Pressor Response to Norepinephrine in Essential Hypertension
A Study in Families

Jose Jayme Galvão De Lima, Marta Machado Dias, Helio Bernardes-Silva, and Giovanni Bellotti

Study of pressor response to graded, increased doses of infused norepinephrine in patients with essential hypertension, their normotensive siblings, and normotensive control subjects unrelated to the patients and without a family history of hypertension indicated an increased response in the two former groups. Comparison of the dose-response curves in the three groups showed that the difference in response was due to a reduced threshold to norepinephrine in patients and their siblings and not to differences in the slopes of the dose-response curves. These alterations were not paralleled by differences in heart rate responses. (Hypertension 1990;15(suppl I):I-137-I-139)

Familial aggregation of blood pressure is a well-known phenomenon, and several cardiovascular disturbances have been reported in relatives of hypertensive subjects. The study of these deviations from normal is important because it might contribute to understanding the pathogenesis of essential hypertension and identifying the individuals with a greater predisposition to developing the disease.

The literature on blood pressure response to norepinephrine in essential hypertension is controversial. Some authors have found responses similar to those observed in normoten- sive individuals, whereas others have reported increased responses. The aim of this study was to evaluate the pressor response to norepinephrine in patients with essential hypertension and their normotensive siblings and in normotensive subjects unrelated to the patients and with a negative family history of hypertension.

Methods

Essential hypertensive patients and their siblings were recruited from the hypertension clinic, Instituto do Coração, São Paulo. Arterial hypertension was defined as diastolic blood pressure equal to or greater than 95 mm Hg on three different occasions with the individuals having taken no medication for at least 2 weeks. Patients with obesity, diabetes, malignant hypertension, or apparent involvement of heart, kidneys, or central nervous system were excluded. Secondary forms of hypertension were ruled out by routine tests.

Control subjects were selected from normoten- sive individuals unrelated to the patients and with no hypertensive first-degree relatives. All subjects in the groups, including the relatives of the control subjects, were examined by one of the authors (J.J.G.L.). There were 26 hypertensive patients and 30 normotensive siblings in 15 families and nine control subjects. Clinical features of all three groups are shown in Table 1.

Blood pressure was measured with a mercury sphygmomanometer. Mean blood pressure (MBP) was calculated as the sum of the diastolic and one third of pulse pressure. The protocol was approved by the Institutional Ethical and Scientific Commission. All subjects gave their informed consent.

Norepinephrine infusions were performed between 8:00 and 11:00 AM with the individuals in supine position. An intravenous infusion of 5% dextrose in water was initiated at the rate of 1.0 ml/min for 30 minutes. At the end of this period, five blood pressure and heart rate (HR) measurements were taken, and the averages of the last three were used as the baseline values. The dextrose infusion was then replaced by a solution of norepinephrine 8 \( \mu g/ml \) in 5% dextrose in water. Norepinephrine was initially infused at the rate of 0.025 \( \mu g/kg/min \) with subsequent doses of 0.050, 0.075, 0.10, 0.15, and 0.20 \( \mu g/kg/min \). Each dose was infused for 10–15 minutes, and an equal interval was allowed between each dose for recovery. The test was stopped if diastolic blood pressure increased by 25 mm Hg or if cardiac arrhythmias occurred. During the infusion, blood pressure and HR were measured every
TABLE 1. Clinical Data and Basal Values of Parameters in Patients With Essential Hypertension, Their Normotensive Siblings, and Normal Control Subjects Without Family History of Hypertension

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>MBP (mm Hg)</th>
<th>HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EH</td>
<td>26</td>
<td>33.8±8</td>
<td>13/13</td>
<td>20/6</td>
<td>65±9</td>
<td>160±10</td>
<td>109±9.6</td>
<td>74±10</td>
</tr>
<tr>
<td>S</td>
<td>30</td>
<td>27.3±7</td>
<td>16/14</td>
<td>24/6</td>
<td>61±6</td>
<td>160±6</td>
<td>90±7.5</td>
<td>70±7</td>
</tr>
<tr>
<td>NC</td>
<td>9</td>
<td>28±6</td>
<td>3/6</td>
<td>7/2</td>
<td>56±15</td>
<td>161±10</td>
<td>86±6.2</td>
<td>75±8</td>
</tr>
</tbody>
</table>

Values given for basal values are mean±SD.

n, number; M, male; F, female; C, caucasoid; N, negroid; MBP, mean blood pressure; HR, heart rate; EH, patients with essential hypertension; S, normotensive siblings; NC, normal control subjects.

2 minutes after the start of each infusion dose. The values for each period correspond to the average of the last three determinations.

Statistical Methods

The pressor and HR responses to norepinephrine infusions in the three groups were evaluated with an adjusted model of linear regression. In this model, the dose of norepinephrine was the independent variable, whereas the difference between basal and observed MBP or HR (ΔMBP or ΔHR) for each dose of norepinephrine was the dependent variable. The logarithm of ΔMBP was used instead of the absolute value because the former followed a Gaussian distribution. For evaluation of HR, no logarithm transformation was necessary. The slopes and intercepts for each regression were then calculated and compared.

