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Research Article

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Postural Augmentation of Plasma Renin Activity and Aldosterone Excretion in Normal People *

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Summary. Peripheral plasma renin activity and aldosterone excretion rates have been measured in normal people during recumbency, recumbent exercise, tilting, and continuous ambulation. Upright posture induces a prompt elevation in peripheral plasma renin activity beginning in 15 minutes and peaking between 60 and 120 minutes. Aldosterone excretion is increased during 120 minutes of upright posture and correlates directly with the elevation in renin activity. Upright posture induces increased plasma renin activity regardless of the level of sodium intake in the preparatory diet. Concomitant measurements of endogenous creatinine clearance and the rates of excretion of sodium and potassium suggest that a fall in renal arterial perfusion resulting from upright posture induces increased release of renin and the subsequent secondary stimulation of aldosterone secretion. Our data indicate that the changes in plasma renin activity are due to changes in the amount of the enzyme rather than to changes in other elements of the renin–angiotensin systm. This report discusses the physiologic importance of postural augmentation of renin production, emphasizing that for proper interpretation of values of plasma renin activity, posture as well as dietary factors must be considered and controlled.

Introduction

This study of the renin–angiotensin–aldosterone system has had two purposes: *a*) to elucidate the normal physiology of the system in man's daily life and *b*) to establish norms under standard conditions of testing that would best enable us to recognize those clinical conditions in which function of the system has been altered by disease. We have studied the effects of various factors on each end of this system, using as our tools *a*) measurements of renin activity in peripheral plasma (1) and *b*) determinations of the rates of excretion of aldosterone (2).

Early in this work we were able to confirm the findings of Veyrat, de Champlain, Boucher, and Genest (3) and of Brown, Davies, Lever, and Robertson (4) that sodium restriction increases plasma renin activity and that sodium loading diminishes it. In addition, we observed that aldosterone production increased and decreased in parallel with plasma renin activity.

Normal people excrete more aldosterone during a period in the upright position than they do during a similar period of recumbency (5, 6), and various ideas have been put forward to explain this phenomenon (7, 8). We have observed that the upright posture is a strong stimulus for increasing both plasma renin activity and aldosterone

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production. These data are herein recorded, and their importance in relation to levels of plasma renin activity in certain abnormal clinical states is discussed.

Methods

Renin activity was measured by the method of Boucher and associates (1). During this study 10 ml of plasma was used for each measurement, and a single value after 3 hours of incubation served to estimate the rate of angiotensin II generation. The final diluting solution before bioassay was changed; in place of 20% ethanol, we used 0.9% saline containing 100 mg per 100 ml polyvinylpyrrolidone (PVP) [1] and 200 mg per 100 ml neomycin sulfate. This solution is nontoxic and has no significant pressor effect. Recovery of added angiotensin II (added to the eluate just before sublimation, and reconstituted with this solution) was 98 ± 8.7% (mean ± SD, N = 6).

To test reproducibility of the total system, we incubated, extracted, and bioassayed six aliquots of the same plasma on different days. The range of values was 492 to 579 ng per 100 ml, with a mean and SD of 547 ± 32 ng per 100 ml. The variability of the bioassay itself was tested by assaying another plasma sample on six different assay animals. The range was 381 to 416 ng per 100 ml, with a mean and SD of 398 ± 12.5 ng per 100 ml.

Recovery of valine-5-angiotensin II (free acid) added to a plasma blank [2] before pH adjustment was 58 ± 6.3% (mean ± SD, N = 19). Amounts of angiotensin II ranging between 10 and 200 ng were added to 10 ml of plasma blank for this study, since the resultant concentration of angiotensin II was similar to that seen in normal plasma after incubation. Recovery of 100 ng angiotensin II added at the completion of incubation of 10 ml of plasma blank was 58.4 ± 5.5% (mean ± SD, N = 5).

The rat pressor assay was performed according to the following specifications. Bilaterally nephrectomized (14 to 20 hours), pentolinium-blocked, pentobarbital-anesthetized male Sprague–Dawley strain rats weighing 160 to 200 g were employed. Pressor response was recorded from the right carotid artery with a Statham P23Db physiologic pressure transducer, and recording was accomplished with a potentiometric (Leeds–Northrup, Speedmax G) recorder. A consistent response of the assay animal of at least 3.2 mm Hg above base line for 0.4 ng angiotensin II standard was required, or the animal was discarded as insensitive. The usual response was from 4 to 6.8 mm Hg. Evidence of a proportional rise of blood pressure (6.8 to 12 mm Hg) to 1 ng of angiotensin II was also required. The volume of injected unknown varied between 10 and 80 μl. Valine-5-angiotensin II free acid (90% carrier free) [3] dissolved in saline PVP–neomycin solution at a concentration of 0.1 ng per μl was used as the standard. Hamilton syringes with automatic dispensers were connected to two PE 10 catheters placed in the left jugular vein. Unknown was assayed at two dose levels and compared to standard angiotensin II at two similar dose levels. The entire bioassay for each unknown was bracketed at the beginning and the end, with either the same dose of unknown or with the standard to demonstrate the absence of significant change (1.2 mm Hg or less) in the responsiveness of the animal with time. Bioassay was performed below 2.4 ng on the dose–response curve. In the range between 0.2 ng and 2.4 ng, the slope of the dose–response curve was relatively steep, and calculation was performed in a linear manner. Each dose of unknown and its respective standard were assayed in close proximity on the curve, usually within 2 mm Hg of each other. Two dose levels were chosen, one dose twice the other, and four points (two unknown and two respective standards) were used for calculation. If calculation of angiotensin II equivalent at the two dose levels did not agree within 20%, the procedure was repeated. The disparity was usually below 10% in specimens measuring 75 ng per 100 ml or greater. Angiotensin II standard of 0.4 ng was the lower limit for the higher comparison standard, and 1 ml of saline–PVP–neomycin was used as the final volume of diluent for the unknown. Therefore, the lower limit of sensitivity of the assay was set arbitrarily at 50 ng angiotensin II per 100 ml of plasma generated in 3 hours' incubation. Eight to 15 specimens can be assayed on a single animal with this procedure. Figure 1 is a reproduction of typical assay recordings.

