JCI The Journal of Clinical Investigation

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J Clin Invest. 1971;50(10):2184-2190. https://doi.org/10.1172/JCI106713.

Research Article

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The lower metabolic clearance rate could account for elevated plasma concentrations of aldosterone even when the secretion rate is normal or low. Measurement of secretion rate or urinary excretion only is therefore insufficient to establish the presence and/or mode of evolution of hyperaldosteronism. Failure of the aldosterone secretion to adapt fully to a decreased aldosterone metabolic clearance rate (MCR) could explain the state of relative hyperaldosteronism in patients with benign essential hypertension, even when the secretion rate and the urinary excretion rate are in the normal range.

A Decreased Metabolic Clearance Rate of Aldosterone in Benign Essential Hypertension

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ABSTRACT Aldosterone secretion rate, metabolic clearance rate, and/or plasma concentration were determined in 16 patients with benign, uncomplicated essential hypertension and compared with those of control subjects. The mean metabolic clearance rate of aldosterone in 10 patients was significantly ($P < 0.001$) lower (mean 867 liters of plasma/day per m^2 ±270 SD) than in a group of 7 healthy subjects (mean 1480 liters/day per m^2 ±265 SD). Secretion rates in 13 patients (including the 10 already mentioned) tended to be low (83 ±43 vs. 109 ±54 μg/day) and plasma concentrations tended to be high (13.6 ±4.6 vs. 7.5 ±4.8 ng/100 ml), but neither of these differences was statistically significant.

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INTRODUCTION

The role of hyperaldosteronism in the pathogenesis of hypertension is well established in primary aldosteronism and malignant hyptertension but still controversial in benign essential hypertension. Aldosterone excretion is elevated in patients with benign and severe essential hypertension as it has been shown by several investigators (1–11), using physicochemical methods to determine urinary aldosterone after chromatographic purification. These findings were later confirmed by Conn (12–14), who used a double-isotope dilution assay. Other workers (15–19), measuring daily secretion and excretion rate of aldosterone by double-isotope dilution methods, confirmed the observations in severe essential and malignant hypertension, but did not find an increased secretion or excretion rate in the great majority of patients with benign essential hypertension. Katsushima (20) found normal or even decreased secretion rates for aldosterone in benign essential hypertension.

We have investigated this discrepancy by measuring the metabolic clearance rate (MCR),[1] secretion rate (SR), and plasma concentration of aldosterone in normal subjects and in patients with benign, uncomplicated, essential hypertension.

Subjects. This study was conducted under controlled metabolic conditions, with due attention given to eliminate patients under acute stresses, anxiety states, and in the second phase of the menstrual cycle. The daily dietary intake contained 135 mEq of Na and 90 mEq of K. The blood pressure was taken every hour from 8 a.m. to 10 p.m. every day. At the time of the study, all the patients except one had blood pressures above 140/90 mm Hg (Table I). The mean age of the 16 patients studied was 37 yr (range, 19–59 yr). Patients in whom the effect of rest and reassurance in our Clinical Investigation Unit resulted in a persistent lowering of blood pressure to normal were not studied. Older patients with overt signs of arteriosclerosis and a wide pulse pressure were not studied either. Normal sub-

Results reported at the 43rd session of the American Heart Association, Atlantic City, N. J., 12–15 November 1970. *Circulation.* **43** (4, Suppl. 3): (Abstr. 311), and in part in a review on Aldosterone and Electrolyte Balance in Human Hypertension at the 6th World Congress of Cardiology, 6–12 September 1970 London. *J. Roy. Coll. Physicians.* 1: 77.

Received for publication 6 July 1970 and in revised form 3 February 1971.

