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Original Research

SLEEP DISORDERS

Increased Dietary Sodium Is Related to Severity of Obstructive Sleep Apnea in Patients With Resistant Hypertension and Hyperaldosteronism

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Background: **Obstructive sleep apnea (OSA) is a strong and independent risk factor for the development of hypertension, particularly resistant hypertension, and cardiovascular diseases. Patients with resistant hypertension have a high prevalence of OSA in association with elevated aldosterone levels, high salt intake, and salt-sensitive BP. The objective of this study was to determine whether dietary salt and aldosterone are associated with severity of OSA in patients with resistant hypertension.**

Methods: **Ninety-seven patients with resistant hypertension were prospectively evaluated by overnight polysomnography and 24-h urinary sodium and aldosterone levels while maintaining their usual diet. Hyperaldosteronism was defined as a plasma renin activity of < 1 ng/mL/h and urinary aldosterone level of ≥ 12 μg/24 h.**

Results: **Overall, patients' mean clinic BP was $156.3 \pm 22.4/88.9 \pm 13.3$ mm Hg while taking an average of 4.3 ± 1.1 antihypertensive medications. Prevalence of OSA was 77.3%. Twenty-eight (28.9%) patients had hyperaldosteronism. Urinary sodium level was an independent predictor of severity of OSA only in patients with hyperaldosteronism.**

Conclusions: **The findings suggest that dietary salt is related to the severity of OSA in patients with resistant hypertension and hyperaldosteronism. The results support dietary salt restriction as a treatment strategy for reduction of OSA severity in these patients.**

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Abbreviations: AHI = apnea-hypopnea index; CrCl = creatinine clearance; OSA = obstructive sleep apnea; PRA = plasma renin activity; Ualdo = urinary aldosterone; UNa = urinary sodium

Obstructive sleep apnea (OSA) secondary to periodic collapse of the upper airway during sleep is a strong and independent risk factor for hypertension and cardiovascular diseases.[1-5] The prevalence of OSA is reported as 23% to 35% in unselected hypertensive populations[6-9] and 65% to 85% among patients with resistant hypertension.[10-12] Cross-sectional studies reported that the severity of OSA is related to BP and that hypertension in subjects with OSA is more likely to be severe and resistant to treatment.[2,5,13]

Observational studies and clinical trials performed in general and hypertensive populations have related high salt intake to high BP and cardiovascular morbidity and mortality.[14-17] Dietary salt reduction by 3 g/d has been projected to reduce the annual number of new cases of coronary heart disease in the United States by 60,000 to 120,000, stroke by 32,000 to 66,000, and myocardial infarction by 54,000 to 99,000 and to reduce the annual number of deaths from any cause by 44,000 to 92,000.[18]

Furthermore, excessive dietary sodium ingestion contributes importantly to the development of resistant hypertension. We have previously reported that in patients with resistant hypertension, low compared with high dietary intake of salt decreased office systolic and diastolic BP by 22.7 and 9.1 mm Hg, respectively.[19] High salt intake is required for the expression of the deleterious effects of aldosterone excess. Experimental and human studies have shown that target-organ damage related to aldosterone occurs only in

the presence of high dietary sodium intake.[20-23] Because patients with resistant hypertension are characterized by a relative excess of aldosterone, a high degree of salt sensitivity, and a high prevalence of OSA, we hypothesized that effects of excess dietary salt and aldosterone combine to increase the severity of OSA.

Materials and Methods

Patients

Consecutive patients with resistant hypertension referred to The University of Alabama at Birmingham Hypertension Clinic were evaluated prospectively. The protocol was approved by the university's Institutional Review Board for Human Use (IRB number F080821013), and all patients provided written informed consent before study participation.