Estimation of substrate activity was accomplished by adding 0.58 dog U of human renin [4] to 5 ml of plasma diluted to 10 ml by the addition of 5 ml of ammonium acetate buffer. After pH adjustment to 5.5, each sample was incubated, extracted, and bioassayed as described above. Human renin in increasing concentration was added to similarly diluted aliquots of a plasma pool prepared by mixing 427 human plasma samples (10 ml each) in order to determine that 0.58 dog U was an excess of renin for this particular concentration of plasma. We were able to recover 60% of 10,000 ng (100,000 ng per 100 ml) angiotensin II added to a 10-ml aliquot of plasma pool, demonstrating that the quantity of Dowex exchange resin employed was adequate for this study.

Aldosterone excretion was determined by the double isotope dilution derivative technique of Kliman and Peterson (2). Forty to 50 ml of urine was extracted and 3,000 dpm of *d*-aldosterone-4-^{14}C added before acidification. The acid-hydrolyzable conjugate of aldosterone, together with free aldosterone, was purified by paper chromatography and then acetylated with acetic anhydride-^{3}H (100 mc per mmole). After two more paper systems, the diacetate was oxidized, and after one more paper system, ^{14}C and ^{3}H radioactivity was determined in a liquid scintillation spectrometer optimized for minimal counting error of both isotopes. Each specimen was counted at least three times (30 minutes each time), and

[1] Average mol wt, 40,000.

[2] Specimens measuring below 100 ng per 100 ml were pooled to serve as a blank for recovery studies. The value of this blank was 50 ng per 100 ml.

[3] We are indebted to Drs. H. Kappeler and W. Rittel, Ciba Ltd., Basel, Switzerland, for providing this standard.

[4] Kindly supplied by Dr. Oscar Helmer.

