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Captopril Suppression Versus Salt Loading in Confirming Primary Aldosteronism

Mohsen Agharazii, Pierre Douville, John H. Grose, Marcel Lebel

Abstract—This prospective study was designed to compare the captopril suppression test with the salt-loading approach to confirm the diagnosis of primary aldosteronism. A total of 49 patients were referred with a presumed diagnosis of primary aldosteronism. The captopril test was performed in the morning with patients in the seated position after overnight fasting. Blood samples for plasma aldosterone were obtained before captopril administration (25 mg PO) and again 2 hours later. Patients were then subjected to a high salt diet (300 mmol sodium per day for 3 days). On the third day, urinary sodium (24 hours) was measured, and plasma aldosterone levels were measured at 8:00 AM (recumbent) and at noon (standing). Of the 49 patients, 44 had nonsuppressible aldosterone concentrations with all the clinical characteristics of primary aldosteronism: 22 patients had surgically confirmed unique adenoma, and 22 patients had presumed bilateral hyperplasia. There was a significant correlation between plasma aldosterone values of salt-loaded patients (mean of 8:00 AM and noon results) and the values 2 hours after captopril administration ($r=0.8$, $P<0.01$). Plasma aldosterone cumulative distribution curves in primary aldosteronism patients (adenoma and hyperplasia) were not significantly different between the 2 suppression tests. Our results showed that the captopril suppression test is as effective as sodium loading in confirming the diagnosis of primary aldosteronism. (*Hypertension*. 2001;37:1440-1443.)

Key Words: aldosterone ■ captopril ■ sodium, dietary ■ hypertension, essential ■ renin

Classic primary aldosteronism is characterized by hypertension, hypokalemia, high urinary potassium levels, low renin levels, and an elevated aldosterone secretion rate. Most often, it is due to idiopathic adrenal bilateral hyperplasia or to a solitary aldosterone-producing adrenal adenoma. Rarer subtypes have also been documented.¹⁻⁴ The use of the ratio of plasma aldosterone to renin levels appears to be the preferred screening approach for distinguishing patients with essential hypertension from those with primary aldosteronism.⁵⁻⁸ The definite biochemical diagnosis is confirmed by demonstrating an inappropriate autonomous hypersecretion of aldosterone. Salt loading is currently used as a physiological approach to establish a nonsuppressible state of aldosteronism; a plasma aldosterone level of <240 pmol/L (8.5 ng/dL) while undergoing salt loading usually rules out primary aldosteronism.⁹⁻¹¹

Captopril inhibits the enzymatic conversion of angiotensin I to angiotensin II. When administered to patients with a normal renin-angiotensin axis, captopril decreases angiotensin II and aldosterone production in the presence of increased renin release because of negative inhibition. In patients with autonomous production of aldosterone, such as primary aldosteronism, it has been suggested that captopril has little or no effect on aldosterone secretion or renin production and, thus, can be used to differentiate primary aldosteronism from essential hypertension.¹² The efficacy of the captopril test has

never been compared with oral salt loading in establishing a diagnosis of primary aldosteronism. The present prospective study was designed to compare the captopril test with the salt-loading approach in patients referred to a tertiary care center for confirmation of a diagnosis of primary aldosteronism.

Methods

Patients and Protocol

The present study was conducted in the Clinical Research Unit of the CHUQ, L'Hôtel-Dieu de Québec Hospital. The protocol was approved by the local ethics committee, and the patients gave informed consent. All patients were hospitalized during the investigation. Between October 1989 and September 1999, a total of 49 patients with sustained hypertension and a past history of unprovoked hypokalemia were referred with a presumed diagnosis of primary aldosteronism. Secondary aldosteronism (renovascular hypertension) and diuretic-induced hypokalemia had previously been ruled out. The aldosterone/renin ratio was not measured in these patients before referral. None had a family history of hypokalemia associated with hypertension.