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

TABLE I

*Clinical Data for the 16 Patients with Benign Essential Hypertension**

Patients	Blood pressure	Known duration of hypertension	Serum electrolytes			Renal function PSP		Creatinine clearance	Plasma renin activity	
			Na	K	Total CO_2 content	15 min	60 min		Recumbent	Upright
	mm Hg	*yr*	*mEq/liter*			%		*ml/min*	*ng/ml per hr*	
1. S. D.; 38 yr; M	220/110	10	140	5.4	23	40	75	91	0.29	—
2. L. L.; 39 yr; M	165/110	25	145	4.8	27	—	51	101	0.19	—
3. L. L.; 59 yr; M	200/120	2	143	4.4	26	29	58	—	0.26	0.38
4. D. G.; 35 yr; M	160/90	3	144	5	22	37	69	110	0.27	0.34
5. A. M.; 38 yr; F	230/140	14	141	4.4	29	27	—	98	0	0.4
6. L. B.; 42 yr; M	160/115	20	139	4.2		83	—	105	0.15	—
7. O. F.; 31 yr; M	140/80	15	140	4.6	22	44	79	148	0.33	0.57
8. R. P.; 42 yr; M	150/100	4	143	3.9	29	0	72	78	0	—
9. B. F.; 28 yr; F	150/105	1.5	142	4.3	26	47	90	92	0	1.53
10. R. P.; 32 yr; M	170/120	2.5	140	4.5	31	24	—	80	0	0.37
11. M. L.; 47 yr; M	240/140	5	149	4.2		23	—	80	0	—
12. C. H.; 48 yr; M	225/130	7	147	3.5	25.5	—	65	133	0.28	0.57
13. C. B.; 19 yr; F	180/130	2	143	4.1	23	46	76	118	0	1.23
14. F. F.; 42 yr; F	220/130	20	145	4.8	22	35	77	78	0.78	0.8
15. N. L.; 22 yr; F	160/115	3	144	4.1	27	31	56	—	0.33	0.85
16. P. E. M.; 42 yr; M	190/120	20	147	4.2	27	56	78	124	0	—

* Renal angiography, performed in all patients, except patient 7, showed no abnormality except for partial stenosis of the superior branch of the renal artery in patient 11.

jects of both sexes, aged 20–45 yr, were used as controls. Women were investigated only in the postmenstrual phase of the cycle.

The diagnosis of benign, essential hypertension was made on the basis of a thorough physical examination and numerous tests. Those patients had normal serum electrolytes, urine analysis, vanillyl-mandelic acid excretion, renal function tests, rapid sequence intravenous pyelography and renal angiography, and the absence of any other known causes of hypertension. However, one patient had an insignificant partial stenosis of the superior branch of the renal artery without elevated peripheral plasma renin activity, and another patient was investigated after having presented a hypertensive crisis, but showing no other symptoms of malignant hypertension. Renal and renovascular disease was positively excluded in all cases, and there was no clinical or laboratory evidence pointing to an aldosterone-producing adenoma.

Peripheral plasma renin activity, measured (24) in all patients in the recumbent and/or upright position, on normal sodium intake (135 mEq/day), was within the normal range (0.18 ng/ml per hr ±0.05 SD recumbent, and 0.70 ng/ml per hr ±0.12 SD upright), which is (24) 0.29 ng/ml per hr ±0.3, SD recumbent, and 0.71 ng/ml per hr ±0.3 SD upright, for 12 control subjects.

The study was usually begun on the 4th day of the diet, after the sodium balance has been established, by injecting aldosterone-^{3}H between 8:00 and 10:00 a.m., into patients kept in a recumbent position since the previous night. Urine was collected for a 24 hr period for the determination of aldosterone secretion rate. 2–3 days later, after complete elimination of the radioactivity, the MCR for aldosterone was determined.

The blood specimen for determination of aldosterone plasma concentration was obtained either immediately before beginning the determination of secretion rate, or else immediately before the administration of the priming dose for the MCR.

