Primary Aldosteronism and Hypertensive Disease

Lorena Mosso, Cristian Carvajal, Alexis González, Adolfo Barraza, Fernando Avila, Joaquín Montero, Alvaro Huete, Alessandra Gederlini, Carlos E. Fardella

Abstract—Recent studies in hypertensive populations that have used the serum aldosterone (SA) to plasma renin activity (PRA) ratio as a screening test have demonstrated a high prevalence of primary aldosteronism (PA). This frequency is higher than that previously described when hypokalemia was used as a screening tool. However, other factors, such as the characteristics of hypertensive disease, could also influence the prevalence of PA. We studied 609 essential hypertensive patients, classified according to the Joint National Committee VI (JNC VI), in 3 different stages depending on the severity of their hypertensive disease. We measured SA and PRA and calculated the SA-PRA ratio for all patients. An SA-PRA ratio > 25 was detected in 63 of 609 patients, and the fludrocortisone test confirmed the PA diagnoses in 37 of 609 (6.1%) cases. PA prevalence according to hypertension stage was as follows: stage 1, 6 of 301 cases (1.99%); stage 2, 15 of 187 cases (8.02%); and stage 3, 16 of 121 cases (13.2%). PA patients were slightly younger than the other hypertensive patients (48.4 ± 10.5 vs 53.6 ± 10.2 years; P < 0.05). Serum potassium levels were normal in 36 of 37 PA patients; only 1 patient had minor hypokalemia. Computed tomography scans showed bilateral adrenal enlargement in 7 and an adrenal nodule in 2 cases. In summary, we found a high frequency of PA in essential hypertensives classified in stages 2 and 3 according to the JNC VI. The low frequency of computed tomography scan abnormalities and hypokalemia suggests that the diagnosis for most PA patients corresponds to attenuated forms of the disease.

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Key Words: hypertension, essential ■ aldosterone ■ renin ■ hypokalemia

Recent studies have demonstrated that primary aldosteronism (PA) is the most common form of secondary hypertension when determinations of serum aldosterone (SA), plasma renin activity (PRA), and the SA-PRA ratio are used as screening tools and the fludrocortisone, saline infusion, or captopril tests are used to confirm the diagnosis.

In a previous work, we reported a PA prevalence of 9.5% in 305 unselected “essential” hypertensive (EH) subjects after using the SA-PRA ratio as a screening method and the fludrocortisone suppression test (FST) to confirm the diagnosis.1 This value was similar to that reported by Gordon et al2 (8.5%) in a different population. In the present millennium other works have been published; 3 of these studies were performed with a similar diagnostic approach as the 1 used in our previous study.3–5 These studies (including our work) included 2140 unselected hypertensive subjects, which yielded a total prevalence of PA close to 7% (range, 4.6% to 9.5%). However, controversies about the true prevalence of PA persist, because the classic studies reported a very low frequency of the disease (< 1%) when a similar population of hypertensive subjects was studied.6–7

The different prevalences of PA could be explained by the method used to screen for the disease. The most recent investigations have used the SA-PRA ratio, and the classic studies used the presence of hypokalemia. Because hypokalemia is variably present in patients with PA, the true prevalence could be underestimated. We have reported that hypokalemia is present only in 16% of PA patients and probably reflects the most severe forms of the disease.8 Another factor that could also explain the differences in PA prevalence might be related to the characteristics of hypertensive disease, such as hypertension severity or the difficulty to reach adequate blood pressure control. PA is clinically suspected as part of “secondary hypertension,” characterized by moderate to severe hypertension in young people and/or refractory hypertension. However, clinical and biochemical features vary widely, and normotensive PA patients have been described.1,9

The aim of this study was to evaluate the prevalence of PA and to relate this to a clinical profile of hypertensive disease. We considered hypertension severity, age at onset, and quantity of drugs necessary for blood pressure control. It could be important to delineate a clinically based strategy to identify a subgroup of patients with the highest likelihood of having PA.