Spironolactone was discontinued at least 6 weeks before the investigation. β -Blockers and clonidine were progressively reduced and withdrawn 1 week before hospitalization. α_1 -Blockers (postsynaptic) and calcium channel blockers were maintained to control severe hypertension, and the morning dose was avoided before the renin-aldosterone measurements. None of the patients was taking ACE inhibitors. During the first part of the study, patients were on a usual hospital diet (120 to 130 mmol sodium and 70 to 80 mmol

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potassium). Blood samples were drawn at 8:00 AM after overnight recumbency to determine plasma renin concentration, plasma aldosterone, and serum potassium and bicarbonate. After normal ambulation, a second blood sample was taken at noon to measure the plasma aldosterone level. On the same day, 24-hour urinary potassium excretion was measured. The captopril test was performed the next morning. The patients fasted overnight and were studied while they were in the seated position. Blood samples for plasma aldosterone and plasma renin concentration were obtained just before the patient received an initial 25-mg dose of captopril orally and then another 2 hours later. With patients in the sitting position, blood pressure was measured with a mercury sphygmomanometer before the test, at 60 minutes, and at the end of the test (120 minutes). The patients were then subjected to a high sodium diet (300 mmol sodium per day for 3 days). Salt was inserted into gelatin capsules and distributed with meals throughout the day. On the last day of the high salt diet, a 24-hour urine collection was obtained to measure urinary sodium excretion. Plasma aldosterone was measured under the same conditions at 8:00 AM and at noon. To distinguish primary aldosteronism subtypes, all patients underwent computed tomographic scanning, 7 patients underwent scintigraphy of the adrenal glands with the use of $6\beta^{31}$ -iodomethyl-19-norcholesterol after dexamethasone suppression, and adrenal venous blood was obtained from 3 patients.

Biochemical Determinations

Plasma active renin concentrations were determined by using an immunoradiometric assay kit (sandwich technique) from ERIA Diagnostics (Pasteur). Reference values ranged from 7 to 25 ng/L in the recumbent position and at noon, after normal ambulation, from 12 to 43 ng/L. Plasma aldosterone was measured by a specific radioimmunoassay after purification of plasma extracts by Sephadex LH-20 column chromatography as previously reported.¹³ Reference values with patients in the recumbent position ranged from 90 to 290 pmol/L (3.2 to 10.4 ng/dL) and from 290 to 730 pmol/L (10.4 to 26.3 ng/dL) at noon after normal ambulation. Plasma and urinary electrolytes were measured with an autoanalyzer system (Ilab 1800). The captopril test was performed as originally described by Lyons et al¹² and briefly summarized above. By use of this test, mean plasma aldosterone concentrations in essential hypertension (n=12) were 259 ± 40 pmol/L (9.3 ± 1.4 ng/dL), with a range of 150 to 576 pmol/L, before captopril administration and 131 ± 18 pmol/L (4.7 ± 0.65 ng/dL), with a range of 80 to 235 pmol/L, 2 hours after captopril administration ($P < 0.01$). The aldosterone/renin ratios in the same patients before and after captopril administration were 45 ± 12 and 19 ± 8 , respectively.

Statistical Analysis

The *t* test for paired measurements was used to establish statistically significant differences observed in subjects over the study period. Results are expressed as mean \pm SEM. The Pearson product-moment correlation coefficient *r* was used to assess the association between individual logarithmically transformed values on both suppression tests. Cumulative distribution of aldosterone values versus the fraction data (deciles) was used to illustrate the concordance between the 2 suppression tests. The comparison between both distribution curves was performed with the Kolmogorov-Smirnov test.¹⁴ Because plasma aldosterone concentrations tend to decrease from 8:00 AM to noon in patients with unique adenoma but the values increase from 8:00 AM to noon in patients with bilateral adrenal hyperplasia, the integrated mean of both 8:00 AM and noon aldosterone values during loading was used to assess the correlation coefficient and also the plasma aldosterone cumulative distribution for the 2 suppression tests.

