ORIGINAL INVESTIGATION

Characterization of Resistant Hypertension

Association Between Resistant Hypertension, Aldosterone, and Persistent Intravascular Volume Expansion

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Background: Resistant hypertension is a common clinical problem and greatly increases the risk of target organ damage.

Methods: We evaluated the characteristics of 279 consecutive patients with resistant hypertension (uncontrolled despite the use of 3 antihypertensive agents) and 53 control subjects (with normotension or hypertension controlled by using ≤2 antihypertensive medications). Participants were prospectively examined for plasma aldosterone concentration, plasma renin activity, aldosterone to renin ratio, brain-type natriuretic peptide, atrial natriuretic peptide, and 24-hour urinary aldosterone (UAldo), cortisol, sodium, and potassium values while adhering to a routine diet.

Results: Plasma aldosterone ($P<.001$), aldosterone to renin ratio ($P<.001$), 24-hour UAldo ($P=.02$), brain-type natriuretic peptide ($P=.007$), and atrial natriuretic peptide ($P=.001$) values were higher and plasma renin activity ($P=.02$) and serum potassium ($P<.001$) values were lower in patients with resistant hypertension vs controls. Of patients with resistant hypertension, men had significantly higher plasma aldosterone ($P=.003$), aldosterone to renin ratio ($P=.02$), 24-hour UAldo ($P<.001$), and urinary cortisol ($P<.001$) values than women. In univariate linear regression analysis, body mass index ($P=.01$), serum potassium ($P<.001$), urinary cortisol ($P<.001$), urinary sodium ($P=.02$), and urinary potassium ($P<.001$) values were correlated with 24-hour UAldo levels. Serum potassium ($P=.001$), urinary potassium ($P<.001$), and urinary sodium ($P=.03$) levels were predictors of 24-hour UAldo levels in multivariate modeling.

Conclusions: Aldosterone levels are higher and there is evidence of intravascular volume expansion (higher brain-type and atrial natriuretic peptide levels) in patients with resistant hypertension vs controls. These differences are most pronounced in men. A significant correlation between 24-hour urinary aldosterone levels and cortisol excretion suggests that a common stimulus, such as corticotropin, may underlie the aldosterone excess in patients with resistant hypertension.

Arch Intern Med. 2008;168(11):1159-1164

RESISTANT HYPERTENSION IS defined as blood pressure (BP) that remains higher than the goal value despite the use of 3 antihypertensive medications, 1 ideally being a diuretic, with all agents prescribed at doses that provide optimal benefit.[1,2] Although the prevalence of resistant hypertension is unknown, evidence from the National Health and Nutrition Examination Survey and from large randomized clinical studies[3-6] indicates that 20% to 30% of hypertensive persons may require 3 or more antihypertensive agents to achieve treatment goals. Patients with resistant hypertension are at a disproportionately high risk for target organ damage and cardiovascular events.[7] Some factors associated with poor BP control include older age, more severe hypertension, chronic kidney disease, female sex, black race, obesity, and diabetes mellitus.[3,4] Although these patient characteristics are known to be associated with poorly controlled hypertension, mechanisms that underlie resistant hypertension remain poorly elucidated.

Recent studies indicate that primary aldosteronism (PA) is a common cause of resistant hypertension. A study[8] of 88 consecutive patients with resistant hypertension reported a 20% prevalence of PA (defined as plasma renin activity <1.0 ng/mL/h and a urinary aldosterone [UAldo] level >12 µg/24 h during high urinary sodium [UNa] excretion [>200 mEq/24 h]). Consistent with these findings, other medical centers have reported a prevalence of PA of 17% to 22% in patients with resistant hypertension.[9-11] The reason for the high prevalence of aldosterone excess in patients with resistant hypertension is unknown.

We hypothesize that aldosterone contributes broadly to antihypertensive drug treatment resistance. In the present study, we seek to identify potential stimuli of ex-

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cessive aldosterone secretion in patients with resistant hypertension.

