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Predictors of antihypertensive response to a standard dose of hydrochlorothiazide for essential hypertension

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Background. Determinants of inter-individual variation in blood pressure (BP) response to antihypertensive therapy remain largely unknown. Although differences in race, age and measures of the renin-angiotensin-aldosterone system (RAAS) have been associated with variation in blood pressure response to hydrochlorothiazide, whether these characteristics make additive contributions to predicting response has not been established. We conducted a comprehensive search for predictors of BP response to a standard dose of hydrochlorothiazide in a biracial sample to estimate how much inter-individual variation in BP response could be explained by all of the identified predictors.

Methods. After withdrawal of antihypertensive medications for at least four weeks (baseline) and stabilization on a diet approximating 150 mmol sodium per day, 225 African American and 280 Caucasian subjects with diagnosed essential hypertension were treated for four weeks with hydrochlorothiazide 25 mg per day. At baseline and the end of treatment, subjects were admitted to the General Clinical Research Center for measurement of activity of the RAAS and other regulators of BP. Characteristics measured at study enrollment, at baseline, and in response to drug treatment were incorporated stepwise into linear regression models in order to quantify their additive contributions to predicting BP responses to hydrochlorothiazide.

Results. Black race and female gender were both associated with significantly greater systolic (SBP) and diastolic (DBP) blood pressure responses to hydrochlorothiazide. Together the combined effects of race and gender accounted for 11% inter-individual variation in SBP response ($P < 0.0001$) and 4% of inter-individual variation in DBP response ($P < 0.0001$). Additional statistically significant predictors of greater systolic and diastolic responses to hydrochlorothiazide included, shorter duration of diagnosed or treated hypertension ($P < 0.001$), higher baseline BP level ($P < 0.0001$), lower baseline plasma renin activity ($P < 0.05$), lower baseline urinary aldosterone excretion ($P < 0.002$), and greater decrease in urinary sodium excretion ($P \leq 0.004$). Greater decrease in weight was an additional statistically significant predictor of SBP but not DBP response, and older age was a predictor of diastolic but not SBP response. The combined effects of all identified predictors accounted for 38% of inter-individual variation in SBP response ($P < 0.0001$) and 20% of inter-individual variation in DBP response ($P < 0.0001$).

Conclusions. A systematic search reveals numerous predictors of BP response to a standard antihypertensive dose of hydrochlorothiazide. However, because the majority of inter-individual variation in SBP and DBP responses remains unexplained, there is considerable opportunity for future investigations to improve the ability to predict individual BP responses to antihypertensive drug therapy.

Key words: African American, Caucasian, hypertension, blood pressure, renin-angiotensin-aldosterone system.

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Hypertension affects 43 million Americans, of whom approximately 85% have stage I-II (mild-moderate) essential hypertension. Despite the availability of multiple classes of antihypertensive agents with different mechanisms of action, less than 40% of treated patients achieve adequate blood pressure control [1, 2]. It has been suggested that blood pressure (BP) responses to particular classes of antihypertensive drugs provide insight into the mechanisms responsible for the hypertension [3]. Therefore, the question is what clinical characteristics can be measured to identify those individuals most likely to respond to a given antihypertensive agent.

Hydrochlorothiazide is one of the preferred drugs for treatment of uncomplicated mild-moderate hypertension [1]. Characteristics previously associated with greater blood pressure response to hydrochlorothiazide are black race, older age, and lower plasma renin activity (PRA) [4]. As with all antihypertensive agents, greater baseline BP also predicts greater blood pressure response [5]. Whereas black race and older age are associated with higher BP, lower PRA, increased sodium and decreased potassium intake [6–8], the additive contributions of these characteristics to predict the BP response to hydrochlorothiazide remains uncertain. Moreover, BP response to a diuretic is one measure of "sodium sensitivity," which also has been associated with obesity, insulin

resistance, activation of the sympathetic nervous system, and decreased potassium intake [4, 9, 10]. Finally, because of under-representation of women in many antihypertensive drug trials [11, 12], it is uncertain if gender contributes to the prediction of BP response to hydrochlorothiazide.

The present study undertook a systematic search for predictors of BP response to hydrochlorothiazide in a bi-racial sample of community and clinic-based patients with previously diagnosed essential hypertension. We systematically considered as potential predictors a comprehensive variety of characteristics measured (*1*) at study enrollment, (*2*) at least four weeks after withdrawal from previous antihypertensive drug therapy and stabilization on a standard sodium diet, and (*3*) after four weeks of hydrochlorothiazide therapy. In addition to establishing whether race, age, and measures of the renin-angiotensin-aldosterone system (RAAS) make additive contributions to the prediction of BP response, our specific objectives were to identify additional predictors of response and to estimate how much inter-individual variation in response to hydrochlorothiazide could be explained by the combined effects of all identified predictors.