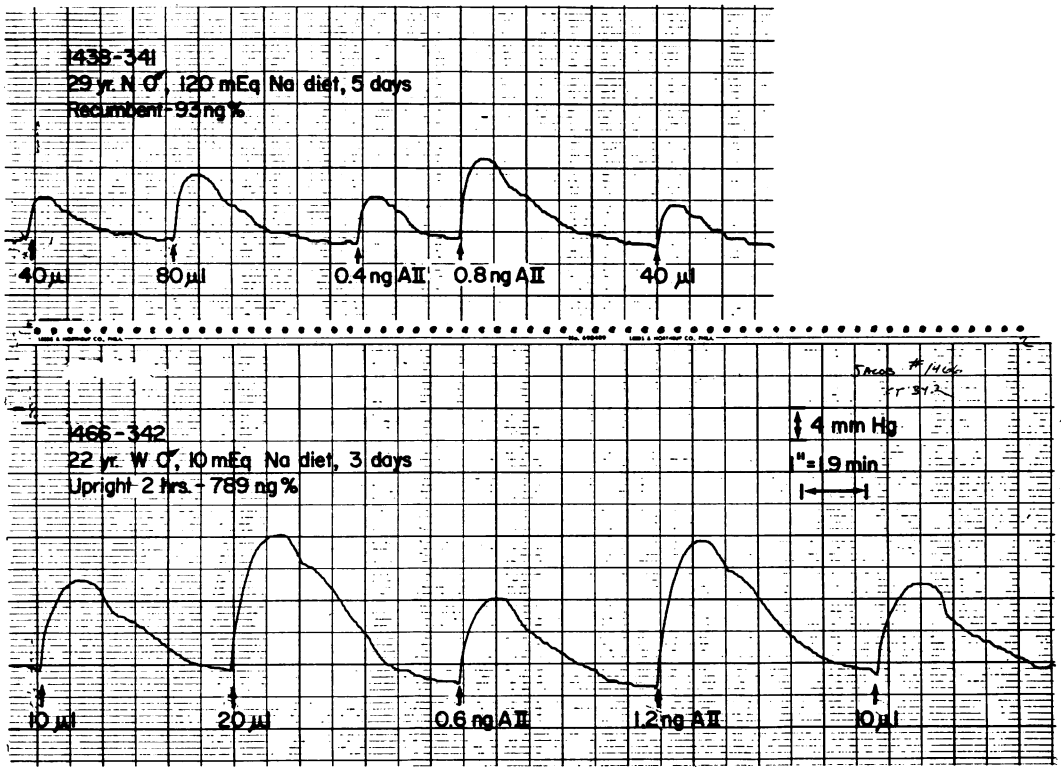

FIG. 1. RECORDINGS OBTAINED FROM TWO NORMAL SUBJECTS. Vertical scale, 0.5 inch (12.5 mm) = 4 mm Hg; horizontal scale, 1 inch (25 mm) = 1.9 minutes. AII = angiotensin II.

the total data were utilized in determining excretion rates through the use of a large high speed digital computer (IBM 7090). The error of counting in each sample was consistently less than 5%.

Serum and urinary sodium and potassium were determined by standard flame photometric technics. Serum and urinary creatinine were determined by the picric acid method (9).

Healthy normotensive men and women, ranging in age between 19 and 38 years, were studied after they had been ingesting the following types of diets: *a*) unrestricted, *b*) low sodium (10 mEq), *c*) moderate sodium (120 mEq), *d*) high sodium (180 mEq), and *e*) very high sodium (360 mEq), each of the latter four for at least 3 days. Twenty-four-hour urine specimens, refrigerated during collection, were frozen for future determination of aldosterone. Venous blood of 50 to 70 ml was drawn from the brachial vein for each measurement of peripheral plasma renin activity.

The various postural changes imposed are described with the individual groups of experiments.

Results

The effects of posture and activity on peripheral plasma renin activity

Figure 2 compares data obtained from three groups of normal people ingesting an unrestricted diet. The first column of data was obtained from 16 subjects on 28 separate occasions. The subjects had been continuously recumbent and fasting (overnight) for at least 7 hours before sampling. Blood was drawn between 7 and 9 a.m. The mean renin activity in fasting recumbent subjects was 182 ± 15 ng per 100 ml, with a range of 61 to 392 ng per 100 ml. The second column (random) represents measurements obtained from 14 people from whom blood was drawn without any prior control of posture, activity, or food ingestion. The mean value, 309 ± 43 ng per 100 ml, was significantly higher than in fasting recumbent subjects ($p < 0.005$), with a broader range, 88 to 657 ng per 100 ml. The data in the third column (4-hour upright) were obtained in the following way. Ten of the first group of subjects (fasting recumbent) ingested a breakfast containing 40 mEq of sodium immediately after the first sampling and then remained on their feet (ambulatory) for 4 hours before the second sampling, which was done with the subject standing. All of these subjects (Figure 3) exhibited a rise in renin activity.

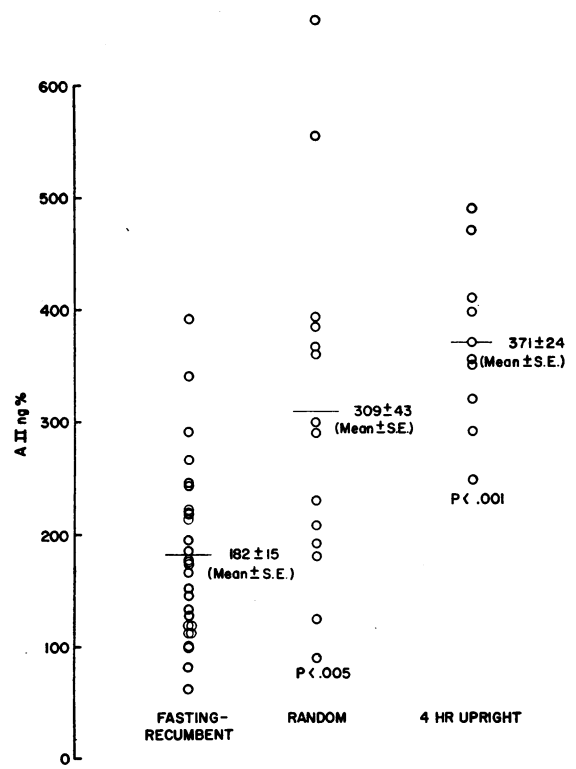

FIG. 2. EFFECT OF POSTURE ON PLASMA RENIN ACTIVITY IN NORMAL SUBJECTS INGESTING AN UNRESTICTED DIET. Values suggest that the position of the patient is important.

The mean for this group, 371 ± 24 ng per 100 ml, was significantly higher ($p < 0.001$) than the mean value obtained on the same subjects when they had been fasting and recumbent.

Two of the same ten subjects were restudied on another day. This time they remained in bed (recumbent) for 4 hours after the initial sampling. They ingested the same breakfast as before while remaining recumbent. In both subjects (Figure 4) renin activity failed to rise.

