Hyperaldosteronism Among Black and White Subjects With Resistant Hypertension

David A. Calhoun, Mari K. Nishizaka, Mohammad A. Zaman, Roopal B. Thakkar, Paula Weissmann

Abstract—Recent reports suggesting that the prevalence of primary hyperaldosteronism may be higher than historically thought have relied on an elevated plasma aldosterone concentration/plasma renin activity ratio to either diagnose or identify subjects at high risk of having primary hyperaldosteronism and have not included suppression testing of all evaluated subjects. In this prospective study of 88 consecutive patients referred to a university clinic for resistant hypertension, we determined the 24-hour urinary aldosterone excretion during high dietary salt ingestion, baseline plasma renin activity, and plasma aldosterone in all subjects. Primary hyperaldosteronism was confirmed if plasma renin activity was <1.0 ng/mL per hour and urinary aldosterone was >12 μg/24-hour during high urinary sodium excretion (>200 mEq/24-hour). Eighteen subjects (20%) were confirmed to have primary hyperaldosteronism. The prevalence of hyperaldosteronism was similar in black and white subjects. Of the 14 subjects with confirmed hyperaldosteronism who have been treated with spironolactone, all have manifested a significant reduction in blood pressure. In this population, an elevated plasma aldosterone/plasma renin activity ratio (>20) had a sensitivity of 89% and a specificity of 71% with a corresponding positive predictive value of 44% and a negative predictive value of 96%. These data provide strong evidence that hyperaldosteronism is a common cause of resistant hypertension in black and white subjects. The accuracy of these results is strengthened by having done suppression testing of all evaluated subjects. (Hypertension. 2002;40:892–896.)

Key Words: hyperaldosteronism ■ hypertension, essential ■ blacks ■ diuretics ■ renin

Primary hyperaldosteronism (PA) has historically been thought to be an uncommon cause of hypertension, with an estimated prevalence of <2% among the general hypertensive population. Recent studies, however, have suggested that the prevalence of PA may be as high as 8% to 30% in selected hypertensive populations.1–10 These reports have been based on either a high plasma aldosterone/plasma renin activity ratio (ARR) or a lack of suppression of plasma or urinary aldosterone in patients identified by an elevated ARR. As PA is generally remediable by treatment with an aldosterone antagonist or, in the case of adrenal adenoma, by adrenalectomy, knowing the true prevalence of PA in selected hypertension populations is clinically important for maximizing diagnosis and treatment.

Prior studies determining the prevalence of PA have been based on an elevated ARR or confirmatory suppression testing in subjects preselected for a high ARR. The former approach would tend to overestimate the prevalence of PA, because patients with a falsely elevated ARR would be included, whereas the latter approach would underestimate the prevalence of PA because of the exclusion of patients with a falsely low ARR. Diagnosis of PA by confirmatory suppression testing of all evaluated patients would be necessary to overcome these limitations.

The prevalence of PA has not been systematically determined in a population that has included a large proportion of African American subjects. Although multiple studies have demonstrated that plasma renin activity (PRA) is lower in hypertensive black subjects compared with white subjects,11–13 which suggests that aldosterone-associated hypertension may be more common in blacks, prospective assessment of PA prevalence has not been reported in hypertensive populations enriched for African Americans.

The purpose of this study was to prospectively determine the prevalence of PA in black and white patients referred to a hypertension specialty clinic for resistant hypertension. We hypothesized that PA would be common in patients with resistant hypertension and that it would be as prevalent or more so among blacks than among similarly hypertensive white subjects. Diagnosis of PA was based on a suppressed PRA and a lack of suppression of urinary aldosterone during high dietary salt ingestion.

Methods

Subjects
Consecutive patients referred to the University of Alabama at Birmingham (UAB) Hypertension Clinic for resistant hypertension...
were studied prospectively over a 14-month period (January 2001–February 2002). Patients were enrolled if referred for resistant hypertension, which was defined as hypertension requiring 3 or more different antihypertensive medications at pharmacologically effective doses. Three subjects with resistant hypertension were not enrolled. Two of the three were thought to be at high risk for renal artery stenosis based on history and/or physical examination, and it was thought clinically inappropriate to delay medical evaluation. The third subject was a lung transplant recipient receiving immunosuppressive therapy, including high-dose prednisone, which precluded evaluation of possible intrinsic mineralocorticoid-induced hypertension.