Resistant hypertension was defined as uncontrolled hypertension (> 140/90 mm Hg) determined at two or more clinic visits despite the use of three or more antihypertensive medications at pharmacologically effective doses.[24] Patients whose office BP was controlled (≤ 140/90 mm Hg) on four or more antihypertensive medications were also considered to have resistant hypertension. Twenty-four-hour ambulatory BP monitoring was not used to rule out the white-coat effect. All patients were on a stable antihypertensive regimen for at least 4 weeks before biochemical evaluation. No medications were discontinued. All patients on a diuretic were taking hydrochlorothiazide 25 mg daily, and no patients were taking spironolactone, triamterene, or amiloride.

After having the patient sit for at least 5 min, office BP was measured with a mercury sphygmomanometer according to American Heart Association guidelines.[25] Secondary causes of hypertension other than hyperaldosteronism, such as renovascular hypertension, pheochromocytoma, or Cushing syndrome, were excluded by laboratory analysis and radiologic imaging as clinically indicated. Patients with a history of atherosclerotic disease (myocardial infarction or stroke < 6 months), congestive heart failure, current smoking, or diabetes treated with insulin were excluded from study participation.

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OSA Evaluation

All participants underwent overnight attended polysomnography. Polysomnographic evaluation included airflow monitoring with thermocouple, nasal pressure, or both; respiratory effort with piezo belts at the chest and abdominal positions; oxygen saturation as measured by pulse oximetry; heart rate with a single-lead ECG; EEG (C4-A1, C3-A2, O2-A1, O1-A2); submental and tibial electromyograms; and bilateral electrooculograms. Apnea was defined as a cessation in airflow for ≥ 10 s. Hypopnea was defined as a reduction in the amplitude of airflow of at least 30% for ≥ 10 s followed by either a decrease in oxygen saturation of 4% or signs of physiologic arousal (at least 3 s of α activity). Apnea-hypopnea index (AHI) was calculated as the total number of apneas plus hypopneas divided by the hours of sleep. Sleep stage was scored according to Rechtschaffen and Kales criteria.[26] Sleep stage and nocturnal events were continuously supervised by a registered polysomnographic technologist. Scoring of all studies was confirmed by an American Board of Sleep Medicine diplomat. OSA, which is characterized by preserved and increased respiratory effort despite partial or complete occlusion of the upper airway, was defined as an AHI ≥ 5.[26] Mild, moderate, and severe OSA were defined as an AHI of 5 to 14, 15 to 29, and ≥ 30, respectively.

Laboratory Assessment

Biochemical evaluation was carried out in all participants on an outpatient basis. An early morning plasma aldosterone concentration to plasma renin activity (PRA) ratio and serum potassium and creatinine levels were determined in ambulatory patients after sitting for 5 min. A 24-h urinary collection for creatinine, aldosterone (Ualdo), and sodium (UNa) was obtained while the patient maintained his or her routine diet and was performed within 2 weeks before the overnight sleep study. Creatinine clearance (CrCl) was calculated from the serum creatinine level and the 24-h urinary excretion of creatinine and was not corrected for body surface area. Urine collection was considered appropriate if the urinary creatinine level was in the range of 14 to 26 mg/kg/d for men and 11 to 20 mg/kg/d for women. UNa was measured by commercial laboratory tests using standard techniques. PRA and Ualdo levels were measured by radioimmunoassay (Mayo Medical Laboratories).

Statistical Analysis

Values are expressed as mean ± SD unless stated otherwise. Hyperaldosteronism was defined as PRA < 1 ng/mL/h and Ualdo ≥ 12 μg/24 h according current guidelines.[27] Continuous variables were compared by two-sample *t* test or Wilcoxon rank sum test, where appropriate. Pearson correlation coefficient was used to assess the relationship between AHI and clinical and biochemical parameters. Because of evidence suggesting that salt and aldosterone have combined effects,[20-23] predictors of severity of OSA were assessed by multiple regression analysis for all patients and for patients with and without hyperaldosteronism separately. Multiple linear regression analysis was used to test the associations between AHI and the covariates, which were age, race, sex, neck circumference, BMI, Ualdo, and UNa. $P < .05$ was considered significant.

