Effect of Antihypertensive Treatment on the Behavioral Consequences of Elevated Blood Pressure

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SUMMARY It was shown in a prior study that mildly hypertensive patients performed significantly less effectively on several sensory-perceptual, cognitive, and psychomotor tests than did matched normotensive controls. To determine whether these deficits are attributable to elevated blood pressure per se, hypertensive and control subjects were recalled for reexamination 15 months after the original tests. Results indicated that those hypertensives in whom blood pressure had been lowered with antihypertensive drugs showed significant restoration of performance scores toward the levels of normotensive subjects. Hypertensives who had not received active treatment remained deficient as compared with controls. These results indicated that behavioral deficits in mild hypertension may be reversible consequences of the effects of elevated blood pressure on the central nervous system.

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KEY WORDS • mild hypertension • effect of treatment • behavioral consequences • psychological tests

E SSENTIAL hypertension has been a disease of special interest to behavioral scientists for many years. Franz Alexander,1 in his classic psychoanalytic study of hypertension, discussed the hostility/dependency conflicts that seemed to be involved in the etiology of high blood pressure. Over the past 40 years and persisting today, there have been many studies in both animals and humans directed at clarifying psychological factors that may eventuate in elevated blood pressure. Despite this research effort, the mechanisms by which personality and environmental variables are translated into chronic, fixed hypertensive disease remain unclear, as do their implications for prevention and treatment.2-5

The role of psychological factors in the etiology of hypertension, while capturing most of the research endeavor, has not been the only interest of investigators. Over the years a smattering of reports has suggested that high blood pressure may produce some impairment of psychological function.6-20 Although this research has not attracted a great deal of attention, some literature indicates impaired performance in hypertensive patients of various cognitive, perceptual, and psychomotor tasks as compared with normotensive controls. The deficits are subtle and require sensitive psychological tests for detection, yet the evidence suggests that hypertensive subjects tend to be slower and less accurate in psychomotor movements, slower and more prone to error in cognitive and memory tasks, and impaired in some sensory tests. The extent of deficit is generally unobtrusive to ordinary life activities, although it may become more significant in aging hypertensive patients19-20 and may have some bearing on personality patterns.5

Since some of these studies were conducted with highly selected subjects,7,18 often with small numbers,6,11 and with populations with high levels of psychopathology,6,7,12,16 we decided to assess a broad battery of psychological functions in a reasonably large sample of newly detected, untreated hypertensive patients and carefully matched normotensive controls.21 Generally young and otherwise healthy, these patients were representative of early mild hypertensives in the general population. The results of this earlier study demonstrated that, even in these early and mild cases, there were significant differences in performance scores on a number of the tests — all in the direction of impaired behavioral scores in the hypertensives. The data also seemed to suggest that young women were
more adversely affected by elevated blood pressure than were men, although there was no explanation for this finding. As expected, not all of the tests in the battery discriminated between the hypertensive patients and normotensive controls, but in each of the areas — sensory, cognitive, and psychomotor — the hypertensives showed some deficiency in some tasks.

One could postulate several possible links between elevated blood pressure and impairment of central nervous system (CNS) functioning. Individuals susceptible to the development of high blood pressure disease may have performance impairments that precede the onset of high blood pressure, that is, they may be part of the genetic-environmental history of hypertensive individuals. An investigation of prehypertensive subjects known to have a diathesis for the disease (i.e., children of hypertensive parents) would provide a means of determining whether the behavioral deficits precede the blood pressure disorder.

A second hypothesis is that essential hypertension is related to subtle CNS changes, which might also read out as behavioral change. In this case, the blood pressure elevation and the behavioral deficits might appear at the same time, but treatment for elevated blood pressure would not necessarily have any effect on behavioral performance.

A third hypothesis is that elevated blood pressure per se has detrimental functional effects on the CNS early in its course, just as it does on the heart and kidneys, and thus subtle effects on behavior are consequent to the hypertension. If that were the case, therapeutic interventions to reduce blood pressure might also ameliorate the behavioral impairment.

