High Prevalence of Primary Aldosteronism Using Postcaptopril Plasma Aldosterone to Renin Ratio as a Screening Test Among Italian Hypertensives

Ermanno Rossi, Giuseppe Regolisti, Aurelio Negro, Carlo Sani, Simona Davoli, and Franco Perazzoli

The prevalence of primary aldosteronism (PA) was assessed in a specialized hypertension center. Baseline and postcaptopril (50 mg orally) aldosterone to plasma renin activity ratio (A/R) as a screening tool were preliminarily tested in a sample including 22 patients with histories of PA and 53 patients with low-renin essential hypertension (EH). Sensitivity and specificity of A/R ≥35 were 95.4% and 28.3% at baseline, compared with 100% and 67.9% after captopril. Using postcaptopril A/R ≥35 and confirmation by acute saline loading, a PA prevalence of 6.3% was found among 1046 consecutive hypertensive patients with normal renal function. Of those 66 PA patients, 16 (24.2%) had a unilateral adenoma, whereas 50 (75.8%) had idiopathic hyperaldosteronism. At presentation, 45.4% of the PA and 16.3% of EH patients were treated with two or more antihypertensive drugs ($\chi^2 = 33.117, P < .0001$).

However, among untreated patients ($n = 553$), the prevalence of mild-to-moderate hypertension (ie, <180/110 mm Hg) was not different between patients with PA and those with EH (70.6% vs 76.7%, $\chi^2 = 0.086, P = .770$). Serum potassium ≥3.6 mEq/L was found in 60.6% of PA patients. In conclusion, we observed the following: 1) postcaptopril compared with baseline A/R is a better screening tool for PA; 2) PA is relatively frequent among hypertensive individuals; 3) PA is not necessarily associated with severe hypertension; and 4) hypokalemia is an insensitive screening criterion for PA. Am J Hypertens 2002;15:896–902 © 2002 American Journal of Hypertension, Ltd.

Key Words: Hyperaldosteronism, hypertension, aldosterone, renin, captopril.

The traditional view that primary aldosteronism (PA) is a rare cause of hypertension has recently been challenged, mainly as a result of the use of plasma aldosterone (ALDO) to the plasma renin activity (PRA) ratio as a screening test in hypertensive patients, whatever the serum potassium concentration may be. The validity of the aldosterone to plasma renin activity ratio (A/R), which was initially proposed by Hiramatsu et al, has been assessed in several studies demonstrating its effectiveness as a screening test for diagnosing PA. Limitations of the test concern a possible reduction of its accuracy by various antihypertensive drugs, as well as an increased false-positive rate in subjects with chronic renal failure.5

Using A/R as a screening test and a standard suppression test for diagnostic confirmation, a high prevalence of PA (ranging from 5% to 9.5%) has been found in Australia, Singapore, the United Kingdom, and Chile. Although the A/R has emerged as a reliable screening method for PA, a variable but substantial overlap of its values exists between patients with PA and subjects with essential hypertension (EH), above all those with low-renin EH, resulting in a false-positive rate ranging from 6% to 25%. The A/R after administration of a single oral dose of captopril may potentially be more advantageous than the basal A/R. In fact, the postcaptopril inhibition of angiotensin II production normally increases renin release by inhibiting negative feedback and decreases aldosterone secretion, resulting in a reduction in the A/R. In patients with PA, who are characterized by a relatively autonomous production of aldosterone, converting enzyme inhibition should have little effect on both aldosterone secretion and renin release. Therefore, the persistence of a high A/R despite captopril administration may ameliorate the test specificity.
The aims of the present study were: 1) to assess the validity of both basal and postcaptopril A/R, as compared with the intravenous saline suppression test as a criterion standard, for the separation of PA patients from patients with low-renin EH; and 2) to look for the prevalence of PA among 1046 subsequent hypertensive patients with preserved renal function, using an elevated postcaptopril A/R as a screening test.

Methods
Study Population

The validity of the captopril test for the screening of PA was preliminarily assessed in a separate group of 75 hypertensive patients. The group consisted of 53 patients with EH with baseline upright PRA <1 ng/mL/h after 4 days of controlled Na intake (approximately 100 mmol/day) and 22 patients with a history of PA, including 16 subjects with idiopathic hyperaldosteronism (IHA) and six with an aldosterone-producing adenoma (A). In all subjects, a captopril test and an intravenous saline test (as a criterion standard) were performed according to the procedures described later here. Sensitivity, specificity, and positive and negative predictive values for A/R before and after captopril were calculated, and the best cut-off was selected with receiver operating characteristic (ROC) curve analysis.