Results

Of the 49 patients, 5 were diagnosed with essential hypertension; of these 5 patients, plasma potassium normalized during investigation, and plasma aldosterone was determined to be

Patient Characteristics and Basal Biochemical Measurements

Variables	Adenoma	Hyperplasia
Total patients, n (total women)	22 (12)	22 (3)
Age, y (range)	50 (37–68)	54 (45–65)
Systolic blood pressure, mm Hg	158 \pm 5	154 \pm 5
Diastolic blood pressure, mm Hg	92 \pm 2	95 \pm 3
Serum potassium, mmol/L	3.0 \pm 0.08	3.2 \pm 0.06
Urinary potassium, mmol/d	82 \pm 6	76 \pm 6
Serum bicarbonate, mmol/L	29.5 \pm 0.57	28.6 \pm 0.42
Plasma renin concentration (8:00 AM), ng/L	3.3 \pm 0.6	4.3 \pm 1.4
Plasma renin concentration (noon), ng/L	4.9 \pm 0.9	4.6 \pm 1.1
Plasma aldosterone (8:00 AM)		
pmol/L	1026 \pm 153	491 \pm 57*
ng/dL	37.0 \pm 5.5	17.7 \pm 2.1
Plasma aldosterone (noon)		
pmol/L	978 \pm 124	840 \pm 146
ng/dL	35.3 \pm 4.5	30.3 \pm 5.3

Values are mean \pm SEM.

* $P < 0.01$ vs patients with adenoma.

normal by both suppression tests (2 hours after captopril, 118 ± 22 pmol/L [4.2 ± 0.8 ng/dL]; during salt-loading conditions [means of 8:00 AM and noon], 171 ± 36 pmol/L [6.2 ± 1.3 ng/dL]). Computed tomographic scanning was normal. The aldosterone/renin ratios before and after captopril administration were 33 ± 14 and 10 ± 4 , respectively. The diagnosis of primary aldosteronism was established in 44 patients. Twenty-two had surgically removed unique adenoma, and 22 had presumed bilateral adrenal hyperplasia. The Table presents the patients' characteristics and basal biochemical determinations. Figure 1 shows plasma aldosterone values before and 2 hours after the administration of 25 mg PO captopril. There was no significant decrease in plasma aldosterone concentrations for both groups of patients who received captopril. Blood pressure values before and 60 and 120 minutes after captopril administration were $149 \pm 7/95 \pm 3.2$, $148 \pm 6/93 \pm 2$, and $146 \pm 6/95 \pm 3$ mm Hg, respectively, in patients with adenoma and $151 \pm 4/99 \pm 3$, $140 \pm 4/95 \pm 3$, and $146 \pm 4/99 \pm 3$ mm Hg, respectively, in patients with hyperplasia. Plasma renin concentrations before and after captopril administration were 5.9 ± 1.3 and 8.9 ± 1.6 ng/L, respectively, in patients with adenoma and 4.6 ± 1.0 and 6.5 ± 1.3 ng/L, respectively, in patients with hyperplasia. The aldosterone/renin ratios before and after captopril administration were 530 ± 160 and 312 ± 93 , respectively, in patients with adenoma and 318 ± 83 and 248 ± 64 , respectively, in patients with hyperplasia. On the last day of the high salt diet, urinary sodium was 344 ± 14 mmol in patients with adenoma and 343 ± 17 mmol in patients with hyperplasia. Plasma aldosterone values under the same conditions at 8:00 AM and noon were 1012 ± 152 pmol/L (36.5 ± 5.5 ng/dL) and 842 ± 100 pmol/L (30.4 ± 3.6 ng/dL), respectively, in patients with adenoma and 478 ± 59 pmol/L (17.2 ± 2.1 ng/dL) and 732 ± 125 pmol/L (26.5 ± 4.5 ng/dL), respectively, in patients with hyperplasia. Figure 2 illustrates the correlation between individual logarithmically transformed plasma aldosterone

