Psychological Characteristics and Responses to Antihypertensive Drug Therapy

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The objective of this study was to explore the relationship between psychological characteristics and responses to antihypertensive drug therapy. Twenty-two hypertensive subjects underwent psychological evaluation and treatment with 1) a diuretic, hydrochlorothiazide (HCTZ); 2) an angiotensin-converting enzyme (ACE) inhibitor, quinapril; and 3) combined α + β blockade (doxazosin + betaxolol). Anger-Out scores on the State-Trait Anger Expression Inventory were positively correlated with the HCTZ-induced fall in systolic blood pressure (p<0.01); Anger-In was negatively correlated with the quinapril-induced fall in systolic pressure (p<0.05). The target systolic blood pressure (130 mm Hg) was achieved with either HCTZ or quinapril in 79% of subjects without, vs. 25% of subjects with, childhood trauma (p=0.03). Responses to doxazosin + betaxolol were not correlated with psychological characteristics. The authors conclude that both inhibited anger expression and childhood trauma are associated with reduced response to a diuretic or ACE inhibitor. Combined α/β blockade may be preferable to an ACE inhibitor or diuretic in treating selected hypertensive patients. Further studies should include examination of psychological factors in terms of the response to combined ACE inhibitor + diuretic therapy. (J Clin Hypertens. 2002;4:25–34) ©2002 Le Jacq Communications, Inc.

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Despite pharmacologic advances, hypertension is controlled in only 24% of hypertensive Americans, and in only 45% of those under treatment.[1] A lingering problem is that no single antihypertensive agent is effective in more than approximately 50% of those who take it.[2] Clearly, hypertension is a heterogeneous disorder and the efficacy of each agent varies from individual to individual. However, despite considerable research, the means to identify the drug or drugs most likely to work in a given individual remain limited.

An intriguing question, and the subject of this study, is whether psychological factors contribute to the heterogeneity of responses to antihypertensive drug therapy. To date, remarkably few studies have examined this question. Pasik et al.[3] reported that subjects with low hostility levels on the Cook Medley Scale responded better than those with high hostility to antihypertensive treatment with a diuretic. Nonresponders had higher scores for indirect, but not direct, forms of expression of hostility. In another study,[4] responses to propranolol, captopril, and methyldopa were greater in subjects with high rather than low hostility. Esler et al.[5] reported that high-renin essential hypertension was associated with suppressed hostility and with sympathetic nervous system (SNS) overactivity, and responded better to combined autonomic blockade than did normal-renin essential hypertension. The relationship between anxiety or depressed mood and responses to antihypertensive agents is virtually unstudied. An association between emotional defensiveness and response to antihypertensive drugs is suggested by a report that subjects with refractory hypertension displayed a lower intensity of emotion and less emotional attachment than subjects with well controlled hypertension.[6]

Another inadequately examined psychological factor is childhood experience. Ekeberg and colleagues[7] reported that a history of childhood trau-

ma was more prevalent among hypertensive than among normotensive subjects, and Pennebaker and Susman[8] reported that written disclosure of prior traumatic events is associated with an acute fall in blood pressure. The relationship between childhood trauma and response to antihypertensive agents has not been previously studied.

This study was based on the belief that psychological factors are involved in the hypertensive process in some individuals but not in others. We hypothesized that, in individuals in whom psychological factors contribute to hypertension, blood pressure elevation is sustained more by a neurogenic mechanism (i.e., the SNS), and less by mechanisms related to blood volume or the renin-angiotensin system (RAS), than in others. We further hypothesized that such individuals would therefore have a reduced response to antihypertensive drugs targeted at volume or the RAS, such as diuretics or angiotensin-converting enzyme (ACE) inhibitors.

To test these hypotheses, and to assess which psychological factors are associated with responsiveness to drug therapy, we examined the relationship between selected psychological parameters and responses to treatment with 1) a diuretic, hydrochlorothiazide (HCTZ); 2) an ACE inhibitor, quinapril; and 3) an α blocker + β blocker combination, doxazosin + betaxolol.

METHODS
The study was approved by the New York Hospital–Cornell Medical Center Committee on Human Rights in Research and was conducted between January, 1998 and December, 1999. Subjects with uncomplicated stage 1 or 2 essential hypertension, without concomitant major illness or contraindications to use of the study drugs, were recruited from the patient population of the Hypertension Center.