The effects of recumbent exercise and of passive tilting upon peripheral plasma renin activity

To be certain that the exercise associated with the 4–hour period of ambulation was not responsible for the rise of plasma renin activity rather than the change of posture, we carried out two sets of studies on seven healthy young men who had been eating unrestricted diets: *a*) the effects of exercise in the recumbent position and *b*) the effects of passive tilting without exercise.

a) *Recumbent exercise.* Each subject remained fasting and continually recumbent for at least 7 hours before base–line sampling at 8 a.m. and then, still recumbent, ate his breakfast containing 40 mEq of sodium. Still recumbent, he performed exercise against a bicycle ergometer at 50 foot pounds per minute intermittently for 10–minute periods during a 4–hour period. This constituted an attempt to simulate the exercise of ordinary ambulation. Blood was drawn at the end of 4 hours during the last exercise period. Figure 5 demonstrates the inconsistent effects of exercise upon peripheral plasma renin activity (open triangles). Three subjects exhibited an elevation of renin activity, one a fall, and three showed no change.

b) *Passive tilting.* Seven days later, after

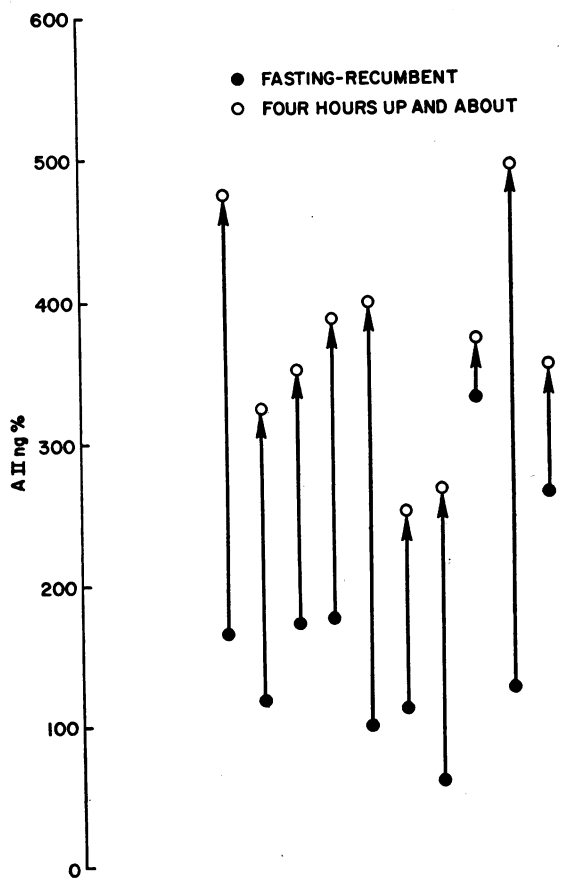

FIG. 3. COMPARISON OF PLASMA RENIN ACTIVITY VALUES OF TEN NORMAL SUBJECTS INGESTING AN UNRESTRICTED DIET WHILE FASTING AND RECUMBENT WITH VALUES AFTER 4 HOURS OF AMBULATION. In each subject the value rises after 4 hours of ambulation.

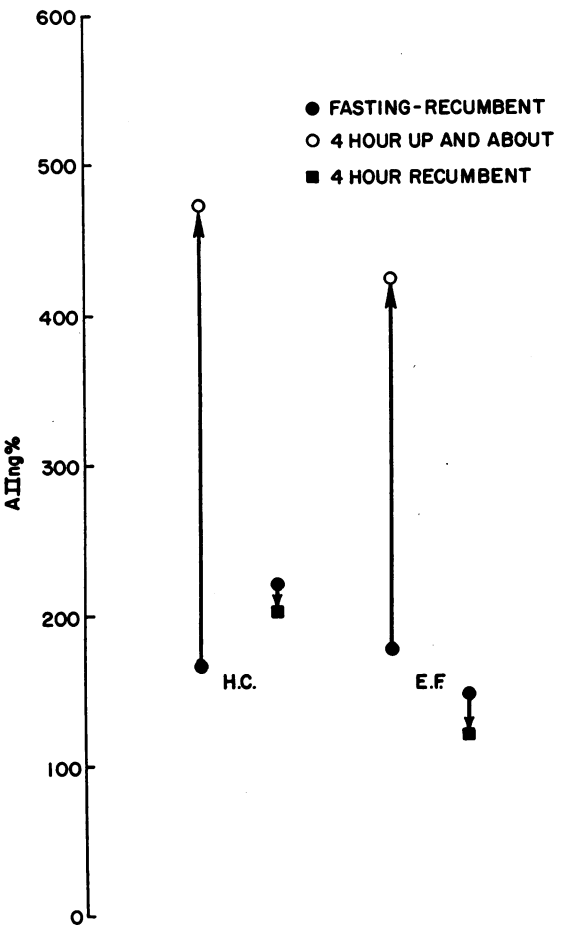

FIG. 4. COMPARISON OF PLASMA RENIN ACTIVITY VALUES IN TWO NORMAL SUBJECTS ON UNRESTRICTED SODIUM DIETS WHILE AMBULATORY WITH VALUES WHILE SUPINE. In one study on each subject, ambulation was allowed for 4 hours after the sample had been drawn with the subject recumbent; in the second study recumbency continued after the initial blood specimen had been drawn.

the overnight base–line sample had been drawn, each of the same seven subjects was placed on a tilt table and promptly tilted to 82°. At no time before tilting did any subject sit, stand, or walk. Syncope or hypotension did not occur. Renin activity was sampled after the 4–hour tilt. Figure 5 (open circles) demonstrates the consistent elevation of renin activity in each subject. An impressive difference between recumbent exercise and passive tilting was observed in all subjects except H.C.

