Aldosterone Excretion Among Subjects With Resistant Hypertension and Symptoms of Sleep Apnea*

David A. Calhoun, MD; Mari K. Nishizaka, MD; Mohammad A. Zaman, MD; and Susan M. Harding, MD, FCCP

Objective: The severity of obstructive sleep apnea (OSA) correlates with the difficulty of controlling BP. The mechanism, however, by which sleep apnea contributes to the development of resistant hypertension remains obscure. Having observed a high prevalence of OSA among hypertensive subjects with primary hyperaldosteronism, we hypothesized a possible association between sleep apnea and aldosterone excretion.

Design: In consecutive subjects referred to a university clinic for resistant hypertension, we prospectively determined plasma renin activity (PRA), plasma aldosterone concentration (PAC), and 24-h urinary aldosterone excretion during high dietary salt ingestion. In addition, all subjects completed the Berlin Questionnaire, a survey designed to identify subjects at risk of having sleep apnea. Primary hyperaldosteronism (PA) was defined as a PRA < 1.0 ng/mL/h and 24-h urinary aldosterone excretion > 12 μg/day during high urinary sodium excretion (> 200 mEq/24 h).

Results: Of the 114 subjects evaluated, 72 subjects had a high probability and 42 subjects had a low probability of having sleep apnea based on their responses to the Berlin Questionnaire. Subjects at high risk for sleep apnea were almost two times more likely to have PA diagnosed (36 vs 19%, p < 0.05), tended to have lower PRA (1.2 ± 1.8 ng/mL/h vs 1.9 ± 4.1 ng/mL/h), and had significantly greater 24-h urinary aldosterone excretion (13.6 ± 9.6 μg vs 9.8 ± 7.6 μg, p < 0.05) compared to subjects at low risk of sleep apnea.

Conclusion: These data provide evidence of increased aldosterone excretion in subjects with resistant hypertension and symptoms of sleep apnea. While the causality of this association is unknown, it is hypothesized that sleep apnea contributes to the development of resistant hypertension by stimulating aldosterone excretion.

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Key words: hyperaldosteronism; hypertension; renin; sleep apnea

Abbreviations: BMI = body mass index; CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea; PA = primary hyperaldosteronism; PAC = plasma aldosterone concentration; PRA = plasma renin activity; RDI = respiratory disturbance index; UAB = University of Alabama at Birmingham

There is a high degree of correlation between obstructive sleep apnea (OSA) and hypertension, particularly among patients with resistant hyperten-

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Large epidemiologic studies1–3 demonstrate that BP and the number of patients with hypertension increase with sleep apnea severity as indicated by the respiratory disturbance index (RDI). In a large randomly sampled cohort of an adult working population, the Wisconsin Sleep Cohort Study4 observed that an RDI > 15 was associated with an almost three times higher risk of acquiring hypertension over a 4-year period, compared to nonapnea control subjects. In a study of patients with resistant hypertension, defined as poorly controlled hypertension in spite of use of three different antihypertensive agents, Logan et al5 diagnosed previously unsuspected OSA in 34 of 41 evaluated subjects (83%). Lastly, in subjects with OSA, resistance to antihypertensive therapy is associated with a higher RDI compared to patients with more easily controlled hypertension.3
Reports from multiple clinics worldwide have suggested that primary hyperaldosteronism (PA) is a much more common cause of hypertension than thought historically. Early studies\(^4,5\) reported PA to be an uncommon secondary cause of hypertension, occurring in 1 to 2% of the hypertensive population. More recent studies\(^6\)–\(^12\) however, suggest that PA is more common than suggested by these earlier studies, occurring in 6 to 20% of selected hypertensive populations. Our laboratory has recently reported that PA is present in 20% of subjects with resistant hypertension.\(^13\) Reasons for this increased prevalence of PA remain undetermined.

In spite of the strong correlation between OSA and hypertension, the mechanism by which OSA contributes to the development of resistant hypertension remains poorly elucidated. In evaluating subjects with resistant hypertension, we observed that a large percentage of subjects with confirmed PA had a previous diagnosis of OSA, leading us to hypothesize a potential interaction between OSA and hyperaldosteronism. This preliminary study was designed to test this hypothesis by determining if there is an association between symptoms of OSA and aldosterone excretion in subjects with resistant hypertension. Although the study did not allow for determination of causality, we question whether OSA could contribute to the development of resistant hypertension by stimulating aldosterone excretion.

