Plasma Norepinephrine Response to Tilting in Essential Hypertension

By Roger B. Hickler, M.D., James T. Hamlin III, M.D., and Roe E. Wells, Jr., M.D.

A significant increase in the plasma concentration of norepinephrine on tilting 19 normal subjects from the horizontal to 60° upright is described. Evidence that this represents an increased neuroadrenergic activity to maintain cerebral circulation despite the peripheral pooling of blood has previously been reported. When 9 subjects with severe essential hypertension were similarly tilted, the rise in plasma norepinephrine concentration was insignificant. This may indicate a diminished neuroadrenergic activity in essential hypertension due to compensatory reflexes from the baroreceptor regions.

There is sufficient evidence to indicate that essential hypertension is not due to increased neuroadrenergic activity. The demonstration of elevated levels of urine norepinephrine excretion in only 16.4 per cent of 500 hypertensive patients is additional evidence. Conversely, there is suggestive evidence of a diminished neuroadrenergic activity in essential hypertension. Gellhorn, in his monograph "Autonomic Imbalance and the Hypothalamus" cites the classical investigation of earlier workers to support the general thesis that a "fall of the blood pressure leads to increased sympathetic and adrenal discharges, and that a rise of blood pressure causes increased parasympathetic discharges." Sandin demonstrated a 3- to 4-fold increase in urine norepinephrine excretion on tilting normal subjects from the horizontal to an upright position. In hypertensive subjects the rise was only about 60 per cent. He suggested that the chronically elevated pressure in the baroreceptor areas in essential hypertension leads to a state of diminished endogenous norepinephrine production.

A previous report from this laboratory described the measurement of a significant increase in the concentration of plasma norepinephrine within minutes of tilting normal subjects from the horizontal to 60° upright. A failure to detect a significant rise in subjects with postural hypotension was also described. In order to investigate further the thesis of a diminished neuroadrenergic activity in essential hypertension, this method was extended to hypertensive subjects.

Method

Nineteen normotensive subjects (resting diastolic pressure below 90 mm. Hg), with a mean age of 59 years (range 29 to 80), served as a control group. These were compared with 9 subjects with essential hypertension (resting diastolic pressure above 100 mm. Hg), with a mean age of 60 years (range 43 to 73). Thirteen subjects formed an "intermediate" group (resting diastolic pressure 90 to 100 mm. Hg). All were ambulatory and none was on medication. The usual clinical and laboratory methods were used to eliminate patients with an identifiable cause for their hypertension. After a 30-minute rest in the supine position on a standard tilt table, each subject was tilted 60° upright for a 30-minute period. Brachial blood pressures were recorded every minute by auscultation and a standard aneroid blood pressure cuff. Pulse rate was determined by counting the radial pulse. Venous samples were drawn through an indwelling needle with stylet in the right antecubital vein during the control period and at 2.5, 5, 10, 20, and 30 minutes after tilting upright. The samples were heparinized and the plasma separated by centrifugation and stored at -18 C. The Aronow and Howard modification of the Weil-Malherbe and Bone method was used for subsequent determination of norepinephrine concentration. While nonhormonally active hydroxyphenol compounds in the plasma may also be detected by this fluoro-
TABLE 1.—Effect of Essential Hypertension on the Plasma Norepinephrine Response to Tilting

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Plasma norepinephrine—mean (µg./L. plasma)</th>
<th>Increment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Diastolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90 mm. Hg)</td>
<td>19</td>
<td>3.2±1.3</td>
<td>1.9±1.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&quot;Intermediate&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Diastolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-100 mm. Hg)</td>
<td>13</td>
<td>3.6±1.2</td>
<td>1.5±1.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Diastolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;100 mm. Hg)</td>
<td>9</td>
<td>3.3±1.3</td>
<td>0.9±0.8</td>
<td>&gt;0.2</td>
</tr>
</tbody>
</table>

nometric method, any abrupt changes on tilting are considered to be due to the labile hormonal fraction. The normal range for plasma norepinephrine in this laboratory in the resting subject is 1.5 to 5.5 µg. per L. The repeatability of the method is ±10 per cent, so that changes of 1 or more micrograms per liter plasma between control and peak norepinephrine concentration after tilting are considered to be significant.