Results

In total, 97 patients with resistant hypertension were evaluated. Overall, 47.4% were men, 48.5% were black, the mean age was 55.2 ± 9.0 years, and the mean office BP was 156.3 ± 22.4/88.9 ± 13.3 mm Hg (Table 1).

Table 1—*Demographic and Biochemical Values for All Patients*

Characteristic	Value
No. patients	97
Male sex	46 (47.4)
Black race	47 (48.5)
Age, y	55.2 ± 9.0
Neck circumference, cm	41.6 ± 4.5
BMI, kg/m²	33.5 ± 6.7
Duration of hypertension, y	17.2 ± 10.3
No. medications	4.3 ± 1.1
Serum potassium, mEq/L	3.9 ± 0.4
CrCl, mL/min	115.5 ± 37.4
PAC, ng/dL	11.1 ± 6.3
PRA, ng/mL/h	2.4 ± 3.9
Aldosterone/renin ratio	14.3 ± 15.1
UNa, mEq/24 h	178.4 ± 76.7
Ualdo, μg/24 h	11.9 ± 6.5
AHI	16.8 ± 17.2
Office BP, mm Hg	
Systolic	156.3 ± 22.4
Diastolic	88.9 ± 13.3

Data are presented as No. (%) or mean ± SD unless otherwise indicated. AHI = apnea-hypopnea index; CrCl = creatinine clearance; PAC = plasma aldosterone concentration; PRA = plasma renin activity; Ualdo = urinary aldosterone; UNa = urinary sodium.

Patients took an average of 4.3 ± 1.1 antihypertensive medications, which included angiotensin-converting enzyme inhibitors (61.2%), angiotensin receptor blockers (57.3%), calcium channel blockers (76.7%), β-blockers (77.7%), and diuretics (91.3%). None of the patients were taking mineralocorticoid receptor blockers. Patients were characterized by a long duration of hypertension, normal renal function, high normal Ualdo levels, low PRA levels, and high dietary salt intake (Table 1).

Overall, the prevalence of OSA was 77.3%. Prevalence of mild, moderate, and severe OSA was 37.1%, 24.7%, and 15.5%, respectively. The mean AHI was significantly greater in men than in women (23.0 ± 19.5 vs 11.2 ± 12.7, $P = .0001$). AHI was similar in blacks and whites. Patients with moderate to severe OSA were more likely to be men (66.7% vs 34.5%, $P = .0357$), had a significantly larger neck circumference (44.1 ± 3.6 cm vs 39.9 ± 4.2 cm, $P < .0001$), and had a higher UNa level (203.0 ± 68.8 mEq/24 h vs 161.8 ± 77.7 mEq/24 h, $P = .0088$) compared with those with no or mild OSA. Age, CrCl, PRA, Ualdo level, and office systolic and diastolic BP were similar between groups.

Twenty-eight patients (28.9%) had hyperaldosteronism. Age, sex, BMI, neck circumference, UNa level, and systolic and diastolic BP were similar between patients with and patients without hyperaldosteronism (Table 2). CrCl was significantly higher among patients with hyperaldosteronism compared with patients with normal aldosterone levels.

Multiple regression analysis showed no significant relationship between AHI and any of the covariates among the entire population (Table 3). After model selection on the basis of stepwise criteria, only neck circumference correlated significantly with AHI ($P < .0001$). Sex, neck circumference, and UNa level were significantly positively related to AHI in patients with hyperaldosteronism (Table 4). The relationship between UNa level and AHI was linear, and there was no threshold. None of the variables were related to AHI in patients without hyperaldosteronism (Table 5). Notably, BMI showed no correlation among patients with or without hyperaldosteronism.

