.	0.6	3.5	11.7	13.5	4.0	8.8
	2.4	3.6	10.0	10.9	6.3	9.8
E. S.	1.3	4.9	20.0	3.9	4.9	18.8
				0.6	5.0	—
				19.4	6.6	7.1
J. Br.	1.2	2.3	12.3	2.7	5.2	19.1
				11.3	7.3	19.7
J. Ba.	0.8	4.9	9.8	7.9	4.8	11.5
	21.2	5.4	11.2	60.2	7.8	11.2
				36.5	7.9	—
H. S.	0.5	4.4	9.2	1.1	5.2	7.6
D. W.	2.7	5.0	13.6	8.3	5.8	10.0
Mean	2.6	4.1	13.3	10.5	5.7	11.9
±SEM	±1.2	±0.3	±1.4	±3.7	±0.2	±1.2

Metabolic clearance rate of aldosterone. The MCR of aldosterone in three anephric patients on a 2nd day postdialysis, supine and sitting, is shown in Fig. 3. The change in posture from supine to sitting produced no alteration in the MCR of aldosterone in two of the patients and was associated with a decrease in the MCR in one patient.

Effect of heparin administration. Three anephric patients received infusions of heparin (80 or 100 mg) during a period of 7 hr on a day before dialysis to determine the effect of heparinization on plasma aldosterone. Clotting times (Lee-White) exceeded 45 min during the infusion of heparin in each of the studies. Plasma aldosterone concentrations before the infusions, at the end of the infusions, and on the following morning are shown in Table VIII. Serum potassium concentrations immediately before the infusions and on the following morning are shown for each patient. There was no evidence from these studies that heparin administration, over the same period of time and in the same total dosage as during hemodialysis, suppresses the level of plasma aldosterone; indeed, plasma aldosterone concentrations at the end of the infusions were increased, and were still higher in two patients on the following morning than before the infusions.

DISCUSSION

Our studies on normal subjects demonstrate that the concentration of plasma aldosterone is increased significantly after 2 hr of upright posture, as compared to the concentrations after 8 hr in the supine position, during periods of both low and high sodium intake. Comparable data for normal subjects on ad libitum sodium intake (8) and on a moderately restricted sodium intake (14) have previously been reported. In our studies on sodium-restricted subjects, this effect of upright posture on plasma aldosterone was similar qualitatively to the effect on PRA. Although the change in the con-

TABLE VI

Potassium Balance Data for Two Anephric Patients on Severely Restricted Potassium Intake and Kayexalate Administration

Patients	Potassium intake	Potassium loss		Cumulative potassium balance
		Dialysate	Feces	
		mEq		
E. S.	127.8	30.0	71.4	+26.4
D. W.	108.8	54.5	67.3	−13.0

centration of plasma aldosterone was in general more consistent than the change in PRA, concordance in these changes was readily apparent.

PRA was suppressed to levels that could not be detected by the bioassay in the majority of the normal subjects on a high sodium intake; and in the small number of subjects who had detectable PRA, no difference between the levels after upright activity and the levels while supine could be demonstrated. These observations are in agreement with the findings of de Champlain, Genest, Veyratt, and Boucher who were also unable to detect PRA in sodium–loaded normal subjects receiving 10 g of salt per day plus an unrestricted diet (15). The studies reported by Cohen, Conn, and Rovner (16) have indicated, however, that postural stimulation of renin release is not totally suppressed by a high sodium intake. Despite our inability to demonstrate a postural variation in the level of PRA in our sodium–loaded normal subjects, which may well be related to the low order of sensitivity of the assay procedure, it is evident in these studies that the effect of upright posture on plasma aldosterone is not abolished by sodium loading.

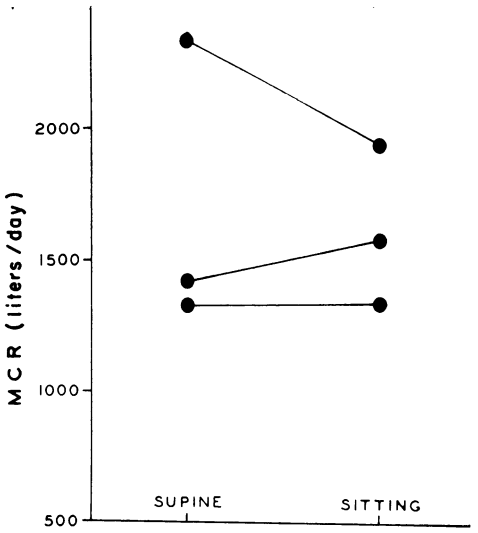

FIGURE 3 Metabolic clearance rate of aldosterone in three anephric patients, supine and sitting. Studies were performed on a 2nd day postdialysis.