METHODS

Consecutive patients referred to the University of Alabama at Birmingham Hypertension Clinic for resistant hypertension were studied prospectively during a 6-year period (January 1, 2001, to December 31, 2006). Patients with resistant hypertension included those with uncontrolled hypertension (>140/90 mm Hg) at 2 clinic visits despite the use of 3 antihypertensive medications at pharmacologically effective doses. We reported a high prevalence of obstructive sleep apnea and a correlation between aldosterone levels and the severity of obstructive sleep apnea in patients with resistant hypertension.[12] Hence, consecutive patients referred to the University of Alabama at Birmingham Sleep/Wake Disorders Center for possible obstructive sleep apnea and without resistant hypertension (with normotension or BP controlled by taking ≤2 antihypertensive medications) were recruited as control subjects to match the patients with resistant hypertension for age, sex, race, body mass index, and the likelihood of obstructive sleep apnea. The study was approved by the University of Alabama at Birmingham institutional review board and was conducted according to institutional guidelines. All the patients provided written informed consent before study enrollment.

All the patients had been adhering to a stable antihypertensive drug regimen for at least 4 weeks before examination. Patients were examined during continuation of their normal medication regimens except for spironolactone, amiloride hydrochloride, and eplerenone, which were discontinued at least 6 weeks before enrollment. Secondary causes of hypertension other than PA, such as renovascular hypertension, pheochromocytoma, and Cushing syndrome, were excluded by laboratory analysis or radiologic imaging as clinically indicated. Patients with a history of congestive heart failure, chronic kidney disease (creatinine clearance <60 mL/min/1.73 m^2 [to convert to milliliters per second per square meter, multiply by 0.0167]), or long-term corticosteroid therapy were excluded from study participation.

Seated clinic BP was measured manually using a mercury sphygmomanometer and an appropriate-sized cuff after 5 minutes of rest. A mean of 2 readings was taken. All patients with resistant hypertension underwent 24-hour ambulatory BP monitoring (model 90207 [Spacelabs Healthcare, Issaquah, Washington] or model 0413 [Suntech Medical, Morrisville, North Carolina]).

Biochemical evaluation was performed for all the patients on an outpatient basis. Early morning (7-9 AM) blood samples were collected from patients in the seated position for serum chemistry results, plasma aldosterone concentration (PAC) (reference range, 4-31 ng/dL [to convert to picomoles per liter, multiply by 27.74]) and plasma renin activity (PRA) (reference range, 1.31-3.95 ng/mL/h). Twenty-four hour urine collection for the measurement of UAldo (reference range, 2-16 µg/24 h), UNa, and creatinine was performed while the patient followed a routine diet. Measurement of plasma metanephrines (reference range, 0-90 pg/mL [to convert to picomoles per liter, multiply by 5.459]), normetanephrines (reference range, 0-163 pg/mL [to convert to picomoles per liter, multiply by 5.459]), brain-type natriuretic peptide (BNP) (reference range, 0-100 pg/mL [to convert to nanograms per liter, multiply by 1.0]), atrial natriuretic peptide (ANP) (reference range, 0-100 pg/mL [to convert to picomoles per liter, multiply by 0.325]), 24-hour urinary potassium (UK), and 24-hour urinary cortisol (UCort) (reference range, 56-286 µg/24 h) was added to the protocol after study initiation. From that point forward, all the patients with resistant hypertension (n=135) and all the control subjects underwent this additional testing. The PAC, PRA, and UAldo levels were measured at commercial laboratories (Quest Diagnostics, Atlanta, Georgia, and Mayo Medical Laboratories, Rochester, Minnesota) using standard techniques. Blood samples for ANP measurements were collected in EDTA tubes and were centrifuged after adding the protease inhibitor aprotinin, which stabilizes ANP. Samples were frozen at –80°C. The ANP level was measured by means of radioimmunoassay using commercially available kits (Phoenix Pharmaceuticals Inc, Burlingame, California). The aldosterone to renin ratio (ARR) was calculated as PAC divided by PRA. Patients with UAldo excretion of 12 µg/24 h or greater and PRA of 1.0 ng/mL/h or less were considered to have a high aldosterone status. All other patients were considered to have a normal aldosterone status.