Male and female individuals, aged 21–65 years, who either had untreated hypertension, or who had treated hypertension but could safely stop their medication, were eligible. Female subjects with potential for pregnancy were included if they agreed to employ nonhormonal means of birth control throughout the duration of the study.

Exclusion criteria included the presence of diabetes, symptomatic cardiovascular or cerebrovascular disease, prior myocardial infarction or stroke, renal disease (creatinine of >1.5 mg/dL), serum potassium of <3.5 mmol/L, or known hypersensitivity or contraindication to any of the study medications. Secondary causes of hypertension were excluded where clinically appropriate. Although subjects were excluded if there were manifestations of overt psychiatric illness, formal psychological screening was not performed. Subjects taking psychotropic medication were excluded.

At the initial visit, after written informed consent was obtained, the medical history was reviewed and a physical examination was performed. Height, weight, heart rate, and blood pressure (casual blood pressure after sitting for 5 minutes) were recorded, and an electrocardiogram and blood for routine chemistries were obtained. Untreated subjects with a mean arterial pressure (MAP) of <105 mm Hg were excluded.

Protocol
The protocol consisted of self-reported psychological assessment, followed by assessment of home blood pressure, and then administration of the study drugs in crossover fashion.

Psychological Assessment. Eligible subjects completed the following self-assessment questionnaires, which were administered by the principal investigator (SJM): State-Trait Personality Inventory (STPI), State-Trait Anger Expression Inventory (STAXI), Marlowe-Crowne Scale of Social Desirability, and the Childhood Trauma Questionnaire (CTQ).

The STPI (Form X-2) contains three 10-item scales of trait anxiety, curiosity, and anger.[9] Subjects respond how they generally feel on a 4-point scale. The score for each scale represents the sum of the 10 items, with a minimum score of 10 and a maximum of 40. The scale is reported to show high internal consistencies (alpha coefficients greater than 0.85), factorial validity, and concurrent validity.

The STAXI provides a number of scales pertinent to the experience and expression of anger.[10,11] It is a 24-item questionnaire comprising three eight-item constructs: anger-in, anger-out, and anger control, with subjects responding on a 4-point scale. Total scores for each subscale are obtained by summing the response values.

The management of anger is assessed by the scales of Anger-Out (outward expression of anger), Anger-In (the covert withholding of anger), and Anger Control (including reduction of suppressed anger and prevention of the outward expression of anger). A total anger expression score is calculated from the following formula[10]:

anger-out + anger-in – anger control +16

For both males and females, scales are reported to show alpha coefficients of 0.76 or greater,[10] factorial and concurrent validity,[12] and associations with high blood pressure and hypertension.[11]

The Marlowe-Crowne Scale of Social Desirability consists of 33 true/false statements about behaviors that are socially desirable but not adhered to

by most people, or socially undesirable but true of most people.[13] The total score represents the number of socially desirable responses, with a maximum of 33. It contains both facets of defensiveness (i.e., self-deception and other deception).[14] Internal consistency of 0.88 has been obtained.[15] A recent meta-analysis[16] showed that defensiveness exhibited a greater size effect in relation to blood pressure than did negative affect or anger expression.

The CTQ is a 28-item self-report inventory that screens for histories of abuse and neglect.[17] It includes five items for each of five types of maltreatment: emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse, and a three-item Minimization/Denial scale for detecting false-negative trauma reports. Responses are on a 5-point Likert-type scale according to frequency, ranging from Never True to Very Often True. For each of the five categories, scores for the five items are added. Threshold scores for mild, moderate, and severe abuse have been established.[17] The CTQ is reported to show high internal consistency (alpha coefficients greater than 0.85, with the exception of the physical neglect category), test-retest reliability (r=0.8), and content and concurrent validity.[18] In this study, the CTQ score was considered indicative of trauma if the score of at least one category met the criterion for severe abuse.[8]

Home Blood Pressure Assessment. Subjects were given a blood pressure monitor (OMRON HEM-704c™, OMRON Corp., Tokyo, Japan), along with instructions on its use and forms on which to record pill taking and blood pressure measurements. Readings were validated with a mercury manometer, and if the averages of three recordings of systolic blood pressure (SBP) by each method were within 5 mm of each other, the monitor was taken home by the subject and used for the study.