METHODS

Subjects

African American and Caucasian men and women between 30 and 59 years of age with essential hypertension were recruited at Emory University in Atlanta, Georgia and Mayo Clinic in Rochester, Minnesota, respectively. The study protocol was reviewed and approved by the Institutional Review Boards of both institutions. In Atlanta, African American subjects were recruited through outpatient medical clinics at Grady Memorial Hospital, the Hypertension and Renal Diseases Research Center at Emory University, advertisements in public media, and mailing lists of registered voters. In Rochester, non-Hispanic whites were recruited from a list of all residents of Olmsted county with the diagnosis of essential hypertension who had been seen by a health care provider in the previous three years prior to recruitment [13]. A letter was sent to potential study subjects providing information about the study. Interested candidates who contacted the study centers were considered for recruitment. Essential hypertension was defined as a blood pressure greater than 140/90 mm Hg or a previous diagnosis of essential hypertension and current prescription antihypertensive medications.

After giving informed written consent, candidates were evaluated in similar fashion at both sites. Potential subjects were considered ineligible for study for the following reasons: diseases causing secondary hypertension; >3 antihypertensive medications for blood pressure control; allergy to hydrochlorothiazide; inability to discontinue antihypertensive medications; use of non-steroidal anti-inflammatory medications including daily aspirin >325 mg per day; congestive heart failure, liver or renal disease (serum creatinine concentration >1.5 mg/dL); diabetes mellitus (fasting blood glucose level >140 mg/dL) or hypoglycemic medications. Women taking oral contraceptive medications were disqualified; however, those receiving post-menopausal hormone replacement were allowed.

At enrollment, subjects underwent dietary evaluation by trained dietitians to determine sodium and potassium intake. Subjects were counseled to maintain a standard sodium intake of 2 mmol/kg/day. Dietary sodium and potassium intake was determined weekly throughout the study from 24-hour urine collections alternating with 24-hour dietary recall diaries. Individuals who demonstrated a sodium intake outside the range of 1.25 to 2.75 mmol/kg/day were contacted and re-counseled with regard to appropriate intake. If subjects had a weight change ≥2% from entry during the washout phase or ≥2% from baseline during the treatment phase, caloric intake was adjusted as necessary.

Subjects had antihypertensive medications discontinued and were evaluated every other week during the washout period, which lasted at least four weeks. If blood pressure increased above 180/110 mm Hg or symptoms developed due to elevated BP, the subject was withdrawn, pre-study blood pressure medications were restarted, and the subject was followed-up by his/her primary physician. If diastolic BP remained <90 mm Hg, the washout period was extended up to four more weeks. If diastolic BP still remained <90 mm Hg, the subject was excluded from further participation.

At least four weeks after withdrawal of previous antihypertensive medications, qualifying subjects were admitted to the General Clinical Research Center (GCRC) for overnight evaluation. Subjects provided 24-hour urine collections on the day of admission for measurement of sodium, potassium, aldosterone, norepinephrine, epinephrine, dopamine, and creatinine excretion. After admission, weight, body mass index, and waist-to-hip ratios were determined [14]. Subjects were required to retire to bed rest by 10:00 PM. At 4:00 AM, subjects arose to void, returned to bed, and an indwelling intravenous catheter was placed in the non-dominant arm. Subjects remained supine until after blood samples were obtained. At 6:00 AM, BP was measured in the dominant arm. Initial blood samples were drawn without a tourniquet for determination of plasma catecholamine concentrations. Additional blood was drawn to determine serum sodium and potassium concentrations and angiotensin-converting enzyme (ACE) activity, PRA, and aldosterone, insulin, cholesterol, and triglyceride concentrations. All samples were collected into pre-chilled

tubes and placed on ice. Tubes were immediately centrifuged and separated and frozen at −80°C until the assays were performed.

Following the initial blood drawing, subjects arose and ambulated for 30 minutes. Then, blood pressure was remeasured after the subject sat for at least five minutes, and additional blood was drawn for determination of seated PRA, aldosterone concentration, and serum ACE activity.

Upon completion of the baseline evaluation, subjects were given 25-mg hydrochlorothiazide tablets to be taken daily and then discharged from the GCRC. They returned at least every other week and collected 24-hour urine specimens after two and four weeks of hydrochlorothiazide therapy for determination of sodium, potassium, creatinine, and aldosterone excretion. Compliance was assessed by pill counts and adequacy of the 24-hour urine collections was assessed by creatinine excretion per kg body weight. At the two-week GCRC visit, blood pressure was measured and blood was drawn with subjects in the seated position for determination of serum potassium and plasma renin activity and aldosterone concentrations. After four weeks of therapy, subjects returned for overnight admission to the GCRC and underwent evaluation in identical fashion to the baseline visit.