All patients had been on a stable antihypertensive regimen for at least 4 weeks before evaluation. No antihypertensive medications were discontinued except for spironolactone, amiloride, or triamterene, for which hydrochlorothiazide was substituted for at least 6 weeks before evaluation. Serum potassium levels were corrected as necessary with oral supplementation to maintain a serum level >3.5 mEq/L. The study was approved by the UAB Institutional Review Board and was conducted according to institutional guidelines. All subjects provided written informed consent before study enrollment.

Biochemical evaluation was done in all patients on an outpatient basis. Initial evaluation included an early morning PRA and plasma aldosterone concentration (PAC) and a 24-hour urine collection for sodium, creatinine, and aldosterone on the subject’s ad libitum diet. A PRA ≥1.0 ng/mL per hour or a urinary aldosterone excretion ≤12 μg/24-hour excluded the diagnosis of PA. If the urinary aldosterone was elevated but the urinary sodium was <200 mEq/24-hour, the 24-hour urinary assessments were repeated after 3 days of dietary salt supplementation. A suppressed PRA (<1.0 ng/mL per hour) and elevated urinary aldosterone (>12 μg/24-hour) in the setting of high dietary sodium ingestion (>200 mEq/24-hour) confirmed the diagnosis of PA. Three patients, despite repeated efforts, did not return 24-hour urine collections with adequate sodium excretion, and their data were not included in the analysis.

**Laboratory Methods**

PRA, PAC, urinary aldosterone, and urinary sodium were measured by commercial laboratories using standard techniques. PRA and PAC levels were measured by radioimmunoassay (Quest Diagnostics). The reference range for an upright PRA is 1.3 to 3.95 ng/mL per hour. The reference range for PAC is 4.0 to 31.0 ng/dL. Urinary aldosterone was measured by radioimmunoassay (Mayo Clinic Laboratories). The reference range for urinary aldosterone is 2 to 16 μg/24-hour.

**Statistics**

Values are reported as mean±SD. Values between groups are compared by Student t test. A probability value <0.05 was considered significant.

**Results**

Eighty-eight consecutive patients with resistant hypertension were evaluated. Eleven evaluated subjects were normotensive by our assessment. Two of these subjects were receiving 3 antihypertensive agents; the remaining 9 were receiving 4 or more agents. Forty-three of the subjects were black and 45 were white. Demographics of the studied patients are described in Table 1. The majority of the subjects were receiving an ACE inhibitor or angiotensin receptor blocker (ARB), a beta-blocker, and/or diuretic therapy. Sixty-three percent of the subjects had low-renin hypertension, defined as a PRA <1.0 ng/mL per hour.

Eighteen of the 88 subjects were confirmed to have PA, for an overall prevalence of 20%. Ten of the subjects with confirmed PA were black and 8 were white, for a prevalence of 23% and 18%, respectively. This racial difference was not statistically significant.

**Subjects with confirmed PA were younger than subjects without PA, but otherwise were similar in age and baseline blood pressure (Table 2). Plasma aldosterone concentration (19.2±10.7 versus 10.8±7.7; range 5 to 47 versus 3 to 30 ng/dL), PRA (0.3±0.2 versus 3.2±5.4; range 0.2 to 0.8 versus 0.2 to 25 ng/mL per hour), and baseline 24-hr aldosterone excretion (21.0±10.3 versus 7.9±4.8; range 13 to 55 versus 1 to 24 μg/24-hour) were significantly different between the 2 groups (P<0.05). Patients with PA tended to require more medications (4.2±1.1 versus 3.8±1.1) and were more likely to be prescribed a beta-blocker, but these differences were not statistically significant. There was a significant difference between PA and non-PA subjects in the tendency for hypokalemia. That is, 72% of the PA patients were hypokalemic (<3.6 mEq/L) on presentation or were receiving oral potassium supplementation versus only 20% of the non-PA subjects (P<0.001).

All 18 of the subjects with confirmed PA have had high-resolution adrenal CAT scan imaging. Eight subjects had normal-appearing adrenal glands. Three subjects had unilateral adrenal masses consistent with adrenomas. Six subjects had diffusely enlarged adrenal glands suggestive of hyperplasia (3 bilateral and 3 unilateral). One subject had evidence both of adrenal hyperplasia and a unilateral mass. None of the subjects with confirmed biochemical PA has undergone adrenal vein sampling or adrenalectomy.

Compared with a diagnosis of PA confirmed by 24-hr aldosterone excretion, an ARR >20 had a sensitivity of 89% and a specificity of 71%. This corresponded to a positive predictive value of 44% and a negative predictive value of 96%.