Home Blood Pressure Measurement Protocol. Each study week and drug treatment period began on a Wednesday. Subjects were instructed to take the medication daily and to obtain home blood pressure readings on six occasions each week: Sunday evening, Monday morning and evening, Tuesday morning and evening, and Wednesday morning. On each of these six occasions, subjects were instructed to take three consecutive measurements of blood pressure and heart rate after 5 minutes of sitting quietly, and to record the second and third readings. Compliance with blood pressure recording was encouraged by requiring subjects to fill out a data sheet each day and by weekly telephone contact with a coinvestigator (LMG). A minimum of eight valid readings was required for a week's readings to be eligible for analysis.

Using this measurement protocol, run-in blood pressure was assessed after subjects were off medication for at least 2 weeks. Untreated subjects proceeded directly to the run-in week. Subjects taking a single agent discontinued that agent and began recording blood pressure the first Sunday evening after being off medication for at least 14 days. For β blockers, the dose was tapered weekly to a minimum dose (the equivalent of atenolol 12.5 mg/day) before the drug was stopped. Subjects taking more than one drug were tapered off medication one drug at a time under the supervision of the investigator until they were taking a single drug, which was then tapered and stopped as described above. If any weekly blood pressure averaged above 180 mm Hg systolic or 110 mm Hg diastolic, the subject was excluded from the study.

Treated subjects whose office blood pressure was >180 mm Hg systolic or >110 mm Hg diastolic were instructed to monitor their home blood pressure for 1 week before reducing medication. If the home blood pressure was also >180/>110, the subject was excluded from the study.

Subjects returned for a second visit upon completion of the run-in week. The home blood pressure recordings were reviewed and subjects with an MAP of ≥110 mm Hg or with an MAP of ≥105 mm Hg and an SBP of ≥140 were entered into the study.

Crossover Treatment Protocol. Subjects meeting the entry criteria were then given the study medications, which included the diuretic HCTZ, the ACE inhibitor quinapril, and the α blocker + β blocker combination of doxazosin + betaxolol. The α/β blocker labetalol was not used because of the unreliable α and β blockade it provides.[19,20] Betaxolol was used rather than atenolol because its more gradual onset of action and longer duration of effect assure a 24-hour duration of action.

The medications were given in randomized order, and in open-label fashion, at the dosages summarized in Table I. Subjects with a heart rate of <55 were excluded from the doxazosin/betaxolol arm, and subjects with a heart rate of <60 on the lowest betaxolol dosage were not given the higher dose. Home blood pressure was monitored each week, as described above. Subjects were contacted by telephone each Wednesday by a coinvestigator, who was blinded to the psychometric data, to assess blood pressure responses and adverse effects, and titrate drug dosage. Each medication was taken for 2 weeks, with dosage titrated after the first

week if the SBP exceeded 125 mm Hg. Treatment was extended to a third week in subjects who did not achieve the target SBP of 130 mm Hg after week 2. If, for any week, the average weekly home blood pressure exceeded 180 mm Hg systolic or 110 mm Hg diastolic, the subject was excluded from the study.

After completion of each drug treatment period, medication was withdrawn for a washout period of 2 weeks. The washout period was reduced to 1 week if the home MAP had returned to ≥105 mm Hg or if the SBP was >140 mm Hg after the first week, and was extended up to 4 weeks in subjects whose blood pressure did not achieve these criteria after 2 weeks.

STATISTICAL ANALYSIS
For each drug regimen, the average home blood pressure recorded during the final week of treatment was used for analysis. The fall in SBP, and the proportion of subjects achieving the target SBP of 130 mm Hg, were used for analyses, consistent both with the increasing clinical focus on SBP and with the use of SBP as the criterion for dose titration in this study.

The decrease in blood pressure achieved by the three drug regimens was compared with paired-samples t tests. The percent of subjects achieving target SBP on the three drug regimens was compared with the McNemar test. Carryover and order effects were examined by analysis of variance. Pairwise correlation coefficients were calculated for psychological test measures and the fall in SBP with each antihypertensive drug.

Blood pressure responses of subgroups defined by the presence or absence of severe childhood trauma on the CTQ were compared by repeated-measures analysis of variance, where the within-person factor was pre- and post-treatment blood pressure and the between-person factor was the presence or absence of trauma. Fisher's exact test was used to compare the percentage of subjects achieving the target SBP by childhood trauma status.

