Alterations in the Responses of the Sympathetic Nervous System and Renin in Borderline Hypertension

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SUMMARY We investigated the effect of stimuli that activate the sympathetic nervous system on plasma catecholamines, renin activity, urinary metanephrine and normetanephrine, and various hemodynamic parameters in normal subjects (NIs) and borderline hypertensive (BH) subjects. No differences were observed in sympathetic nervous system activity or renin activity when the subjects were in the resting state on a 150 mEq sodium diet. However, the BH group exhibited greater responses in terms of plasma catecholamines and plasma renin activity in response to sodium deprivation and treadmill exercise. Although hemodynamic differences in the cold pressor test and handgrip exercise did not emerge, the ratio of atrial size decrement to venous tone increment during the Valsalva maneuver was significantly reduced in the BH group. The investigations suggest that in the basal state, BH subjects have appropriate levels of activation of the sympathetic and renin systems for a normal level of pressure but that perturbations of pressure and volume factors lead to unmasking of abnormalities in regulation of both systems. The data are also consistent with the suggestion that venous compliance is reduced in these patients. (Hypertension 1: 118-124, 1979)

KEY WORDS • borderline hypertension • plasma renin activity • norepinephrine • epinephrine • sodium balance • Valsalva maneuver • sympathetic nervous system

The hypothesis that essential hypertension results from disordered function of the sympathetic nervous system has been attractive. However, in spite of the efforts of many investigators to obtain evidence in support of such a relationship, controversy still abounds. The introduction of improved assay methodology for catecholamines has resulted in much new data but a number of problems in interpretation have arisen. Plasma norepinephrine (NE) has been shown to increase with age, with caffeine, with smoking, with sodium restriction, and with activity, and studies which do not control for these variables must be interpreted with caution. Mild essential hypertension associated with high plasma renin activity has been proposed as a neurogenic disease. In comparison with normal subjects, these patients had a raised plasma norepinephrine but no differences in plasma epinephrine were noted. Other workers have also reported increased plasma norepinephrine in certain subgroups of essential hypertension, but there have also been well-controlled negative studies.

Rather than a continuing overactivity of the sympathetic and renin systems, it is possible that the borderline hypertensive individual differs by responding with an excessive sympathetic and renin activation to stimuli that tend to reduce arterial pressure. To test this possibility, we evaluated the responsiveness of the sympathetic nervous system and renin to sodium deprivation, a maneuver known to reduce blood volume. After a modest reduction in blood volume, such as that evoked by sodium deprivation, it is known that increased sympathetic activity and renin release occur as feedback control mechanisms to maintain arterial pressure. The effect of sodium deprivation was evaluated in both the supine and upright postures. In addition, the more complex stimulus
of treadmill exercise, which includes sympathetic activation, was employed.

In the sodium deprivation studies, evidence was sought that any change in plasma norepinephrine or epinephrine was reflected in increased release of amine rather than reduced clearance. This was achieved by concomitant measurement of the urinary excretion of their metabolites, normetanephrine and metanephrine, with a newly developed stable isotope ratio method employing mass spectrometry.

In addition to assessment of the adrenergic and renin responses to these stimuli, we also characterized study subjects in terms of plasma volume, venous reflex response, and echocardiographic left atrial size change during the Valsalva maneuver.

It seemed preferable to test the adrenergic and renin responses to these stimuli in individuals who had not developed advanced vascular and cardiac consequences of increased arterial pressure. Accordingly, our studies were conducted in “borderline” hypertensive subjects, individuals who had normal blood pressures interspersed between hypertensive levels in the outpatient setting. As this is a younger subset of the hypertensive population, they were compared with a group of similar average age.