Methods

Study Subjects

This work was designed as a cross-sectional study. The patients included were selected from 2 government-supported, outpatient,
primary care centers. All hypertensive patients at both centers and whose blood pressure was under control were invited to participate in this study. We reviewed the clinical records of each patient, and we considered hypertensive those patients with a diastolic blood pressure (DBP) >90 mm Hg and a systolic blood pressure (SBP) >140 mm Hg on at least 2 occasions on different days who were not taking antihypertensive drugs at the time of diagnosis. All patients underwent a clinical examination and serum determinations of creatinine, calcium, urea, glucose, and hepatic profile. With this screening, we excluded those with renal disease, diabetes mellitus, hepatic failure, hypercalcemia, clinical Cushing’s syndrome, or acromegaly. Using these criteria, we selected 609 EH patients for whom we reviewed their medical records, with emphasis on the history and treatment of hypertensive disease. The mean ±SD duration of hypertension was 5.4±3.6 years. We classified the patients according to their SBP and DBP determined without medications at the time of diagnosis. The classification of BP for adults (ages 18 years and older) was taken from the Joint National Committee VI (JNC VI), which has established 3 different stages: stage 1, SBP 140 to 159, DBP 90 to 99; stage 2, SBP 160 to 179, DBP 100 to 109; and stage 3, SBP >180, DBP >110 mm Hg.10 When the patient’s SBP and DBP were in different categories, the higher category was selected to classify the individual’s BP status. Informed consent was obtained from all participants, according to the guidelines of the Declaration of Helsinki, and the protocol was approved by the Research Commission of the School of Medicine at the Catholic University of Chile.

Patients were evaluated between 8 and 9 AM after a 12-hour fast. Because most patients were taking antihypertensive drugs at the time of the study, we instituted a washout period of at least 15 days for any drugs that could affect the renin-angiotensin system, such as β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptors blockers, diuretics, spironolactone, and aspirin. All subjects consumed a normal diet, with no attempt to control sodium intake. On admission, a catheter was placed in an antecubital vein, and after the patient had been seated for 15 minutes, free-flowing blood was withdrawn to measure sodium, potassium (SK), SA, and PRA. The clinical and laboratory finding of EH patients are shown in Table 1.

### Procedures

SA was measured by radioimmunoassay with the use of a commercial kit (Diagnosis Products Corp). The intra-assay and interassay coefficients of variation for SA were 4.8% (9.7±0.5 ng/dL) and 6.3% (10.2±0.6 ng/dL), respectively, and the normal range was 1 to 16 ng/dL. The PRA was determined as previously described.13,14 Its intra-assay coefficient of variation was 5.9% (1.1±0.1 ng·mL⁻¹·h⁻¹), and the inter-assay coefficients of variation were 8.4% (0.53±0.04 ng·mL⁻¹·h⁻¹) and 8.1% (4.0±0.03 ng·mL⁻¹·h⁻¹); we assumed that intermediate values had the same variation. The normal range was 1 to 2.5 ng·mL⁻¹·h⁻¹, and the lower limit of determination was 0.1 ng·mL⁻¹·h⁻¹. An SA-PRA ratio >25 was considered high, a value that has been validated in previous reports.1,16-18 An FST was performed to confirm the diagnosis of PA in all patients with an SA-PRA ratio >25. For the FST, supine SA levels were measured under baseline conditions and after 4 days of fludrocortisone (0.4 mg/d orally; 0.1 mg every 6 hours), with supplemental dietary salt in the form of 2 g 3 times a day with meals (110 mmol). In all patients, the urinary sodium excretion was determined after the FST, being >260 mEq/L. Blood samples were taken on the fifth day at 8 AM. An FST result was considered positive when SA levels failed to suppress <5 ng/dL.19,20 A computed tomography (CT; 3-mm slices) scan of the adrenal area was performed to screen for an adrenal mass or nodule in all patients whose results were positive on the FST. The adrenal CT scan was judged compatible with hyperplasia when any area thicker than 10 mm was detected.21

### Statistical Analysis

Values are reported as mean±SD. We used the Student t test to compare values that were normally distributed and the Kruskal-Wallis test to compare values that were not normally distributed. Univariate and multivariate logistic regressions were performed to analyze the influence of clinical and biochemical variables on the risk of having a positive FST result.