Afterward, a prospective study was carried out on 1065 consecutive hypertensive patients referred by general practitioners to our hypertension center between 1 January 1997 and 31 December 1999. Of these, 19 patients were excluded because of renal impairment (serum creatinine >1.6 mg/dL). The remaining 1046 patients underwent a captopril test.

Antihypertensive drugs except α1-blockers were withdrawn at least 4 weeks before the test (8 weeks for aldosterone antagonists); doxazosin was substituted if necessary. Patients were instructed to follow a diet containing 100 mmol NaCl and 80 mmol KCl for 5 days before the test. Compliance was checked by measurement of 24-h urinary excretion of electrolytes the day before the test.

All 75 patients who participated in the preliminary study underwent two separate PRA (ng/mL/h) and ALDO (ng/dL) measurements on the day of the test, which was carried out between 7:30 and 10:00 AM. A blood sample for the measurement of ALDO, PRA, serum creatinine, and electrolytes was drawn after 1 h with the patient seated (baseline value), and 50 mg of captopril was then administered orally. After 90 min with the patient seated, another blood sample was drawn for ALDO and PRA measurements.

In the 1046 subjects participating in the prospective study, only ALDO and PRA determination 90 min after captopril administration was considered for further diagnostic workup. In each patient with postcaptopril A/R ≥35, an intravenous saline load (2 L 0.9% NaCl over 4 h from 8 AM to 12 noon with the patient supine) was performed on a separate occasion, as a confirmatory test.16–18

The study was approved by the local Hospital Ethics Committee, and informed consent was obtained from all participants.

Hypertension was defined by blood pressure (BP) levels ≥140/90 mm Hg on at least three separate occasions or by use of antihypertensive drugs. Essential hypertension was established after exclusion of secondary hypertension by appropriate biochemical and instrumental examinations.

In the preliminary study for evaluating the accuracy of the captopril test, diagnosis of PA had been based on the presence of a PRA value <1.5 ng/mL/h with the patient in the upright position after 2 h of ambulation, after 5 days on a sodium-restricted diet (<20 mmol/day)16, supine ALDO at a normal sodium intake above the normal reference values in our laboratory (>12 ng/dL) and ALDO ≥7.5 ng/dL at the end of the intravenous saline load.16–18 In the six patients with A, the diagnosis was subsequently confirmed upon surgery.

In the prospective study, the diagnosis of PA was established by the presence of each of the following findings: 1) A/R ≥35 after 50 mg of oral captopril (on the basis of the results of the preliminary study); and ALDO ≥7.5 ng/dL at the end of the intravenous saline load.

All patients with biochemically confirmed PA underwent a high-resolution, thin-section CT scan of the adrenal glands and dexamethasone (0.5 mg 4 times daily for 4 days) suppressed scintigraphy with 131I-6-iodomethyl-norcholesterol. The diagnosis of A was based on CT evidence of a unilateral adrenal nodule combined with concordant unilateral accumulation of radioisotope at scintigraphic scan. The diagnosis of IHA was made in all other cases. In all subjects with PA, genetic testing for glucocorticoid-remediable aldosteronism (GRA) was performed.

Analytical Techniques

We determined PRA by radioimmunoassay using a commercial kit (Radim, Pomezia, Italy). Intra- and interassay coefficients of variation were 7.6% and 9.1%, respectively. In our laboratory, normal reference values for PRA are 0.20 to 2.80 ng/mL/h in the supine position and 1.50 to 5.70 ng/mL/h in the upright position; the lower limit of detection of PRA assay is 0.1 ng/mL/h. Values <0.1 ng/mL/h were considered equal to 0.1 ng/mL/h. Aldosterone was measured by radioimmunoassay with a commercially available kit (Biorad, Marnes-La-Coquette, France). Normal reference values for ALDO in our laboratory are 2 to 12 ng/dL and 4 to 32 ng/dL in the supine and upright position, respectively. Intra- and interassay coefficients of variation were 5.3% and 8.6%, respectively. We excluded the presence of GRA by a long polymerase chain reaction–based method.19
Statistical Analysis

Exploratory analysis was carried out to verify normal distribution of continuous data. Whenever this condition was not met, log transformation was performed before subsequent analyses. Differences in continuous variables among groups were assessed by t test for independent samples. Frequencies were analyzed by means of a χ² test. Stepwise linear multiple regression was used to identify variables significantly related to A/R in the subgroup of patients in whom sensitivity and specificity of the captopril test were assessed. Analysis of covariance was then applied to A/R to control for possible confounders. Classical ROC curve analysis was performed according to Hanley and McNeil.20,21 A two-sided α level of 0.05 was considered significant. All statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL).