**Materials and Methods**

**Subjects**

Consecutive subjects referred to the University of Alabama at Birmingham (UAB) Hypertension Clinic were prospectively evaluated over a 24-month period (December 2000 to November 2002). Resistant hypertension was defined as requiring three or more different antihypertensive medications at pharmacologically effective doses. The study was approved by the UAB Institutional Review Board, and all subjects provided written informed consent prior to study participation.

All subjects were receiving a stable antihypertensive regimen for at least 4 weeks prior to evaluation. No antihypertensive medications were discontinued, except for spironolactone, amiloride, or triamterene, for which hydrochlorothiazide was substituted for at least 6 weeks prior to evaluation. Serum potassium levels were corrected as necessary with oral supplementation to maintain a serum level > 3.5 mEq/L.

**Biochemical Evaluation**

Biochemical assessment of all subjects was done on an outpatient basis.\(^14\) Initial evaluation included an early morning plasma renin activity (PRA) and plasma aldosterone concentration (PAC), and a 24-h urine collection for sodium, creatinine, and aldosterone on the subject’s ad-lib diet. A PRA ≥ 1.0 ng/mL/h or 24-h urinary aldosterone excretion ≥ 12 µg excluded the diagnosis of PA. If the urinary aldosterone was elevated, but the urinary sodium was < 200 mEq/24 h, the 24-h urinary assessments were repeated after 3 days of dietary salt supplementation. Primary hyperaldosteronism (PA) was defined as a suppressed PRA (< 1.0 ng/mL/h) and elevated 24-h urinary aldosterone excretion (≥ 12 µg) in the setting of high dietary sodium ingestion (≥ 200 mEq/24 h).\(^13\)–\(^15\)

**OSA Screening**

Prior to undergoing biochemical evaluation for PA, all subjects completed the Berlin Questionnaire in order to quantify severity of OSA symptoms. The Berlin Questionnaire is a validated instrument for identification of subjects at risk for sleep apnea syndrome. It has been used successfully in > 700 adults in a primary care setting where portable monitoring was used to assess the validity of the risk grouping strategy.\(^16\) Determination of high risk or low risk for OSA was based on responses in the three symptom categories. In category 1, high risk was defined as persistent symptoms (more than three to four times per week) in two or more questions about snoring. In category 2, high risk was defined as persistent (more than three to four times per week) wake time sleepiness, drowsy driving, or both. All subjects were defined as high risk in category 3 because of their history of hypertension. To be considered at high risk for OSA, a subject had to qualify for at least two symptom categories (ie, category 1 or 2 in addition to category 3).\(^17\) Subjects at high risk in category 3 only (that is, subjects who denied having persistent symptoms in categories 1 and 2) were placed in the low-risk group for having OSA.

**Laboratory Methods**

PRA, PAC, 24-h urinary aldosterone, and urinary sodium were measured by commercial laboratories using standard techniques. PRA and PAC levels were measured by radioimmunoassay (Quest Diagnostics; Atlanta, GA). The reference range for an upright PRA is 1.31 to 3.95 ng/mL/h. The reference range for PAC is 4.0 to 31.0 ng/dL. Urinary aldosterone was measured by radioimmunoassay (Mayo Clinic Laboratories; Rochester, MN; or Quest Diagnostics; Atlanta, GA). The reference range for 24-h urinary aldosterone excretion is 2 to 16 µg.

**Statistics**

All values are reported as mean ± SD. Values between groups were compared by two-tailed t test or \(\chi^2\) test where appropriate; \(p < 0.05\) was considered significant. A potential correlation between body weight and body mass index (BMI) with 24-h urinary aldosterone excretion was evaluated by linear regression analysis.

**Results**

Biochemical assessment and completion of the Berlin Questionnaire was done in a total of 114 consecutive patients referred for resistant hypertension. The demographic and mean biochemical values for all of the evaluated subjects are listed in Table 1. An equal number of African-American and nonblack subjects were included.

