Published in final edited form as:
Arch Intern Med. 2008 June 9; 168(11): 1159–1164. doi:10.1001/archinte.168.11.1159.

RESISTANT HYPERTENSION CHARACTERIZED BY INCREASED ALDOSTERONE LEVELS AND PERSISTENT INTRAVASCULAR VOLUME EXPANSION

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Abstract

Background—Resistant hypertension is a common clinical problem and greatly increases risk of target organ damage. We sought to evaluate the characteristics of resistant hypertensive patients (uncontrolled in spite of use of 3 antihypertensive agents) compared to controls (normotensive or hypertension controlled with ≤2 antihypertensive medications).

Methods—Consecutive subjects with resistant hypertension (RHTN) (n=279) and controls (n=53) were prospectively evaluated for plasma aldosterone (PAC), plasma renin activity (PRA), aldosterone-renin ratio (ARR), brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), 24-hr urinary aldosterone (UAldo), cortisol (UCort), sodium (UNa) and potassium (UK) on their routine diet.

Results—PAC (13±0.5 vs. 8.4±0.7 ng/dl, p=0.0005), ARR (22±1.7 vs. 6±0.7, p < 0.0001), UAldo (13±0.6 vs. 9.7±0.9 μg/24hr, p=0.02), BNP (37.2±3.1 vs. 22.5±3.4 pg/ml, p=0.007) and ANP (95.9 ±5.8 vs. 54.8±4.9 pg/ml, p=0.001) were higher, PRA (2.3±0.2 vs. 3.8±0.9 ng/ml/hr, p=0.02) and serum potassium (3.9±0.03 vs. 4.3±0.06 mEq/L, p < 0.0001) were lower in patients with RHTN compared to controls. Among subjects with RHTN, males had significantly higher PAC, ARR, UAldo, and UCort than their female counterparts. In univariate linear regression analysis, BMI, serum potassium, UCort, UNa and UK were correlated with UAldo. Serum potassium, UK and UNa were significant predictors of UAldo in multivariate modeling.

Conclusion—These findings indicate that aldosterone levels are higher and there is evidence of intravascular volume expansion (higher BNP and ANP levels) in patients with resistant hypertension compared to controls. These differences are most pronounced in males. A significant correlation between 24-hr urinary aldosterone and cortisol excretion suggests that a common stimulus, such as ACTH, may underlie the aldosterone excess in patients with resistant hypertension.

Keywords

resistant hypertension; aldosterone; cortisol; natriuretic peptide; intravascular volume

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Introduction

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

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

We hypothesize that aldosterone contributes broadly to antihypertensive treatment resistance. In the current study, we sought to identify potential stimuli of excessive aldosterone secretion in subjects with resistant hypertension.

Methods

Consecutive patients referred to the University of Alabama at Birmingham (UAB) Hypertension Clinic for resistant hypertension were studied prospectively over a 6 year period (January 2001-December 2006). Patients with resistant hypertension included those with uncontrolled hypertension (>140/90 mm Hg) at 2 clinic visits, in spite of use of 3 antihypertensive medications at pharmacologically effective doses. We have reported a high prevalence of obstructive sleep apnea (OSA) and a correlation between aldosterone levels and the severity of OSA among patients with resistant hypertension.[12] Hence consecutive subjects referred to the UAB Sleep/Wake Disorders Center for suspicion of OSA and without resistant hypertension (normotensive or BP controlled on ≤2 antihypertensive medications) were recruited as control subjects in order to match the resistant hypertensive subjects for age, gender, race, BMI and likelihood of OSA. The study was approved by the UAB Institutional Review Board and was conducted according to institutional guidelines. All subjects provided written informed consent prior to study enrollment.

All patients had been on a stable antihypertensive regimen for at least 4 weeks before evaluation. Subjects were evaluated during continuation of their normal medical regimens except for spironolactone, amiloride or eplerenone which were discontinued at least 6 weeks prior to enrollment. Secondary causes of hypertension other than PA, such as renovascular hypertension, pheochromocytoma or Cushing's syndrome had been excluded by laboratory analysis and/or radiological imaging as clinically indicated. Subjects with a history of congestive heart failure, chronic kidney disease (creatinine clearance <60 ml/min) or chronic steroid therapy were excluded from study participation.