Values are reported as mean (SEM) for continuous variables. Differences between groups are compared using the unpaired *t* test for continuous variables and the Fisher exact test for categorical variables (sex and race). Predictors of aldosterone levels were assessed by means of univariate and multiple regression analysis using a software program (SAS, version 9.1; SAS Institute Inc, Cary, North Carolina). Because UAldo levels in this study population were not normally distributed, the natural log of UAldo was used in the multivariate model to predict UAldo levels. $P<.05$ was considered statistically significant.

RESULTS

A total of 279 patients with resistant hypertension (135 men and 144 women) and 53 controls (29 men and 24 women) were examined. Overall, 60% of the patients with resistant hypertension had suppressed PRA (<1.0 ng/mL/h) vs only 40% of controls. Thirty-five percent of the patients with resistant hypertension had an elevated ARR (>20), and 29% had elevated 24-hour UAldo levels (≥12 µg/24 h) and suppressed PRA (≤1.0 ng/mL/h). In contrast, only 4% of controls had an elevated ratio with the use of either plasma or urinary aldosterone levels. Of the patients with resistant hypertension, 84.9% were taking thiazide diuretics (3.6% were receiving both a loop and a thiazide diuretic), 76.3% were taking calcium channel antagonists, 71.0% were taking β-blockers, 57.3% were taking angiotensin-converting enzyme inhibitors, 51.6% were taking angiotensin receptor blockers, 10.0% were taking α-antagonists, and 44.4% were taking other antihypertensive medications, including centrally acting agents or vasodilators.

Patients with resistant hypertension were older and more likely to be African American than were control subjects (**Table 1**). The clinic systolic and diastolic BP, PAC, UAldo, ARR, BNP, and ANP values were all higher in patients with resistant hypertension than in controls (Table 1 and **Figure 1**A). The ANP and BNP values were incrementally higher in patients with a high aldosterone status (UAldo level ≥12 µg/24 h and PRA ≤1.0 ng/mL/h) vs patients with a normal aldosterone status (UAldo level <12 µg/24 h or PRA >1.0 ng/mL/h) vs controls (Figure 1B). The PRA levels were lower in patients with resistant hypertension despite widespread use of agents known to increase PRA, and serum potassium levels were also lower, perhaps as a consequence of greater diuretic use or higher aldosterone levels (Table 1).

Table 1. Characteristics of the Study Participants

Characteristic	Patients With Resistant Hypertension (n=279)[a]	Controls (n=53)[a]
Male sex, %	48.3	54.7
Black race, %	47.3[b]	28.3
Age, y	54 (0.7)[b]	50 (1.4)
BMI	33.0 (0.4)	33.9 (0.9)
Clinic systolic/diastolic BP, mm Hg	146 (1.2)[c]/86 (0.9)[c]	125 (1.4)/79 (1.0)
No. of BP medications	4.1 (0.07)[c]	0.5 (0.10)
Potassium, mEq/L	3.9 (0.03)[c]	4.3 (0.06)
Plasma aldosterone, ng/dL	13.0 (0.5)[c]	8.4 (0.7)
Plasma renin activity, ng/mL/h	2.3 (0.2)[b]	3.8 (0.9)
Plasma ARR	22 (1.7)[c]	6 (0.7)
Plasma metanephrines, pg/mL	36.6 (1.8)	36.6 (1.8)
Plasma normetanephrines, pg/mL	122.7 (5.5)	108.1 (5.5)
Urinary aldosterone, µg/24 h	13.0 (0.6)[b]	9.7 (0.9)
Urinary cortisol, µg/24 h	91.2 (3.7)	97.4 (5.4)
Urinary sodium, mEq/24 h	187 (5.2)	181 (14.1)
Urinary potassium, mEq/24 h	64 (2.1)	66 (3.1)
BNP, pg/mL	37.2 (3.1)[b]	22.5 (3.4)
ANP, pg/mL	95.9 (5.8)[c]	54.8 (4.9)

Abbreviations: ANP, atrial natriuretic peptide; ARR, aldosterone to renin ratio; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BNP, brain-type natriuretic peptide; BP, blood pressure.