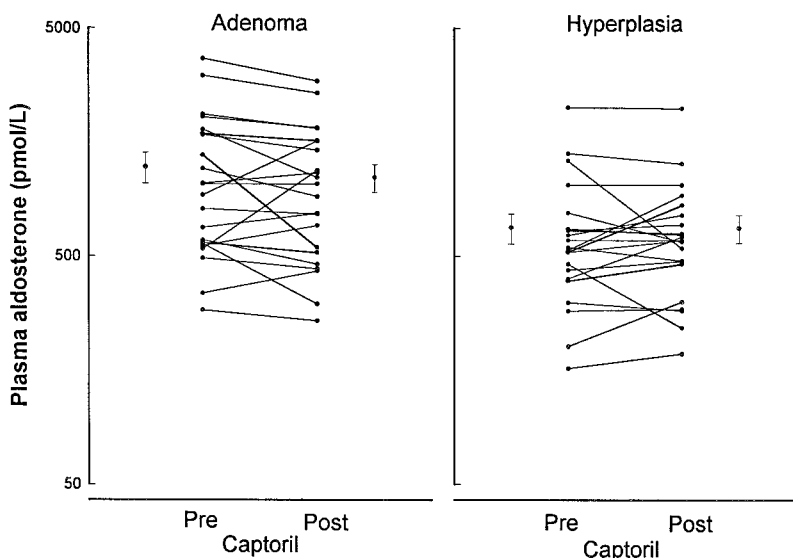


Figure 1. Plasma aldosterone values before and 2 hours after captopril administration in patients with unique adenoma and bilateral hyperplasia. Values are mean \pm SEM. The mean values before and after captopril administration were not significantly different.

values during captopril and salt-loading conditions. With 240 pmol/L (8.5 ng/dL) used as the arbitrary cutoff point for confirming the diagnosis of primary aldosteronism, all 44 salt-loaded patients had aldosterone values >240 pmol/L (sensitivity 100%); with the captopril test, 1 patient with hyperplasia had a suppressed aldosterone value at 187 pmol/L (sensitivity 97%). The same patients had a post-salt-loading aldosterone value close to the cutoff point (242 pmol/L). Figure 3 shows cumulative distribution curves for plasma aldosterone values during captopril and salt-loading conditions. The 2 cumulative distribution curves were not statistically significantly different.

Discussion

In the present study, we compared the efficacy of the pharmacological captopril test with the “gold standard” phys-

iological salt-loading test in confirming the diagnosis of primary aldosteronism. Of the 49 patients referred with a presumed diagnosis of primary aldosteronism, 44 had non-suppressible aldosterone concentrations and all the clinical characteristics of primary aldosteronism. Both suppression tests (captopril and salt loading) exhibited comparable sensitivity. Because only 5 patients with essential hypertension were investigated in the same experimental conditions, it was not possible to assess precisely the specificity. However, these 5 patients exhibited plasma aldosterone concentrations below the cutoff value of 240 pmol/L (8.5 ng/dL) under captopril. A similar suppression of plasma aldosterone levels was also observed in the 12 patients with essential hypertensive reported in Methods. It is noteworthy that the plasma aldosterone concentrations that were achieved in the 44 patients with primary aldosteronism were similar in both tests

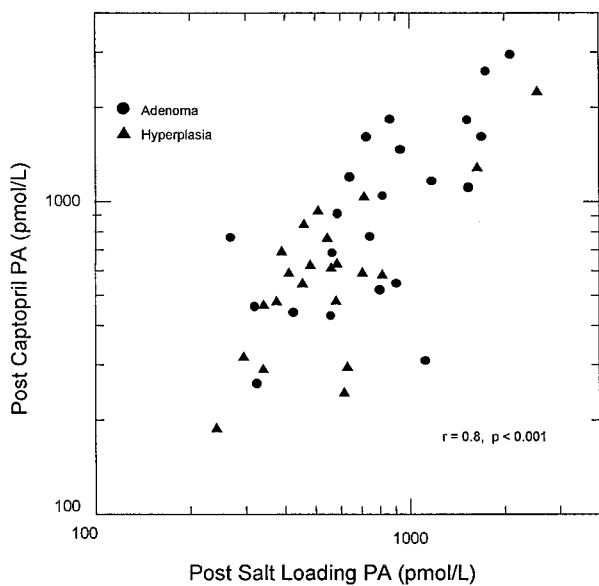


Figure 2. Correlation between individual logarithmically transformed plasma aldosterone (PA) values during salt loading and after administration of captopril in patients with primary aldosteronism.