Seated clinic blood pressures were measured manually with a mercury column sphygmomanometer and an appropriate size cuff after 5 minutes of rest. An average of 2 readings was taken. All resistant hypertensive subjects underwent 24-hr ambulatory blood

pressure monitoring (ABPM) using a Space Labs (Redmond, WA; model # 90207) or Suntech (Morrisville, NC; model # 0413) monitor.

Biochemical evaluation was performed for all subjects on an outpatient basis. Early morning (0700-0900) blood samples were collected from patients in the seated position for serum chemistries, plasma aldosterone concentration (PAC) (reference range 4 to 31 ng/dl) and plasma renin activity (PRA) (reference range 1.31 to 3.95 ng/mL/h). Twenty-four hour urine collection for measurement of aldosterone (UAldo) (reference range 2 to 16 μg/24-hr), sodium (UNa) and creatinine was obtained during the subject's routine diet. Measurement of plasma metanephrines (P-met) (reference range 0 to 0.49 nMol/L), nor-metanephrines (P-nmet) (reference range 0 to 0.89 nMol/L), brain natriuretic peptide (BNP) (reference range 0 to 100 pg/mL), atrial natriuretic peptide (ANP) (reference range 0 to 100 pg/mL), 24-hr urine potassium (UK) and 24-hr urine cortisol (UCort) (reference range 56 to 286 μg/24-hr) was added to the protocol after study initiation. From that point forward, all resistant hypertensive subjects (n=135) and all of the control subjects had this additional testing. PAC, PRA, and urinary aldosterone were measured by commercial laboratories (Quest Diagnostics, Atlanta, GA and Mayo Medical Laboratories, Rochester, MN) using standard techniques. Blood samples for ANP measurements were collected in EDTA tubes and centrifuged after adding the protease inhibitor aprotinin that stabilizes ANP. Samples were frozen at -80°C. ANP was measured by radioimmunoassay using commercially available kits (Phoenix Pharmaceuticals, Burlingame, CA). Aldosterone renin ratio (ARR) was calculated as PAC divided by PRA. Subjects with urinary aldosterone excretion (≥12 mcg/24-hr) and PRA (≤1.0 ng/ml/h) were considered to have high aldosterone status (high-aldo). All other subjects were considered to have normal aldosterone status (normal-aldo).

Statistics

Values are reported as mean ± s.e.m for continuous variables. Differences between groups were compared using Student *t* test for continuous variables and Fisher's exact test for categorical variables (gender and race). Predictors of aldosterone levels were assessed by univariate and multiple regression analysis using SAS (version 9.1). As urinary aldosterone in our study population was not normally distributed, the natural log of urine aldosterone (log UAldo) was used in the multivariate model to predict UAldo. A probability (p value) of < 0.05 was considered significant.

Results

A total of 279 resistant hypertensive subjects (135 men and 144 women) and 53 controls (29 men and 24 women) were evaluated. Overall, 60% of the resistant hypertensive subjects had a suppressed PRA (<1.0 ng/ml/hr) vs. only 40% of the control subjects. Thirty-five percent of the resistant hypertensive subjects had an elevated plasma aldosterone/PRA ratio (>20), while 29% had elevated 24-hr urinary aldosterone levels (≥12 mcg/24h) and suppressed PRA (≤1.0 ng/ml/h). In contrast, only 4% of control subjects had an elevated ratio with use of either plasma or urinary aldosterone levels. Among the resistant hypertensive subjects, 85% were on thiazide diuretics (4% were receiving both a loop and a thiazide diuretic), 76% were on calcium channel antagonists, 71% were on β-blockers, 57% were on ACE inhibitors, 52% were on ARBs, 10% were on α-antagonists, and 44% were on other antihypertensive medications including centrally acting agents and/or vasodilators.