Fourteen of the 18 subjects with confirmed PA have been treated with spironolactone, with doses ranging from 25 to 50 mg daily, and have had follow-up of between 6 to 12 weeks (Figure). Other prescribed medications remained unchanged. All 14 subjects had a significant improvement in blood pressure.
pressure (defined as >20 mm Hg reduction in systolic blood pressure or >10 mm Hg reduction in diastolic blood pressure or normalization of blood pressure). The mean blood pressure reduction at follow-up was \(-26 \pm 15.7/\text{12} \pm 12.6 \text{ mm Hg}\).

### Discussion

In this prospective evaluation of 88 consecutive patients referred to a hypertension specialty clinic for resistant hypertension, 18 (20%) were diagnosed as having PA, based on a suppressed PRA (<1.0 ng/mL per hour) and lack of suppression of urinary aldosterone (>12 \(\mu g/24\)-hour) during high dietary sodium ingestion (>200 mEq/24-hour). The study population included equal numbers of black and white subjects, with the prevalence of PA being similar in the 2 groups, 23% versus 18%, respectively. These results demonstrate that PA is common among both black and white patients referred to a specialty clinic for resistant hypertension.

An increasing number of reports suggest that PA is much more common than historically thought. In one of the earliest reports, Gordon et al. found that, of 199 patients referred to a hypertension clinic in Brisbane, Australia, 8.5% were confirmed to have PA, based on fludrocortisone suppression testing (FST) of patients with a persistently elevated ARR. In a recent report from the United States, Galley et al. reported a prevalence of PA of 17% among patients with poorly controlled hypertension. PA was diagnosed on the basis of an elevated ARR and demonstration of a functionally active adrenal adenoma with iodine 131 norcholesterol uptake scan and/or good therapeutic response to adrenalectomy or treatment with spironolactone. Other studies have reported a high prevalence of PA among general hypertensive populations or referral populations selected for resistant hypertension. In an early study suggesting that PA may not be uncommon among selected hypertensive populations, Holland et al. found a prevalence of PA, based on suppression of aldosterone excretion with saline infusion, of approximately 15% among 120 patients with low or normal renin hypertension.

Prior studies have generally relied on a high ARR to estimate the prevalence of PA and/or have carried out suppression testing only in patients identified by a high ARR. The former approach would tend to overestimate the prevalence of PA because of the inclusion of patients with a falsely high ARR, whereas the latter would tend to underestimate the prevalence of PA because of the exclusion of patients with a falsely low ARR.

In the current study, PA was confirmed by suppression testing in all evaluated patients. The ARR was determined but was not used to diagnose PA or to identify patients at high risk of PA. Of the 88 evaluated subjects, 2 were confirmed as having PA despite having an ARR <20. These results demonstrate that an elevated ARR has a very low false-negative rate, but by identifying such subjects, it has allowed for a more accurate

### Table 2. Comparison of Subjects With and Without Primary Hyperaldosteronism

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>PA Subjects (n=18)</th>
<th>Non-PA Subjects (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51.2±10.5 (34–71)</td>
<td>57.9±11.7 (31–82)*</td>
</tr>
<tr>
<td>Black/white</td>
<td>10/8</td>
<td>34/36</td>
</tr>
<tr>
<td>Male/female</td>
<td>10/8</td>
<td>23/67</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>33.8±8.2 (23.4–62.5)</td>
<td>32.1±8.2 (18.3–69.9)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>158±17.9 (128–190)</td>
<td>159±25.8 (102–228)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>92±11.7 (74–112)</td>
<td>89±16.9 (48–128)</td>
</tr>
<tr>
<td>No. of antihypertensive medications</td>
<td>4.2±0.9 (3–6)</td>
<td>3.8±0.9 (3–7)</td>
</tr>
<tr>
<td>Patients with potassium &lt;3.6 mg/dL or on potassium supplements</td>
<td>13 (72%)</td>
<td>14 (20%)†</td>
</tr>
<tr>
<td>Subjects on ACE inhibitor or ARB, %</td>
<td>94</td>
<td>84</td>
</tr>
<tr>
<td>Subjects on diuretic, %</td>
<td>78</td>
<td>80</td>
</tr>
<tr>
<td>Subjects on beta-blocker, %</td>
<td>78</td>
<td>61</td>
</tr>
<tr>
<td>PAC, ng/dL</td>
<td>19.2±10.7 (5–47)</td>
<td>10.8±7.7 (2–30)†</td>
</tr>
<tr>
<td>PRA, ng/mL per hour</td>
<td>0.3±0.2 (0.2–0.8)</td>
<td>3.2±5.4 (0.2–25)*</td>
</tr>
<tr>
<td>Ratio</td>
<td>80.6±53.0 (12.5–235)</td>
<td>22.9±32.8 (0.1–150)†</td>
</tr>
<tr>
<td>Urinary aldosterone, (\mu g/24)-hour</td>
<td>21.0±10.3 (13–55)</td>
<td>7.9±4.8 (1–24)†</td>
</tr>
</tbody>
</table>

Values are mean±SD (range). PA indicates primary hyperaldosteronism; PAC, plasma aldosterone concentration.