The relationship between psychological parameters and blood pressure responses was also assessed using the better of each individual's responses to HCTZ and quinapril. This analysis

was performed because many responders to monotherapy respond to either an ACE inhibitor or a diuretic without responding to the other; the lack of response to one of these agents is not an indicator of refractoriness to monotherapy.[21–24] Hence, responsiveness to monotherapy was defined as the better of the two responses.

Two-tailed probability levels for statistical significance tests are reported, with $p<0.05$ considered statistically significant.

RESULTS
Forty-one subjects met the eligibility criteria and performed run-in home blood pressure measurement. Twelve of the 41 did not meet the entry blood pressure criteria (seven were too high and five were too low) and were excluded, and three decided not to participate. The remaining 26 were entered into the study. Three dropped out during the protocol, and the data of one subject, who was unable to tolerate titration of any of the study medications, were discarded, leaving 22 who satisfactorily completed the protocol. One subject was not given betaxolol + doxazosin because of sinus bradycardia. All provided a minimum of eight valid readings for each week of the study. Subject characteristics

Table II. Subject Characteristics (n=22)	
	MEANS±SD
Age (years)	49.3±7.9
Body mass index (kg/m²)	25.8±5.3
Run-in home BP (mm Hg)	
Systolic	148.4±7.0
Diastolic	99.4±6.2
Gender (% male)	54.5
Ethnicity (%)	
White/African American/other	54.5/22.7/22.7
	PSYCHOMETRIC SCORES
	MEANS±SD
STAXI	
Anger-out	13.8±3.0
Anger-in	16.4±4.8
Anger-control	25.8±4.0
Anger total	20.4±6.7
STPI	
Trait anger	18.4±5.5
Trait anxiety	18.0±5.3
Marlowe-Crowne Social Desirability Scale	17.7±6.8

BP=blood pressure; STAXI=State-Trait Anger Expression Inventory; STPI=State-Trait Personality Inventory
Psychometric scales are described in the Methods section.

Table I. Drug Dosage (mg/day)			
	WEEK 1	WEEK 2	WEEK 3
Hydrochlorothiazide	12.5	25	25
Quinapril	10	20	40
Doxazosin + betaxolol	1/5	2/10	4/10

and psychometric scores are displayed in Table II. Ten of the 22 subjects who completed the study were untreated at the time of recruitment. Twelve were on medication, including three who were on one of the study regimens (two on ACE inhibitor monotherapy, one on α/β blockade). Four were on calcium channel blocker monotherapy and five were on various drug combinations.

The mean fall in blood pressure was significantly greater after treatment with the combination of doxazosin + betaxolol than after treatment with either HCTZ or quinapril (Table III). No significant order effects or carryover effects were observed.

Seven of the 22 subjects achieved the target SBP of 130 mm Hg after treatment with HCTZ, nine after quinapril treatment, 13 after treatment with one or the other of these two agents, and 15 after doxazosin + betaxolol therapy (Table IV).

Relationship Between Psychological Characteristics and Responses to Antihypertensive Agents

As shown in Table V, SBP responses were not related to anger scores on the STPI, but were strongly correlated with more specific measures of anger expression assessed by the STAXI.

There was a significant positive correlation between anger-out and response to HCTZ, and a significant negative correlation between anger-in and response to quinapril (Table V). Responses to doxazosin + betaxolol were not significantly related to psychometric scores.

There was also a significant relationship between the childhood trauma score on the CTQ and achievement of the target SBP by either HCTZ or quinapril (Table IV). The target SBP was achieved in 25% of subjects with reported trauma, vs. 79% of subjects without trauma (p=0.03). There was no relationship between CTQ scores and achievement of the target SBP with doxazosin + betaxolol treatment. The mean fall in blood pressure after treatment with HCTZ, quinapril, or either of these medications was also greater in subjects without trauma, but these differences did not reach statistical significance (Table VI).

Blood pressure responses were not associated with the trait anxiety score (STPI) or with the Marlowe-Crowne score (Table V).

DISCUSSION

The study results support the hypothesis that there is a relationship between psychological characteristics and responses to antihypertensive agents. The results suggest that both inhibited anger expression and childhood trauma are predictive of a reduced response to diuretics and ACE inhibitors. Responses to α/β blockade appear less affected. No relationship was found between responses to the drugs and measures of either anxiety or defensiveness.