METHODS

Measurements of MCR of aldosterone. Our procedure uses the constant infusion principle as described by Tait, Little, Tait, and Flood (21). A priming dose of about 2 μCi of 1,2-^{3}H-labeled aldosterone (5 Ci/mmole) in 10 ml of sterile isotonic saline was injected intravenously during 1 min to fasting, recumbent subjects hospitalized during the previous night at about 8:00 a.m. Neither the normal subjects nor the hypertensive patients were allowed out of bed before the end of the experiment. 1 hr later, a continuous infusion, at a constant rate, was begun with a Sage infusion pump (Sage Instruments, White Plains, N. Y.) fitted with a 10 ml disposable syringe, containing an accurately measured total of about 2 μCi of aldosterone-^{3}H in 10 ml of isotonic saline. The infusion was given into the left cubital vein via a 21 gauge needle. Whole blood (20 ml) was drawn into heparinized disposable plastic syringes from the right arm at 90, 100, and 110 min after the start of the infusion.

The blood was immediately centrifuged in order to separate the plasma. 0.5 ml of ethanol containing 50 μg of carrier aldosterone and about 300 dpm of a ^{14}C-labeled aldos-

terone indicator was mixed with 10 ml of plasma and 0.5 ml of 1 N NaOH in a 100 ml cylinder fitted with a ground glass stopper. The mixture was then extracted once with 7 volumes of dichloromethane (22). After evaporation of the solvent, the dried extract was applied to a thin layer of silica gel (22) and chromatographed in methanol-toluene 15:85. The carrier aldosterone was located under 254 mμ ultraviolet lamp, the spot was cut out and eluted with methanol. The material was rechromatographed in the Eberlein-Bongiovanni E_2B system (5, 23) and again in the Bush B_5 system (5, 23).

The final dried extract was transferred to counting vials. The MCR was calculated as the constant rate of infusion (R_{inf}; μg/24 hr), divided by the plasma concentration of the labeled aldosterone at equilibrium (Conc; μg/liter), and corrected for recovery (see below). The final result was expressed in liters of plasma per 24 hr/m² of body surface. Determinations were based on tritium determined on the methylene chloride–extracted aldosterone, purified by chromatography, with corrections for losses based on the recovery of an aldosterone-^{14}C internal standard.

Plasma concentration and secretory rate of aldosterone. The procedure used was developed in this laboratory and reported in detail earlier (22). It is a double-isotope derivative assay that uses aldosterone-^{14}C as marker and acetic anhydride-^{3}H with high specific activity as acetylating agent. About 400 dpm of the marker (56.7 Ci/mole) was added to each sample. The methanol and ethanol used in this study were purified first by distillation over silver nitrate and KOH pellets, and then a second distillation with 2,4-dinitrophenylhydrazine; both reagents contained a trace of 2,4-dinitrophenylhydrazine. Without this precaution, the free aldosterone or its diacetate is often modified by the alcohol. The normal range for peripheral plasma aldosterone in 20 normal subjects was 1.4–16.0 ng/100 ml (mean 7.49, SD ±4.84, SE ±1.08) corrected for blank (22) in recumbent position and on a diet containing normal amounts of sodium.

The secretion rate of aldosterone was determined by the double-isotope dilution method (22). Aldosterone-^{3}H (2 μCi, 5 Ci/mole) was injected into the antecubital vein. Urinary oxo-conjugate was used for the determination after the formation of a diacetate with acetic anhydride-^{14}C (3 mCi/

TABLE II

Aldosterone SR, PL, and MCR in Patients with Benign Essential Hypertension and MCR in Control Subjects