Results

Figure 1 demonstrates a typical response in a normotensive subject, age 70. The blood pressure was well maintained after tilting. The rise in diastolic pressure and pulse rate are probably manifestations of the increased neuroadrenergic activity attending the orthostatic stress. The slight fall in norepinephrine concentration between the first and second control samples prior to the tilt probably represents an approach to a baseline level on resting horizontally on the tilt board. After tilting to 60° the norepinephrine concentration rose, reached a peak after 10 minutes, and then returned toward the control level. The increment is taken as the difference between the last control sample just prior to the tilt and the peak value after the tilt. In this instance the increment was 1.8 µg. per liter plasma. In the 19 normotensive subjects studied the mean increment was 1.9 ± 1.07 µg., representing a significant rise over the control levels (p < 0.01). In only 2 instances was the rise less than 1 µg. (0.1 and 0.8 µg.).

Figure 2 demonstrates the response in a hypertensive subject, age 48. There was a maximum fall in systolic pressure of 30 mm. Hg associated with a relatively small rise in norepinephrine concentration of only 0.7 µg. per L. plasma after 30 minutes of tilting. In 9 hypertensive subjects studied the mean increment was 0.9 ± 0.77 µg., representing an insignificant rise over the control levels (p > 0.2). In the "intermediate" group (13 subjects with a diastolic pressure 90 to 100 mm. Hg) the mean increment was 1.5 ± 1.02 µg., a significant rise (p < 0.01) of a degree intermediate between the normotensive and distinctly hypertensive groups (table 1). It is notable that the mean control values for the 3 groups showed no significant difference
TABLE 2.—Effect of Age on the Plasma Norepinephrine Response to Tilting in Normotensive Subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No. of Subjects</th>
<th>Plasma norepinephrine—mean (µg./L. plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Peak</td>
</tr>
<tr>
<td>Young (Mean age 35)</td>
<td>7</td>
<td>2.8±1.0</td>
</tr>
<tr>
<td>Old (Mean age 73)</td>
<td>12</td>
<td>3.5±1.3</td>
</tr>
</tbody>
</table>

TABLE 3.—Effect of Essential Hypertension on the Hemodynamic Response to Tilting

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean change in pulse rate (beats/min.)</th>
<th>Mean change in systolic pressure (mm. Hg.)</th>
<th>Mean change in diastolic pressure (mm. Hg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>+12</td>
<td>-16</td>
<td>+6</td>
</tr>
<tr>
<td>(15 subjects)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>+22</td>
<td>-29</td>
<td>+3</td>
</tr>
<tr>
<td>(9 subjects)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TABLE 4.—Effect of Age on the Hemodynamic Response to Tilting in Normotensive Subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No. of Subjects</th>
<th>Mean change in pulse rate (beats/min.)</th>
<th>Mean change in systolic pressure (mm. Hg.)</th>
<th>Mean change in diastolic pressure (mm. Hg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young (mean age 35)</td>
<td>7</td>
<td>+19</td>
<td>-10</td>
<td>+13</td>
</tr>
<tr>
<td>Old (mean age 73)</td>
<td>12</td>
<td>+9</td>
<td>-19</td>
<td>+1</td>
</tr>
</tbody>
</table>

(normotensive group, 3.2 µg.; "intermediate" group, 3.6 µg.; hypertensive group, 3.3 µg.). Thus the relatively insignificant rise in the hypertensive group could not be related to a higher baseline.

Age difference could not account for the difference, since the mean ages of the normotensive and the hypertensive groups were both 59 years. To determine the effect of age per se on the norepinephrine response to tilting, independent of hypertension, the 19 normotensive subjects were divided into 2 groups: 7 subjects under age 60 (mean of 35 years) and 12 over age 60 (mean of 73 years) (table 2). Both groups showed a significant rise: mean rise of 2.3±1.3 µg. for the young (p < 0.01) and 1.8±0.9 µg. for the old (p < 0.01). The difference in mean increases between the young and old groups was not significant (p > 0.3).

The hemodynamic data were analyzed by comparing the pulse rate and systolic and diastolic pressure just prior to the tilt with the maximum change observed following the tilt (table 3). In the hypertensive group the mean increment in the pulse rate was almost double that for the normotensive group; the diastolic pressure rise was only half and the systolic pressure fall was almost double that of the normotensive group.

An analysis of the effect of aging, independent of hypertension, was accomplished by comparing the pressure and pulse response in the 7 young and 12 old normotensive subjects. Table 4 illustrates the smaller pulse and diastolic pressure rise and the greater systolic pressure fall in the old group, consistent with the vascular "brittleness" of advancing age.