The resistant hypertensive subjects were older and more likely African American than control subjects (Table 1). The clinic systolic and diastolic BP, PAC, UAldo, ARR, BNP and ANP were all higher in resistant hypertensive subjects compared with controls (Table 1 & Figure 1, upper panel). ANP and BNP values were incrementally higher in high-aldo (urinary

aldosterone ≥12 μg/24-hr and PRA ≤1.0 ng/mg/hr; high-aldo) vs. normal-aldo (urinary aldosterone <12 μg/24-hr and/or PRA >1.0 ng/mg/hr; normal-aldo) vs. control subjects (Figure 1, lower panel). PRA levels were lower in the patients with resistant hypertension in spite of wide spread use of agents known to increase renin activity while serum potassium levels were lower, a consequence of, perhaps greater diuretic use and/or higher aldosterone levels.

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

Blacks with resistant hypertension had higher clinic systolic (148±1.8 vs. 144±1.7 mm Hg; p=0.07), diastolic (89±1.4 vs. 83±1.1 mm Hg; p<0.001), 24-hr ambulatory systolic (146±1.8 vs. 140±1.4 mm Hg; p=0.01) and 24-hr ambulatory diastolic BP (86±1.2 vs. 81±1.1 mm Hg; p<0.001) compared to whites. PAC was significantly lower in blacks (11.2±0.7 vs. 14.6±0.8 ng/dl; p<0.001) while no significant racial differences were noted in UAldo or PRA.

Mean 24-hr ambulatory blood pressures in all the resistant hypertensive subjects were 143 ±1.7/83±1.4 mm Hg). Consistent with prior reports from this laboratory[13], multivariate analysis indicated that older age, male gender, black race and high aldosterone status were associated with higher ABPM levels.

Univariate linear regression analysis showed that among the patients with resistant hypertension, 24-hr urinary aldosterone excretion correlated with BMI (r=0.15, p=0.01), serum potassium (r=-0.23, p<0.007), UCort (r=0.29, p=0.0007) (Figure 2), UNa (r=0.2, p=0.02), and UK (r=0.55, p < 0.0001). Multivariate regression modeling with age, gender, race, BMI, serum potassium, UK, UNa and UCort as covariates indicated that serum potassium (coefficient=-0.325, p=0.001) and UNa (coefficient=-0.001, p=0.03) were negatively related UK (coefficient=0.012, p=<0.0001) positively related to UAldo. The R-squared equaled 43.6% for this model.

Discussion

The current study adds to the body of literature relating aldosterone excess to the pathogenesis of resistant hypertension by demonstrating that: 1) both plasma aldosterone and 24-hr urinary aldosterone excretion are significantly higher in patients with resistant hypertension compared to 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 increased intravascular volume as a common characteristic of resistant hypertension; and 4) 24-hr urinary excretion of aldosterone and cortisol are positively correlated in patients with resistant hypertension suggesting a stimulus common to both as the underlying cause of the excessive aldosterone secretion.

While prior studies, including our own, have reported a prevalence of PA of approximately 20% in patients with resistant hypertension, none specifically compared aldosterone levels to a control group. In the current study we make such a comparison and confirm overall higher levels of both plasma and 24-hr urinary aldosterone in patients with resistant hypertension. In addition, almost 30% of the resistant hypertensive subjects had an elevated aldosterone/renin ratio compared to only 4% of the control subjects. These findings suggest a potentially greater

role of aldosterone in causing resistance to antihypertensive than just patients with classically defined PA. Such an effect is supported by recent studies documenting the broad antihypertensive benefit of aldosterone antagonists in treating resistant hypertension.[14-16]

The current results demonstrate significantly higher levels of aldosterone in male subjects with resistant hypertension compared to female subjects. This gender difference is the opposite of findings from studies of normotensive or mildly hypertensive subjects in which plasma aldosterone levels were higher in female subjects.[17,18] Accordingly, the current data indicate that patients with resistant hypertension are distinct from the more general hypertensive population with males having higher aldosterone levels than females of similar age and body weight. In a post-hoc evaluation of our female subjects with resistant hypertension, aldosterone levels were not related to post-menopausal status or to the use of menopausal hormone therapy, suggesting that the gender difference in aldosterone levels is not likely related to presence or absence of female sex hormones.