Methods

Nineteen volunteers were studied. They ranged in age from 16 to 39 years. Eighteen were male and one was female; none varied from ideal weight by more than 10%. Seventeen were white and two were black. None had evidence by history, physical examination, or laboratory screening of any intercurrent illness. Nine subjects had borderline hypertension (BH), defined as blood pressure readings (by cuff method) greater than 150/95 on two occasions that were not associated with evidence of any unusual stress, separated by an intervening normal (<140/90) reading. While there was no selection of patients by renin status, our BH group included no subjects with low or suppressed plasma renin activities, although such subjects are relatively frequently encountered in clinical practice. None of these patients had had antihypertensive therapy. Ten volunteers had normal blood pressure (N1). Mean age for the BH subjects was 25 ± 7 years while the N1 subjects averaged 27 ± 3 years of age. All volunteers had normal urinalyses, creatinine clearances, and electrolytes and eight of the volunteers with BH had had normal intravenous pyelograms. In one patient with BH an intravenous pyelogram was not performed. None of the normal subjects had a history of hypertension in siblings or parents, but four of the BH individuals had positive family histories. Average supine blood pressure was 111/73 in the N1 subjects and 131/86 in the BH subjects during balance on the 150 mEq sodium diet. All of the volunteers abstained from all medications, including aspirin, in the 3 weeks before the study. They also abstained from methylxanthine and alcohol-containing beverages and from smoking for the 24 hours before the study and throughout the course of the study.

All participants in the study were admitted to the Elliot V. Newman Clinical Research Center of Vanderbilt University Hospital before the study. A diet containing 150 mEq sodium and 60 mEq potassium was provided. It usually took 3 to 5 days to bring the subjects into sodium balance on this diet: daily urinary sodium, potassium and creatinine were monitored. Each subject had echocardiography as well as blood and plasma volume determinations by a dual tracer method. Venous reflex testing was carried out by monitoring the pressure in a superficial hand vein during transient sphygmomanometric cuff occlusion of arterial and venous blood flow at the wrist. The stimuli employed to assess alteration in tone were the Valsalva maneuver and deep inspiration, each of which was carried out twice.

On another occasion the Valsalva maneuver was repeated during echocardiographic monitoring of left atrial size. The Valsalva maneuver was carried out with 40 mm Hg of positive intrathoracic pressure generated for a period of 20 seconds as previously described. The parameter assessed was the percent reduction in left atrial diameter associated with the strain phase of the Valsalva maneuver.

Treadmill testing consisted of 3 minutes of exercise at 4 mph with grade adjusted according to the subject’s weight to give a total of 10,000 footpounds of work. Blood pressure, heart rate, plasma norepinephrine, epinephrine and dopamine were monitored before and after testing.

Each subject also had cold pressor and isometric handgrip testing. In the cold pressor test, the subject’s left hand was placed in a container of half ice and half water for 1 minute. For the isometric test, the subject held 30% of his maximum handgrip capacity for a period of 3 minutes. Blood pressures and heart rates were determined before and at 1-minute intervals during the stimulus. Because we have observed individual variability on the first occasion these tests are carried out, while there is greater reproducibility on subsequent trials, cold pressor and isometric tests were performed several times on different days.

After the conclusion of the above procedures, a 24-hour urine was collected for determination of metanephrine and normetanephrine excretion. For assessment of plasma catecholamines, participants in the study were instructed to remain supine and to take no food or beverage after midnight. A 19-gauge heparin-lock needle was placed in the right forearm at 7:30 a.m. After 30 minutes continued rest, blood samples for plasma catecholamines and plasma renin activity were taken. Following this, the subject was ambulatory until 11:00 a.m., at which time a second set of samples was taken. The heparin-lock needle was then removed.

The participants in the study were then brought into balance on a 10 mEq sodium diet. This usually required 5 to 7 days. When balance was achieved, they
remained supine and took nothing by mouth after midnight. As before, 8:00 a.m. supine and 11:00 a.m. ambulatory samples for catecholamines and plasma renin determinations were taken via heparin-lock needles. Again a 24-hour urine was collected for metanephrine and normetanephrine.