Seventy-two of the 114 evaluated subjects were at high risk and 42 subjects were at low risk of having
OSA based on their responses to the Berlin Questionnaire. Sixteen of the evaluated subjects had a previous diagnosis of OSA by polysomnography. Based on their questionnaire responses, 11 of these subjects were assigned to the high-risk Berlin category. Nine of these subjects reported use of continuous positive airway treatment (CPAP). Five subjects with a prior diagnosis of OSA were assigned to the high-risk Berlin category. Among the subjects at high risk of having OSA, 26 of 72 subjects (36%) received a diagnosis of PA. In contrast, in subjects at low risk of having OSA, 8 of 42 subjects (19%) received a diagnosis of PA. This difference was statistically significant (p < 0.05).

To evaluate a possible relationship between body weight and aldosterone excretion, we correlated body weight and BMI with 24-h urinary aldosterone excretion by linear regression analysis in all 114 evaluated subjects. This analysis indicated that there was no significant correlation with either parameter.

Table 1—Baseline Characteristics of All Evaluated Subjects (n = 114)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>57 ± 11</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>42/72</td>
</tr>
<tr>
<td>Black/nonblack race, No.</td>
<td>55/59</td>
</tr>
<tr>
<td>BMI</td>
<td>33.0 ± 8.6</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>164 ± 25</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>91 ± 16</td>
</tr>
<tr>
<td>Antihypertensive medications</td>
<td>3.6 ± 1.3</td>
</tr>
<tr>
<td>Plasma aldosterone, ng/dL</td>
<td>13.6 ± 8.9</td>
</tr>
<tr>
<td>PRA, ng/mL/h</td>
<td>1.5 ± 2.9</td>
</tr>
<tr>
<td>Plasma aldosterone/PRA ratio, (ng/dL)/(ng/mL/h)</td>
<td>35.5 ± 40.1</td>
</tr>
<tr>
<td>Urinary aldosterone, µg/24 h</td>
<td>12.2 ± 9.0</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.

Table 2—Demographic and Biochemical Characteristics of Subjects at High and Low Probability of Having OSA Based on the Berlin Questionnaire*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>High OSA</th>
<th>Low OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, No.</td>
<td>72</td>
<td>42</td>
</tr>
<tr>
<td>Age, yr</td>
<td>55 ± 11†</td>
<td>60 ± 12</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>32/40†</td>
<td>10/32</td>
</tr>
<tr>
<td>Black/nonblack race, No.</td>
<td>36/36</td>
<td>19/23</td>
</tr>
<tr>
<td>BMI</td>
<td>36 ± 9†</td>
<td>28 ± 6</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>165 ± 25</td>
<td>162 ± 24</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>93 ± 17</td>
<td>88 ± 14</td>
</tr>
<tr>
<td>BP medications</td>
<td>3.9 ± 1.2†</td>
<td>3.3 ± 1.3</td>
</tr>
<tr>
<td>PAC, ng/dL</td>
<td>13.7 ± 9.0</td>
<td>13.5 ± 8.8</td>
</tr>
<tr>
<td>PRA, ng/mL/h</td>
<td>1.2 ± 1.8</td>
<td>1.9 ± 4.1</td>
</tr>
<tr>
<td>Plasma aldosterone/PRA</td>
<td>37 ± 41</td>
<td>34 ± 38</td>
</tr>
<tr>
<td>ratio, (ng/dL)/(ng/mL/h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary aldosterone, µg/24 h</td>
<td>13.6 ± 9.6†</td>
<td>9.8 ± 7.6</td>
</tr>
<tr>
<td>Confirmed PA, No. (%)</td>
<td>26 (36%)</td>
<td>8 (19%)</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.
†Different from low OSA group (p < 0.05).
‡Different from low OSA group (χ² = 4.24; p < 0.05).