When corrected for urinary potassium excretion, the gender differences in aldosterone levels were no longer significant. This suggests 2 possibilities, greater dietary potassium intake by males is stimulating increased aldosterone release or that higher aldosterone levels in males are inducing greater potassium excretion. Intuitively, it seems that if greater dietary potassium is stimulating the increased aldosterone release in males, there would be concomitantly higher serum potassium levels as this should better reflect the stimulatory effects of potassium at the level of the adrenal gland. However, just the opposite is observed, with males having lower serum potassium levels (3.85±0.04 vs. 3.94±0.04 mEq/L, p=0.08). 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 current 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 to be the best predictors of UAldo. The inverse relation with UNa is consistent with high dietary sodium intake suppressing aldosterone release while the positive relation with UK and the negative relation with serum potassium are consistent with high dietary potassium stimulating aldosterone release and/or aldosterone excess promoting urinary potassium excretion.[19,20] Again, separating cause from effect in terms of aldosterone and potassium may help be important in explaining the high degree of aldosterone excess in patients with resistant hypertension.

The current study is the first to report significantly higher BNP and ANP levels in patients with resistant hypertension compared to controls. ANP is mainly produced in the cardiac atria while BNP is produced mostly in the cardiac ventricles in response to volume or pressure overload.[21-24] Our findings of higher BNP and ANP levels in patients with resistant hypertension in spite of widespread diuretic use supports 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 resistant hypertensive patients suggests that persistent fluid retention is not just limited to patients with measurable evidence of aldosterone excess.

Interpretation of the current results to suggest persistent fluid retention separate from higher arterial BP as an important cause of the higher natriuretic peptides is consistent with findings from Mayo Clinic investigators who reported that higher intravascular volumes as indexed by thoracic impedance predicted a favorable response to increased diuretic use in subjects with resistant hypertension.[25] The fact that the large majority (85%) of subjects in our study were already receiving chronic 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.

Our finding of a significant positive correlation between urinary aldosterone and cortisol excretion in patients with resistant hypertension but not in controls suggests in the former group a stimulus common to both aldosterone and cortisol. If so, adreno-corticotropic hormone (ACTH) would be an obvious suspect as it is known to stimulate release of both aldosterone and cortisol.[19,20] Consistent with the current findings, a cross sectional study comparing hypertensive to normotensive African Americans found that the hypertensive subjects had higher aldosterone, lower renin, and higher salivary cortisol levels.[26] Additional studies are needed to determine whether ACTH levels are higher in patients with resistant hypertension compared to controls or whether the resistant hypertensive patients may be more sensitive to the stimulatory effects of ACTH.

Adipocyte-derived secretagogues and genetic polymorphisms affecting 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 have suggested that sympathetic nervous system activation may stimulate aldosterone and cortisol release.[30,31] However, in the current study we found no differences in the sympathetic activation based on measurement of plasma metanephrines and normetanephrines, although admittedly, such values are an insensitive index of sympathetic activity.

The current study is strengthened by its prospective design, inclusion of a large number of subjects with resistant hypertension, and comparison to a control group without resistant hypertension. Additional strengths include assessment of aldosterone, cortisol, sodium and potassium excretion by 24-hr urine collection. This study is limited in having carried out all biochemical evaluations during ongoing antihypertensive treatment. Although assessment of aldosterone and renin activity is ideally done after withdrawal of medications, this was not possible for safety reasons in these high risk patients. Although β-blockers predictably suppress and diuretics, ACE inhibitors, and ARBs increase PRA, effects on aldosterone release are minimal or absent.[9]

In conclusion, the current 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 either, that factors other than aldosterone contribute to fluid retention or that 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 male subjects indicating a sexual dichotomy that has not been previously described. Lastly, in subjects with resistant hypertension, a significant positive correlation between aldosterone and cortisol excretion suggests a common but as of yet unidentified stimulus as a potential mediator of the aldosterone excess in these subjects.