In Table I are recorded for each subject the additional data collected in the course of both the recumbent exercise studies and the passive tilt studies. Two–hour voided urine specimens had been obtained during each 4–hour test period, and blood samples for plasma renin activity and for serum sodium, potassium, and creatinine had been drawn at the beginning and end of each 4–hour test period. Aldosterone was determined on the 4–hour urine sample, and sodium, potassium, and creatinine determinations were made on each 2–hour specimen. All subjects, except O.H., exhibited sharply lower endogenous creatinine clearance values during the first 2–hour period of tilt than during the first 2–hour period of recumbent exercise. With the same exception (subject O.H.), sodium and potassium excretion rates diminished greatly during the tilt.

All subjects demonstrated a higher 4–hour excretion of aldosterone during the 4–hour tilt than during the 4–hour recumbent exercise period, and

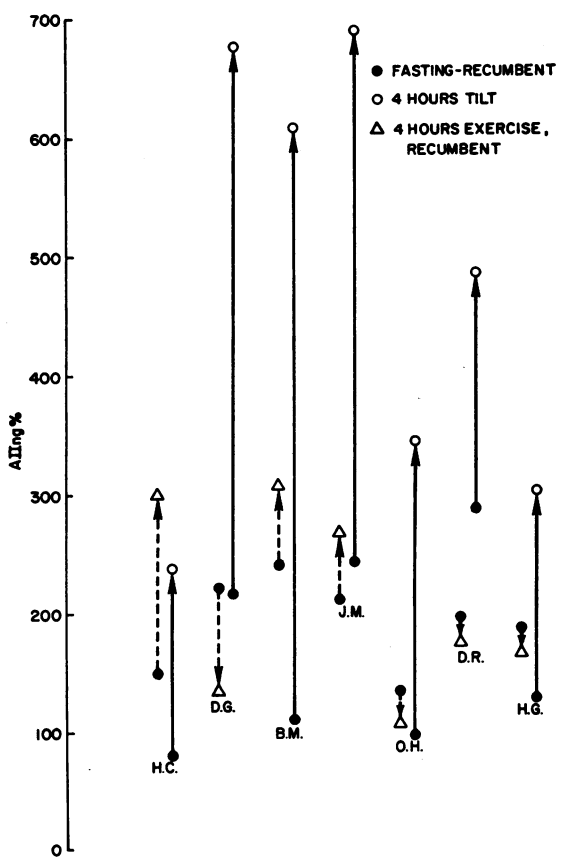

FIG. 5. PLASMA RENIN ACTIVITY VALUES AFTER 4 HOURS OF INTERMITTENT RECUMBENT EXERCISE COMPARED WITH THOSE OBTAINED AFTER 4 HOURS OF PASSIVE TILTING (82°). Each of the seven normal subjects had been ingesting an unrestricted diet.

TABLE I

Effects of recumbent exercise and of passive tilting on plasma renin activity, aldosterone excretion, creatinine clearance, and the rates of excretion of sodium ($U_{Na}V$) and potassium (U_KV)

		Renin activity					
		Base line → 4 hours	Aldosterone	Creatinine	$U_{Na}V$	U_KV	Time
		ng/100 ml	*μg/4 hours*	*ml/min*	*mEq/min*	*mEq/min*	*hours*
H.C.	A*	152 → 298	1.7	151 134 112	0.17 0.24 0.04	0.06 0.07 0.03	0–2 2–4 0–2
	B†	81 → 235	6.2	150	0.05	0.03	2–4
D.G.	A	222 → 138	2.6	168 120 120	0.11 0.47 0.03	0.04 0.13 0.02	0–2 2–4 0–2
	B	219 → 676	12.3	155	0.03	0.02	2–4
J.M.	A	213 → 265	0.64	135 129 113	0.12 0.24 0.03	0.10 0.14 0.02	0–2 2–4 0–2
	B	246 → 699	2.4	110	0.05	0.06	2–4
W.M.	A	244 → 316	1.0	170 154 130	0.29 0.47 0.04	0.12 0.13 0.03	0–2 2–4 0–2
	B	112 → 607	7.1	147	0.10	0.10	2–4
D.R.	A	195 → 180	1.1	147 142	0.42 0.44	0.15 0.14	0–2 2–4
	B	291 → 486	2.0	103	0.06	0.04	0–4
O.H.	A	133 → 112	0.94	149 161 157	0.17 0.20 0.09	0.03 0.05 0.03	0–2 2–4 0–2
	B	99 → 345	2.7	167	0.17	0.07	2–4
H.G.	A	185 → 174	2.8	145 145 100	0.19 0.33 0.08	0.06 0.09 0.03	0–2 2–4 0–2
	B	118 → 302	4.2	119	0.14	0.06	2–4
Mean ± SE	A	192 ± 15 → 212 ± 30.5 $p > 0.5$	1.54 ± 0.32‡	153 ± 4.8§ 141 ± 5.4‖	0.27 ± 0.04‡	0.09 ± 0.01‡	
Mean ± SE	B	166 ± 31.5 → 478 ± 71.4 $p < 0.005$	5.27 ± 1.38‡ $p < 0.01$	119 ± 7.4§ 141 ± 9‖	0.07 ± 0.01‡ $p < 0.001$	0.04 ± 0.004‡ $p < 0.001$	