Rationale: Why the Psychological Profile Should Affect Responses to Drug Therapy

Although the antihypertensive effects of agents such as diuretics and ACE inhibitors are roughly equivalent to each other, studies suggest that ACE inhibitors are more likely to be effective in individuals

Table III. Mean Fall in Blood Pressure in Response to Antihypertensive Treatment (n=21)

	SYSTOLIC (MEANS±SD)	DIASTOLIC (MEANS±SD)
Drug (mean daily dose) Hydrochlorothiazide		
(HCTZ) (23 mg)	11.5±10.1	7.5±6.9
Quinapril (30 mg)	12.9±13.0	8.8±8.5
Betaxolol/doxazosin (7.1/2.5 mg)	21.2±11.0‡	16.5±7.1**

‡p=0.001 vs. HCTZ and p=0.002 vs. quinapril;
**p<0.001 vs. HCTZ and quinapril

Table IV. Percentage of Subjects Achieving Target Systolic Blood Pressure: Effect of Childhood Trauma Status

	PERCENT ACHIEVING TARGET SYSTOLIC BLOOD PRESSURE (SBP)				
	N	BASELINE SBP	HCTZ	QUINAPRIL	HCTZ OR QUINAPRIL	DOXAZOSIN + BETAXOLOL
Overall	22	148.4±7.0	32% (7/22)	41% (9/22)	59% (13/22)	71% (15/21)*
Childhood trauma						
Yes	8	148.0±6.1	13% (1/8)	25% (2/8)	25% (2/8)	71% (5/7)
No	14	148.6±7.7	43% (6/14)	50% (7/14)	79% (11/14)**	71% (10/14)

HCTZ=hydrochlorothiazide; *p=0.04 vs. HCTZ and p=0.03 vs. quinapril (McNemar Test);
**p=0.03 (Fisher's exact test [two-tailed], comparing yes vs. no)

Table V. Correlation Coefficients Between Psychological Test Measures and Fall in Systolic Blood Pressure (n=22)

VARIABLE	HCTZ	QUINAPRIL	HCTZ OR QUINAPRIL	DOXAZOSIN + BETAXOLOL
STPI				
Anger	−0.10	−0.24	−0.19	−0.12
Anxiety	−0.18	−0.13	−0.21	0.06
STAXI				
Anger-out	0.55**	0.21	0.39	0.07
Anger-in	−0.32	−0.52*	−0.49*	−0.39
Anger control	−0.22	0.24	0.13	0.07
Total anger	0.14	−0.43*	−0.26	−0.30
Marlowe-Crowne Scale of Social Desirability	−0.25	0.16	0.07	−0.14

HCTZ=hydrochlorothiazide; STPI=State-Trait Personality Inventory; STAXI=State-Trait Anger Expression Inventory; *$p<0.05$; **$p<0.01$. Psychometric scales are described in the Methods section.

Table VI. Response to Antihypertensive Agents by Childhood Trauma Status (n=22)

| | CHILDHOOD TRAUMA | |
	YES N=8	NO N=14
Fall in SBP (means±SD)		
Hydrochlorothiazide	8.4±10.7	12.5±9.8
Quinapril	8.9±14.1	14.3±12.3
Better monotherapy response*	11.9±14.0	18.8±10.9
Doxazosin + betaxolol	19.0±10.5	22.3±11.4

SBP=systolic blood pressure; *for each subject, the larger response achieved by the two monotherapy arms (hydrochlorothiazide and quinapril)

with increased activation of the RAS, as reflected by plasma renin activity.[25,26] Similarly, agents such as diuretics are more likely to be effective in individuals with volume-dependent hypertension and reduced levels of plasma renin activity.[22]

These agents address hypertensive mechanisms related predominantly to the RAS or to volume. One could expect them to be most effective in individuals whose hypertension is linked pathophysiologically to these factors. The hypothesis tested in this study is that in individuals with certain psychological characteristics, in whom hypertension might be related more to increased sympathetic tone than to the RAS or volume, responses to these agents would be reduced. This possibility has not previously been explored and is difficult to test, both because the causes of increased sympathetic tone are not well understood and because of the lack of reliable, convenient, and clinically applicable means of assessing sympathetic tone in individual subjects.

The results of this study confirm this hypothesis and suggest that psychological factors, including anger-in and childhood trauma history, are associated with a reduced response to ACE inhibitors and diuretics. The findings suggest that assessment of psychological parameters might be helpful in identifying those individuals less likely to respond to these agents. We hypothesize that in such subjects, the link between psychological characteristics and the hypertensive process is mediated by increased SNS activity, which is why α/β blockade was effective. Alpha/beta blockade was also effective in subjects without these characteristics, attributable at least partly to the renal suppressing effect of β blockade.