Acknowledgments

This work was supported by NHLBI Grants HL077100, and HL075614 received by D.A.C and NHLBI Grant HL007457 received by K.K.G GCRC Grant M01-RR00032 Dr. Yiu-Fai Chen - ANP measurements

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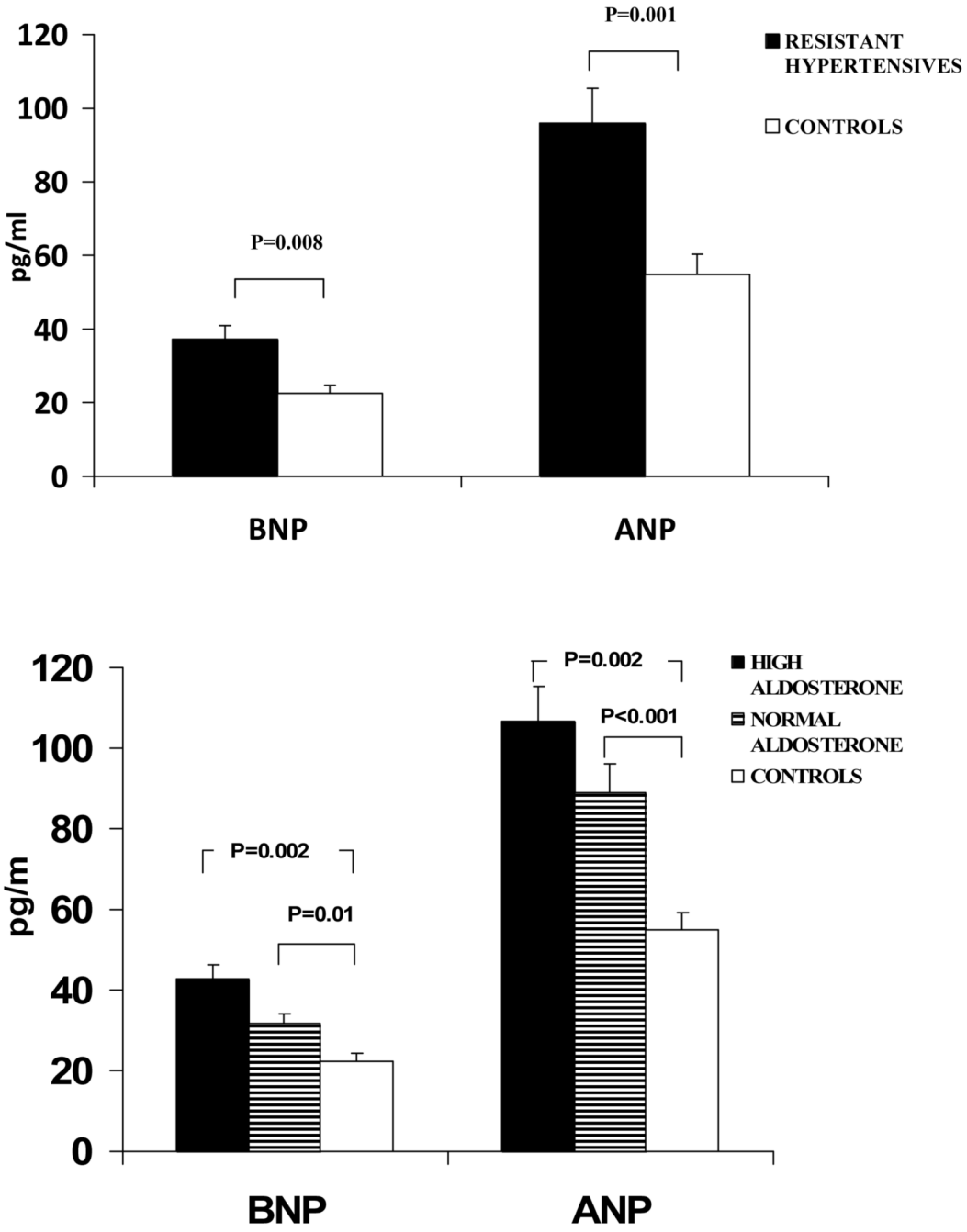

Figure 1.