Goldman et al. studied a group of seven essentially hypertensive men before and after biofeedback training designed to reduce their blood pressure. The subjects were given the Category Test, a subtest of the Halstead-Reitan Neuropsychological Test Battery, before the biofeedback training and again 9 weeks after it. The data revealed that there were significant correlations between the amount of reduction in blood pressure and improvement in scores on the Category Test. These results suggest that blood pressure elevation does have effects on cognitive function and that a reduction in pressure may restore CNS functioning to within normal limits.

Although the Goldman et al. experiment demonstrated an important relationship between blood pressure levels and cognitive function, it did not resolve a number of important issues. The efficacy and applicability of treatment with biofeedback procedures are limited, and most patients are managed with antihypertensive medications. Indeed, there has been an increasing emphasis on early and aggressive pharmacological treatment of blood pressure elevation in an attempt to reduce the risk for heart disease and stroke.

It is also entirely possible that the type of antihypertensive agent employed plays a significant role in CNS changes. Thus, agents that act peripherally to reduce blood pressure through non-neurogenic mechanisms may have substantially different effects on behavior and performance functions than do substances that reduce pressures through autonomic or CNS action.

Our present study was designed as a follow-up to our previous study of matched groups of normotensive subjects and newly detected, untreated hypertensive patients. Subsequent to that study, the hypertensive patients had continued to be seen at the Hypertension Clinic of the University Health Center or by private physicians, but pharmacological treatment was left to their physicians' decisions and was not prescribed as part of our study protocol. We contacted as many of the subjects as possible, both controls and hypertensives, and asked them to return for a second examination on the behavioral test battery 15 months after their first test. Thus, it was possible to compare original performance scores with those obtained after 15 months of medical supervision for early and mild blood pressure elevation. These data would permit an examination of the extent of the relationship between therapeutic control of hypertensive disease and change in CNS functioning and offer insight concerning the third of the hypotheses suggested above, namely, whether blood pressure reduction is associated with an improvement in CNS function.

### Methods

#### Subjects

From the 41 matched pairs of normotensives and hypertensives (82 subjects) who had been tested in the previous study, we were able to retest 58 subjects, consisting of 12 normotensive men, 16 hypertensive men, 12 normotensive women, and 18 hypertensive women.

Since the hypertensive subjects enlisted in the initial sample were newly identified, generally young, and had only mild elevations in blood pressure, a number of them had not been placed on pharmacologic agents during the intervening 15 months. Six of the hypertensive men and seven hypertensive women were taking no active medication but had been advised to restrict salt intake and, if indicated, lose weight. Ten hypertensive men and 11 hypertensive women had been placed on antihypertensive medication regimens. All of these hypertensive patients were on diuretic therapy, and four men and two women were also taking beta-blockers. One man had been placed on a combination of a diuretic and alphamethyldopa. Since the number of subjects on Step 2 drugs was small, we decided to perform statistical analysis on those who were "treated" with any pharmacological regimen (including those with Step 2) and those who were "untreated" with any drugs.

Table 1 provides a demographic breakdown of the six groups of subjects in the follow-up investigation. These data indicate that the groups were not ideally matched on all of the variables of interest. The men were more highly educated than the women \( (p < 0.001) \) and there was a higher proportion of black women in the sample than black men \( (p < 0.01) \). There were no significant differences in ages.
While it would have been desirable to have obtained more homogeneity in education and race among the groups, the analyses of interest in this investigation are concerned with changes in behavioral performance over the two sessions separated by 15 months of treatment. Thus, the important comparisons could be made in Within Subjects’ Scores with each subject serving as his or her own control. There is no inherent reason to suspect that education or race introduced a bias in these change scores, especially since an analysis of variance (ANOVA) revealed that there was neither a race nor education effect on the type of treatment administered to the hypertensive subjects.

**Procedure**

The subject was first interviewed for a medical history over the past 15 months, including a careful drug history with particular emphasis on antihypertensive treatment, and then underwent a physical examination including standing and recumbent blood pressure determinations. The purpose of the experiment was explained to the subject, and informed consent was obtained before the behavioral examination was begun.

In the behavioral testing laboratory, the identical battery of tests that had been administered in the initial testing was repeated, making use of alternate forms of certain tasks that might be expected to show practice effects from that earlier experience (Benton Memory for Design, Visual Recognition, Perception of Spaced Stimuli).