In the studies on anephric patients, low concentrations of plasma aldosterone were detected on the 1st day postdialysis, in both the supine position and after 2 hr of ambulation. In contrast, by the 3rd or 4th day postdialysis, the concentration of plasma aldosterone was significantly higher. Changes in the concentration of plasma aldosterone in relation to upright activity were less consistently demonstrable than in the studies on normal subjects, although the data are insufficient to exclude the possibility that postural variation in plasma aldosterone may also occur in the anephric state.

As shown by the studies of Balikian, Brodie, Dale, Melby, and Tait (14) the rate of secretion of aldo-

TABLE VII

Plasma Aldosterone, Serum Potassium Concentrations, and Plasma Corticoid Concentrations in Three Anephric Patients During Low Potassium Studies

Patients		Day before K restriction + Kayexalate predialysis	K restriction + Kayexalate			
			Post-dialysis	Pre-dialysis	Post-dialysis	Pre-dialysis
A. D.	Plasma aldosterone, *ng/100 ml*	—	0.5	0.5	0.5	0.5
	Serum K, *mEq/liter*	6.2	4.4	4.2	3.8	4.3
	Plasma corticoid, *μg/100 ml*	—	8.5	8.8	10.3	8.3
E. S.	Plasma aldosterone, *ng/100 ml*	19.4	2.0	10.4	0.5	0.5
	Serum K, *mEq/liter*	6.6	4.9	3.9	4.2	3.7
	Plasma corticoid, *μg/100 ml*	7.1	11.7	8.0	10.7	10.9
D. W.	Plasma aldosterone, *ng/100 ml*	8.3	2.2	0.5	0.5	0.5
	Serum K, *mEq/liter*	5.4	4.5	3.9	3.4	3.3
	Plasma corticoid, *μg/100 ml*	—	11.9	9.6	10.4	7.8

sterone is the primary determinant of the plasma aldosterone concentration, and the metabolic clearance rate (MCR) of aldosterone is not a major factor. The aldosterone MCR in three of our patients was in the range of normal values reported by Balikian et al. (14) and by Tait, Little, Tait, and Flood (17), and even though the MCR might be expected to have a greater effect on the plasma aldosterone concentration under circumstances in which aldosterone secretion is reduced, neither the absence of an increase in the concentration of plasma aldosterone in the upright position nor a change in the concentration between the 1st day postdialysis and the 3rd or 4th day postdialysis could be attributed to this mechanism.

Plasma renin activity or renin-like activity was detected by the bioassay in one anephric patient, a 15-yr old female who exhibited sporadic menstruation, and by the more sensitive technique of radioimmunoassay in one additional patient, a 46 yr old male. Renin or a renin-like enzyme has been demonstrated in the plasma of female anephric patients by Capelli, Wesson, Aponte, Faraldo, and Jaffe (18), and assay of the extracts of various tissues obtained from one of these patients at autopsy revealed renin-like activity only in the uterus. McKenzie and Montgomerie reported the detection of renin-like activity in the plasma of nephrectomized male patients (19). The source of this substance in male subjects, however, has not been determined. Although one of our male patients exhibited substantial renin activity in stored plasma samples obtained on the 4th day postdialysis, there was no increase in PRA induced by 2 hr of upright posture.

Although the concentration of plasma aldosterone in the anephric patients was quite low on the 1st day after hemodialysis, it did increase significantly between the 1st day postdialysis and the 3rd or 4th day postdialysis. Furthermore, this increase occurred despite an increase in body weight (1.05, SEM ±0.84 kg), implying retention of sodium and water. A similar increase in body weight in the group of normal subjects during the period of high sodium intake produced the opposite effect, i.e., a marked reduction in the concentration of plasma aldosterone. Thus, it seems clear from these data that aldosterone secretion, as reflected in the concentration of plasma aldosterone, does not respond normally, in the absence of the kidneys, to progressive volume expansion. However, the increase in the concentration of plasma aldosterone between the 1st day postdialysis and the 3rd or 4th day postdialysis indicates clearly that aldosterone secretion in anephric patients is responsive to other stimuli.