SI conversion factors: To convert ANP to picomoles per liter, multiply by 0.325; to convert BNP to nanograms per liter, multiply by 1.0; to convert plasma aldosterone to picomoles per liter, multiply by 27.74; to convert plasma metanephrines and normetanephrines to picomoles per liter, multiply by 5.459; and to convert potassium to millimoles per liter, multiply by 1.0.

[a] Data are given as mean (SEM) unless otherwise indicated.

[b] Different from controls, $P<.05$.

[c] Different from controls, $P<.001$.

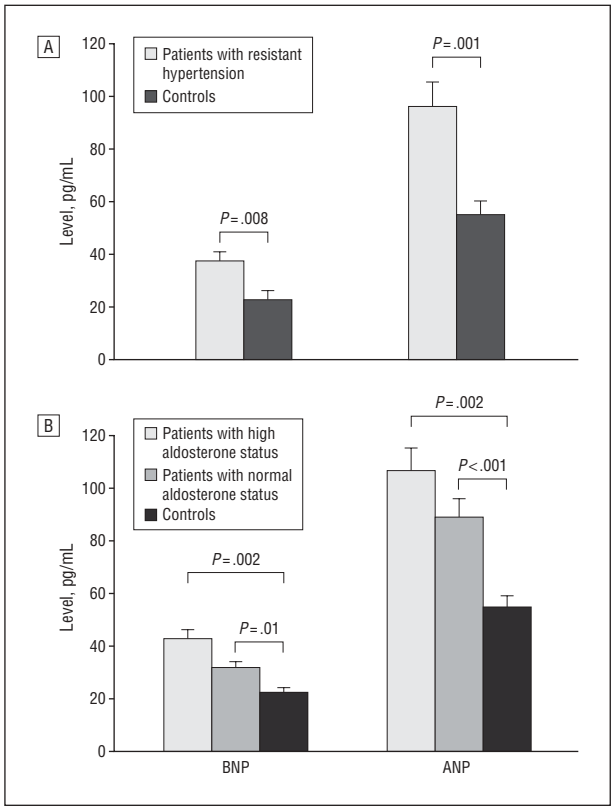

Figure 1. Atrial natriuretic peptide (ANP) and brain-type natriuretic peptide (BNP) values in patients with resistant hypertension (n=279) vs controls (n=53) (A) and in patients with resistant hypertension with a normal aldosterone status (n=197) or a high aldosterone status (n=82) vs controls (n=53) (B). There was a significant incremental increase in ANP and BNP values among controls, patients with resistant hypertension with a normal aldosterone status, and patients with resistant hypertension with a high aldosterone status. To convert ANP to picomoles per liter, multiply by 0.325; to convert BNP to nanograms per liter, multiply by 1.0. Error bars represent SEM.

Of patients with resistant hypertension, men had significantly greater PAC, ARR, UAldo, UCort, UNa, and UK values compared with women (**Table 2**). Men had higher aldosterone levels despite greater dietary sodium intake, as evident from greater UNa excretion. In women, aldosterone levels were not related to menopausal status (determined based on patient report or surgical menopause) or to the use of menopausal hormone therapy. The PAC, ARR, UAldo, and UNa values did not differ between male and female control subjects. The UCort level was significantly higher in male than in female controls. This sex difference in aldosterone remained significant after correcting for serum potassium concentration. However, no such sex difference was noted when corrected for UK concentration.

Black patients with resistant hypertension had higher clinic systolic BP (148 [1.8] vs 144 [1.7] mm Hg; $P=.07$), diastolic BP (89 [1.4] vs 83 [1.1] mm Hg; $P<.001$), 24-hour ambulatory systolic BP (146 [1.8] vs 140 [1.4] mm Hg; $P=.01$), and 24-hour ambulatory diastolic BP (86 [1.2] vs 81 [1.1] mm Hg; $P<.001$) compared with white patients. The PAC was significantly lower in black patients (11.2 [0.7] vs 14.6 [0.8] ng/dL; $P<.001$), and no statistically significant racial differences were noted in UAldo levels or PRA.

The 24-hour ambulatory systolic/diastolic BP in all the patients with resistant hypertension was 143 [1.7]/83 [1.4] mm Hg. Consistent with previous reports from this laboratory,[13] multivariate analysis indicated that older age, male sex, black race, and high aldosterone status were associated with higher ambulatory BP monitoring levels.