Differences in threshold values were established from equations obtained from the adjusted linear model. A p value of less than 0.05 was considered significant.

Results

MBP increased linearly with the doses of norepinephrine infused in all groups (Figure 1). Equations derived from the adjusted regression model were as follows:

Hypertensive patients: Log(ΔMBP) = 0.3832 + 6.4813 × dose norepinephrine
Siblings: Log(ΔMBP) = 0.1681 + 7.7383 × dose norepinephrine
Control subjects: Log(ΔMBP) = 0.0440 + 7.7278 × dose norepinephrine

Further analysis allowed the following conclusions: 1) The three regressions differed significantly from each other (F = 9.2579; p = 0.0001). 2) The threshold (or intercepts) were different in the three groups: Hypertensive patients versus normotensive siblings, F = 8.3980, p = 0.0040; hypertensive patients versus normotensive control subjects, F = 17.3241, p = 0.0001; and normotensive siblings versus control subjects, F = 4.2404, p = 0.0402. 3) The slopes of the three relations were comparable (F = 2.2575, p = 0.1016; NS).

HR decreased with increased doses of norepinephrine in the three groups, yielding the following equations:

Hypertensive patients: ΔHR = 0.3718 - 91.3182 × dose norepinephrine
Siblings: ΔHR = 0.7671 - 103.1097 × dose norepinephrine
Control subjects: ΔHR = 1.6742 - 119.8502 × dose norepinephrine

FIGURE 1. Graph and scatterplots showing effect of norepinephrine (μg/kg/min) on logarithm of changes in mean arterial pressure in normotensive subjects from normotensive families (□), patients with essential hypertension (○), and their normotensive siblings (△).
The differences between the regressions were not statistically significant ($F=1.0628; p=0.3750$).

**Discussion**

The aim of this study was to verify whether patients with essential hypertension and their normotensive siblings display different pressor responses to infused norepinephrine from those observed in normotensive subjects belonging to normotensive families. We have used two parameters to characterize the pressor response to stepwise increased doses of norepinephrine, the slope of the dose-response relation and the threshold dose, that is, the smallest pressor dose of norepinephrine for each group. We found that the slopes of the dose-response relations did not differ among the three groups, whereas hypertensive subjects and their normotensive siblings presented a lower threshold to norepinephrine. This means the hypertensive individuals and their normotensive relatives responded to reduced doses of norepinephrine, but once the response was initiated, it progressed in parallel with that observed in normal control subjects, causing the dose-response curves to be displaced to the left. These results are in agreement with those reported by Bianchetti et al.\cite{3} and Philipp et al.\cite{8} Others, however, found a steeper dose-response slope to infused norepinephrine in subjects with essential hypertension.\cite{7} Pressor response to norepinephrine indistinguishable from that documented in normal subjects, has also been described.\cite{4-6} These discrepancies might be related to differences in methodology, especially regarding the severity of hypertension in the hypertensive population.\cite{5,6,12}

Age, race, and dietary salt intake influence the dose-response curve.\cite{5} We have not controlled for salt intake. Age, race, and gender, however, were similar in the three groups. Differences in metabolic handling of circulating catecholamines could influence cardiovascular response to infused norepinephrine; however, it has been reported that normotensive members of hypertensive families do not differ from normal control subjects in this regard.\cite{3} Moreover, expressive reduction in norepinephrine clearance rates seems to predominate in older individuals,\cite{11} whereas all of our subjects were under 45 years old.

Direct assessment of baroreceptor reflex response could not be made under the present experimental circumstances. Nevertheless, modification of baroreceptor activity\cite{4} seems unlikely because HR changed proportionally in the three groups, a finding also reported by others.\cite{5,5} Therefore, the altered pressor response in patients and in their normotensive siblings might be a consequence of differences in cardiovascular responsiveness to norepinephrine rather than to changes mediated by the autonomic nervous system.

An augmented pressor response to norepinephrine might reflect a primary supersensitivity of the end organ, or it might be secondary to structural abnormalities of the cardiovascular system, developing in response to elevations in blood pressure.\cite{12} In the present investigation, the pressor response of relatives of hypertensive patients was situated midway between those observed in the two other groups and differed significantly from both. Because these individuals had normal blood pressure, our observations point to a functional rather than structural disturbance in norepinephrine responsiveness and support the concept that cardiovascular hyperreactivity is involved in the pathogenesis of essential hypertension. Follow-up studies are necessary to verify whether the development of essential hypertension in normotensive siblings of hypertensive individuals can be anticipated from a disturbed cardiovascular response to norepinephrine.

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**References**


**Key Words** • norepinephrine • essential hypertension • pressor response
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