* A = recumbent exercise period.
† B = passive tilt period.
‡ Four hours.
§ $p < 0.005$.
‖ $p > 0.5$.

in all, except H.C., the higher aldosterone value was accompanied by a much higher level of renin activity. Statistical evaluation of the over–all data (Table I) indicates *a*) that a significant rise in renin activity occurs with tilting ($p < 0.005$) but not with exercise, *b*) that tilting is accompanied by a significant rise in aldosterone excretion ($p < 0.01$), and *c*) that significant decreases in creatinine clearance (first 2 hours, $p < 0.005$) and in sodium excretion ($p < 0.001$) and potassium excretion ($p < 0.001$) occur during the tilting experiments.

Table II shows data on subject J.M., who was studied under all three conditions: recumbent exercise, tilt, and ambulation. It is of interest to compare the results of the recumbent exercise test done twice (4 months apart) on the same person. It is apparent, too, that the results obtained during 4 hours of ambulation are very similar to those during the 4–hour tilt.

TABLE II

*Recumbent exercise and upright tests repeated in the same person**

	Renin activity				
	Base line	4 hours	Aldosterone	Creatinine	Time
	ng/100 ml		*μg/4 hours*	*ml/min*	*hours*
4-hour exercise	213	→ 265	0.64	135	0–2
(9/13/64)				129	2–4
4-hour tilt	246	→ 699	2.4	113	0–2
(9/20/64)				110	2–4
4-hour exercise	106	→ 169	1.07	152	0–2
(1/24/65)				125	2–4
4-hour ambulation	122	→ 453	2.99	107	0–2
(1/31/65)				115	2–4

* J.M., normal male, general diet.

The effects of posture in modifying the effects of different levels of sodium intake upon peripheral plasma renin activity

The sodium intake of 17 normal subjects (Table III) was carefully controlled at 10 mEq daily (potassium 70 mEq daily) for 3 days. On the morning of the fourth day, the mean value (recumbent) for renin activity, 451 ± 53 ng per 100 ml, was significantly elevated when compared to the mean value (recumbent) of 182 ± 15 ng per 100 ml for subjects on an unrestricted diet. More striking, however, was the 2.5-fold further rise when the subjects assumed the upright position (1,181 ± 117 ng per 100 ml). This value was also significantly higher than the mean value (upright) of 371 ± 24 ng per 100 ml for subjects studied on an unrestricted diet.

TABLE III

Effect of low sodium intake and upright posture on plasma renin activity in 17 normal subjects*

	Recumbent	Ambulatory 4 hours
	ng/100 ml	
R.K.	884	1,770
J.J.	484	862
D.K.	920	1,472
W.A.	767	1,337
D.P.	377	709
D.R.	426	1,211
D.R.	587	1,136
H.R.	628	1,427
C.L.	274	1,180
C.K.	400	2,371
H.P.	341	630
D.H.	293	1,724
M.R.	196	1,182
K.P.	372	1,712
M.W.	388	695
P.Z.	220	446
D.Z.	141	964
Mean ± SE	451 ± 53	1,181 ± 117

* Ten mEq per day for 3 days.

In Table IV are shown values for plasma renin activity (recumbent and upright) from eight normal subjects, each on three different levels of sodium intake (10 mEq, 180 mEq, and 360 mEq), together with the corresponding aldosterone excretion rates. Potassium intake was constant (70 mEq). Recumbent and 4-hour ambulatory renin activity measurements were made on each subject after 3 days of the low sodium diet and after 5 days on each of the higher sodium regimens. Aldosterone was measured on the 24-hour urine specimen completed just before blood was drawn

TABLE IV

Effects of recumbency and ambulation upon plasma renin activity and aldosterone excretion of eight normal subjects on three levels of sodium intake

Sodium:	10 mEq/day			180 mEq/day			360 mEq/day		
	Renin activity			Renin activity			Renin activity		
	→*	↑†	Aldosterone	→	↑	Aldosterone	→	↑	Aldosterone
	ng/100 ml		*μg/day*	*ng/100 ml*		*μg/day*	*ng/100 ml*		*μg/day*
C.L.	274	1,185	63	<50	117	12	<50	119	3
H.P.	341	630	22	100	310	12	<50	109	5
C.K.	400	2,371	63	72	603	20	<50	96	4
M.W.	388	695	75	107	167	7	<50	63	4
R.K.	884	1,770	15	‡	‡	4	121	163	2
J.J.	484	862	21	‡	‡	6	114	171	3
L.B.	231	757	51	122	469	10	185	320	6
B.M.	402	648	32	133	491	10	145	238	2

* → = recumbent.
† ↑ = upright.
‡ Renin activity not determined.

