Pressor Responses to Noxious Stimuli in Hypertensive Patients
Effects of Reserpine and Chlorothiazide

By Alvin P. Shapiro, M.D.

Clinical studies of hypotensive drugs have been concerned primarily with the effects of these agents on basal or casual levels of blood pressure. Little attention has been given to alterations in the reactivity of the blood pressure to noxious stimuli during the course of chronic drug therapy. Persistent reactivity in treated patients is implied from such data as those indicating that blood pressures in treated patients frequently are lower when measured at home than during clinic or office visits. Moreover, in view of the hypersensitivity of denervated organs, drugs that inhibit the autonomic nervous system might even exaggerate the pressor response to any stimulus that may act through a humoral, rather than a neurogenic mechanism.

Data pertinent to this problem were obtained during the course of a previous study in which the pressor responses of hypertensive patients to a number of different noxious stimuli were evaluated. Subjects had been included in this study who were receiving several different types of drug therapy. Although increased reactivity to both psychological and physical stimuli was demonstrated in the hypertensive group as a whole, patients receiving drugs at the time of testing showed responses quantitatively similar to those of untreated subjects. Accordingly, the present study was designed specifically to compare the pressor response in the same patient before and during therapy, in order to obtain systematic information about the effects of certain hypotensive drugs on reactivity.

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Materials and Methods

Thirty hypertensive patients with mild to moderate hypertensive vascular disease were divided into three groups of 10 each, and their pressor responses to noxious stimuli were tested before and during therapy. One group received reserpine; a second, chlorothiazide or one of its congeners; a third, a combination of both these drugs. The severity of the hypertension in each group is indicated in Table 1, and the average dose and duration of therapy are shown in Table 2. All patients were ambulatory and were seen regularly in the Hypertension-Renal Clinic throughout the study.

The techniques employed to test pressor responses have been described fully in the previous publication. Briefly, after a 30-minute rest period three noxious stimuli were administered at 15- to 30-minute intervals: (1) the intravenous injection of 10 ml. of normal saline during which the subject was asked to "count backwards from 100 as rapidly as possible"; (2) a standard cold pressor test; (3) the reading of a chart on which the names of colors were printed in colors different from the actual names, the subject being told to "read the color the words are printed in and not the words themselves, as fast as you can." In the previous study, the mean elevations of blood pressure and their standard deviations following these three stimuli in a group of 60 hypertensive subjects were 27/13 ± 13/6, 36/27 ± 21/11, and 21/6 ± 17/8 mm. Hg, respectively; increases in pulse rate during these three tests were 12, 12, and 11 per minute, respectively.

All blood pressures were determined on the Gilford automatic recorder with simultaneous registration of the pulse rates by means of a Gilford cardiocochronometer. To maintain a reasonably constant relationship between the time of drug administration and the tests of reactivity, the latter were performed during the hours from 10 a.m. to 3 p.m. In order to estimate any differences in mood and attitude of the patients between the two periods of testing, the Clyde Mood Scale was administered in most subjects at the conclusion of each session. The Mood Scale is a self-admin-

*Gilford Instrument Laboratories, Inc., Oberlin, Ohio.
istered psychological test devised by Dr. Dean Clyde of the Psychopharmacology Center, National Institutes of Health. Its use in our investigations has been described; as before, the patient was asked to sort two sets of cards, one to describe his own feelings and one to describe his estimate of the investigator's feelings. The calculated scores deviate from a norm of 50 and estimate the mood of the subject in six categories, i.e., friendly, energetic, clearthinking, aggressive, jittery, depressed.

**Results**

The "resting" blood pressures and pulse rates immediately before exposure to each of the noxious stimuli are indicated for the three groups of patients before and during therapy in table 2. The method of paired differences was used to test the significance of the changes. It is apparent that the resting blood pressures declined significantly in most instances during treatment. Although resting pulse rates appeared to be lowered by reserpine alone and by reserpine plus chlorothiazide, and to be slightly elevated by chlorothiazide alone, these changes—with one exception—were not significant statistically.

The pressor responses to each stimulus before and during therapy are depicted in figure 1 (reserpine group), figure 2 (chlorothiazide group), and figure 3 (chlorothiazide plus reserpine group). The declines in resting blood pressures also are illustrated in these figures. In all three treatment groups,

**Table 1**

Clinical Data before Therapy in Hypertensive Subjects in Study

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number of patients</th>
<th>Male</th>
<th>Female</th>
<th>Average age</th>
<th>Grading of fundi I</th>
<th>II</th>
<th>III</th>
<th>Number with cardiac hypertrophy</th>
<th>Average blood urea nitrogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reserpine</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>49</td>
<td>3</td>
<td>7</td>
<td>0</td>
<td>8</td>
<td>14.2</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>44</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>13.1</td>
</tr>
<tr>
<td>Reserpine plus chlorothiazide</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>51</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>9</td>
<td>16.3</td>
</tr>
</tbody>
</table>