If serum potassium was <3.6 mmol/L at the screening visit, an oral potassium supplement (K-Dur, 20 mmol/day; Key Pharmaceuticals, Kenilworth, NJ, USA) was prescribed. After two weeks of diuretic therapy, serum potassium concentration was remeasured; if the value was <3.6 mmol/L, an oral potassium supplement (20 to 40 mmol/day) was prescribed.

Laboratory analyses

Sodium and potassium were determined by ion selective electrode or flame photometry. Plasma renin activity was determined by radioimmunoassay (RIA) of angiotensin I in the presence of reagents that inhibit angiotensin-I converting enzyme and angiotensinases (Dupont Company, Boston, MA, USA). Plasma and urinary aldosterone concentrations were determined by RIA (Diagnostic Products Corporation, Los Angeles, CA, USA). Serum ACE activity was determined spectrophotometrically. Serum and urine creatinine concentrations and plasma glucose concentrations were determined by automated spectrophotometric methods implemented on the IL Monarch Chemistry System 760 (Instrumentation Laboratories, Lexington, MA, USA). Insulin concentrations were determined using a simultaneous one-step immunoenzymatic sandwich assay (Access Ultrasensitive Insulin; Sanofi Diagnostics, Chaska, MN, USA). Cholesterol and triglyceride concentrations were determined spectrophotometrically using Roche reagents on a Cobas Mira analyzer. Norepinephrine concentrations were determined radioenzymatically.

Statistical analysis

Data were summarized by calculating means and standard deviations for quantitative variables and percentages for categorical variables. In all analyses, statistical significance was inferred when $P < 0.05$. Contrasts between race and gender subgroups were based on analysis of variance (ANOVA) with Sheffe's correction for pairwise contrasts of differences in mean values (for quantitative variables) or on chi-square contingency tests of differences in proportions (for categorical variables).

Systolic and diastolic blood pressure responses to hydrochlorothiazide were defined as the final value (at the end of drug therapy) minus the baseline value (at the end of the washout period). Analyses considered the responses to hydrochlorothiazide as continuous variables. The large number of potential predictor variables and the co-linearity among these variables dictated that a multi-stage analysis strategy be employed. Three classes of potential predictor variables were considered: (*1*) characteristics measured at the enrollment visit (screening), (*2*) those measured at the end of the washout period (baseline), and (*3*) those reflecting response to hydrochlorothiazide therapy (final − baseline). At the first stage of analysis, each potential predictor trait was assessed in the entire study group, in each race, in each gender, and in each race-gender subgroup. For each quantitative predictor trait, the significance of its correlation coefficients with the systolic and diastolic BP responses was determined. For categorical traits, the ANOVA was used to assess the significance of differences in mean systolic and diastolic BP responses among categories, with appropriate corrections for multiple comparisons, as described above.

Those variables significantly associated with systolic or diastolic BP responses in any of the above analyses progressed to the next stage of analyses, in which stepwise multiple linear regression analyses were performed to identify combinations of traits that made additive contributions to the prediction of systolic and diastolic BP responses to hydrochlorothiazide. Race and gender were forced into all regression models prior to the stepwise addition of other predictors. Separate analyses were done for predictors measured at study enrollment, for those measured at baseline, and for their changes in response to hydrochlorothiazide. Upon completion of each stepwise selection process, the percentage of the inter-individual variation in BP response explained by the combined effects of the included predictor variables was estimated.

In the final stage of analyses, multiple linear regression was again used to construct a final model by further stepwise selection from among all three sets of predictor

Table 1. Reasons for withdrawal of subjects from the study

	African American		Caucasian		
	Male	Female	Male	Female	*P* value
Total enrolled	120	199	217	250	
Number withdrawn	38	56	59	128[a,b]	<0.0003
BP too high	27.7%	16.9%	14.5%	9.9%	0.080
BP too low	21.5%	25.4%	41.9%	58.3%[a,b]	<0.017
Abnormal lab	10.8%	6.8%	0.0%	0.8%	0.217
Other	40.0%	50.9%	43.6%	31.0%	0.297

Abbreviations are: BP, blood pressure; lab, laboratory.
[a] Significant difference between races within genders
[b] Significant difference between genders within races

traits included in the models built at the previous stage. As before, race and gender were forced into the models before the stepwise addition of other predictors began. Upon completion of the final selection process, the percentage of inter-individual variation in BP response to hydrochlorothiazide explained by all of the identified predictors was estimated.