	Benign essential hypertension						Control subjects					
			Aldosterone metabolic clearance									MCR
Patients	Aldosterone SR	Plasma aldosterone	Corrected aldosterone-^{3}H concentration during infusion of plasma 90 min	100 min	110 min	MCR liters of plasma/24 hr per m² of body surface	Initials	Sex	Corrected aldosterone-^{3}H concentration during infusion of plasma 90 min	100 min	110 min	1 plasma/24 hr per m² body surface
	μg/day	*ng/100 ml*		*dpm/liter*						*dpm/liter*		
1	*55**	8.3	25,590	26,430	26,490	669	J. C.	M	27,006	27,634	24,762	1031
2	61	12.3	61,680	63,350	62,390	387	G. H.	F	—	39,235	39,366	1660
3	78	15.3	45,320	—	44,700	767	C. H.	F	51,352	52,563	52,059	1457
4	*55**	8.3	28,350	34,140	28,790	670	J. B.	F	18,246	18,600	19,200	1588
5	30	6.8	18,425	18,654	18,009	976	P. P.	M	87,226	93,845	88,846	1519
6	78	*7.9**	18,300	18,940	18,990	990	W. M.	M	13,013	13,812	12,660	1287
7	*139**	16	22,500	22,530	23,450	869	V. V.	M	17,007	16,662	16,884	1851
8	86	7.8	21,180	18,150	19,080	1324						
9	74	12.5	23,510	22,800	25,490	1187						
10	91	12.8	15,600	14,430	15,840	833						
11	148	11.4	—	—	—	*1298**						
12	28	23.6	—	—	—	*119**						
13	164	14.3	—	—	—	*1147**						
14	61	13	—	—	—	*469**						
15	151	28	—	—	—	*539**						
16	35	14	—	—	—	*250**						
Mean	83.46	13.62				867						1484
±SE	12.54	1.48			±SE:	85.49					±SE	100.5
					←				$P < 0.001$			→
*Mean	83				*Calculated mean*	*637**						
±SE	28				±SE	*196**						
Control subjects	(n = 10)	(n = 20)										
Mean	109	7.5										
±SE	17	1.3										

SR, PL, and MCR of aldosterone in 16 patients with benign essential hypertension. MCR of aldosterone in seven normal control subjects. Actual values for corrected aldosterone-^{3}H concentration at 90, 100, and 110, demonstrate that the calculation of the MCR was made after the achievement of a constant level of aldosterone-^{3}H during the infusion. Plasma levels were determined either before SR or before MCR. There was always a 48 hr interval between the SR and the MCR determinations. Figures marked with asterisks represent values calculated from two actually measured parameters according to the equation SR/PL = MCR. There is little no difference between the measured and calculated mean of MCR.

* *Calculated value.*

mole in 20% benzene v/v). There was always an interval of at least 48 hr between the determination of SR and MCR.

RESULTS

We have determined the aldosterone secretion rate, plasma concentration, and MCR (Table II, Fig. 1) in the 16 patients who have benign, uncomplicated, essential hypertension as shown by their clinical and laboratory data (Table I). However, in some cases we do not have all three parameters. The missing ones were calculated and are shown in parentheses in Table II. Values are also given for normal subjects. Table II also summarizes the actual values for corrected aldosterone-^{3}H concentration at 90, 100, and 110 min for the MCR experiments, giving evidence that a constant level of aldosterone-^{3}H had been reached during the infusion.

The mean MCR for the patients was significantly ($P < 0.001$) lower than that of the seven normal subjects, with only two of the values falling within 1 SD of the mean control value.

7 out of the 13 patients in whom we measured the secretion rate of aldosterone gave values within the normal range (109 ± 17 [SD] μg/day); 3 had subnormal values and only 3 had values above the normal mean. The mean was lower than the normal mean.

The mean aldosterone secretory rate in 10 normal controls was 109 μg/day ± 54 SD (Fig. 1) ranging from 40 to 210 μg/day.

13 of the 15 determined plasma aldosterone concentrations were within the normal range, but with a statistically insignificant tendency to be higher than in normal subjects (Table II, Fig. 1).