*P<0.05, †P<0.001, both versus PA subjects.
determination of the PA prevalence rate in this selected population.

In this study population of patients with resistant hypertension, an elevated ARR had a high sensitivity (89%), but a lower specificity (71%). As such, our data suggests that, in this selected population, an elevated ARR is an effective screening technique (high negative predictive value) but lacks the specificity to be reliable in confirming the diagnosis of PA. In the current study, an elevated ARR had a high false-positive rate (20 of 88 or 23%), that is, patients who had an elevated ARR but were excluded from having PA based on suppression of urinary aldosterone excretion. Accordingly, to rely on an elevated ARR to diagnose PA in patients with resistant hypertension would result in a large percentage of falsely positive assessments.

Our finding that an elevated ARR has a high sensitivity in identifying patients with PA is consistent with the findings of other investigators.\textsuperscript{16–18} The relatively lower specificity of the ARR, however, is in disagreement with these same investigators, in that they found an elevated ARR to have both a high sensitivity and a high specificity. This disagreement is likely related to differences in study design. In the current study, the predictive value of an elevated ARR was compared with a lack of suppression of 24-hour urinary aldosterone excretion during high dietary salt ingestion. In other studies, FST, saline infusion, or captropil-suppression of aldosterone were used as the gold standard for diagnosing PA. Differences may also be related to the study population. In the current study, all subjects were evaluated on a stable antihypertensive regimen that included, in the majority of patients, an ACE inhibitor or ARB, a beta blocker, and a diuretic. The specificity of the ARR may be different in normotensive or more general hypertensive populations and/or in subjects evaluated after having been withdrawn from antihypertensive therapy. Lastly, in the current study, sensitivity and specificity determinations were based on a single determination of ARR. These values may improve if based on additional assessments.

This is the first prospective evaluation of a hypertensive population that included a large proportion of African American subjects. Blacks tend to have lower PRA levels compared with white controls, possibly suggesting a greater prevalence of aldosterone-related hypertension.\textsuperscript{11–13} However, prospective evaluation of racial differences in the prevalence of PA had not been previously reported. In a study evaluating the validity of saline infusion for confirming PA, Stree et al\textsuperscript{16} reported that, in their hypertensive study population of mostly white subjects, more black subjects (approximately 8%) than whites (approximately 2%) were diagnosed with PA. Although provocative, this study was not designed to specifically determine the prevalence of PA in the study population, because only a very small percentage of the subjects underwent mineralocorticoid suppression, considered by the authors to be the gold standard for diagnosis of PA. Our data suggest that PA is not a more common cause of resistant hypertension in blacks than in whites. Overall, PRA and plasma aldosterone levels tended to be lower in black than in white subjects, but this tendency did not reflect a greater likelihood of having PA.

In the current study, patients were evaluated while being maintained on their prescribed antihypertensive medications, including ACE inhibitors, ARBs, calcium channel blockers, beta blockers, and diuretics. ACE inhibitors, ARBs, and diuretics have been reported to increase PRA, calcium channel blockers to suppress aldosterone release, and beta blockers to suppress PRA, thereby potentially confounding biochemical assessment of PA.\textsuperscript{2,5–7} These possible effects were unavoidable in the present population. For safety reasons, prescribed therapies could not be discontinued because of the lack of blood pressure control in the large majority of patients. Although some investigators have suggested that PA can be screened for without discontinuing antihypertensive medications,\textsuperscript{2,15,17} the overall effect of the different classes of agents on the biochemical assessment of PA is not known. If there were an unrecognized confounding effect on the current data, it would most likely result in an underestimation of the prevalence of PA, because the most commonly used antihypertensive agents in the current study (ACE inhibitors, ARBs, and diuretics) tend to increase PRA, resulting in an increased number of falsely negative results (PRA >1.0 in the presence of true PA). Conversely, beta-blockers may have suppressed PRA in some patients to result in a falsely high ARR. This later effect, however, would not have confounded the main objective of our study, ie, determining the prevalence of PA based on suppression testing, but might have altered assessment of the sensitivity and specificity of the ARR. This possibility may be reflected by the fact that a greater proportion of patients with a falsely elevated ARR were receiving a beta-blocker compared with other evaluated patients (80% versus 60%, respectively, \(P=0.11\)).