Discussion

To our knowledge, this study is the first to demonstrate in a hypertensive cohort that dietary salt and aldosterone are associated with severity of OSA. UNa, which could be used for the estimation of dietary salt intake, was positively correlated with AHI in patients with resistant hypertension and hyperaldosteronism. The study also confirms that OSA is highly prevalent among patients with resistant hypertension. In a recent prospective analysis of 125 patients with resistant hypertension, OSA (defined as AHI > 15) was diagnosed in 64% of subjects.[10] In a separate study, OSA (defined as AHI ≥ 10) was diagnosed in 83% of 41 patients with resistant hypertension seen in a hypertension specialty clinic.[11]

Table 2—*Demographic and Biochemical Characteristics of Patients With or Without Hyperaldosteronism*

Characteristic	Without Hyperaldosteronism (n = 69)	With Hyperaldosteronism (n = 28)	*P* Value
Male sex	31 (44.9)	15 (53.6)	.440
Age, y	53.5 ± 9.5	54.9 ± 7.7	.839
Neck circumference, cm	41.3 ± 4.7	42.3 ± 3.8	.343
BMI, kg/m²	33.2 ± 7.0	34.3 ± 6.0	.452
CrCl, mL/min	109.7 ± 36.4	129.9 ± 36.5	.015
UNa, mEq/24 h	174.1 ± 74.8	188.9 ± 81.4	.392
Office BP, mm Hg			
Systolic	155.1 ± 23.2	159.0 ± 20.5	.448
Diastolic	88.9 ± 13.9	89.0 ± 11.8	.987

Data are presented as No. (%) or mean ± SD. See Table 1 legend for expansion of abbreviations.

Table 3—*Multiple Regression Analysis in the Entire Population*

Variable	Parameter Estimate	95% CI	*P* Value
Age	−0.00424	−0.41 to 0.40	.9833
Race	−2.28585	−9.52 to 4.95	.5313
Sex	3.96949	−6.92 to 14.86	.4704
Neck circumference	1.23393	−0.10 to 2.57	.0694
BMI	0.02613	−0.73 to 0.78	.9452
Ualdo	−0.01959	−0.58 to 0.54	.9451
UNa	0.02159	−0.03 to 0.07	.3978

See Table 1 legend for expansion of abbreviations.

Table 5—*Multiple Regression Analysis for Patients Without Hyperaldosteronism*

Variable	Parameter Estimate	95% CI	*P* Value
Age	−0.01778	−0.49 to 0.45	.9401
Race	−4.30479	−13.02 to 4.42	.3271
Sex	10.23554	−3.03 to 23.51	.1280
Neck circumference	0.81173	−0.83 to 2.45	.3265
BMI	0.21264	−0.73 to 1.15	.6519
Ualdo	−0.11912	−1.01 to 0.77	.7900
UNa	−0.00925	−0.08 to 0.06	.7782

See Table 1 legend for expansion of abbreviations.

Aldosterone excess may play a pathophysiologic role in the relationship between hypertension and OSA.[28,29] In a cross-sectional analysis of 114 patients with resistant hypertension, those at high risk for OSA (according to the Berlin Questionnaire) were almost twice as likely to have primary aldosteronism, tended to have lower PRA, and had significantly greater 24-h Ualdo excretion compared with those at low risk for OSA.[30] However, the relationship between aldosterone levels and severity of OSA is unclear. In a prospective study, patients with moderate to severe OSA without coexisting cardiovascular disease and normal BP had a plasma aldosterone concentration and PRA similar to that of healthy subjects.[31]