TABLE VIII

Effect of Heparin Administration in Anephric Patients

Patients	Plasma aldosterone			Serum K	
	Pre-infusion	End of infusion	Next morning	Pre-infusion	Next morning
	ng/100 ml			*mEq/liter*	
A. D.	2.7	5.4	3.0	5.8	6.3
E. S.	6.7	10.7	4.5	5.0	5.8
D. W.	2.6	29.4	16.7	—	6.8

Aldosterone secretion can be stimulated acutely by ACTH (20). However, as shown by the studies of Bledsoe, Island, and Liddle (21), cortisol and corticosterone secretion are increased by small quantities of ACTH which have no effect on the secretion of aldosterone, and since the concentration of plasma corticoids did not change in these studies between the 1st day postdialysis and the 3rd or 4th day postdialysis, the increase in the concentration of plasma aldosterone in this period cannot be attributed to ACTH.

The finding of a highly significant correlation between the concentration of plasma aldosterone and the serum potassium concentration suggests that the primary regulator of plasma aldosterone concentration in the anephric state may be serum potassium. There is an abundance of evidence from earlier studies which indicates that aldosterone secretion can be stimulated by increased serum potassium concentration (4, 22–24). Davis, Urquhart, and Higgins reported that increments in the serum potassium concentration as small as 1.3 mEq/liter were sufficient to produce increased secretion of aldosterone in hypophysectomized dogs (24); the effect of increased serum potassium concentration on aldosterone secretion in these studies was not abolished by subsequent nephrectomy, and increased aldosterone output from isolated adrenals could be demonstrated after the infusion of potassium salts directly into the adrenal arterial blood supply. A direct effect of serum potassium concentration on aldosterone secretion has also been shown in studies in which potassium salts were infused directly into the adrenal artery of sheep with adrenals transplanted to the neck (4).

This relationship in man has not been so clearly defined. Gann, Delea, Gill, Thomas, and Bartter observed that potassium administration, after moderate potassium and sodium depletion, produced further augmentation of aldosterone excretion in the absence of continuing sodium loss, and despite plasma volume expansion (25). However, it was not possible, in these studies, to separate the effect of serum potassium concentration on aldosterone excretion from the effect of potassium balance. In other studies on man, Cannon, Ames, and Laragh noted that potassium administration produced marked increases in aldosterone secretion with only minor changes in the serum potassium con-

centration (26). These investigators postulated that tissue potassium accumulation, possibly in the adrenal cortex, may be more important than the serum potassium concentration in the regulation of aldosterone secretion. It was also noted in these studies that the magnitude of enhancement of aldosterone secretion produced by potassium administration was directly related to the preexisting level of aldosterone production.

In our studies on three anephric patients during a period of severely restricted potassium intake and Kayexalate administration, plasma aldosterone concentration fell to barely detectable levels. After the initial loss of potassium during the hemodialysis that preceded these studies, the potassium balances measured in two of these patients showed neither further depletion nor retention of potassium. The serum potassium concentration, on the other hand, decreased slightly (1.2 mEq/liter in both of these patients) during the period included in the balances, possibly in association with moderate expansion of the extracellular fluid volume due to the increment in sodium intake provided by Kayexalate. These observations suggest that the reduction in the concentration of plasma aldosterone may be correlated more closely with the serum potassium concentration than with potassium balance. In addition, these studies show clearly that without the continued stimulus of potassium accumulation, aldosterone secretion in anephric patients, as indicated by the marked reduction in the plasma aldosterone concentration, is promptly reduced to a low level.

One additional factor which must be considered is the effect of heparin administration during each of the dialyses. Heparin in doses of 300–400 mg per day has been shown to suppress aldosterone excretion and promote natriuresis and potassium retention (27, 28). However, this effect occurs gradually, and maximal suppression of aldosterone excretion is observed after several days of continued heparin administration. When heparin was administered to three of our patients on a day before dialysis, the concentration of plasma aldosterone was consistently increased at the end of the infusions (7 hr) and returned to lower levels by the following morning. Only one of these patients exhibited a lower concentration of plasma aldosterone on the morning after the infusion than before the infusion. Although additional studies are clearly indicated, it seems unlikely on the basis of these observations that heparin administration during hemodialysis contributed significantly to the reduction of the concentration of plasma aldosterone on the 1st day postdialysis. The rise in the concentration of plasma aldosterone during heparin administration on the off-dialysis day is presently unexplained and requires further elucidation.

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