Univariate linear regression analysis showed that in patients with resistant hypertension, 24-hour UAldo excretion correlated with body mass index ($r=0.15$, $P=.01$), serum potassium ($r=-0.23$, $P<.001$), UCort ($r=0.29$, $P<.001$) (**Figure 2**), UNa ($r=0.20$, $P=.02$), and UK ($r=0.55$, $P<.001$) values. Multivariate regression modeling with age, sex, race, body mass index, serum potassium, UK, UNa, and UCort as covariates indicated that serum potassium (coefficient=–0.325, $P=.001$) and UNa (coefficient=–0.001, $P=.03$) levels were negatively related and UK (coefficient=0.012, $P<.001$) was positively related to UAldo level. The R^2 was 43.6% for this model.

COMMENT

The present study adds to the body of literature relating aldosterone excess to the pathogenesis of resistant hypertension by demonstrating that (1) PAC and 24-hour

Table 2. Characteristics of Male and Female Patients With Resistant Hypertension

Characteristic	Men (n=135)[a]	Women (n=144)[a]
Black race, %	39[b]	56
Age, y	54 (0.92)	55 (0.93)
BMI	32.6 (0.46)	33.4 (0.68)
Clinic systolic/diastolic BP, mm Hg	146 (1.8)/88 (1.16)[c]	145 (1.7)/84 (1.35)
24-h ambulatory systolic/diastolic BP, mm Hg	144 (1.5)/86 (0.9)[b]	143 (1.8)/81 (1.4)
No. of BP medications	4.18 (0.10)	4.10 (0.09)
Potassium, mEq/L	3.85 (0.04)	3.94 (0.04)
Plasma aldosterone, ng/dL	14.8 (0.8)[b]	11.3 (0.7)
Plasma renin activity, ng/mL/h	2.20 (0.3)	2.35 (0.3)
Plasma ARR	26 (2.8)[c]	18 (1.9)
Plasma metanephrines, pg/mL	42.1 (1.8)	44.0 (1.8)
Plasma normetanephrines, pg/mL	122.7 (9.2)	122.7 (7.3)
Urinary aldosterone, µg/24 h	16.0 (0.9)[d]	10.2 (0.7)
Urinary cortisol, µg/24 h	107.8 (5.0)[d]	76.5 (4.9)
Urinary sodium, mEq/24 h	214 (7.7)[d]	161 (6.1)
Urinary potassium, mEq/24 h	77 (3.2)[d]	52 (2.0)
BNP, pg/mL	31.5 (4.0)	42.2 (4.6)
ANP, pg/mL	88.9 (7)	103.3 (9.3)

Abbreviations: See Table 1.

SI conversion factors: To convert ANP to picomoles per liter, multiply by 0.325; to convert BNP to nanograms per liter, multiply by 1.0; to convert plasma aldosterone to picomoles per liter, multiply by 27.74; to convert plasma metanephrines and normetanephrines to picomoles per liter, multiply by 5.459; and to convert potassium to millimoles per liter, multiply by 1.0.

[a] Data are given as mean (SEM) unless otherwise indicated.

[b] Different from women, $P<.005$.

[c] Different from women, $P<.05$.

[d] Different from women, $P<.001$.