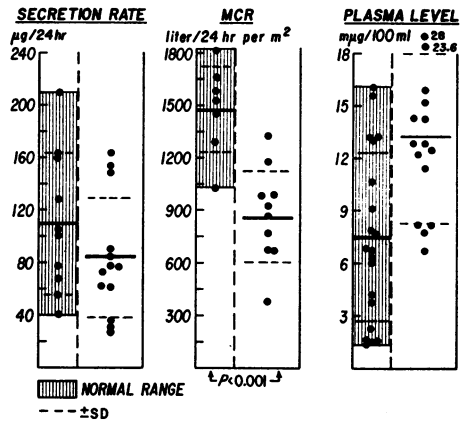

FIGURE 1 MCR, SR, and PL of aldosterone in normal control subjects and patients with benign essential hypertension.

DISCUSSION

An excess of circulating aldosterone may occur by several mechanisms, such as an increase in the adrenal secretion rate, a decrease in the metabolic clearance rate (which can be defined as a rate of disappearance of aldosterone from the circulation and is predominantly due to hepatic inactivation [85%] and renal excretion [15%] [21]), or by a combination of both.

Therefore, the assessment of the role of aldosterone in hypertension by only one of the parameters, such as the plasma level, secretion rate, or urinary excretion, may lead to contradictory results.

These contradictions, as summarized in the Introduction to this paper are also necessarily reflected in our own results reported previously (25, 26). In those particular studies, the mean plasma aldosterone concentration in 42 patients with benign essential hypertension was statistically higher than that in control subjects. This statistical difference is mainly due to the inclusion of some high values in the results of our original 42 patients, even though two-thirds of them had plasma aldosterone values within the normal range (25, 26). The same tendency to higher values is evident in the present study (Fig. 1). High values for plasma aldosterone might result from a hyperresponsiveness to stress or other stimuli during the drawing of the blood for the determinations. Recently we have found (27, 28) that a certain percentage of patients with essential hypertension, such as those with hyperkinetic circulation, shows a greater response of plasma renin activity and of urinary aldosterone excretion to upright posture than normal subjects. Although patients and subjects in the present study remained recumbent, so that the above finding has no direct bearing on the results, it exemplifies the responsiveness of the measured parameters to possibly unsuspected influences.

The main purpose of the present study has been to determine whether or not some of the discrepancies existing in the literature on this subject could be explained by measuring the metabolic clearance rate of aldosterone, a factor not yet investigated in essential hypertension. As evident from our data, this clearance rate is significantly lower for patients with benign essential hypertension. The secretory rates tended to be low and the plasma concentrations high; since MCR = SR/PL, these changes reinforce each other in leading to a significantly low figure for MCR and a more consistent result (low in 8/10 patients) than for plasma aldosterone (high in 6/15 patients) here, and one-third of the patients in the previous study.

Independent measuring of the secretory rate and the plasma level of aldosterone in these patients, which shows a decrease in most of the MCR values, also presented aldosterone secretory rate in the low range of normal, between 60 and 90 μg/day with three very

evident subnormal values and only three values above the normal mean.

The agreement between calculated and measured values for secretion rate or plasma concentration is good (see Table II, and footnote), especially if we consider the normal physiological fluctuations occurring during the lapse of at least 48 hr between the determination of the secretion rate and that of the MCR.

The heterogenous, hemodynamic, and hormonal character of essential hypertension as a clinical entity, as we have recently reported (28), is the main difficulty for a more general interpretation of our data. The outcome of these studies is obviously dependent on the selection of the patients who have been clinically diagnosed as having benign essential hypertension, and who are all possibly in various stages of the disease. Since plasma renin activity is one of the criterion in the subdivision of essential hypertension as a clinical entity, a relative homogeneity of our series is reflected by the fact that all patients in this study had a normal plasma renin activity (PRA). The series of patients so far studied, however, selected only by the exclusion of known causes of hypertension, may be representative only for a certain type or stage of development of "essential" hypertension.