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Table 2

Basal Blood Pressure (BP) and Pulse Rates (PR) Prior to Test Stimuli before and during Therapy

<table>
<thead>
<tr>
<th>Groups</th>
<th>Reserpine</th>
<th>Chlorothiazide</th>
<th>Reserpine and chlorothiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average dose (mg./day)</td>
<td>0.45</td>
<td>950</td>
<td>0.38 + 700</td>
</tr>
<tr>
<td>Average duration of therapy (wk.)</td>
<td>13</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Basal BP before each test (mm. Hg)</td>
<td>Basal PR before each test (mm. Hg)</td>
<td>Basal BP before each test (mm. Hg)</td>
<td></td>
</tr>
<tr>
<td>Before Rx</td>
<td>During Rx</td>
<td>Δ</td>
<td>P</td>
</tr>
<tr>
<td>Test 1 (saline)</td>
<td>177</td>
<td>161</td>
<td>-16.3</td>
</tr>
<tr>
<td>(cold pressor)</td>
<td>106</td>
<td>94</td>
<td>-12.7</td>
</tr>
<tr>
<td>Test 3 (color)</td>
<td>183</td>
<td>173</td>
<td>-10.0</td>
</tr>
<tr>
<td></td>
<td>110</td>
<td>105</td>
<td>-5.7</td>
</tr>
<tr>
<td>Basal PR before each test (per min.)</td>
<td>Basal PR before each test (per min.)</td>
<td>Basal PR before each test (per min.)</td>
<td></td>
</tr>
<tr>
<td>Test 1</td>
<td>72</td>
<td>66</td>
<td>- 6.4</td>
</tr>
<tr>
<td>Test 2</td>
<td>72</td>
<td>65</td>
<td>- 7.4</td>
</tr>
<tr>
<td>Test 3</td>
<td>70</td>
<td>65</td>
<td>- 5.2</td>
</tr>
</tbody>
</table>

*Significant values.
the medications had minimal effects on the actual magnitude of the pressor response to each stimulus. With the method of paired differences, in only one test—the pressor response of the reserpine plus chlorothiazide group during test 1 (saline)—was there a change of probable statistical significance, and this consisted actually of an increased response during therapy. The "ceilings" following the responses were of course lower with therapy, since the resting pressures had been decreased.

The ranges in the magnitude of the pressor responses for the six tests done with each stimulus were 24 to 38/11 to 14 mm. Hg for test 1; 27 to 45/20 to 26 mm. Hg for test 2; and 17 to 29/8 to 12 mm. Hg for test 3; all were within the range for each of these responses as determined in our previous study.\(^3\)

The pulse rate responses also are demonstrated in figures 1 to 3. The elevations similarly were within the ranges noted previously, and like the pressor responses, were not significantly affected by therapy.

The mean scores describing the patient’s "mood" and his estimate of the investigator's "mood," the latter a rating that gives some indication of the doctor-patient relationship in the test situation, were slightly different before and during therapy in certain categories (table 3). These differences, however, were only rarely of statistical significance and occurred in both positive and negative directions with different therapies; e.g., the self-rating "friendly" score was lower during therapy in patients treated with chlorothiazide and reserpine, higher in those treated with reserpine alone, and essentially unchanged in those receiving chlorothiazide alone. Accordingly, it seemed unlikely that patients’ attitudes about themselves and the investigator, insofar as these can be determined by the Clyde Mood Scale, differed significantly on the two test days.

**Discussion**

Therapeutic doses of chlorothiazide and reserpine, alone or in combination, failed to diminish the response of the blood pressure and pulse rate to both psychological and physical noxious stimuli, in spite of the abil-
Effect of reserpine plus chlorothiazide.

The effect of these drugs to lower resting blood pressure significantly. The magnitude of the pressor responses was similar to that noted previously in a large group of hypertensive subjects, in whom hyperreactivity, which was influenced by the type of noxious stimuli and the sex and age of the patient but not by the level of the resting blood pressure, was demonstrated.  This hyperreactivity also is present in normotensive subjects with a family history of hypertension.  Taken together, these findings support the hypothesis that the reactivity of the blood pressure in the hypertensive subject is a constitutional characteristic, which is present even prior to the development of the clinical disease, and may be unaffected by treatment, at least with these mildly hypotensive drugs.