The urinary metanephrine and normetanephrine levels were determined using a highly sensitive and accurate gas chromatography-mass spectrometric method which depends on selected ion monitoring with deuterated metanephrine and deuterated normetanephrine as internal standards.\textsuperscript{18}

The assay of norepinephrine, epinephrine and dopamine was accomplished by a radioenzymatic method.\textsuperscript{1} We added 50 \textmu l of plasma without further extraction or deproteinization directly to incubates containing catechol-O-methyltransferase and \textit{S}-adenosyl-L-methionine-(\textsuperscript{3}H-methyl) (New England Nuclear Corp., specific activity 8.1-11.5 Ci/nmole). The total incubation volume was 100 \textmu l. To an identical incubation mixture containing a second 50-\textmu l aliquot of the plasma sample was added 100 pg each of norepinephrine, epinephrine and dopamine as internal standards. Blank tubes contained each of the above reagents except plasma. After incubation for 60 minutes at 37°C, the \textit{S}-H-0-methyl-catecholamines were extracted and then separated by means of thin-layer chromatography. Radioactivity in each catecholamine derivative was determined by scintillation counting.

Results

Response to Sodium Deprivation

While in balance on the 150 mEq sodium diet, there was no difference between the normal (NI) and borderline hypertensive (BH) groups with respect to either plasma norepinephrine (fig. 1), or plasma renin activity (PRA) (fig. 2) in either the supine or standing position. Urinary normetanephrine excretion over a 24-hour period also was not significantly different on this intake of sodium (fig. 3).

After coming into balance on a 10 mEq sodium diet, differences between the hypertensive and normotensive groups emerged. The average plasma norepinephrine concentration was significantly higher in the BH group in the supine position (NI = 213 ± 51; BH = 333 ± 100, \textit{p} < 0.02), and also after upright posture (NI = 554 ± 76; BH = 698 ± 174, \textit{p} < 0.05) (fig. 1). Urinary excretion of normetanephrine over a 24-hour period (fig. 3) also was significantly higher in the BH group (NI = 470 ± 91; BH = 636 ± 136, \textit{p} < 0.02), confirming a higher net release of norepinephrine from adrenergic neurons in the BH group during sodium deprivation.

Plasma renin activity rose during sodium deprivation to a higher level in the BH group than in the normal group (fig. 2). In the upright position, the differences were most striking (NI = 9.0 ± 1.5 ng/ml/hr\textsuperscript{1}; BH = 35.6 ± 14.8 ng/ml/hr\textsuperscript{1}, \textit{p} < 0.001).

\textbf{Figure 1.} Plasma norepinephrine levels in normal and borderline hypertensive subjects as a function of posture and sodium balance.
In contrast to the changes in norepinephrine release evoked by sodium deprivation, neither plasma epinephrine nor urinary metanephrine were significantly increased by the 10 mEq sodium diet in either group (table 1).

Weight loss incurred during transition from the 150 mEq sodium balance to the 10 mEq sodium balance was similar in both groups: NL = 1.7 ± 0.4 kg; BH = 1.7 ± 0.8 kg. The average reduction in mean blood pressure associated with this change in sodium balance was rather modest, 1.7 ± 1.6 mm Hg in the NLs and 4.4 ± 2.5 mm Hg in the BH group. These changes are not significantly different, but the data obviously do not exclude the possibility that the hypotensive responses to sodium deprivation differed in the groups studied. No significant associated change in heart rate occurred in either group.

Response to Exercise

The concentration of NE in plasma rose in both groups after exercise on a treadmill (fig. 4). The postexercise NE was significantly greater in the BH group (NL = 916 ± 195; BH = 1553 ± 729 pg/ml, p < 0.05).

The concentration of epinephrine in plasma immediately after exercise was not significantly different between the two groups. The level of epinephrine in the pre-exercise period (just before stepping onto the treadmill) was greater in the BH group (table 1).

FIGURE 2. Plasma renin activity in normal and borderline hypertensive subjects as a function of posture and sodium balance.