RESULTS

Two hundred and twenty-five African Americans (82 men, 143 women) and 280 Caucasians (158 men and 122 women) completed the study protocol. Caucasian women were more likely to be discontinued from the protocol than Caucasian men or African American women (52% vs. 27% and 28%, respectively; $P < 0.05$ for both contrasts), chiefly because diastolic BP did not increase ≥90 mm Hg during the wash-out period (Table 1).

Characteristics measured at study enrollment and at the end of the washout period (baseline) are shown in Tables 2 and 3, respectively, for those who completed the study protocol. Mean values (or percentages) for most characteristics differed significantly among race-gender groups. In particular, African Americans of both genders were characterized by significantly more frequent smoking and greater mean values for duration of hypertension and baseline systolic BP than Caucasians; whereas Caucasians of both genders were characterized by significantly more frequent ethanol use, and greater mean waist-to-hip ratio, serum potassium, plasma triglycerides, and urinary potassium excretion than African Americans. Males of both races were characterized by significantly greater mean waist-to-hip ratio, serum potassium concentration, and urinary excretion of sodium than females, whereas females of both races were characterized by significantly more frequent previous antihypertensive drug therapy and potassium supplementation than males.

Among women, the frequency of menopause did not differ significantly between African Americans and Caucasians (Table 2). However, among the post-menopausal women, only 37% of African Americans but 67% of Caucasians were taking hormone replacement therapy ($P < 0.01$).

The distributions of systolic and diastolic BP responses to hydrochlorothiazide are shown in Figures 1 and 2 for all subjects. In each gender-race subgroup, the systolic and diastolic BP responses appeared normally distributed (not shown). In response to hydrochlorothiazide, the mean decrease in systolic BP was significantly greater in African Americans of both genders than in Caucasians ($P < 0.05$ for each contrast). Women of both races also demonstrated greater systolic BP and diastolic responses to hydrochlorothiazide than men ($P \leq 0.01$ for each contrast). In multiple regression models, the combined effects of race and gender accounted for 11% of interindividual variation in systolic BP response ($P < 0.0001$) and 4% of interindividual variation and DBP response ($P < 0.0001$).

The time courses of systolic and diastolic BP responses to hydrochlorothiazide are shown in Figures 3 and 4. Maximal decline in BP was achieved at two weeks of therapy in Caucasian men and women, whereas four weeks was required in African American men and women. No such differences in time course were apparent between men and women in either race. The dose of hydrochlorothiazide per kilogram of body weight was significantly greater in females of both races than in men (for African Americans, 0.30 ± 0.07 vs. 0.27 ± 0.06 mg/kg, $P < 0.005$; for Caucasians, 0.31 ± 0.07 vs. 0.26 ± 0.05 mg/kg, $P < 0.0001$), but did not differ significantly between races in either gender.

Predictors of blood pressure response

Characteristics measured at study enrollment. In univariate analyses, enrollment characteristics that were significantly associated or correlated with systolic or diastolic BP responses to hydrochlorothiazide included race, gender, age, level of education, duration of diagnosed hypertension, duration of antihypertensive drug treatment, current smoking, potassium supplementation, alcohol intake, waist-to-hip ratio, body weight, and age at diagnosis of hypertension (Table 2). Of these significant correlates of response, stepwise multiple linear regression analyses indicated that only black race, female gender, older age, and shorter duration of diagnosed hypertension made additive contributions to prediction of greater systolic BP response, together accounting for 14% of inter-individual variation ($R^2 \times 100\%$) in the response to hydrochlorothiazide ($P < 0.0001$). For diastolic BP response, the predictors were similar except duration of antihypertensive drug treatment replaced duration of diagnosed hypertension and together with race, gender, and age explained 9% of inter-individual variation in diastolic BP response to hydrochlorothiazide ($P < 0.0001$).