The Roles of Different Psychological Characteristics

Anger and Anxiety. The relationship observed between anger expression and drug responses is consistent with the findings of Pasik et al.,[3] who demonstrated that indirect expression of hostility was associated with a reduced response to diuretic therapy. We did not observe a relationship between blood pressure responses and measures of anxiety, which is consistent with a previous case-control study that similarly indicated that anxiety and depression scores were unrelated to responsiveness to antihypertensive drug therapy.[27]

Childhood Trauma. The present study is the first to explore whether or not a relationship exists between childhood trauma and responses to antihypertensive agents. The CTQ was used rather than other questionnaires of stressful events, such as the Holmes-Rahe,[28] PERI,[29] and Paykel[30] scales, because of its specific focus on childhood experiences and on different forms of abuse or neglect.

Childhood abuse and trauma are highly prevalent[31,32] and can clearly have major and persisting psychological effects.[33] Their potential for physical sequelae in adulthood has only recently become recognized, as, for example, in reports linking childhood sexual abuse to irritable bowel syndrome.[34] However, their potential impact as a persisting, albeit unrecognized, stressor underlying the later development of hypertension has been the subject of little study.

Ekeberg et al.[7] reported that a history of childhood trauma was more prevalent among hypertensive than among normotensive subjects. Childhood trauma has also been reported to be a cause of unexplained paroxysmal hypertension.[35] The association of paroxysms with increased catecholamine levels, and the efficacy of treatment with antidepressants, further suggest a relationship between emotional factors and the SNS.[35]

A number of mechanisms could link childhood events to the eventual development of essential hypertension. Meaney and coworkers[36] demonstrated a relationship between perinatal events and neuroendocrine responses to stress in later life. Alexithymia, defined as the inability to recognize or verbalize feelings, is more prevalent in hypertensive than in normotensive individuals[37,38] and has been linked to childhood history, including overt trauma[39] and poor maternal bonding.[40] Traumatic stress has been associated with persisting consequences, including a sustained increase in sympathetic tone, distancing of emotions, loss of attachment, and alexithymia.[40,41] Thus, one can postulate a link connecting early trauma, alexithymia, lack of attachment, increased sympathetic tone, and essential hypertension.

Clearly, not all trauma survivors develop hypertension. Genetic and lifestyle factors are also important determinants of whether or not hypertension will develop. The study findings, however, do suggest that in those in whom hypertension does develop, normalization of blood pressure with agents directed at volume or the RAS is less likely to occur than in individuals without a history of childhood trauma.

Emotional Defensiveness. Studies fairly consistently document an association between essential hypertension and emotional defensiveness.[42–44] Some epidemiologic studies also provide evidence that essential hypertension may be linked more to reduced awareness of emotional distress than to measures of negative affect.[45–47]

In the present study, there was no relationship between Marlowe-Crowne scores and drug effects. However, the Marlowe-Crowne scale contains elements both of self-deception, an unconscious process, as well as impression management, i.e., the conscious deception of others.[48] Studies using psychometric instruments that separate these two components could be helpful in further clarifying whether or not drug responses are related to defensiveness.

Study Strengths

An important strength of the study is that the study population, entry blood pressure criteria, medications, and dosages were highly representative of clinical practice. The entry blood pressure criteria are consistent with those recently advocated for diagnosing hypertension.[49,50] The target home SBP of 130 mm Hg is consistent both with the recent emphasis on SBP as a predictor of cardiovascular events[51] and with data that the widely used office blood pressure target of 140 mm Hg corresponds most closely with a home systolic pressure of 130 mm Hg.[49]

The study population consisted of volunteers interested in learning more about drug treatment of their hypertension, rather than of volunteers primarily interested in psychological aspects of hypertension. Thus, the study population was likely no more psychologically-minded than the general hypertensive population. Intensive psychological screening of subjects was not performed, just as such screening is not routinely performed in medical practice.

Another major strength of the study is the use of home blood pressure monitoring, whose use is supported by the documented accuracy of self-monitoring devices[52–54] and by the greater correlation of home readings, as compared with clinic readings, with measures of target organ damage.[55] The multiple readings obtained over 3 days increased the likelihood of obtaining representative blood pressure levels in individual subjects. The alternative of 24-hour ambulatory blood pressure monitoring was not employed because of concern about the reluctance of subjects to wear the ambulatory monitor as many as three or four times, and the inconvenience of repeated clinic visits to do so. The low drop-out rate in this study (12%) is largely attributable to the convenience and availability of the home monitoring technology.