FIGURE 3. Urinary normetanephrine excretion over a 24-hour period in normal and borderline hypertensive subjects as a function of sodium balance.
TABLE 1. Plasma Epinephrine Levels in Normal and Borderline Hypertensive Subjects

<table>
<thead>
<tr>
<th>Epinephrine level</th>
<th>Normal subjects</th>
<th>Labile hypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mEq Na⁺ balance 8:00 a.m. supine</td>
<td>36 ± 20*</td>
<td>51 ± 24</td>
</tr>
<tr>
<td>150 mEq Na⁺ balance 11:00 a.m. upright</td>
<td>57 ± 31</td>
<td>64 ± 34</td>
</tr>
<tr>
<td>10 mEq Na⁺ balance 8:00 a.m. supine</td>
<td>29 ± 7</td>
<td>55 ± 33†</td>
</tr>
<tr>
<td>10 mEq Na⁺ balance 11:00 a.m. upright</td>
<td>46 ± 14</td>
<td>58 ± 14</td>
</tr>
<tr>
<td>Upright before treadmill</td>
<td>38 ± 9</td>
<td>62 ± 33†</td>
</tr>
<tr>
<td>Upright after treadmill</td>
<td>96 ± 39</td>
<td>115 ± 51</td>
</tr>
</tbody>
</table>

*Values represent mean ± sd in pg/ml. †p < 0.05.

Hemodynamic Evaluation

Echocardiographic evaluation revealed no difference in left ventricular systolic or diastolic dimension, stroke volume, or mitral valve closure. The left atrial dimension, one of the earliest cardiac indices of hypertension was also not significantly different between the normal (2.4 ± 0.4 cm) and the BH group (2.8 ± 0.3 cm).

The diminution in left atrial diameter during the strain phase of the Valsalva maneuver was 36 ± 5% in the Nls and 24 ± 4% in the BH group (p = 0.06).

The venous reflex response to the Valsalva maneuver was 14.6 ± 1.5 mm Hg in the Nls and 19.7 ± 3 mm Hg in the BH subjects (p = 0.09). The comparable figures for the venous reflex response to deep breath were 18.2 ± 2 mm Hg and 24.2 ± 4 mm Hg, respectively (p = 0.10).

The ratio of atrial size decrement during the Valsalva maneuver to the venous pressure increment during the venous response testing to the same maneuver showed a significant divergence between the two groups: the ratio was 2.5 ± 0.4 in the Nls and 1.2 ± 0.2 in the BH subjects (p < 0.05).

While plasma volume was 1.9 ± 0.1 liters/m² in the Nls, it was 1.6 ± 0.6 liters/m² in the BH group. These differences were not statistically significant.

The cold pressor test resulted in mean blood pressure increases of 24 ± 8 mm Hg in Nls and 22 ± 9 mm Hg in BH with no significant difference between these groups on either initial or subsequent cold pressor tests. The handgrip response was also similar in the Nls (19 ± 6 mm Hg) and BH group (18 ± 5 mm Hg).

Discussion

Neither the activity of the sympathetic nervous system nor the levels of plasma renin activity were increased in borderline hypertensive subjects at rest in 150 mEq sodium balance. However, the borderline hypertensive group exhibited greater response to both sodium deprivation and exercise.

Reduction of sodium intake to 10 mEq daily evoked an increased release of the noradrenergic neurotransmitter in all subjects as reflected by increased plasma levels of norepinephrine and increased urinary levels of normetanephrine. In the borderline hypertensive group, this response was exaggerated, as evidenced by both plasma norepinephrine and urinary normetanephrine levels.

The release of epinephrine from the adrenal medulla would appear to be controlled independently of the release of the noradrenergic neurotransmitter. Neither epinephrine nor metanephrine increased significantly with sodium deprivation. The higher epinephrine in the hypertensive subjects under certain circumstances such as the anticipation of treadmill exercise is noted. However, it is recognized that the psychic stress in such situations in the hypertensive patients (all of whom were aware that their blood pressure was in the borderline range) may not be comparable to that in the normal volunteers.
In the case of treadmill exercise, there is evidence that differences in conditioning contribute to the interindividual differences in plasma catecholamine responses to a given workload. By history, both the NI and the BH subjects appeared to have approximately equivalent physical conditioning, but small differences between the two groups in this characteristic obviously cannot be ruled out.

