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 m² ± 270 sd) than in a group of 7 healthy subjects (mean 1480 liters/day per m² ± 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.

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.

INTRODUCTION

The role of hyperaldosteronism in the pathogenesis of hypertension is well established in primary aldosteronism and malignant hypertension 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), 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-

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*Abbreviations used in this paper: MCR, metabolic clearance rate; PL, plasma level; PRA, plasma renin activity; SR, secretion rate.*
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 s.d. recumbent, and 0.70 ng/ml per hr ±0.12 s.d. upright), which is (24) 0.29 ng/ml per hr ±0.3 s.d. recumbent, and 0.71 ng/ml per hr ±0.3 s.d. 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-4H 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 used the constant infusion principle as described by Tait, Little, Tait, and Flood (21). A priming dose of about 2 μCi of 1.2-4H-labeled aldosterone (5 Ci/m mole) 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-4H 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 14C-labeled aldoste-
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 μm ultraviolet lamp, the spot was cut out and eluted with methanol. The material was rechromatographed in the Eberlein-Bongiovanni EeB system (5, 23) and again in the Bush Bs system (5, 23).

The final dried extract was transferred to counting vials. The MCR was calculated as the constant rate of infusion (Rinf; 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-4C 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-4C as marker and acetyladosterone-5C with high specific activity as acetylator 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, ±4.84, ±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-5C (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-4C (3 mCi/

**Table II**

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

<table>
<thead>
<tr>
<th></th>
<th>Benign essential hypertension</th>
<th>Control subjects</th>
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<tbody>
<tr>
<td>Aldosterone metabolic clearance</td>
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<tr>
<td>MCR</td>
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<td>Aldosterone SR</td>
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<tr>
<td>Plasma aldosterone</td>
<td>Corrected aldosterone-4H concentration during infusion of plasma</td>
<td>Corrected aldosterone-4H concentration during infusion of plasma</td>
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<tr>
<td></td>
<td>µg/day</td>
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<tr>
<td>Patients</td>
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<td>55*</td>
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<tr>
<td>3</td>
<td>78</td>
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<tr>
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<td>12.54</td>
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<tr>
<td><em>Mean Calculated mean 637</em></td>
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<td>±SE Calculated mean 196*</td>
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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-4H concentration at 90, 100, and 110, demonstrate that the calculation of the MCR was made after the achievement of a constant level of aldosterone-4H 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 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 \((109 \pm 17 [sd] \mu g/day)\); 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 \(\mu g/day\) \(\pm 54 sd\) (Fig. 1) ranging from 40 to 210 \(\mu g/day\).

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).

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 \(\mu g/day\) 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 determina-
tion of the secretion rate and that of the MCR.

The heterogenous, hemodynamic, and hormonal char-
acter 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 diag-
nosed 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 en-
tity, 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 “es-
tential” 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 param-
eters were studied, the individual analysis of each pa-
tient 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 hyperten-
sion, 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 hyperaldosteron-
ism even when the secretion rate is at a “normally”
depressed level under sodium loading, and lead to in-
adquate sodium elimination.

Conversely, it may also be possible that other anom-
alties in the aldosterone response to stimuli in benign
essential hypertension (lack of aldosterone responsive-
ness to severe sodium restriction [30, 31], sodium de-
pletion 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 secre-
tion 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 suppres-
sion, but also to stimulation.

The mechanism of the decreased aldosterone MCR
in benign essential hypertension remains to be eluci-
dated. 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 hy-
pertension is normal. Another factor could be a de-
crease in the activity of the liver enzyme that catalyzes
the reduction of the Δ3-3-ketone of aldosterone. In nor-
mal subjects, a small portion of secreted hormone
is excreted as free aldosterone, another as the acid-hydro-
lyzable 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 in-
fluence the distribution volume and clearance rate be-
tween 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 pro-
tein 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 mea-
urements 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 aldoster-
one 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.

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