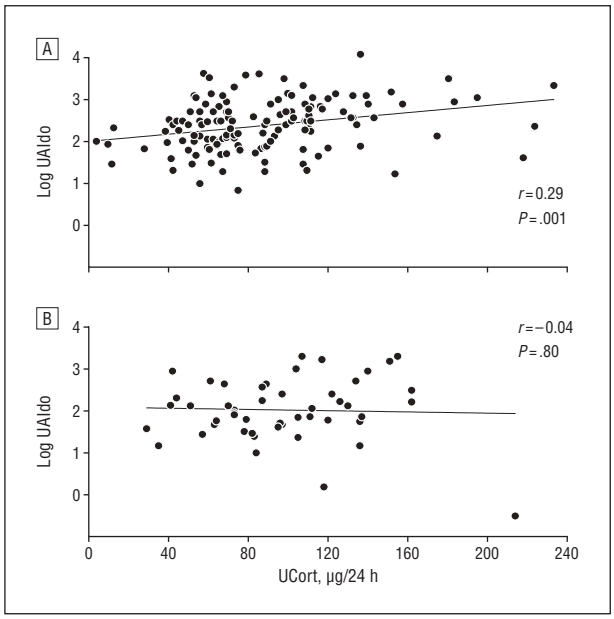

Figure 2. Correlation between 24-hour urinary aldosterone (UAldo) (reference range, 2-16 µg/24 h) and urinary cortisol (UCort) (reference range, 56-286 µg/24 h) levels in patients with resistant hypertension (A) and controls (B).

UAldo excretion are significantly higher in patients with resistant hypertension vs control subjects; (2) aldosterone levels are higher in men than in women with resistant hypertension; (3) BNP and ANP levels are higher in patients with resistant hypertension, irrespective of aldosterone levels, suggesting that increased intravascular volume is a common characteristic of resistant hypertension; and (4) 24-hour excretion of UAldo and UCort is positively correlated in patients with resistant hypertension, suggesting a stimulus common to both as the underlying cause of the excessive aldosterone secretion.

Although previous studies, including our own, have reported a prevalence of PA of approximately 20% in patients with resistant hypertension, none specifically compared aldosterone levels in a control group. In the present study, we make such a comparison and confirm overall higher levels of plasma and 24-hour urinary aldosterone in patients with resistant hypertension. In addition, 34.7% of the patients with resistant hypertension had an elevated ARR compared with only 3.7% of control subjects. These findings suggest a potentially greater role of aldosterone in causing resistance to antihypertensive agents than only in patients with classically defined PA. Such an effect is supported by recent studies[14-16] documenting the broad antihypertensive benefit of aldosterone antagonists in treating resistant hypertension.

The present results demonstrate significantly higher levels of aldosterone in men with resistant hypertension compared with women. This sex difference is the opposite of findings from studies[17,18] of patients with normotension or mild hypertension in which PACs were higher in female patients. Accordingly, the present data indicate that patients with resistant hypertension are distinct from the more general hypertensive population, with men having higher aldosterone levels than women of similar age and body weight. In a post hoc examination of the present female patients with resistant hypertension, aldosterone levels were not related to postmenopausal status or to the use of menopausal hormone therapy, suggesting that the sex difference in aldosterone levels is not likely to be related to the presence or absence of female sex hormones.

When corrected for UK excretion, the sex differences in aldosterone levels were no longer significant. This suggests 2 possibilities: the greater dietary potassium intake by men is stimulating increased aldosterone release or higher aldosterone levels in men are inducing greater potassium excretion. Intuitively, it seems that if greater dietary potassium is stimulating the increased aldosterone release in men, there would be concomitantly higher serum potassium levels because this should better reflect the stimulatory effects of potassium at the level of the adrenal gland. However, just the opposite is observed, with men having lower serum potassium levels (3.85 [0.04] vs 3.94 [0.04] mEq/L; $P=.08$) (to convert potassium to millimoles per liter, multiply by 1.0). This observation seems to argue against potassium intake stimulating increased aldosterone release as opposed to excess aldosterone promoting increased potassium wasting. However, the observational design of the present study cannot distinguish between these 2 possibilities, and interventional studies are needed to determine which is the predominant effect.

Similarly, multivariate modeling identified UNa, serum potassium, and UK levels to be the best predictors of UAldo levels. The inverse relation with UNa is consistent with high dietary sodium intake suppressing aldosterone release, whereas the positive relation with UK and the negative relation with serum potassium are consistent with high dietary potassium intake stimulating aldosterone release or aldosterone excess promoting UK excretion.[19,20] Again, separating cause from effect in terms of aldosterone and potassium may be important in explaining the high degree of aldosterone excess in patients with resistant hypertension.