The original test battery was retained in its entirety except for the Movement Reversal Test (a measurement that had been newly developed and was of questionable reliability in the first experiment), even though several of the tests had not discriminated between normotensive and hypertensive subjects. The rationale for including all of the tests was that the effects of antihypertensive medication could be reflected in tasks that had shown no differences initially. The test battery is described in the previous paper and was designed to assess three functional areas: sensory-perceptual, cognitive, and psychomotor.

**Results**

**Blood Pressure Changes**

Table 2 presents the data on systolic and diastolic blood pressure. Normotensive men and women experienced no change in blood pressure during the 15-month interval between tests, nor did the pharmacologically untreated hypertensive subjects. The treated hypertensives, on the other hand, did show statistically significant reductions in pressures: systolic and diastolic in the men and systolic only in the women.

**Behavioral Tests**

The primary analysis of the repeat test data was accomplished with repeated measures ANOVAs so that change over time as a function of antihypertensive medication could be examined.
treatment could be evaluated. On those variables where significant differences had occurred at Session 1, a covariate analysis was used to compensate for the initial differences. In addition, univariate ANOVAs at Session 2 were performed so that comparisons could be drawn with the results reported in the earlier study.

Sensory-Perceptual Tests

The amount of change in performance scores on sensory-perceptual tasks for controls, untreated hypertensives, and treated hypertensives is shown in Figure 1. At Session 1, hypertensive subjects had been significantly impaired on Visual Recognition Time ($p < 0.05$) and had also evidenced some, but not statistically significant, deficit in each of the other tasks in this category. Analyses of Session 2 scores revealed that the difference between controls and hypertensives in Visual Recognition Time was no longer significant 15 months later and that all groups of subjects were somewhat improved in this task (Figure 1). Although the treated hypertensive subjects displayed improved performance on all of the sensory-perceptual tests, the only statistically significant differential effect was on Two-Flash Threshold ($p < 0.05$). The apparent marked improvement in Perception of Spaced Stimuli in treated as compared to untreated patients failed to reach a level of statistical significance.

In addition, there were marked gender differences with Critical Flicker Fusion ($p < 0.05$) and Two-Flash Threshold ($p < 0.01$), with the scores of men higher than those of women. These same sex differences had been found in Session 1 testing as well.

Cognitive Tests

At the initial evaluation, hypertensive subjects had been found to perform less effectively on the Digit Symbol Test ($p < 0.01$), and they were also deficient in comparison with controls on the other cognitive tasks as well, although these differences did not reach significant levels. At Session 2, the hypertensive subjects still failed to achieve scores as high as the normotensives ($p < 0.01$) but, as Figure 2 reveals, there was a differential rate of improvement in performance on this test over the 15-month interval. Treated hypertensives improved at a much higher rate than did either the untreated or the control groups ($p < 0.007$). Thus, treated subjects were moving in the direction of restoration of normal performance while untreated subjects showed less improvement than did the normotensive controls during the 15 months between tests.

On the initial testing, hypertensive women had been found to be markedly deficient in the Operative Estimation of Time, differing from each of the three groups (normotensive men and women, hypertensive men) at the $p < 0.01$ level. Examination of the change over the 15-month interval produced some unexpected findings. All of the subjects except the treated hypertensive women produced poorer performances on this task on Session 2 than on Session 1. The ANOVA of these data revealed a Sex X Interval X Treatment effect ($p < 0.001$), confirming that the change in performance by the treated women over the 15-month interval was opposite in direction to that found in the other groups. In addition, within-group comparisons revealed that untreated hypertensive women were still significantly less accurate in time estimation than were the untreated men ($p < .01$), but women did not differ from men in either the normotensive or treated hypertensive groups.
Psychomotor Function Tests

Tapping Speed was one of the tests in the battery that had discriminated between hypertensives and normotensives at the time of the original testing \((p < 0.01)\). Hypertensives were still significantly slower than normotensives in Tapping Speed at Session 2 \((p < 0.05)\), but the repeated measures ANOVA revealed that there had been significant improvement in the performance of treated hypertensive subjects as compared with controls \((p < 0.05)\). The rate of improvement in the untreated hypertensives did not differ from that of control subjects (Figure 3).