The study provides evidence of increased aldosterone excretion among subjects with resistant hypertension and symptoms of OSA. In the current results, PA was almost two times more prevalent in subjects at high risk compared to subjects at low risk of having OSA based on the Berlin Questionnaire. Further, in subjects at high risk for OSA, there was greater evidence of increased aldosterone excretion as manifested by a lower mean PRA and a significantly greater mean 24-h urinary aldosterone excretion. The current study did not allow for examination of causality, but the results have led us to hypothesize that OSA may contribute to the development of resistant hypertension by stimulating aldosterone excretion.

Epidemiologic studies have documented OSA to be a strong, independent risk factor for the presence and development of hypertension. In a recent study, Grote et al evaluated 1,190 consecutive patients referred for the possibility of sleep-disordered breathing. The results demonstrated an independent linear association between RDI, BP, and heart rate. The relative risk of hypertension increased as the RDI increased, with an odds ratio of 4.15 for an RDI > 40 as compared with an RDI < 5. These findings
documented a strongly positive association between RDI and the development of hypertension.

Two recent studies have documented the strong association between OSA and resistant hypertension. Lavie and Hoffstein\(^3\) retrospectively examined BP control in 1,485 subjects who had undergone polysomnographic evaluation. They found that subjects whose hypertension remained poorly controlled in spite of antihypertensive therapy had a significantly higher mean RDI than subjects whose BP was controlled with antihypertensive therapy (44 ± 29 events per hour vs 33 ± 25 events per hour). The authors concluded that the severity of OSA as indexed by the RDI correlated with resistance to antihypertensive therapy.

Logan et al\(^2\) reported a very high prevalence of unsuspected OSA among patients with resistant hypertension; in this study, 41 patients with resistant hypertension (BP uncontrolled on multiple antihypertensive medications) but no history of OSA were prospectively evaluated by an overnight polysomnographic study. Of those, 34 subjects (83%) received a diagnosis of OSA, demonstrating a strong association between OSA and pharmacologically resistant hypertension.

The mechanisms through which OSA may contribute to the development of resistant hypertension have not been fully elucidated. Vascular stiffening secondary to repeated intermittent arousals, increased levels of circulating vasoconstrictors such as norepinephrine and endothelin, and sympathetic activation have been suggested by animal models of OSA as possibly contributing to increases in BP.\(^{19-23}\)

In humans, muscle sympathetic activity is elevated in patients with OSA compared to non-OSA control subjects and is improved with CPAP, identifying OSA-induced sympathetic activation as a potential cause of hypertension.\(^{24,25}\)

A number of reports\(^6-12\) have suggested that PA may be a more common cause of hypertension than thought historically, with recent estimates of prevalence ranging from 6 to 20%. Among patients with resistant hypertension, two reports\(^13,26\) have demonstrated a prevalence of PA of approximately 20%. In evaluating 88 consecutive subjects with resistant hypertension, this clinic found a prevalence of PA of 20% in black subjects and white subjects as suggested by a suppressed PRA and high 24-h urinary aldosterone excretion during high dietary salt ingestion.\(^13\) In an evaluation of 90 patients with poorly controlled hypertension, Gallay et al\(^26\) found a prevalence of PA of 17% based on a high aldosterone/PRA ratio and surgical confirmation of adrenal adenoma or control of BP with use of spironolactone.

Neither of the above studies was designed to determine the cause of the seemingly high prevalence of PA. However, in doing our evaluation, we observed that a large number of the subjects with documented hyperaldosteronism had been previously diagnosed with OSA, leading us to hypothesize an association between OSA and aldosterone excretion.

The relationship between OSA and the renin-angiotensin-aldosterone system is complex and remains largely unclear. Animal studies\(^27\) suggest that acute hypercapnia or hypoxia separately increase PAC independent of increases in PRA, while the combination of hypercapnia and hypoxia is a potent stimulus of PRA and PAC.

In humans, observations relating OSA and the renin-aldosterone axis have been inconsistent. In a recent study\(^28\) of seven normotensive subjects with untreated mild-to-severe OSA, nighttime plasma levels of aldosterone were lower while renin levels were generally the same in OSA subjects vs non-OSA control subjects. Follenius et al\(^29\) reported that a single overnight session of CPAP treatment increased nighttime levels of PRA and aldosterone in patients with severe OSA. In contrast, Saarelainen et al\(^30\) found that CPAP therapy significantly reduced PAC at 3 months in 11 obese men with OSA and untreated hypertension. The current results are consistent with the latter report,\(^30\) indicating a possible mechanistic relationship between OSA-related hypoxia and aldosterone excretion.