The present study is the first, to our knowledge, to report significantly higher BNP and ANP levels in patients with resistant hypertension compared with controls. Atrial natriuretic peptide is mainly produced in the cardiac atria, and BNP is produced mostly in the cardiac ventricles in response to volume or pressure overload.[21-24] These findings of higher BNP and ANP levels in patients with resistant hypertension despite widespread diuretic use support persistent intravascular volume expansion as an important cause of resistant hypertension. If elevated secondary to volume expansion, the overall higher levels of natriuretic peptides in patients with resistant hypertension suggest that persistent fluid retention is not limited only to patients with measurable evidence of aldosterone excess.

Interpretation of the present results to suggest persistent fluid retention separate from higher arterial BP as an important cause of the higher natriuretic peptide levels is consistent with findings from Mayo Clinic investigators,[25] who reported that higher intravascular volumes as indexed by thoracic impedance, predicted a favorable response to increased diuretic use in individuals with resistant hypertension. The fact that most patients (84.9%) in the present study were already receiving long-term thiazide diuretic therapy suggests that thiazide diuretics at conventional doses may not be sufficient to overcome this persistent volume expansion. The broad benefit of spironolactone in reducing BP in patients with resistant hypertension indicates that it may represent a more targeted approach, but whether the antihypertensive benefit of spironolactone in this setting is related to increased diuresis needs to be determined.

The finding of a significant positive correlation between UAldo and UCort excretion in patients with resistant hypertension but not in controls suggests that in the former group there is a stimulus common to aldosterone and cortisol. If so, corticotropin would be an obvious suspect because it is known to stimulate the release of aldosterone and cortisol.[19,20] Consistent with the present findings, a cross-sectional study[26] comparing hypertensive with normotensive African American individuals found that hypertensive patients had higher aldosterone, lower renin, and higher salivary cortisol levels. Additional studies are needed to determine whether corticotropin levels are higher in patients with resistant hypertension compared with controls or whether the patients with resistant hypertension may be more sensitive to the stimulatory effects of corticotropin.

Adipocyte-derived secretagogues and genetic polymorphisms that affect aldosterone synthase activity have been implicated as potentially important mediators of aldosterone and cortisol secretion.[27-29] Whether such factors may be contributing to higher aldosterone levels in patients with resistant hypertension is not known. In vitro studies[30,31] have suggested that sympathetic nervous system activation may stimulate aldosterone and cortisol release. However, in the present study, we found no differences in sympathetic activation based on the measurement of plasma metanephrines and normetanephrines, although, admittedly, such values are an insensitive index of sympathetic activity.

The present study is strengthened by its prospective design, the inclusion of many patients with resistant hypertension, and the comparison with a control group without resistant hypertension. Additional strengths include assessment of aldosterone, cortisol, sodium, and potassium excretion by 24-hour urine collection. This study is limited in having performed all biochemical evaluations during ongoing antihypertensive drug treatment. Although aldosterone and renin activity are ideally assessed after the withdrawal of medications, this was not possible for safety reasons in these high-risk patients. Although β-blockers predictably suppress and diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers increase PRA, effects on aldosterone release are minimal or absent.[9]

In conclusion, the present study implicates aldosterone excess and persistent intravascular volume expansion as common underlying causes of resistant hypertension. Increased intravascular volume is not limited to patients with measurable evidence of aldosterone excess, suggesting that either factors other than aldosterone contribute to fluid retention or conventional assessments of aldosterone levels do not accurately reflect the functional role of aldosterone in maintaining fluid excess. In patients with resistant hypertension, hyperaldosteronism is more common in men, indicating a sexual dichotomy that has not been previously described, to our knowledge. Last, in patients with resistant hypertension, a significant positive correlation between aldosterone concentration and cortisol excretion suggests a common but as yet unidentified stimulus as a potential mediator of the aldosterone excess in these patients.

Accepted for Publication: December 28, 2007.
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Financial Disclosure: None reported.
Funding/Support: This study was supported by grant HL007457 (Dr Gaddam) and grants HL077100 and HL075614 (Dr Calhoun) from the National Heart, Lung,

and Blood Institute and by grant M01-RR00032 from the General Clinical Research Center.

Role of the Sponsor: The funding bodies had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Additional Contributions: Yiu-Fai Chen, MD, performed ANP measurements.

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