Characteristics measured at baseline. Baseline charac-

Table 2. Subject characteristics measured at study enrollment

Characteristic	African American		Caucasian		*P* value
	Male	Female	Male	Female	
Number	82	143	158	122	
Age *years*	48.2 ± 6.8	47.6 ± 5.7	48.2 ± 8.2	50.1 ± 6.1	<0.040
Weight *kg*	94.2 ± 19.2	88.7 ± 20.5	97.8 ± 17.5[b]	83.3 ± 16.4	<0.001
BMI	29.8 ± 5.1	32.9 ± 7.2[b]	30.5 ± 4.9	30.8 ± 5.4	<0.001
Waist:hip	0.92 ± 0.1[b]	0.84 ± 0.1	0.97 ± 0.1[a,b]	0.89 ± 0.1[a]	<0.0001
Age HT Dx	40.2 ± 9.4	39.1 ± 8.5	41.8 ± 10.7	45.8 ± 6.0[a,b]	<0.0001
HT duration *years*	8.8 ± 8.6[a]	8.1 ± 7.2[a]	5.8 ± 6.9	3.7 ± 5.0	<0.0001
% on Rx	88	96[b]	90	97[b]	0.038
Rx duration *years*	7.0 ± 7.6	6.9 ± 6.4[a]	5.0 ± 5.9	3.7 ± 4.6	<0.0001
% on K^+	26	39[a,b]	7	16[a,b]	<0.0001
% Smoker	22[a]	13[a]	7	4	<0.001
% Etoh user	62[b]	39	83[a]	82[a]	<0.0001
% College grad	39	31	45[b]	30	<0.035
% Menopause		58		66	0.328
% HRT		37		67[a]	<0.001

Abbreviations are: BMI, body mass index [weight (kg) ÷ height squared (m^2)]; waist:hip, waist-to-hip ratio; HT, hypertension; Dx, diagnosis; Rx, antihypertensive drug treatment; K^+, potassium supplementation; Etoh, ethanol; HRT, hormone replacement therapy.

[a] Significant difference between races within genders

[b] Significant difference between genders within races

Table 3. Subject characteristics measured at end of washout period (baseline)

Characteristic	African American		Caucasian		*P* value
	Male	Female	Male	Female	
Number	82	143	158	122	
Systolic BP *mm Hg*	150 ± 13[a]	153 ± 15[a]	141 ± 13	144 ± 12	<0.0001
Diastolic BP *mm Hg*	98 ± 5	97 ± 5[a]	96 ± 5[b]	94 ± 5	<0.0001
Weight *kg*	96 ± 19	89 ± 20	99 ± 17[b]	85 ± 18	<0.0001
Serum Na^+ *mmol/L*	139 ± 2.6	138 ± 2.7	139 ± 2.0	138 ± 2.6	0.115
Serum K^+ *mmol/L*	3.8 ± 0.3	3.7 ± 0.3	4.1 ± 0.2[a,b]	4.0 ± 0.2[a]	<0.0001
Plasma trig. *mg/dL*	138 ± 68	116 ± 49	187 ± 108[a]	174 ± 72[a]	<0.0001
Plasma glucose *mg/dL*	98 ± 13	97 ± 14[a]	96 ± 11[b]	91 ± 12	<0.0001
Plasma insulin *μIU/mL*	12 ± 9[a]	11 ± 8	9 ± 6	9 ± 7	<0.007
Plasma Epi *pg/mL*	18 ± 17	13 ± 11	20 ± 16[b]	14 ± 13	<0.0001
Plasma Dopa *pg/mL*	24 ± 29[a,b]	16 ± 11	12 ± 11	12 ± 15	<0.0001
Seated PAC *ng/dL*	16 ± 9	20 ± 10[a,b]	16 ± 8	15 ± 10	<0.001
Seated PRA *ng/mL/h*	1.0 ± 1.0	1.0 ± 1.1	1.4 ± 1.2	1.7 ± 1.3[a]	<0.0001
Serum ACE *U/L*	14 ± 7[b]	12 ± 5	13 ± 5	11 ± 5	<0.001
Urine Na^+ *mmol/24 hr*	188 ± 71[b]	154 ± 58	178 ± 78[b]	137 ± 57	<0.0001
Urine K^+ *mmol/24 hr*	56 ± 24	46 ± 18	74 ± 32[a,b]	59 ± 24[a]	<0.0001
Urine Aldo *μg/24 hr*	8.8 ± 6.3	9.7 ± 6.1	10.1 ± 6.8	9.6 ± 4.9	0.543

Abbreviations are: BP, blood pressure; Na^+, sodium; K^+, potassium; Trig, triglycerides; Epi, epinephrine; Dopa, dopamine; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ACE, angiotensin-converting enzyme; Aldo, aldosterone.

[a] Significant difference between races within genders

[b] Significant difference between genders within races

teristics (Table 3) that were significantly correlated with systolic or diastolic BP responses to hydrochlorothiazide included: baseline blood pressure levels; serum concentrations of sodium, potassium, and ACE activity; plasma concentrations of triglycerides, epinephrine, dopamine, and seated PRA; and urinary excretion of sodium, potassium, and aldosterone. Of these significant correlates of response, stepwise multiple regression analyses indicated that after race and gender only greater baseline BP, lower upright PRA, and lower urinary aldosterone excretion made additive contributions to prediction of greater BP responses to hydrochlorothiazide, together accounting for 33% and 13% of inter-individual variation in the SBP and diastolic BP responses, respectively ($P < 0.0001$ for both models).