### Results

We studied 609 EH patients and detected that 63 of them had an SA-PRA ratio >25 (10.2%). An FST was performed in 62 of 63 patients with suspected PA (1 patient refused to undergo the test). The test confirmed the diagnosis of PA in 37 of 62 patients (59.7%), giving a 6.1% prevalence of PA. Twenty-one of 37 patients met all criteria for PA because they had high SA values (16.5 to 41.0 ng/dL), low levels of PRA (<0.5 ng·mL⁻¹·h⁻¹), and a high SA-PRA ratio (>50) on at least 2 determinations. In the remaining 16 of 37 patients, the SA values were between 9 and 16 ng/dL. All patients confirmed as having PA had a baseline SA value >9 ng/dL; patients with SA levels lower than this always tested negative on the confirmatory FST, independent of the magnitude of the SA-PRA ratio. Biochemical features of patients with positive (PA patients) and negative FST results are shown in Table 2.

The prevalence of PA according to hypertension stage (JNC VI classification) demonstrated a higher number of PA patients in stage 2 and 3 but a low frequency in stage 1, a difference that was statistically significant (P<0.01; Figure). We also show the prevalence of PA in normotensive subjects from the same population (Figure), data recently published by our group.17 In that study, we detected a normotensive PA prevalence close to 1.5%, a value that was similar to that in EH stage 1 patients. PA patients were slightly younger (48.4±10.5 years) than the other EH patients (53.6±10.2 years), a difference that reached statistical significant (P=0.005). The BP measured without antihypertensive drugs at the time of diagnosis was significantly higher in PA patients than in EH with respect to both SBP (163.7±11.9 vs 155.6±15.9 mm Hg; P<0.05) and DBP (101.6±9.9 vs 96.3±9.0 mm Hg; P<0.05) values. The numbers of drugs taken for BP control, at the time of the present study, was slightly greater in PA than in EH patients (1.6±0.8 vs 1.2±0.9; P<0.05). We did not observe any differences by gender between patients affected by PA (11/26, male/female) and non-PA, EH (210/362).

### Table 1. Clinical and Laboratory Finding in Hypertensive Patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hypertensives (n=609)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54.1±11.2</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>221/388</td>
</tr>
<tr>
<td>Blood pressure at study, mm Hg</td>
<td>156.1±15.8</td>
</tr>
<tr>
<td>Systolic</td>
<td>96.6±9.1</td>
</tr>
<tr>
<td>Diastolic</td>
<td>9.67±6.93</td>
</tr>
<tr>
<td>SA, ng/dL</td>
<td>2.3±5.4</td>
</tr>
<tr>
<td>PRA, ng·mL⁻¹·h⁻¹</td>
<td>12.32±21.25</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD. SA indicates serum aldosterone; PRA, plasma renin activity.

Informed consent was obtained from all participants, according to Committee VI (JNC VI), which has established 3 different stages: stage 1, SBP 140 to 159, DBP 90 to 99; stage 2, SBP 160 to 179, DBP 100 to 109; and stage 3, SBP >180, DBP >110 mm Hg. When the patient’s SBP and DBP were in different categories, the higher category was selected to classify the individual’s BP status. Informed consent was obtained from all participants, according to the guidelines of the Declaration of Helsinki, and the protocol was approved by the Research Commission of the School of Medicine at the Catholic University of Chile.
The results of this work show a high prevalence (2.4%) of normokalemic PA in an unselected population of EH patients. This prevalence varied, depending on the severity of hypertensive disease, being similar to that found in normotensive subjects or those with stage 1 (1.99%) but significantly higher in stages 2 (8.55%) and 3 (13.50%) of the disease. In our study, we only found 1 patient with mild hypokalemia. The low frequency of hypokalemia can be explained because the hypokalemic patients were previously excluded by the primary care clinicians when they screened for secondary hypertension and then referred them to other secondary health centers. However, we estimated the prevalence of hypokalemic PA from the clinical records of these secondary centers as close to 1.5%. Thus, the total prevalence of PA (normokalemic and hypokalemic) could be estimated at 7.5% of hypertensive patients.