Results

Sensitivity and Specificity of Captopril Test for Screening PA

Demographic, anthropometric, and analytical data for the 75 subjects participating in the preliminary study are reported in Table 1. Empirical ROC curves drawn using fixed cut-off values for A/R are shown in Fig. 1. A value of 35 for postcaptopril A/R proved to be the best cut-off in terms of specificity at a 100% sensitivity (Fig. 2). As a consequence, the positive predictive value increased from 35.6% at baseline to 56.4% after captopril administration (Table 2).

Stepwise linear multiple regression analysis was performed with the A/R ratio as the dependent variable and age, 24-h urinary sodium excretion, serum potassium, systolic, and diastolic BPs as indicator variables. Serum potassium (β = –0.401, P < .0001) and diastolic BP (β = 0.331; P = .002) were significant predictors of the A/R at baseline, whereas age (β = 0.280, P = .008), serum potas-

### Table 1. Characteristics of patients enrolled for validation of captopril test

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PA (N = 22)</th>
<th>EH (N = 53)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>49.0 ± 12.2</td>
<td>49.8 ± 10.1</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>13/9</td>
<td>30/23</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of hypertension (months)*</td>
<td>24 (6–120)</td>
<td>16 (4–138)</td>
<td>NS†</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.0 ± 3.8</td>
<td>21.7 ± 3.0</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>175.8 ± 15.5</td>
<td>162.3 ± 9.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>103.2 ± 8.5</td>
<td>102.0 ± 5.7</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.85 ± 0.18</td>
<td>0.85 ± 0.16</td>
<td>NS</td>
</tr>
<tr>
<td>Serum Na⁺ (mmol/L)</td>
<td>141.3 ± 2.4</td>
<td>140.7 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>PRA, baseline (ng/mL/h)*</td>
<td>0.10 (0.10–0.25)</td>
<td>0.25 (0.10–1.10)</td>
<td>&lt;.0001†</td>
</tr>
<tr>
<td>PRA, after captopril (ng/mL/h)*</td>
<td>0.10 (0.10–0.40)</td>
<td>0.40 (0.25–7.00)</td>
<td>&lt;.0001†</td>
</tr>
<tr>
<td>ALDO, baseline (ng/dL)*</td>
<td>13.7 (7.5–57.0)</td>
<td>14.0 (4.5–27.0)</td>
<td>.047†</td>
</tr>
<tr>
<td>ALDO, after captopril (ng/dL)*</td>
<td>14.2 (6.5–55.0)</td>
<td>10.0 (3.5–24.0)</td>
<td>&lt;.0001†</td>
</tr>
<tr>
<td>ALDO, after saline infusion (ng/dL)*</td>
<td>11.0 (7.5–43.0)</td>
<td>3.5 (1.0–7.0)</td>
<td>&lt;.0001†</td>
</tr>
<tr>
<td>ALDO/PRA, baseline*</td>
<td>107 (32–570)</td>
<td>51 (10–260)</td>
<td>&lt;.0001†</td>
</tr>
<tr>
<td>ALDO/PRA, after captopril*</td>
<td>117 (37–550)</td>
<td>25 (1–240)</td>
<td>&lt;.0001†</td>
</tr>
<tr>
<td>Serum K⁺ (mmol/L)</td>
<td>3.44 ± 0.54</td>
<td>3.91 ± 0.36</td>
<td>&lt;.0001†</td>
</tr>
<tr>
<td>Urinary Na⁺ (mmol/24 h)*</td>
<td>93 (30–166)</td>
<td>81 (22–156)</td>
<td>NS†</td>
</tr>
</tbody>
</table>

PA = primary aldosteronism; EH = essential hypertension; NS = not significant; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; PRA = plasma renin activity; ALDO = plasma aldosterone.

* Values are expressed as mean ± SD unless otherwise indicated.
† Values are expressed as median (range).
† After log transformation.

FIG. 1. Receiver operating characteristic (ROC) curves for aldosterone to renin ratio (A/R) in screening for primary aldosteronism among low-renin hypertensive patients. Curves were constructed using the following fixed cut-off values for A/R (ng/dL per ng/mL/h): 5, 10, 20, 30, 35, 40, 50, 100, 250, 500. The areas under the curves are significantly different (P < .03). Filled circles connected by lines represent baseline A/R; open circles connected by lines indicate postcaptopril A/R.
sium (β = –0.422, P < .0001), and diastolic BP (β = 0.303, P = .005) were significant predictors of the A/R after the captopril challenge. When the variables selected by multiple regression were entered as covariates in an analysis of covariance model, the difference in A/R between EH and PA patients remained highly significant both at baseline (P = .01) and after the captopril test (P < .0001).