It appears unlikely that the failure of these drugs to affect reactivity was due to the absence of significant pharmacologic effects at the time of testing. Certainly placebo effects can be potent hypotensive factors.  The doses used here, however, were those generally considered in the therapeutic range, while the declines in resting pressures were equivalent to those we have observed in previous clinical assays in which the nonpharmacologic variables were controlled carefully and the actual pharmacologic effects of the drugs were isolated.  For instance, the declines in the resting blood pressures before each of the three tests in the group receiving reserpine averaged 12/10 mm. Hg; for the group receiving chlorothiazide and congeners, the average was 17/9 mm. Hg. In the aforementioned drug assays, the declines with reserpine and chlorothiazide averaged 10/10 mm. Hg and 22/10 mm. Hg, respectively. Accordingly, it would seem pertinent to discuss other explanations for the failure to diminish the pressor response.

It was surprising that chlorothiazide and its congeners had no effect. Although this drug does not affect the neurogenic mechanisms responsible for pressor responses, considerable evidence suggests that responses to humoral vasopressor agents are diminished. A number of investigators have shown decreased responses to infused norepinephrine, epineph-
Thiazides do not appear to alter plasma volume and may decrease reactivity when given therapeutically, alone or in combination with reserpine. Recently, Abramson et al. have shown similarly that patients treated with thiazides do not develop decreased reactivity of the vessels of the forearm following vasoconstrictor stimuli. It may be pertinent, that although Eckstein and co-workers have reported a reduction in the response of peripheral resistance to norepinephrine after chlorothiazide, they noted that the response of the cardiac output was enhanced and the elevation of arterial pressure was the same before and after therapy.

The failure of reserpine to affect reactivity is equally puzzling inasmuch as this drug appears to deplete the sympathetic nerve endings of norepinephrine. Since norepinephrine is responsible for transmission of neurogenic vasoconstrictor impulses, its depletion should result in impairment of pressor responses to noxious stimuli. In fact, it has been suggested that patients receiving reserpine may suffer vascular collapse during surgical anesthesia. In the usual therapeutic dose in the hypertensive patient, however, ability to maintain some neurogenic vasoconstriction is indicated by the observation that reserpine usually does not produce postural hypotension. Moreover, it has been shown recently by Markason and co-workers that reserpine in therapeutic doses neither increases catecholamine excretion nor diminishes the pressor response to norepinephrine infusion. Similarly, Chidsley et al. have demonstrated that administration of syrosingopine, a congener of reserpine, produces no change in the response of cardiac output and arterial pressure to hypoxemia or

Table 3

Effect of Therapy on Clyde Mood Scale Scores

<table>
<thead>
<tr>
<th>Category</th>
<th>Reserpine Before Rx During Rx</th>
<th>Chlorothiazide Before Rx During Rx Self-rating score</th>
<th>Reserpine and chlorothiazide Before Rx During Rx n = 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friendly</td>
<td>54.3 57.5</td>
<td>50.8 50.7</td>
<td>49.4 45.9</td>
</tr>
<tr>
<td>Energetic</td>
<td>48.8 54.2</td>
<td>45.7 46.6</td>
<td>52.0 50.5</td>
</tr>
<tr>
<td>Clearthinking</td>
<td>52.0 53.3</td>
<td>50.4 50.7</td>
<td>50.5 42.9*</td>
</tr>
<tr>
<td>Aggressive</td>
<td>41.0 41.0</td>
<td>48.4 48.3</td>
<td>47.8 48.9</td>
</tr>
<tr>
<td>Jittery</td>
<td>44.7 41.8</td>
<td>50.9 51.2</td>
<td>52.9 55.6</td>
</tr>
<tr>
<td>Depressed</td>
<td>44.3 42.7</td>
<td>52.0 51.1</td>
<td>51.6 53.4</td>
</tr>
</tbody>
</table>

*Significant difference; \( P = .05 \).
†Significant difference; \( P = .01 \).

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exercise. Finally, in pharmacologic studies reserpine actually may potentiate responses to humoral agents, providing an example of the hypersensitivity of denervated structures.\textsuperscript{21}

Aside from possible differences in pharmacologic and therapeutic doses, variation in the mechanism—e.g., neurogenic and humoral—that can produce pressor responses, may be responsible for these confusing aspects of reactivity. When one pathway is altered by disease or by drug, another may compensate. For instance, it is generally considered that the cold pressor response is mediated through neurogenic pathways, since it can be diminished by blockade of the sympathetic ganglia,\textsuperscript{22} and may be minimal in individuals with idiopathic orthostatic hypotension.\textsuperscript{23} In both these instances increased reactivity to humoral vasoconstrictors may be seen.\textsuperscript{24, 25}

Recently, increased reactivity to infused norepinephrine has been reported as evidence of sympathetic nervous system neuropathy in patients with diabetes mellitus.\textsuperscript{26} In individuals with pheochromocytoma, in whom a humoral agent elevates blood pressure, cold pressor responsiveness often is reduced,\textsuperscript{27} while patients with unilateral renal disease, toxemia, and acute glomerulonephritis may show no decline in pressure following ganglionic blockade.\textsuperscript{28}