The major strength of the current study is the prospective determination of aldosterone excretion and quantification of OSA symptoms in all evaluated subjects. A limitation of the current study is that the presence of OSA was not confirmed or excluded based on polysomnographic evaluation of all subjects. While ambitious, such an approach will be necessary to definitively categorize subjects as OSA positive or negative. Until such a comparison is done based on definitive assessment of OSA, the current results, based on presence of absence of symptoms of OSA, must be considered preliminary.

In the present study, the likelihood of OSA was based on subject responses to the Berlin Questionnaire. The Berlin Questionnaire has been validated as an effective tool to identify subjects likely to have OSA. In a prospective evaluation of 744 primary care subjects, the Berlin Questionnaire had a sensitivity of 86%, a specificity of 77%, and a positive predictive value of 89% in identifying subjects with OSA.\(^16\) Accordingly, use of the Berlin Questionnaire should have allowed for accurate differentiation of subjects likely and unlikely to have OSA based on the presence of absence of OSA-associated symptoms.

The Berlin Questionnaire was validated in a large cohort of subjects recruited from primary care clinics. As OSA is known to be common in subjects with
resistant hypertension, the prevalence of OSA was likely higher in our population of subjects than in the primary care subjects in which the Berlin Questionnaire was originally validated. This difference in OSA prevalence may have been further increased by the older age of our subjects and the inclusion of a large proportion of African-American subjects.\textsuperscript{31,32} Given the greater pretest probability of having OSA in the current study subjects vs the primary care subjects in which the Berlin Questionnaire was originally validated, it is recognized that the accuracy of the screening instrument, \textit{i.e.}, the Berlin Questionnaire, may not be the same in the two different populations.

To address concern over the validity of the Berlin Questionnaire in subjects with resistant hypertension, we have begun a prospective evaluation of subjects referred to us with resistant hypertension. Subjects first complete the Berlin Questionnaire and are then referred for laboratory polysomnographic evaluation. The polysomnography results are scored by the center physician blinded to the results of the Berlin Questionnaire. To date, 20 subjects with resistant hypertension who were at high risk for OSA based on their responses to the Berlin Questionnaire have undergone polysomnographic evaluation. Of those 20, 18 subjects were confirmed to have OSA and 2 subjects were not. This corresponds to a positive predictive value of 90\%, which is the same as had been reported by Netzer et al\textsuperscript{16} in their validation of the Berlin Questionnaire in primary care subjects. While our evaluation is currently limited to a small number of subjects, it does suggest similar applicability of the Berlin Questionnaire to primary care subjects, in which it was validated, and our study subjects with resistant hypertension.

An alternative explanation for the current observation of the high degree of association between suspected OSA and hyperaldosteronism is that obesity and not OSA underlies the greater aldosterone excretion. Several investigators\textsuperscript{33–35} have reported higher aldosterone levels in obese individuals than in lean control subjects. These reports have generally indicated, however, that the higher aldosterone levels in obese subjects occurred in association with increased renin activity, consistent with a generalized stimulation of the renin-angiotensin-aldosterone system. In the current analysis, BMI did not correlate with urinary aldosterone excretion; in subjects with confirmed PA, aldosterone was elevated in conjunction with suppressed renin activity. The observed disassociation between renin activity and aldosterone excretion in the current subjects is not suggestive of a generalized stimulation of the renin-aldosterone system.

Goodfriend et al\textsuperscript{36} reported that the higher aldosterone levels previously reported in obese hypertensive subjects may be more strongly related to measures of central fat distribution than to general adiposity. Further, these investigators\textsuperscript{37} described an adipocyte-derived factor, likely a free fatty acid derivative, that enhances the release of a hepatic stimulator of aldosterone synthesis. The effect of an adipocyte-derived aldosterone secretagogue independent of renin activity might contribute to the renin-aldosterone disassociation observed in the current report. Additional studies will be needed to evaluate this possibility.

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