**Prevalence of PA in the Referral Center Population**

The general characteristics of the whole population are summarized in Table 3. A total of 134 (12.8%) hypertensive patients screened positive for primary aldosteronism (A/R ≥ 35). Of these, 66 patients (6.3%) of the entire population were finally diagnosed as having PA on the basis of the intravenous saline load test. In the remaining 68 patients (6.5%), the intravenous saline test did not confirm PA. All hypertensive patients with false-positive PA test results were found to have EH. In 16 of 66 PA patients (24.2%), a unilateral A was detected, and the diagnosis was histologically confirmed in all cases at surgery. In the remaining 50 patients (75.8%), a diagnosis of IHA was established. No case of GRA was detected among the 66 patients with PA.

A total of 931 patients (89.0%) were finally diagnosed as having EH; 36 patients (3.4%) were found to have renovascular hypertension, 12 (1.1%) had some kind of renal disease; and one patient (0.1%) had pheochromocytoma. Table 4 summarizes the anthropometric and laboratory data of patients with EH and those with PA.

At the time of the first visit, 30/66 patients (45.4%) with PA were treated with two or more antihypertensive drugs, compared with 152/931 patients (16.3%) with EH (χ² = 33.117, P < .0001). In the former group, 22/50 patients (44.0%) patients had IHA and 8/16 patients (50.0%) had A (χ² = 0.170, P = .615). None of them were receiving aldosterone antagonists. In the group of the patients who were not taking antihypertensive drugs, 536/931 patients (57.6%) had EH and 17/66 patients (25.8%) had PA (χ² = 23.893, P < .0001). In these untreated patients, hypertension was classified as mild to moderate in 411/536 (76.7%) patients with EH and in 12/17 (70.6%) patients with PA (χ² = 0.086, P = .770).

Serum potassium values were significantly lower in patients with PA compared to patients with EH (Table 4). However, 40/66 (60.6%) patients with PA had serum potassium values ≥ 3.6 mEq/L; in this group, 33/50 patients (66.0%) had IHA and 7/16 patients (43.8%) had A (χ² = 1.668, P = .197).

**Discussion**

In the first part of our study, the postcaptopril A/R displayed a significantly higher specificity for the identifica-
Table 4. Anthropometric and laboratory data in patients with essential hypertension (EH) and patients with primary aldosteronism (PA)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EH (n = 931)</th>
<th>PA (n = 66)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>49.3 ± 11.9</td>
<td>54.6 ± 10.8</td>
<td>.001</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>459/472</td>
<td>33/33</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.7 ± 4.5</td>
<td>26.3 ± 3.5</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of hypertension (months)*</td>
<td>28 (2-280)</td>
<td>60 (1-240)</td>
<td>.003†</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>166.9 ± 14.1</td>
<td>171.2 ± 21.5</td>
<td>.001</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>102.8 ± 6.1</td>
<td>103.9 ± 8.2</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.95 ± 0.16</td>
<td>0.93 ± 0.16</td>
<td>NS</td>
</tr>
<tr>
<td>Serum Na+ (mmol/L)</td>
<td>140.5 ± 2.6</td>
<td>141.9 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Serum K+ (mmol/L)</td>
<td>4.0 ± 0.3</td>
<td>3.5 ± 0.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>24-h Urinary Na+ (mmol/24 h)*</td>
<td>101.8 (48-151)</td>
<td>94.4 (53-158)</td>
<td>NS†</td>
</tr>
<tr>
<td>ALDO, after captopril (ng/dL)*</td>
<td>8.4 (0.3-55.0)</td>
<td>17.1 (3.5-59.9)</td>
<td>&lt;.0001†</td>
</tr>
<tr>
<td>PRA, after captopril (ng/mL/h)*</td>
<td>1.30 (0.10-22.5)</td>
<td>0.15 (0.10-1.00)</td>
<td>&lt;.0001†</td>
</tr>
<tr>
<td>ALDO/PRA, after captopril*</td>
<td>5.8 (2-235)</td>
<td>96.7 (35-599)</td>
<td>&lt;.0001†</td>
</tr>
<tr>
<td>ALDO, after saline infusion (ng/dL)*</td>
<td>2.5 (1.0-7.1)†</td>
<td>9.0 (7.5-43.0)</td>
<td>&lt;.0001†</td>
</tr>
</tbody>
</table>