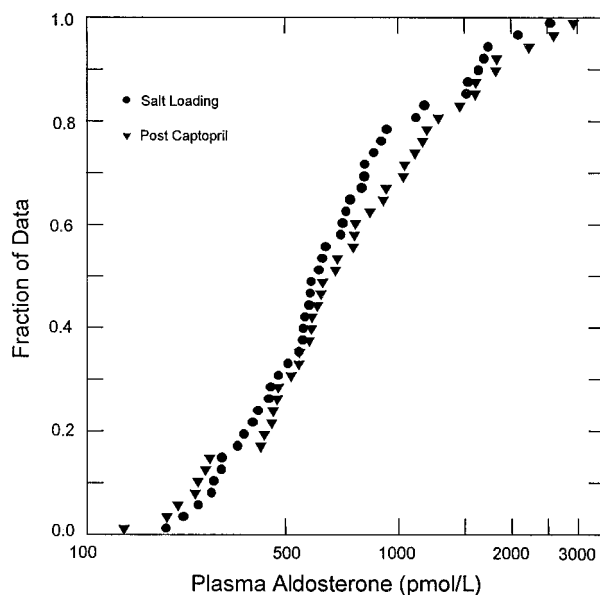


Figure 3. Plasma aldosterone cumulative distribution curves in patients with primary aldosteronism during salt loading and captopril suppression tests. Fraction data are given as deciles.

for any given patient, although blood samples were drawn 3 days apart under completely different experimental conditions. The correlation of individual plasma aldosterone values between the 2 tests was excellent, and the cumulative distribution curves were not significantly different. To our knowledge, this is the first report comparing the efficacy of the captopril test with the oral salt-loading approach for the confirmation of the diagnosis of primary aldosteronism in a series of well-documented patients.

Initially, the captopril test was introduced to differentiate patients with primary aldosteronism from those with essential hypertension.¹² Because the test was simple and specific, it was thought that it might also be superior as a screening test.¹⁵ However, subsequent investigations did not show superiority over criteria using basal plasma aldosterone combined with the aldosterone/renin ratio, but it was equally efficacious.^{16,17} Wambach et al¹⁸ observed a larger fall in plasma aldosterone levels after captopril administration in 16 patients with bilateral adrenal hyperplasia compared with 8 patients with unique adenoma. They proposed that the captopril test might be helpful in distinguishing these 2 subtypes of primary aldosteronism. Our results, obtained in a larger series of patients, do not show any difference in the degree of suppression of plasma aldosterone in adenoma versus hyperplasia.

The main finding of the present study was that the captopril test was as effective as salt loading in confirming the diagnosis of primary aldosteronism. In addition, this test was well tolerated; blood pressure remained relatively stable without an increase or abrupt drop throughout the test. It could also be applied in clinical situations in which the salt-loading procedure is contraindicated, such as severe hypertension or subclinical heart failure. As pointed out by Naomi et al,¹⁹ because the results of the captopril test were unaffected by large individual variations in sodium intake, it can be carried out in outpatients without standardized dietary conditions. It also has time- and cost-saving advantages because an abnormal captopril aldosterone/renin ratio does not require further confirmatory investigations, such as salt loading. However, antihypertensive medication should be modified, as suggested in the present study.

In summary, the captopril suppression test is safe and as effective as sodium loading in confirming the diagnosis of primary aldosteronism.

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