Several patients had high urinary aldosterone excretion rates but were excluded from having PA because their PRA was not suppressed (\(\geq 1.0\) ng/mL per hour). Case reports, however, document that, in patients with renal dysfunction, the PRA is not necessarily suppressed in patients with confirmed PA.\textsuperscript{19} Accordingly, it is possible we have underestimated the true prevalence of PA in the current population by falsely excluding PA based on an elevated PRA. Excluding this possibility would require differentiating primary from secondary hyperaldosteronism based on lateralization of adrenal excretion during adrenal vein sampling. Relatedly, the acid-labile conjugated aldosterone metabolite measured in the urine as an index of overall aldosterone excretion has been observed to be within the normal range in a significant proportion of patients with PA diagnosed by other criteria.\textsuperscript{10,16} Such occurrences in the present study population would have also resulted in an underestimation of PA prevalence.

Seven of the 18 subjects were diagnosed to have PA based on a high urinary aldosterone (range 17 to 55 \(\mu\)g/24-hour) and sodium (range 203 to 349 mEq/24-hour) excretion during their ad libitum diet. In all cases, patients were queried to ensure that they had not altered their routine diet preceding and during the urine collection. It was felt that chronic high dietary salt ingestion would provide sufficient volume expansion to ordinarily suppress renin and aldosterone secretion, obviating the need for additional salt loading. It is possible, however, that in some of these patients supplemental salt ingestion would have suppressed aldosterone below the threshold for diagnosis of PA, in which case the current results will have overestimated the true prevalence of PA.

We observed a relatively high prevalence of low PRA levels in the study population. This reflects, in part, the high incidence
of PA that we documented but also is likely related to the high proportion of black and elderly subjects who were enrolled and to the high dietary salt ingestion observed in this study population. Additionally, 64% of all subjects were receiving beta-blockers at the time of evaluation, which may have contributed to an increased prevalence of low-renin hypertension.

Abdominal CAT scan imaging indicated that 3 of the 18 patients who were confirmed to have PA have a unilateral adrenal mass consistent with adenoma. It should be emphasized, however, that these imaging results are purely descriptive. None of the subjects has undergone adrenal vein sampling or adrenalectomy to confirm that the observed adenoma is relevant to diagnosis of biochemical PA. Reports using adrenal vein sampling for localization of functional adenomas indicate that visualization of tumors by CAT scan imaging has a low sensitivity for identifying hypersecreting tumors.20,21

Concerns have been raised about the potential overdiagnosis of PA in various hypertensive populations.22–26 The major concern has been about relying on the ARR to diagnose PA or to preselect patients for suppression testing. The current protocol was specifically designed to overcome this deficiency by conducting suppression testing in all evaluated subjects. Additionally, all of the patients diagnosed with PA in this study who have been treated with spironolactone have had a significant blood pressure response, suggesting hyperaldosteronism as a significant underlying cause of their hypertension.

Perspectives

Despite increasing use of combination therapy, clinical trials indicate a continued high prevalence of pharmacologically resistant hypertension. One approach to overcoming treatment resistance is to identify potential underlying causes. Results from this and other recent studies indicate that hyperaldosteronism is a more common cause of hypertension than previously thought. Reasons for this increased prevalence remain speculative. Early studies of hyperaldosteronism may have underestimated the prevalence of PA by evaluating only small numbers of selected patients, such as only patients presenting with hypokalemia. Current estimates of an increased prevalence of PA may reflect differences in how the disorder is being defined. Definitions of PA have varied across studies according to a number of different parameters, such as presence or absence hypokalemia, demonstration of aldosterone suppression, resting versus stimulated PRA, and/or lateralization of aldosterone excretion during adrenal vein sampling. Lastly, PA may truly be more prevalent now than several decades earlier. If so, reasons for an increased incidence of PA remain unknown. Whether recent reports of an increased prevalence of PA reflect a change in definition or a true increase in frequency needs to be determined, but the current results indicate a high prevalence of aldosterone-associated hypertension among patients with resistant hypertension, which, when identified, allows for targeted therapy and more effective blood pressure reduction.

Acknowledgments

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References

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