Other abbreviations as in Tables 1 and 3.
*Values are expressed as mean ± SD unless otherwise indicated.
†Values are expressed as median (range).
‡EH patients screened positive (false-positives) by the captopril test (n = 68)

The specificity of postcaptopril A/R in our sample of hypertensive patients turned out to be lower than that found by others. However, unlike previous studies, we intentionally selected, as negative cases, EH patients with PRA <1 ng/mL/h at baseline. In fact, the major diagnostic challenge in identifying PA patients occurs in the subgroup of low-renin hypertensive individuals. Indeed, a substantial proportion of patients with low-renin EH, like PA patients, exhibit a raised A/R, which may reflect inappropriately increased secretion of aldosterone in relation to endogenous angiotensin II. Therefore, when the validity of A/R as a screening tool for PA is tested in a sample of low-renin hypertensive subjects, a lower specificity must be expected as compared with the specificity that would be found if EH subjects were not selected on the basis of PRA values. Moreover, the limited sensitivity of the intravenous saline load as a confirmatory test, in comparison with other suppression tests, might have further reduced the specificity of postcaptopril A/R as a screening test.

We acknowledge the need to validate formally the postcaptopril A/R among hypertensive individuals who are not selected on the basis of PRA profile. In this case, however, the expected specificity would conceivably be higher than that observed in our sample of low-renin hypertensive patients, inasmuch as A/R is not elevated in normal-to-high renin EH. Actually, we measured postcaptopril A/R in 1046 consecutive patients with preserved renal function. A total of 134 patients (12.8%) screened positive for PA. Of the 1046 patients, 66 had biochemically confirmed PA, corresponding to a 6.3% prevalence of PA. Therefore, assuming a 100% sensitivity for postcaptopril A/R ≥35, as indicated in the preliminary study, this data corresponds to a 912/980 (93.1%) specificity and a positive predictive value of 66/134 (49.3%), thus confirming the expected increase in specificity.

Because our study, like others, was carried out in a specialized center for the evaluation of hypertension, the prevalence of PA among our referred hypertensive patients does not necessarily reflect the prevalence among unselected hypertensive individuals. However, the proportion of our untreated patients with severe hypertension was not quite elevated in either the EH (23.3%) or PA (29.4%) group. Moreover, Loh et al found a prevalence of PA of 6.4% in a sample of 350 unselected hypertensive subjects, which may suggest that the prevalence of PA in unselected hypertensive individuals could be close to that observed in referred hypertensive patients.

We have found a proportion of unilateral A among our PA patients (16/66, 24.2%) that is substantially lower than that reported by others; indeed, unilateral adenomas were detected in more than 50% of all patients with PA in several studies. This inconsistency may partly reflect the use of hypokalemia (which is more frequently associated with A than with IHA) as a screening tool for PA in previous studies. Moreover, as we did not perform
adrenal venous sampling, which is the most accurate tool for detecting unilateral A.27–30 we may have overlooked several cases of A. A lower proportion of A in comparison to that reported by previous studies may also depend on the high sensitivity of A/R as a screening test, which allows detection of even mild PA, which is more frequently caused by IHA than by A. Indeed, the systematic application of the A/R in all hypertensive patients has resulted in a decrease of the ratio of A to IHA, even when adrenal venous sampling is performed in all patients with biochemically confirmed PA.23 All the same, even the identification of patients with IHA is a worthwhile aim, as specific medical treatment with aldosterone antagonists may be more effective than standard antihypertensive therapy in these subjects.31 In fact, a greater proportion of our PA patients compared with those with EH were taking two or more antihypertensive drugs before the beginning of the study, which may suggest unsatisfactory BP reduction with nonspecific antihypertensive drugs.

None of our 66 cases of PA was positive for the chimeric gene of GRA, a finding consistent with the absence of this condition in another series of Italian patients with PA.32 Most of our patients with PA (60.6%) were normokalemic. As a consequence, 33/50 cases of IHA and 7/16 cases of A would have gone unrecognized if hypokalemia had been used as a screening test.

In conclusion, our study results indicate that a raised postcaptopril A/R may be a more reliable indicator of PA than a raised basal ratio, given its similar sensitivity associated with a higher specificity. Furthermore, our findings suggest that PA is more frequent than traditionally thought even in Italy, in agreement with similar results reported in other parts of the world.8–11

References