TABLE V

Relation of duration of upright posture to levels of plasma renin activity and aldosterone excretion

Subject	Renin activity						
	0 min	15 min	30 min	60 min	120 min	180 min	240 min
				ng/100 ml			
1	170	496	561	935	718	501	442
2	298	339		494	603	658	675
3	172	246	228	326	241	286	349
4	165	171	259	332	419	317	292
5	25*	102	196	316	448	439	247
6	168	277	384	461	827	650	476
Mean ± SE	166 ± 35	272 ± 56	326 ± 67	477 ± 97	543 ± 87	475 ± 65	414 ± 63
p		<0.2	<0.1	<0.025	<0.005	<0.005	<0.01

	Aldosterone excretion		
	Base (−240 min → 0)	120 min (0 → 120)	240 min (120 → 240)
		μg/hour	
1	1.0	1.4	4.3
2	0.8	2.8	2.6
3	0.4	1.2	1.6
4	0.9	2.2	3.0
5	0.4	1.6	2.9
6	0.7	2.6	3.8
Mean ± SE	0.7 ± 0.1	1.97 ± 2.7	3.03 ± 0.38
p		<0.005	<0.001

* <50 ng per 100 ml (estimated at 25 ng per 100 ml).

for renin determinations. With increasing sodium intake there occurred suppression of both upright renin activity and aldosterone excretion. However, at every level of sodium intake, the stimulus of upright posture on plasma renin activity is readily observed. Further, when the very high intake of sodium suppressed plasma renin activity below the detectable range, the upright posture brought the value into measurable range in every instance.

Rate of elevation of renin activity during upright posture

To study the rate at which renin activity rises after normal people assume the upright posture, we placed six men on diets containing 120 mEq of

TABLE VI

Plasma renin activity and aldosterone excretion during 4 hours of continuous recumbency

Subject	Renin activity						
	0 min	15 min	30 min	60 min	120 min	180 min	240 min
				ng/100 ml			
1	93	93	121	104	61	70	69
2	222	215	190	143	149	167	160
3	77	113	113	117	82	87	96
5	57	65	59	59	100	64	58
Mean ± SE	112 ± 37	122 ± 33	121 ± 27	106 ± 18	98 ± 19	97 ± 24	96 ± 23
p		0.5	0.5	0.5	0.5	0.5	0.5

	Aldosterone excretion		
	Base (−240 min → 0)	120 min (0 → 120)	240 min (120 → 240)
		μg/hour	
1	0.6	0.73	0.56
2	0.85	0.77	0.59
5	1.7	0.75	0.68

TABLE VII

Addition of excess human renin to plasma samples collected during recumbency and after ambulation

Subject	Diet	Renin activity		Substrate activity	
		Recumbent	4 hours upright	Recumbent	4 hours upright
		ng/100 ml		*ng/100 ml*	
1	120 mEq Na	122	302	23,552	26,140
2	10 mEq Na	729	2,311	32,532	30,220
3	10 mEq Na	307	1,151	25,340	25,120
4	10 mEq Na	252	814	29,440	32,000

sodium and 70 mEq of potassium for 5 days and studied them on the morning of the sixth day. Plasma renin activity was measured on 25 to 40 ml of blood taken during the fasting and recumbent state and at 15, 30, 60, 120, 180, and 240 minutes after the subject had assumed the upright posture. He ingested the usual breakfast after the drawing of the specimen while he fasted. Urine specimens were collected at the beginning of the study (4 a.m. to 8 a.m.) and at 120 and 240 minutes after the upright posture had been assumed. These specimens were measured for aldosterone excretion. Table V reviews the data.

Each subject demonstrated a peak in renin activity at the 60- or 120-minute point thereupon reaching a plateau or exhibiting a decline. The means for the absolute values at each time period were significantly different from the base line at 60, 120, 180, and 240 minutes. There was convincing evidence of rise in renin activity within 15 minutes in three of the six subjects.

Aldosterone excretion was also significantly elevated from base-line values at the 120-minute point. Further elevation occurred at 240 minutes.

Four of the same six subjects were restudied after a second 5-day period (Table VI). This time, conditions were unchanged except that continuous recumbency was maintained during the study. Renin activity showed considerable variability during the first 2 hours of study, but no statistically significant elevation was found. Values fell or stabilized by the third and fourth hours. Aldosterone excretion, likewise, showed no elevation when compared with base-line values, and actually fell in two of the three subjects studied.