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) values in resistant hypertensive subjects (n=279) and controls (n=53) (top panel). There was a significant incremental increase in ANP and BNP values between controls (n=53), resistant hypertensive subjects with normal -aldo (n=197) and high-aldo (n=82) (bottom panel).

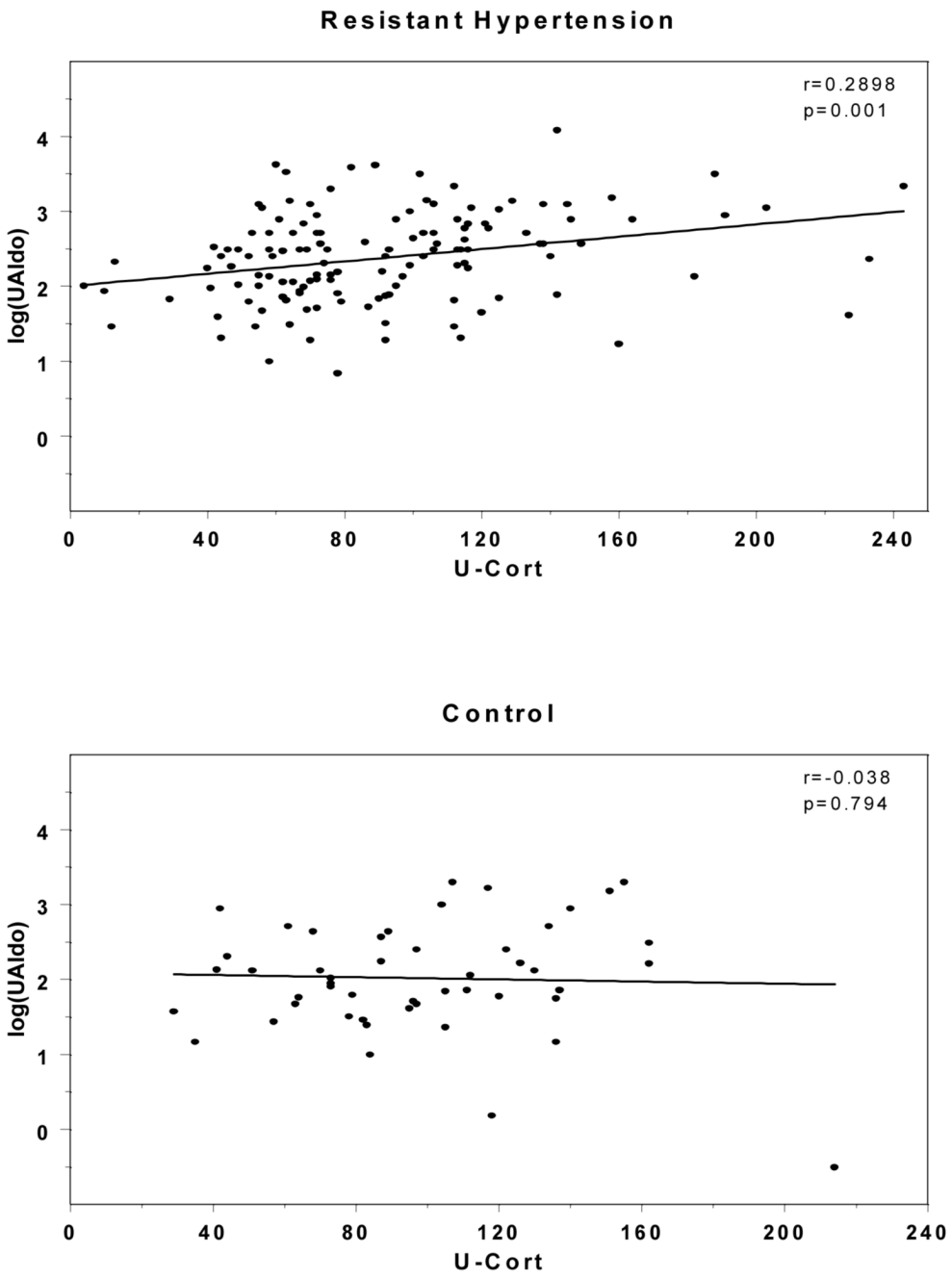

Figure 2.
Correlation between 24-hour urinary aldosterone (reference range 2 to 16 μg/24-hr) and urinary cortisol (reference range 56 to 286 μg /24-hr) among patients with resistant hypertension (top panel) and controls (bottom panel).