Characteristics measured in response to hydrochlorothiazide. Response characteristics that were significantly associated with systolic or diastolic BP responses to hydrochlorothiazide included changes in weight, plasma glucose and triglyceride concentrations, and urinary sodium and aldosterone excretion (not shown). Of these significant correlates of response, stepwise regression analyses indicated that after race and gender, only greater weight loss and greater reduction in urinary so-

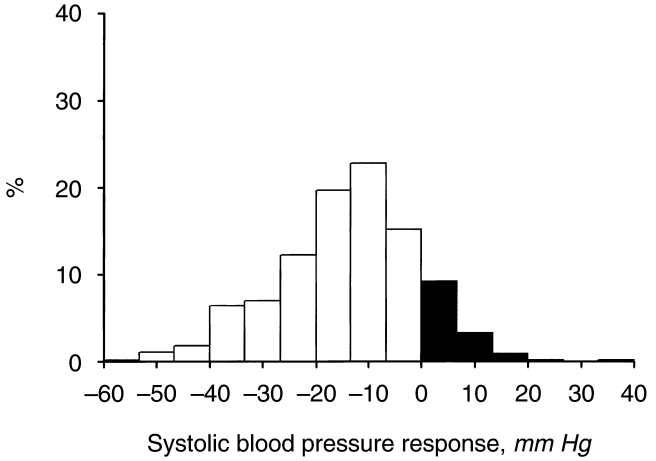

Fig. 1. Frequency distribution histogram of systolic blood pressure (BP) responses to four weeks of hydrochlorothiazide, 25 mg per day, in the combined sample of 225 African Americans and 280 Caucasians. Symbols are: (□) decreases in BP; (■) increases in BP. Data are mean = −14.4, SD = 13.4, $N = 505$.

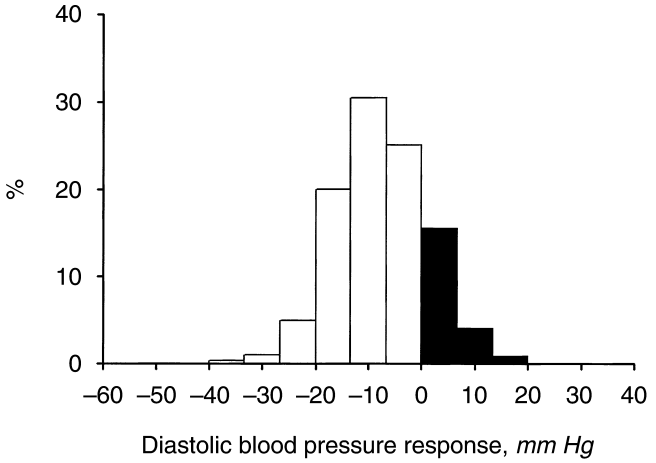

Fig. 2. Frequency distribution histogram of diastolic blood pressure (DBP) response to four weeks of hydrochlorothiazide, 25 mg per day, in the combined sample of 225 African Americans and 280 Caucasians. Symbols are: (□) decreases in BP; (■) increases in BP. Data are mean = −7.8, SD = 8.4, $N = 505$.

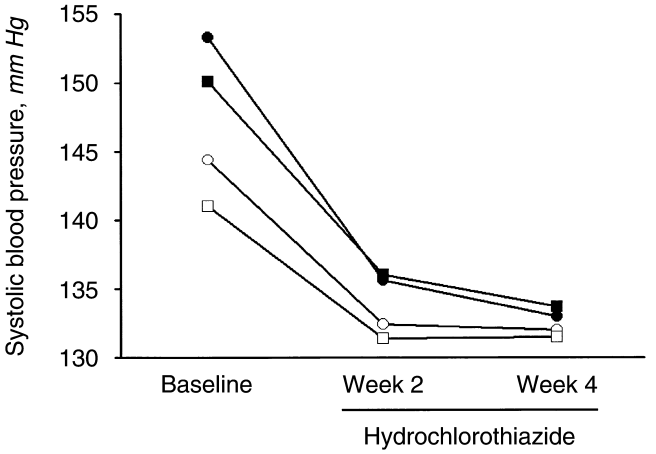

Fig. 3. Time course of systolic blood pressure (SBP) response to four weeks of hydrochlorothiazide, 25 mg per day, in 143 African American women (●), 82 African American men (■), 122 Caucasian women (○), and 158 Caucasian men (□).