OSA is characterized by repetitive interruption of airflow during sleep caused by collapse of the pharyngeal airway. An anatomically small pharyngeal airway and enlarged peripharyngeal soft tissues resulting from obesity are common abnormalities in patients with OSA. Cross-sectional studies have used CT imaging and MRI to measure upper airway and soft tissue dimensions in the oropharyngeal region of patients with sleep-related breathing disorders. The volumes of the tongue and lateral walls of the upper airway independently increase the risk of OSA.[32] More recently, investigators demonstrated that severity of OSA is related to rostral fluid displacement from the legs.[33] Furthermore, an observational study in patients with congestive heart failure demonstrated that sodium intake, according to food diary recordings, is directly, and renal function indirectly, related to the severity of OSA, suggesting that OSA is associated with fluid retention secondary to the combined effects of high sodium intake, impaired renal function, and overnight rostral fluid shift from the legs.[34]

Table 4—*Multiple Regression Analysis for Patients With Hyperaldosteronism*

Variable	Parameter Estimate	95% CI	*P* Value
Age	0.61974	−0.29 to 1.53	.1715
Race	0.52658	−16.00 to 17.04	.9475
Sex	−21.74439	−41.34 to −2.15	.0314
Neck circumference	3.85743	1.32 to 6.40	.0049
BMI	−0.52754	−1.73 to 0.67	.3695
Ualdo	0.43795	−0.58 to 1.46	.3802
UNa	0.10516	0.02 to 0.19	.0137

See Table 1 legend for expansion of abbreviations.

The present study extends the combined effects of aldosterone and salt to OSA, which is independently associated not only with risk and severity of hypertension but also with cardiovascular morbidity and mortality. Similarly to studies in animals, studies in humans have shown that salt is required for aldosterone-induced target-organ deterioration.[21] We have demonstrated that similarly to AHI in the current study, urinary protein excretion increased progressively across tertiles of UNa in patients with hyperaldosteronism but not in patients with normal aldosterone levels.[22] In a separate study, we demonstrated the combined effects of aldosterone and salt in promoting dilatation and hypertrophy of the heart.[23]

Preliminary evidence from our center indicates that medical treatment with mineralocorticoid receptor blockade can improve OSA, supporting the role of aldosterone and fluid retention in the pathogenesis of OSA.[35] In a prospective, open-label study, 12 patients with resistant hypertension and moderate to severe OSA (AHI $\geq$ 15) had spironolactone added to their existing antihypertensive regimen for 8 weeks, after which overnight polysomnography was repeated. In all patients, the AHI was reduced by a mean of about 50%. These results support the concept that aldosterone- and sodium-mediated chronic fluid retention is an important mediator of OSA severity.

The present study is strengthened by its prospective design, sodium excretion measured by 24-h urine collection, and diagnosis of OSA through full-night attended polysomnography. Study limitations include a cross-sectional design and having evaluated patients during ongoing antihypertensive treatment. Although biochemical evaluation of hyperaldosteronism and UNa are best done after withdrawal of antihypertensive medications,[36] this was not possible for safety reasons in high-risk patients with resistant hypertension. All patients were on a stable antihypertensive regimen for at least 4 weeks such that their sodium balance was likely in a steady state. Although different

classes of antihypertensive medications have predictable effects on renin activity (β-blockers suppressing and diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers increasing), medication effects on aldosterone excretion are less pronounced.[37,38] It can be argued that assessment of salt intake on the basis of a single urine collection does not accurately reflect dietary salt intake. However, patients were instructed to collect urine on a day when they were consuming their usual diet and going about their usual activities, prior to receiving dietary education.

In conclusion, the current study suggests that high dietary salt intake contributes to the severity of OSA in patients with resistant hypertension and hyperaldosteronism. Because the study is observational, causality cannot be determined. Interventional studies that use dietary salt restriction as a treatment strategy for OSA in patients with resistant hypertension and hyperaldosteronism are needed to test this hypothesis.

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Dr Pimenta: contributed to the study conception and design; data acquisition, analysis, and interpretation; statistical analysis; and drafting of the manuscript.
Dr Stowasser: contributed to the data interpretation and critical revision of the manuscript for important intellectual content.
Dr Gordon: contributed to the critical revision of the manuscript for important intellectual content.
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