The rise in plasma renin activity evoked by sodium deprivation was considerably greater in the borderline hypertensive subjects than in the normal group. Considering the extent to which this response was exaggerated in our borderline hypertensive subjects, it is pertinent that the release of renin is governed not only by the sympathetic nervous system but also by an intrarenal pressure-sensitive mechanism. Thus, the renin release evoked by sodium deprivation is probably the result of both components. Because of the known influence of angiotensin II on the adrenergic nervous system, it is also possible that the increased plasma renin activity contributed to the increased release of norepinephrine.

Other investigators have found evidence consistent with exaggerated sympathetic or renin responsiveness in some subjects with borderline hypertension to such stimuli as upright posture, mental stress, lower body negative pressure and sodium loading.

Our experiments do not address the mechanism responsible for the exaggerated sympathetic responses and renin release in borderline hypertension. It is possible that sodium loss was greater in our BH group, and that there was accordingly a greater reduction in blood volume and hence a greater stimulus to the baroreceptor. However, the equivalent weight change in the two groups suggests that this was not the case.

It is also possible that the exaggerated response to sodium restriction in the BH group was due to a "normal" contraction of the blood volume in the face of low venous compliance. With reduced venous compliance, a given reduction in volume would provide a greater stimulus for sympathetic and renin activation to maintain arterial pressure.

Our experiments do not provide a direct measure of venous compliance in these two groups. However, the measurements made during the Valsalva maneuver at least suggest a diminution in venous compliance. During the increase in intrathoracic pressure, the decrease in left atrial size occurs as blood is being transferred to the peripheral circulation; the forearm venous tone is a reflection of the resistance to expanding the volume in the venous system. A ratio of the reduction in left atrial size to the venous pressure during the Valsalva maneuver yields a factor that varies directly with the capacity for peripheral pooling during this maneuver.

In the extreme case of peripheral adrenergic neuron blockade by guanethidine, left atrial size change during the Valsalva maneuver is very great while the venous reflex is quite small and thus the ratio of atrial size change to venous pressure is quite large (Robertson, unpublished data). In this study, the ratio of atrial size decrement to venous pressure during the Valsalva maneuver in the normal individuals was 2.5 ± 0.4, whereas in the borderline hypertensive patients it was 1.2 ± 0.2 (p < 0.05). These findings are consistent with the reduced compliance and central redistribution of blood volume which have been found by others. However, alternative explanations for these differences are possible: the left atrium might be structurally different in BH subjects. Differences in parasympathetic tone might also be present.

An enhanced response to equivalent stimulation of arterial baroreceptors could occur at the level of the baroreceptors or in the central nervous system. One possibility is that the medullary vasomotor center in the BH individual is under excessive stimulation from higher centers. This could result in sufficient pressure elevation to bring about baroreceptor-mediated inhibitory input into the vasomotor center, thus reducing overall sympathetic outflow to normal. With removal of baroreceptor inhibition during stimuli, such as sodium deprivation, the greater stimulatory input into the vasomotor center would be unmasked. A similar situation would result from a deficiency of the inhibitory input of the nucleus tractus solitarius into the vasomotor center.

Clearly, additional information will be required to elucidate the mechanism of the altered sympathetic and renin responses observed in borderline hypertension. It is also apparent from these results that in investigations of altered regulation of blood pressure in borderline hypertension, the basal state may not yield valid clues, as the disorder is unlikely to be an autonomous overactivity of either system as exists with pheochromocytoma or a renin-producing tumor.

Rather, we suggest that in the basal state, most borderline hypertensive individuals have levels of activation of the sympathetic and renin systems that are appropriate for normal levels of blood pressure in spite of having pressures that are raised. In the borderline hypertensive subjects, there thus appears to be a disorder in regulation of these factors. These abnormalities of sympathetic and renin regulation are most easily demonstrated in response to perturbations of the pressure and volume factors that provide afferent information to the regulatory system.

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