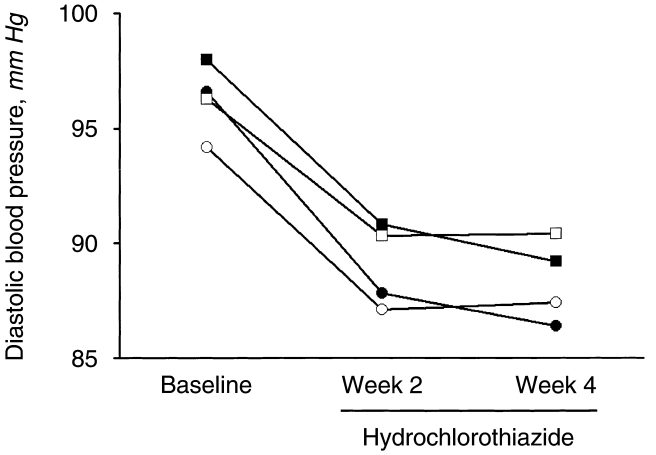

Fig. 4. Time course of diastolic blood pressure response to four weeks of hydrochlorothiazide, 25 mg per day, in 143 African American women (●), 82 African American men (■), 122 Caucasian women (○), and 158 Caucasian men (□).

dium excretion made additive contributions to the prediction of greater SBP response, accounting for 14% of inter-individual variation in the response to hydrochlorothiazide ($P < 0.0001$). Only greater increase in urinary aldosterone excretion and greater decrease in urinary sodium excretion made additive contributions to the prediction of greater DBP response, accounting for 8% of inter-individual variation in the response to hydrochlorothiazide ($P < 0.0001$).

Final model. Selecting from characteristics included in the separate regression models described above, final stepwise multiple linear regression analyses were performed to identify a parsimonious combination of characteristics that explained the most inter-individual variation in BP response to hydrochlorothiazide (Table 4). For the systolic BP response, this analysis indicated that black race, female gender, shorter duration of diagnosed hypertension, greater baseline systolic BP, lower upright PRA, lower urinary aldosterone excretion, greater weight loss, and greater reduction in urinary sodium excretion each made additive contributions to the prediction, and together explained 38% of inter-individual variation in the systolic BP response to hydrochlorothiazide ($P < 0.0001$). For diastolic BP response, the analysis indicated that black race, female gender, older age, shorter duration of antihypertensive drug treatment, higher baseline diastolic BP, lower upright PRA, lower baseline urinary aldosterone excretion, greater increase in urinary aldo-

Table 4. Final model of predictors of blood pressure response to hydrochlorothiazide

Predictor	β-coefficient	SE	*P* value
Systolic BP			
Race	−2.73	1.07	0.011
Gender	−1.89	0.97	0.054
HT duration	0.23	0.07	<0.001
Baseline BP	−0.44	0.04	<0.0001
Seated PRA	1.43	0.42	<0.001
U-Aldo	0.37	0.08	<0.0001
Δ Weight	1.18	0.32	<0.001
Δ U-Na^+	0.02	0.01	0.004
Diastolic BP			
Race	−2.54	0.75	<0.001
Gender	−1.74	0.70	0.014
Age	−0.20	0.05	0.0001
Rx duration	0.24	0.06	<0.0001
Baseline BP	−0.40	0.07	<0.001
Seated PRA	0.60	0.30	0.047
U-Aldo	0.18	0.06	0.002
Δ U-Na^+	0.013	0.004	0.003

The combined predictors explained 38% of interindividual variation in systolic and 20% of interindividual variation in diastolic blood pressure responses ($P < 0.0001$ for both models). Abbreviations are: SE, standard error; BP, blood pressure; HT, hypertension; PRA, plasma renin activity; U, 24-hour urinary excretion; Aldo, aldosterone; Na^+, sodium; Rx, antihypertensive drug treatment.

sterone excretion, and greater decrease in urinary sodium excretion each made additive contributions to the prediction and together accounted for 20% of inter-individual variation in the diastolic BP response to hydrochlorothiazide ($P < 0.0001$).

DISCUSSION

This study of African American and Caucasian men and women with stage I-II essential hypertension describes a systematic search for clinical characteristics that predict BP response to a standard dose of hydrochlorothiazide. The present findings demonstrate that a significant percentage of inter-individual variation in systolic and diastolic BP responses to hydrochlorothiazide (38% and 20%, respectively) can be predicted from characteristics measured at presentation or during the study protocol. Given the complex control of blood pressure and the inherent variability in its measurement, the magnitude of these contributions to the prediction of BP are notable. It is important to emphasize that the models found to best predict systolic and diastolic BP responses in this study were built from measured characteristics chosen by the investigators for their potential influence on BP, and that a particular model-building strategy was applied. Measurement of different characteristics or application of a different model-building strategy may have given different results. However, the present study provides benchmark estimates of our current ability to predict individual BP responses to a preferred monotherapy for the treatment of essential hypertension.