Transfer Coordination Speed, which had also shown a significant deficit in hypertensive subjects in Session 1 \((p < 0.05)\), showed only a trend in that direction at Session 2 \((p < 0.10)\). Figure 3 shows that both the normotensive and treated hypertensive subjects improved their scores slightly on this test, but untreated hypertensives were further impaired on the second testing.

 Traverse Time scores, also significantly impaired in hypertensive subjects in Session 1 \((p < 0.05)\), showed only a trend in that direction at Session 2 \((p < 0.10)\). It can be seen in Figure 3 that treated hypertensive and normotensive subjects both improved on this test while the untreated hypertensives were slightly more impaired.

The Reaction Time tests (Right Lift and Right Jump), which on initial testing had failed to discriminate hypertensives from normotensives, were still not significantly different in any of the Session 2 comparisons. The sex differences, which indicated that men were consistently faster than women in Reaction Time, persisted at Session 2 \((p < 0.01)\).

There was a rather complex shift in Hand Grip Strength over the 15-month interval between tests. Repeated measures ANOVA showed, as expected, a strong effect of Sex \((p < 0.001)\), with men stronger than women in both dominant and nondominant grip strength. Similarly, the main effect of Hand was significant \((p < 0.001)\), with the dominant hand stronger than the nondominant hand. The interaction between Hand and Sex \((p < 0.05)\) indicated that the discrepancy between strength in the dominant vs the nondominant hand was greater in men than women. The interesting finding was a significant interaction between Group X Hand X Session \((p < 0.02)\). Figure 4 reveals that, in contrast to the control and treated hypertensive groups, the untreated hypertensive men and women were both weaker in the nondominant hand on the second test. These data suggest that a more marked laterality developed in the un medicated hypertensive subjects over time than occurred in controls or treated groups.

To estimate the overall changes on the battery of tests, each subject’s change in score from Session 1 to Session 2 was converted to a Z-score for each of the 15 tests in the battery. Then, the average Z-score for each subject was obtained and an ANOVA performed. This analysis revealed a significant \((p < 0.01)\) effect of treatment on the amount of performance change from Session 1 to Session 2. A Tukey test indicated that treated hypertensives showed overall improvement on the battery (mean Z = 0.1594) while the untreated group had a mean decrement in performance (mean Z = -0.3250), a difference that was significant at \(p < 0.05\). The normotensive controls were virtually unchanged overall (mean Z = -0.0261) and did not differ significantly from either of the hypertensive groups. Thus, although some of the analyses of individual tests had not proved to be statistically signifi-
important, a broad view over the entire battery suggests that treated hypertensives showed the greater improvement in performance scores, and untreated hypertensives were the least improved. We are aware that combining the results of a series of "slices" of behaviors in this fashion provides only an estimate of the comparative improvement of the groups. This method did not, for example, account for the initial levels of performance in Session 1 where it was shown that hypertensives differed from the controls on a number of the tests. Hence, it was possible for the treated patients to make quantitatively more improvement than normotensive controls, who were already performing at near optimal levels. Nevertheless, the technique does provide a further indication that treated hypertensives improved overall while untreated hypertensives did not.

**Discussion**

In analyzing the results, a note of caution must be introduced since these subjects were given the same battery of psychological tests that they had previously taken. Although alternate forms, where available, were used in Session 2, and 15 months had passed, some improvement in absolute scores might have been a function of prior practice, familiarity with the instructions and procedures, and acquaintance with the behavioral scientists administering the tests. In fact, examination of the performances of the normotensive control subjects revealed that there were modest gains (5%-7%) in many of the tests on the second administration. The only test in which the normals showed a large change was Time Estimation (Figure 2), where their performance was substantially less accurate than it had been on the first testing occasion. We have no logical explanation for the marked deterioration of performance by the control group on this task.

Nevertheless, the results do indicate that the group of treated hypertensive subjects, whose blood pressure was significantly reduced by medication, showed a pattern of improvement in test performance. Although only several changes were significant, the rate of improvement of treated subjects exceeded that of untreated subjects on 12 of the 15 tests (Figures 1-4), and they improved more than did normal controls on 10 of the 15 tests. The Benton Memory for Design test, a test that did not distinguish between hypertensives and normotensives originally, was the only test that showed substantially poorer performance on Session 2 for treated and untreated hypertensive patients.