Table 1

Characteristics of all subjects.

Parameter	Subjects with Resistant Hypertension	Controls
N	279	53
Males (%)	48	55
Black (%)	47*	28
Age (years)	54±0.7*	50±1.4
BMI (kg/m)	33.0±0.4	33.9±0.9
Clinic BP (mm Hg)	146±1.2†/86±0.9**	125±1.4/79±1.0
Number of BP Meds	4.1±0.07†	0.5±0.1
Potassium (mEq/L)	3.9±0.03†	4.3±0.06
Plasma Aldosterone (ng/dl)	13.0±0.5**	8.4±0.7
Plasma Renin Activity (ng/ml/hr)	2.3±0.2*	3.8±0.9
ARR	22±1.7†	6±0.7
Plasma Metanephrines (nMol/L)	0.2±0.01	0.2±0.01
Plasma Normetanephrines (nMol/L)	0.67±0.03	0.59±0.03
Urinary Aldosterone (μg/24-hr)	13.0±0.6*	9.7±0.9
Urinary Cortisol (μg/24-hr)	91.2±3.7	97.4±5.4
Urinary Sodium (mEq/24-hr)	187±5.2	181±14.1
Urinary Potassium (mEq/24-hr)	64±2.1	66±3.1
BNP (pg/ml)	37.2±3.1*	22.5±3.4
ANP (pg/ml)	95.9±5.8**	54.8±4.9

Values, mean±S.E.M. BMI, body mass index; BP, blood pressure; ARR, plasma aldosterone/plasma renin activity ratio; BNP, brain natriuretic peptide; ANP, Atrial natriuretic peptide.

* different from controls $p < 0.05$

** different from controls, $p < 0.001$

† different from controls, $p < 0.0001$.

Table 2

Characteristics of male and female resistant hypertensive subjects.

Parameter	Males	Females
N	135	144
Black	39**	56
Age (years)	54±0.92	55±0.93
BMI (kg/m)	32.6±0.46	33.4±0.68
Clinic BP (mm Hg)	146±1.8/88±1.16*	145±1.7/84±1.35
24-hr ambulatory BP (mm Hg)	144±1.5/86±0.9**	143±1.8/81±1.4
Number of BP Meds	4.18±0.1	4.10±0.09
Potassium (mEq/L)	3.85±0.04	3.94±0.04
Plasma Aldosterone (ng/dl)	14.8±0.8**	11.3±0.7
Plasma Renin Activity (ng/ml/hr)	2.2±0.3	2.35±0.3
ARR	26±2.8*	18±1.9
Plasma Metanephrines (nMol/L)	0.23±0.01	0.24±0.01
Plasma Normetanephrines (nMol/L)	0.67±0.05	0.67±0.04
Urinary Aldosterone (μg/24-hr)	16.0±0.9†	10.2±0.7
Urinary Cortisol (μg/24-hr)	107.8±5.0†	76.5±4.9
Urinary Sodium (mEq/24-hr)	214±7.7†	161±6.1
Urinary Potassium (mEq/24-hr)	77±3.2†	52±2.0
BNP (pg/ml)	31.5±4.0	42.2±4.6
ANP (pg/ml)	88.9±7	103.3±9.3

Values, mean±S.E.M. BMI, body mass index; BP, blood pressure; ARR, plasma aldosterone/plasma renin activity ratio; BNP, brain natriuretic peptide; ANP, Atrial natriuretic peptide.

*different from females, $p < 0.05$

**different from females, $p < 0.005$

†different from females, $p < 0.0001$.