Estimation of substrate activity during upright posture

Substrate activity was estimated in four pairs of samples by adding human renin in excess (see above). Samples were collected from one subject maintained on a 120 mEq sodium intake (5 days) and three subjects ingesting 10 mEq sodium daily (3 days). Results (Table VII) show that substrate concentration was unchanged in each pair of samples, despite the original elevation of renin activity upon assumption of the upright posture.

Discussion

Skinner, McCubbin, and Page (10) have demonstrated that relatively small decreases in mean renal arterial perfusion pressure stimulate renin output. Vander and Miller (11) have suggested that something associated with the "load" of sodium, which arrives at the macula densa of the distal tubule, is critical in regulating release of renin, the secretion being inversely proportional to the "load of sodium" at the receptor site. Thurau (12) has suggested that renin secretion is directly proportional to sodium concentration in the macula densa, thereby effecting autoregulation of glomerular filtration rate. Though the actual mechanism for the stimulation of renin secretion is undetermined, it would appear that relatively small changes in renal hemodynamics or small changes in sodium concentration at some intrarenal receptor site or both are important factors regulating the renin–angiotensin–aldosterone system.

Smith (13), employing a tilt table, originally showed that the acute effects of upright posture include sharp decreases in the clearance of both inulin and para-aminohippurate, despite maintenance of mean arterial blood pressure. Wesson (14) has reviewed more recent studies which show that upright posture is associated with significant decreases in creatinine and inulin clearances and of sodium excretion. Exercise has an inconsistent effect upon these same variables (15).

The actual mechanism inducing these acute changes in renal hemodynamics upon assumption of upright posture is not yet clear. Acute changes in "effective" blood volume due to pooling of blood in the lower extremities (16–18) could result directly in significant depression of renal arterial perfusion or could stimulate the autonomic nervous system to induce a similar effect. Vander (19) has presented evidence to suggest that a direct effect of the autonomic nervous system upon the renal vasculature results in increased renin

secretion in anesthetized dogs. Similarly, Wathen and his colleagues (20) have demonstrated a rise in renin secretion during infusion of catecholamines into the renal artery of anesthetized dogs. However, intravenous infusion of catecholamines into anesthetized dogs failed to evoke increased renin secretion until the infusion was discontinued. Therefore, the function of the autonomic nervous system and catecholamines in the control of renin secretion remains unsettled. Leyssac (21) has suggested that in the rat angiotensin itself regulates glomerular filtration rate through its effect upon the proximal tubular transport of sodium.

Our observations of consistent sharp falls in endogenous creatinine clearance, as well as greatly decreased rates of sodium and potassium excretion during tilting, are consistent with earlier findings (13, 14). Similarly, we have confirmed the observations of Gowenlock, Mills, and Thomas (6) and of Muller, Manning, and Riondel (5) that upright posture results in increased excretion of aldosterone. In addition, however, our data indicate a direct correlation between the postural rise of plasma renin activity and the increased rate of aldosterone excretion. We choose to interpret all of these findings together as meaning that the acute hemodynamic changes associated with assumption of the upright posture stimulate the release of increased amounts of renin, raising the level of activity of the angiotensin–aldosterone system, and that, in this respect, the renin–angiotensin–aldosterone system represents an important compensatory mechanism, tending to hold blood pressure and expand plasma volume. By such a negative feedback system, the final compensated state for upright posture would be associated with higher activity of the renin–angiotensin–aldosterone system but less high than that triggered acutely by changing from recumbent to upright positions.

The renin–angiotensin reaction is complex, and the reliability of any bioassay system for the estimation of renin is subject to the adequate control of other known variables. The consistency of recovery of angiotensin II added to our system both before and after incubation gives confidence that angiotensinases were effectively controlled. The demonstration that renin substrate does not change significantly upon assumption of the upright posture rules this out as a factor in the elevation of the renin activity. The same line of reasoning can be applied in ruling out other factors such as converting enzyme, inhibitors, or potentiators as playing a role in the phenomenon elicited by upright posture.

The changes of plasma renin activity and of aldosterone excretion that are measurable in normal people as their sodium intakes change, and the demonstration of the relatively rapid superimposable effects of posture regardless of sodium intake, make it clear that the renin–angiotensin–aldosterone system has important regulatory functions, making hour–to–hour and day–to–day adjustments as we change position and diet. When one thus becomes aware of the factors that increase and decrease plasma renin activity, only then is he in a position to set standards for comparison with clinical situations in which this measurement is thought to be abnormal.

We have shown (22–25), for example, that under conditions of low sodium intake (10 mEq per day for 3 days) and upright posture (ambulation for 4 hours, 8 a.m. to noon), conditions that in normal people induce very high levels of plasma renin activity, patients with primary aldosteronism exhibit greatly suppressed levels of plasma renin activity. This, together with overproduction of aldosterone, has been uniquely diagnostic of an aldosterone–producing adrenal tumor. Similarly, we have taken advantage of the enhancing effect on plasma renin activity of upright posture in the diagnosis of renovascular hypertension (26). This has been presented in detail in another communication (27).

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