**Discussion**

These results suggest that in essential hypertension there is a diminished responsiveness of the sympathetic nervous system. Previous studies have shown that bilateral adrenalectomy does not modify the norepinephrine excretion in urine or the plasma norepinephrine response to tilting. The changes therefore must represent a difference between normotensive and hypertensive subjects in the rate of release of norepinephrine (over rate of destruction) by the sympathetic nerve endings.

Subjects with autonomic hypofunction resulting in postural hypotension have also shown a diminished plasma norepinephrine response to tilting. Such a similarity between hypertensive subjects and subjects with postural hypotension might seem at face value to be paradoxical. An analysis in this laboratory of the plasma norepinephrine and hemodynamic response to tilting in 6 subjects with postural hypotension is compared with the
results of the present study (table 5). It can be seen that the subjects with hypertension and postural hypotension in comparison with the normotensive subjects have a relatively "flat" plasma norepinephrine response, associated with a poorer maintenance of systolic and diastolic blood pressure against a gravitational stress. The changes are not so marked in essential hypertension, and it is suggested that the degree of sympathetic unresponsiveness is not so severe.

The rate of renal excretion of a parenteral salt load demonstrates another similarity between essential hypertension and postural hypotension. Studies have demonstrated an exaggerated natriuresis associated with parenteral saline administration in essential hypertension11 and in postural hypotension12 as compared with normal subjects. The factor in common may be a diminished sympathetic regulatory mechanism on renal salt conservation. Indirect evidence of the possible importance of the neuroadrenergic system on sodium excretion may be cited. Norepinephrine infusion has been shown to cause sodium retention.13 Dibenzylamine infusion into the renal artery in dogs with experimental valvular heart lesions has been shown to augment sodium excretion.14

Evidence is accumulating of a hyperreactive response of the vasculature of the hypertensive subject to parenteral administration of catecholamines.15-17 This may be comparable to the postsympathectomy subject in whom increased reactivity to administered pressor substances is characteristic of the state of diminished sympathetic innervation.18, 19 With this in mind the finding of postural hypotension in 50 per cent of subjects with pheochromocytoma may seem less surprising.20 The high level of circulating pressor amine and concomitant hypertension may actually obtund the responsiveness of the neuroadrenergic system, particularly when called upon to respond quickly to an abrupt change in body position.

It is possible that in the labile phase of essential hypertension, normotensive periods are maintained in the face of the basic hypertensive process by virtue of a reflexly diminished neuroadrenergic activity. Situations which then acutely evoke the release of pressor amine may act upon a vasculature rendered hyperresponsive by a chronically diminished endogenous norepinephrine production, resulting in transient periods of hypertension. The hypertensive process, at this point, could be regarded as incompletely compensated.

Summary

An insignificant rise in the venous concentration of norepinephrine was found on tilting 9 hypertensive subjects from the horizontal to 60° upright. A significant rise was found when 19 normotensive subjects were similarly stressed.

The hypertensive group showed a greater fall in systolic pressure and a smaller rise in diastolic pressure following this orthostatic stress. This was comparable to the more striking fall in both systolic and diastolic pressures in subjects with autonomic hypofunction resulting in postural hypotension.

It is concluded that in essential hypertension there may be a diminished reflex responsiveness of the neuroadrenergic system. This could represent an unsuccessful homeostatic mechanism against the hypertensive state.

Summary in Interlingua

Un augmento insignificativo del concentracion venose de norepinephrina esseva consta-
tate post bascular 9 subjectos hypertensive ab
le decubito horizontal a un inclination de 60
grados in alto. Un augmento significative
esseva trovate in 19 subjectos normotensive
post lor exposition al same typo de stress.

Le gruppo hypertensive monstrava un plus
grande reduction del tension systolic e un
piu miere augmento del tension diastolic
post le describite stress orthostatic. Isto es-
seva comparabile al plus frappante reduc-
tiones del tension tanto systolic como etiam
diastolic que es vidite in subjectos con hypo-
function autonomie resultante in hypotension
postural.

Es concludite que in hypertension essential
il existe possibilemente un reducite respons-
vitare reflexe del sistema neuroadrenergic.
Isto representara un non-successose mecha-
nismo homeostatic contra le stato de hyper-
tension.

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