With this limitation in mind, we are able to observe a tendency to a nonlinear inverse relationship between aldosterone secretory rate and plasma level, which in itself implies the existence of a change in the MCR. In the small number of patients in whom all three parameters were studied, the individual analysis of each patient could be interpreted to mean that a low aldosterone MCR is a basic characteristic of the hypertension; adaptation to this MCR may consist in a decrease in secretory rate with maintenance of a normal or only slightly elevated plasma concentration.

The recent work of Luetscher et al. (29) indicates that in some patients with benign essential hypertension, aldosterone secretion and/or urinary excretion fails to be adequately suppressed in response to sodium loading. If these patients have already adapted to a lower than usual MCR by decreasing the secretion rate, they may be unable to decrease it further on sodium loading or at least, not to the same extent as in normal subjects. Such a failure to suppress the aldosterone secretion rate might explain a state of relative hyperaldosteronism even when the secretion rate is at a "normally" depressed level under sodium loading, and lead to inadequate sodium elimination.

Conversely, it may also be possible that other anomalies in the aldosterone response to stimuli in benign essential hypertension (lack of aldosterone responsiveness to severe sodium restriction [30, 31], sodium depletion as a result of the administration of Furosemide, and severe reduction in blood volume [32]) are related to a new equilibrium in which the aldosterone secretion rate, kept at a low-normal level by an internal buffering with a loss of flexibility within the system, responds inadequately not only to aldosterone suppression, but also to stimulation.

The mechanism of the decreased aldosterone MCR in benign essential hypertension remains to be elucidated. The liver plays the most important role in the clearance of aldosterone. A decrease in MCR clearance rate could be caused in the first place by a reduction in the effective volume of blood circulating through the liver. A previous report (33) has shown, however, that hepatic blood flow in patients with benign essential hypertension is normal. Another factor could be a decrease in the activity of the liver enzyme that catalyzes the reduction of the Δ^4-3-ketone of aldosterone. In normal subjects, a small portion of secreted hormone is excreted as free aldosterone, another as the acid-hydrolyzable 18-oxo-conjugate. These two portions were measured by our procedure for the urinary excretion of aldosterone (5).

The plasma protein binding of aldosterone may influence the distribution volume and clearance rate between the outer and inner pool and, therefore, its MCR. The constant infusion method of the MCR offers little information about volumes of distribution, unless the radioactivity in the plasma is followed after the infusion has stopped, which was not done in the present study, as repeated blood withdrawals were already involved.

An increased binding of aldosterone to plasma protein could limit the extraction of the hormone by the liver cells and, therefore, decrease the MCR as suggested by Layne, Meyer, Vaishwanar, and Pincus (34). A humoral factor could be responsible for a disturbance in the protein binding of aldosterone (35), since it has been shown that a high concentration of circulating estrogens results in a decrease in the MCR of cortisol by increasing its protein binding and presumably reducing the hepatic extraction (36).

Whatever the mechanism of this decreased MCR may be, its existence supports the concept that the role of aldosterone in this disease cannot be assessed by measurements of the secretory rate, plasma level, or urinary excretion only. High levels of aldosterone in plasma or other body pools may be due to a decreased aldosterone MCR, uncompensated by an adequate decrease in the secretion rate. Conversely, a secretory rate that appears normal under high sodium intake may not necessarily exclude an "effective" hyperaldosteronism.

ACKNOWLEDGMENTS

It is a pleasure to acknowledge the collaboration of Dr. Jean-Louis Cuche and Dr. Carlos Chavez; Miss L. Gauthier and Miss F. Salvail in the performance of the metabolic

clearance rates and help in documentation; of Miss Pauline Robinson and Gaétane Massicotte for technical assistance.

This work was generously supported by grants from the Medical Research Council of Montreal Canada, Grant MT-1549, MT-2915; the Quebec Heart Foundation; the Banting Research Foundation, Toronto, Canada; and the Searle Company, Chicago, Ill.

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