Limitations and Possible Biases

The study was not intended to determine maximal responses to the study drugs, and some of the nonresponders might have responded to higher doses or to a longer duration of treatment. Nevertheless, the dosages used were highly representative of usual clinical practice and were administered uniformly to all subjects. Further, the magnitude of the

blood pressure reduction was comparable to that observed in other studies.[56–59]

Knowledge of the subjects' history of responses to medications was unlikely to have biased the selection of subjects. Participants were entered strictly on the basis of meeting eligibility requirements and entry blood pressure criteria. In addition, although the small numbers prevented meaningful subgroup analysis, the observed correlations appeared independent of treatment status prior to entry.

The study was performed in open-label fashion, and the possibility of subject or investigator bias must be considered. The possibility of investigator bias was minimized by the administration and titration of medication by a coinvestigator who was blinded to the results of the psychological assessment of the subjects. The possibility of subject bias was unlikely because subjects were not aware of the study hypotheses regarding responses to treatment.

The study did not assess responses to β blocker, α blocker, or calcium channel blocker monotherapy. HCTZ and quinapril were used because their mechanism of action is directed at identifiable mechanisms of hypertension. Beta blocker monotherapy was not given because of the high degree of overlap between responses to ACE inhibitors and β blockers ($r=0.50$), attributable at least in part to suppression of the RAS by each.[21] Alpha blocker monotherapy was not given because it is not widely used as first-step therapy of hypertension. In addition, the recent findings of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[60] in which the reduction in cardiovascular events, particularly congestive heart failure, achieved by the diuretic chlorthalidone exceeded that achieved by doxazosin, have raised concerns about the use of doxazosin monotherapy as first-step treatment of hypertension. In addition, β blocker and α blocker monotherapy are largely ineffective in blocking stress-induced increases in blood pressure, as compared to combined α/β blockade; the efficacy of these two monotherapies in lowering blood pressure in neurogenic hypertension might similarly be limited, further encouraging our use of combined α + β blocker therapy.[61–66] Calcium channel blocker monotherapy was not given because responses to these agents yield less information about specific hypertensive mechanisms. Finally, a central α agonist, such as clonidine, was not used for the sympatholytic arm because of the prominent side effects associated with the use of such agents.

The length of the washout period was based on studies that indicate that 2 weeks of washout are sufficient even after treatment with high-dose diuretics.[67] Although longer washout periods are perhaps preferable, they also confer the potential confounding effect of increasing anxiety in subjects who are monitoring their home blood pressure on a daily basis and obtaining repeatedly elevated readings. Shortening the washout period in subjects in whom the hypotensive effect of the prior treatment has ended offered the advantage of minimizing subject anxiety with a low likelihood of drug carryover effect. Consistent with this, in the present study, there was no evidence of a drug carryover effect.

The potential problem of inaccurate recording by subjects of the blood pressure readings obtained has been recently reported.[68] However, inaccuracy of recording would be likely to equally affect readings on all treatment regimens without a systematic bias that would affect responses to HCTZ and quinapril but not doxazosin + betaxolol. Further, although the study medications were given in open-label fashion, a bias was also unlikely, since the subjects did not know the rationale underlying differential drug responses. In future studies, the use of blood pressure monitors equipped with a memory chip, and double-blinded administration of medication, can further exclude potential bias.

Finally, the association between psychological characteristics and the reduced response to ACE inhibitor and diuretic therapy could be postulated to be a result of disparity in compliance with medication associated with different psychological characteristics. We believe this is unlikely because in that case, responses to α/β blockade would also have been affected. It would seem unlikely that differences in compliance would have differentially affected responses to quinapril and HCTZ but not doxazosin/betaxolol. In future studies, electronic monitoring of compliance can help in addressing this concern.

CONCLUSIONS
Both inhibited anger expression and childhood trauma were associated with a reduced antihypertensive response to an ACE inhibitor and a diuretic. Responses to α/β blockade were less affected. All treatment responses were independent of anxiety and defensiveness. The magnitude of the differences observed suggests that psychological assessment may be of considerable clinical relevance in individualizing the selection of antihypertensive drug therapy in patients with mild or moderate hypertension.

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