The increase in the prevalence of PA according to the severity of hypertensive disease has never been published. However, several authors have recommended that the possibility of PA be investigated in cases of severe hypertension or resistant disease. The present study would support this recommendation, because the prevalence of PA is higher in hypertensives in stage 2 and 3 of the JNC VI classification, and patients with PA needed more drugs than did non-PA, EH patients to achieve adequate BP control. A recent study by Calhoun et al supports our results, providing data on subjects with resistant hypertension and in whom the prevalence of PA is even higher, reaching 20% of studied subjects. Thus, the spectrum of PA in EH seems to be continuous from low frequencies in mild hypertensives, similar to those found in normotensive subjects, to very high frequencies in severe or resistant hypertension.

The prevalence of PA detected in this work was 2.4%, lower than previously communicated by our group 2 years ago, when it reached 9.5% among unselected EH patients. This difference could be related to the severity of hypertensive disease in the hypertensive population. In the first work, we studied 305 EH patients, with 65% of them in stages 2 and 3 versus 50% in the present study. When we reanalyzed our previous data, we also detected a higher frequency of PA in stages 2 (10.4%) and 3 (16.5%), similar to that reported in the present study.

**Discussion**

The results of this work show a high prevalence (≈6%) of normokalemic PA in an unselected population of EH patients.
In the present work, we used a washout period for drugs that could affect the renin-angiotensin system and secondarily modify the SA-PRA ratio, which might yield false-negative or false-positive results. A false-negative result was recently communicated by Mulatero et al,11 with the use of angiotensin II receptors blockers, antihypertensive drugs that were suspended 15 days before the study. The possibility of a false-positive result was excluded with the FST that was performed in all patients with a high SA-PRA ratio.

The diagnostic approach for PA has been extensively discussed in previous communications.27–30 It is important to note that most patients with PA are normokalemic and would not be diagnosed if the screening required the presence of hypokalemia. Recent studies have demonstrated that fewer than 20% of PA patients are hypokalemic.9 In relation to the SA-PRA ratio, we demonstrated that very low levels of PRA could amplify by several times a normal SA value, yielding an inaccurate suspicion of PA. In fact, patients who screened positive for PA but whose SA baseline value was <9 ng/dL were always negative on the confirmatory FST (Table 2). In relation to the FST, inhibition of aldosterone secretion is a supraphysiological maneuver, and some patients with idiopathic hyperaldosteronism who retain some feedback suppression in aldosterone production could be missed, thus understimating the true prevalence of PA.31 Moreover, the FST has been criticized, because an independent and blinded comparison between the different “gold standard” tests has not been performed. However, today most investigators use the FST or salt loading tests to confirm the diagnosis of PA.29

In PA patients, we found a low frequency of CT scan abnormalities. This was also communicated by Lim et al8 and is probably explained because our patients presented attenuated forms of the disease, in which the presence of aldosteroneomas or bilateral enlargement of adrenal gland is less frequent. It is known that patients with aldosteroneomas generally present with the classic features of PA, including severe hypertension and hypokalemia. In this study, we found 9 subjects with CT scan abnormalities who had corresponding PA and who were included in stages 2 and 3 of the JNC VI classification of hypertension. However, the possibility of very small lesions (<3 mm) below the limit of resolution of CT cannot be discounted, and adrenal venous sampling that would contribute to the correct classification of PA was not performed.

Perspectives

This study determined the prevalence of PA and related this to the clinical profile of hypertensive disease. We found a high frequency of PA in EH classified in stages 2 and 3 of the JVC VI, but in stage 1, the frequency of PA was similar to that found in normotensive subjects. The SA-PRA ratio is a useful screening method in the diagnosis of PA, because most patients are normokalemic. The low frequency of CT scan abnormalities in the absence of hypokalemia suggests that most PA patients likely have idiopathic hyperaldosteronism. These data support the need to redefine the concept of PA as a continuous pathologic disorder, in which most patients present with attenuated disease and only a minority of patient present with classic clinical picture of PA. Differentiation between patients with low-renin EH and mild forms of PA would be easier in the future with the development of more sophisticated molecular genetic studies and more reliable and specific biochemical determinations (ie, 18-hydroxycortisol).

Acknowledgments

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References

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