A variety of humoral pressor agents is available for such hemostatic alterations. In addition to norepinephrine, which can be both a circulating humoral agent as well as a peripheral neurogenic transmitter, polypeptides whose prototypes are angiotensin and vasopressin may play an important role as both primary and compensatory vasopressor agents. Some evidence for homeostatic mechanisms in mediating pressor responses was provided by Ferris and co-workers,\textsuperscript{29} who demonstrated the varying responses in individual patients to the intravenous injection of tetraethylammonium chloride, a ganglion-blocking agent. Presumably this variation resulted from changing mechanisms, at times neurogenic and at times humoral, for maintenance of blood pressure elevation. Similarly, in acute studies, Doyle and Black\textsuperscript{30} have demonstrated increased reactivity to pressor agents after ganglionic blockade and have suggested that neurogenic regulatory mechanisms ordinarily may limit pressor responses. With the presently available sympatholytic and ganglion-blocking drugs which can be administered chronically, study of the changes in reactivity to standardized noxious stimuli should help to elucidate further the perplexing interrelationships of the humoral and neurogenic components of the pressor response.

Previously, we have demonstrated a suggestive positive correlation between the degree of anxiety on the day of testing (height of the "jittery" and "depressed" scores in the Clyde Mood Scale) and the intensity of the pressor response to certain noxious stimuli.\textsuperscript{3} Accordingly, it is pertinent that significant differences in mood were absent both in the scores for the patients and for the patients' estimate of the investigator, during the two different testing occasions in the present experiment. Insofar as the Clyde Mood Scale is an adequate measurement, the emotional setting of the testing procedures remained fairly uniform.

Several therapeutic implications stem from these data. It seems clear that lability of the blood pressure may persist unabated even with treatment. A rise in pressure in the patient receiving treatment with reserpine and chlorothiazide thus may represent his response to noxious stimuli, and need not indicate omission of the medication or loss of its therapeutic effect. Precipitously abandoning a previously satisfactory therapeutic regimen for a more potent drug can often be avoided by recognizing the existence of this lability and seeking its causes. Finally, it should be emphasized that although reactivity remained unchanged, the "ceiling" to which the blood pressure rose after the pressor response was lowered. Whether a chronic diminution in the "ceiling" is of value in preventing complications and prolonging survival in mild to moderate hypertensive patients, is of course another problem, the answer to which still remains obscure.
Summary

The pressor and pulse rate responses to three standardized noxious stimuli were determined in groups of hypertensive patients receiving reserpine and chlorothiazide, alone and in combination. Although the drugs caused a significant decline in resting blood pressure, they failed to diminish the actual magnitude of the elevations in pressure and heart rate resulting from either physical or psychological stimuli. The possible physiological interpretations and the therapeutic implications of these data have been pointed out.

References


23. SHAPIRO, A. P.: Unpublished data.
Galvani and the Electrophysiology of Muscular Contraction

Galvani's merits as a physicist and physiologist obscured his contributions to anatomy, yet his morphological investigations by themselves would have been sufficient to secure his reputation. His first publication dated 1762, discussed the anatomy and pathology of bones. These Theses, according to the custom of the times, were publicly discussed by Galvani at the Archiginnasio (to enable him to lecture at the University). His first dissertation inserted in the Commentaries of the Academy is dated 1767 and was concerned with bird kidneys. In order to investigate the disposition and thin structure of renal tubules, Galvani caused a natural injection of the tubules by ligating the ureters and in that way anticipated by almost a century, the approach of Hoppe-Seyler and Zaleski. In that paper, for the first time, the three layers of the ureteral walls as well as the peristaltic and antiperistaltic motions of the ureters were described.

In his second dissertation, read before the Academy on February 19, 1767, Galvani reported the results of his experiments on the nasal mucosa in men and several animals, and described in detail the mucous glands and the tubercles situated in the inferior portion of the septum and the anterior portion of the inferior turbinates. He also read several Latin essays before the Academy on the structure and functions of the ear in birds shortly before Scarpa published his famous paper on the round window and secondary tympanum.

Several historians and anatomists have commented on the great value of Galvani's investigations on the ear. He discussed the variation in diameter of the auditory canal, its straight direction, slight depth and different configurations in various kinds of birds.

He was the first to write of the bony cavity leading to the oval or round window, which he called the antievestibulo. He investigated the function of the two muscles which end and are inserted into the auditory osseous. He also followed the entire course of the chorda tympani by means of a lens.—Giulio Pupilli. Commentary on the Effect of Electricity on Muscular Motion. by Luigi Galvani. Translated by Robert Montraville Green, M.D., Cambridge, Massachusetts, Elizabeth Licht, Publisher, 1953, p. xv.
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