Importantly, this study did not implement other BP-lowering interventions [1]—such as dietary sodium restriction, weight loss, or exercise—so as to avoid confounding the effects of drug therapy or the associated predictors. As much as possible, the study protocol was carried out in an identical fashion in African Americans from Atlanta and Caucasians from Rochester to facilitate our combined analyses of the data. Nevertheless, additional factors may contribute to the observed differences between race-gender subgroups, including differences in geography, lifestyle, preceding diet, and activity. As surrogates for the combined effects of all such unmeasured factors, "race" and "gender" were included in all prediction models and interactions with other identified predictors were evaluated. Unmeasured differences in placebo effects also are possible but unlikely to be correlated with the other predictors of BP response. We selected subjects with stage I-II essential hypertension because these patients represent the majority of hypertensive individuals treated in the United States [12]. Although this cohort was relatively obese (mean BMI was greater than 29 kg/m^2 in each race-gender subgroup), measures of body size did not remain in any of the multiple linear regression models as predictors of systolic or diastolic BP responses to hydrochlorothiazide.

Similar to other studies, African American and Caucasian men had higher baseline systolic and diastolic BP than their Caucasian and female counterparts [6, 7, 15]. We found that African Americans of both genders and women of both races exhibited greater BP declines in response to hydrochlorothiazide therapy than their Caucasian and male counterparts, respectively. These findings are consistent with other reports of racial differences in BP responses to hydrochlorothiazide [4, 11], but new with regard to greater BP response in hypertensive women than men. Among women, neither menopausal status nor hormone replacement therapy was associated with a difference in BP response. Although BP levels, plasma volume, and "sodium-sensitivity" have been reported to be greater during the post-ovulatory (luteal) than the follicular phase of the menstrual cycle [16, 17], pre-menopausal women in our study were not uniformly evaluated pre- and post-hydrochlorothiazide treatment at the same stage of the menstrual cycle.

In the final prediction models, age was among the predictors of diastolic BP response to hydrochlorothiazide, even though the age range of subjects (30 to 59 years) did not include elderly individuals. Previous studies have suggested that older individuals are more salt sensitive [18], demonstrate greater BP response to hydrochlorothiazide [11, 19], and have decreased activation of the RAAS [4, 20]. Although subjects in those studies also had higher baseline BP values, which could have contributed to their greater BP responses to hydrochlorothiazide, our study suggests that age makes an additional contribution to the prediction of diastolic BP re-

sponse to hydrochlorothiazide in younger hypertensive individuals.

Lower upright renin activity and lower urinary aldosterone excretion made additive contributions to the prediction of greater BP responses to hydrochlorothiazide. In some but not all previous studies, PRA alone was found to predict BP response to diuretic therapy [21–24]. For example, studies by Laragh and colleagues of predominantly Caucasian males classified as low, normal, or high renin relative to sodium excretion found that those with a low renin profile demonstrated the largest BP response to hydrochlorothiazide [25, 26]. However, not addressed was the role of PRA in predicting the BP response in African Americans or women, those with the greatest BP responses in this study. The Veterans Administration Cooperative Antihypertensive Trial found that race and age were predictive of blood pressure responses to multiple agents including hydrochlorothiazide [11], with African Americans and older men (>60 years) demonstrating greater blood pressure responses to hydrochlorothiazide [27]. However, when measures of the RAAS, specifically PRA, were included as predictors of BP response, their additional predictive value was marginal and found only in individuals older than 60 years of age [4]. In the VA study, blood samples for the determination of PRA were obtained under conditions that did not control or account for dietary sodium and potassium intake or the subjects' activity, thereby potentially obscuring additional predictive information related to the circulatory RAAS.

Factors other than PRA (for example, dietary potassium intake) may regulate aldosterone excretion and have been associated with sodium sensitivity [28]. This may account for the contribution of urinary aldosterone excretion in addition to PRA to the prediction of BP responses in this cohort of subjects.

In summary, this systematic search reveals numerous characteristics that make additive contributions to the prediction of BP responses to hydrochlorothiazide in African American and Caucasian men and women with mild-moderate essential hypertension. In addition to previously identified predictors of race, age, and measures of the RAAS, other characteristics that further contribute to the prediction of BP responses include gender, duration of diagnosed or treated hypertension, and treatment-associated changes in weight and urinary sodium excretion. Because the combined effects of all identified predictors still leave most inter-individual variation in BP responses unexplained, there is considerable opportunity for future studies to improve our ability to predict the individual patients' responses to antihypertensive drug therapy [29].

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