The untreated hypertensive subjects, on the other hand, performed less well on seven of the 15 tests on the second administration. Again, although not all of these differences were statistically significant, the general pattern for untreated subjects suggests that they did not make the gains seen either in the normotensive controls, perhaps from practice effects, or the improvement found in treated subjects. Further, the Z-score analysis demonstrated a highly significant improvement in the overall battery of tests in the treated hypertensives.

Although it would have been desirable to have retested all 82 subjects instead of only 58, the results of this experiment are of both practical and theoretical interest. They indicate that treated hypertensive subjects showed a restoration of behavioral function approaching that of normotensive controls, while untreated subjects' scores at best improved only modestly on some tasks and deteriorated further on others. As mentioned earlier, the only published report that has examined performance change in subjects undergoing treatment for hypertension is that of Goldman et al., who looked only at a cognitive task and did not study control groups to assess the effects of practice and familiarity.

Similar kinds of studies have not been reported on patients with more severe and long-lasting hypertensive disease. Nor does the evidence from cross-sectional studies resolve the issue. For example, Speith found that hypertensive subjects taking antihypertensive medication did not differ from normotensive controls on a series of behavioral tests, while unmedicated hypertensives were significantly impaired. Light, on the other hand, reported that the medicated hypertensive group showed deficits relative to controls, while untreated subjects did not differ from normotensives. Examination of these two experiments reveals that substantial procedural and sample considerations preclude a meaningful comparison of results. Speith's subjects were aviation personnel undergoing licensure reexamination and were, he assumed, under some emotional stress at the time of testing. Further, the performance of all of his subjects, both diseased and healthy, was higher than would be expected in a sample of the general population because they were a select, highly trained, skilled group. The conditions in Light's study were quite different. Treated hypertensives were required to stop taking their medication 3 to 21 days prior to behavioral testing, and further, on the test day, all of the hypertensive subjects were given a potent diuretic that lowered their blood pressure acutely during the test period to within normotensive limits.

From a theoretical point of view, our results suggest that the degradation of performance that has been reported in hypertensive subjects is likely a consequence, not a cause, of the elevated blood pressure, since the behavioral dysfunctions tended to return to normal as pressure was reduced. Whether the impairment of behavior is a consequence of altered cerebral metabolic processes secondary to the level of blood pressure or a consequence of one of the mechanisms responsible for the elevation, such as renin or catecholamine levels, can only be a matter for speculation at this point. Moreover, further studies are obviously necessary to replicate these results, to compare them with observations on the CNS effects of drugs, and to extend them to test results from hypertensive patients having more severe and long-standing disease.

Clearly, these results do not speak to the etiology of hypertensive disease, whether biological or psychosomatic. The theories that suggest that personality constellation (hostility), in conjunction with genetic, envi-
vironmental, and social factors in varying combinations, plays an important role in the development of high blood pressure. are not assaulted by our findings. Nor do our data conflict with the work of Esler et al., who suggested that a segment of the hypertensive pop-
ulation, which demonstrates high adrenergic tone and high renin levels, has significant emotional and neuro-
genic components in their disorder. These individuals
displayed certain behaviors that included problems with handling aggression. This has been further dem-
strated recently by Perini et al., who described a
"conflict prone personality with suppressed aggres-
sion" in high-renin hypertensives. In fact, our data
may suggest that hypertensive individuals convey an
impression of passivity and a hesitancy to engage in
conflict because they indeed may not be as keen in
responding to environmental stimuli or as efficient in
cognitive processing. Continued studies of behavioral
effects during prehypertensive states and after long-
term blood pressure reduction, now possible, may
serve to delineate these variables into etiologic and/or
consequential factors.

Finally, the extent and nature of performance defi-
cits in our mildly hypertensive populations were not
detectable by the casual observer, nor are they likely to
intrude significantly on everyday activities, other than
in interpersonal relationships in the manner described
above. Suboptimal performance on standardized be-
avioral tests can also be found in a variety of other
conditions, for example, sleep deprivation, alcohol in-
take, and so forth. Nevertheless, any chronic impair-
ment of intellectual, perceptual, or psychomotor func-
tion, particularly over extended periods of time, is
undesirable. Therefore, the demonstration of restored
behavioral performance with blood pressure reduction
may provide another argument for early antihyperten-
sive treatment.

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