Decreased Beta-Adrenoreceptor Responsiveness as Related to Age, Blood Pressure, and Plasma Catecholamines in Patients with Essential Hypertension

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SUMMARY The role of the sympathetic nervous system as it relates to adrenoceptor-mediated hemodynamic responses was investigated in patients with essential hypertension and in normal subjects of similar age. An age-related increase in plasma norepinephrine (PNE) concentrations observed in 36 recumbent normal subjects ($r = 0.623, p < 0.001$) was not found in 56 patients; the latter included some young patients with high values. Sympathetic overactivity in patients ($n = 24$) as compared with normotensive subjects ($n = 20$) was suggested by a greater increase in PNE upon standing ($242 \pm 34 \text{ vs } 155 \pm 25 \text{ pg/ml (SEM), } p < 0.05$) and persistently higher plasma epinephrine (PE) concentrations at rest and during equieffective exercise ($p < 0.05$). In patients, PNE was directly related to systolic ($r = 0.57, p < 0.01$) and diastolic ($r = 0.53, p < 0.01$) blood pressure. Older age was associated with diminished exercise tachycardia and increased blood pressure responses to exercise, which were both more pronounced in hypertensive patients. This higher pressure/lower heart rate pattern was paralleled by an age-related decrease in isoproterenol sensitivity in normal subjects ($0.97 \pm 0.15$ in six below age 34 years, $1.31 \pm 0.30$ in eight between 35–49 years, and $1.82 \pm 0.12 \mu g/m^2\text{ in six above 50 years}$), which was also more pronounced ($p < 0.05$) in hypertensive patients ($1.20 \pm 1.18$ in seven below age 34 years, $2.42 \pm 0.30$ in nine between 35–49 years, and $6.73 \pm 2.44 \mu g/m^2$ in eight above 50 years). Thus, an increase in the patients' blood pressure and age is associated with a progressive reduction in $\beta$-adrenoreceptor sensitivity and/or reactivity. Defective $\beta$-adrenoreceptor-mediated responses may result in unopposed $\alpha$-adrenoreceptor-mediated vasoconstriction and thereby contribute to the development of hypertension. (Hypertension 2: 130–138, 1980)

KEY WORDS • plasma catecholamines • beta adrenoreceptors • isoproterenol • essential hypertension

THE sympathetic nervous system is involved in blood pressure regulation in normal and hypertensive man via postganglionic nerve transmission mediated by norepinephrine and via adreno-medullary epinephrine secretion. Heart rate, cardiac output, and the renin-angiotensin pressor system as well as vascular tone are, in part, controlled via $\beta$ and $\alpha$ adrenoreceptors. The response of the target organ is therefore the result of a balance between neural activity and receptor responsiveness. Sympathetic nervous activity and changes therein are reflected in plasma catecholamine concentrations and in heart rate, particularly when parasympathetic tone is minimized during strenuous physical exercise. Beta-adrenoreceptor response can be assessed selectively by heart rate stimulation with isoproterenol. To obtain a more integrated view of the sympathetic nervous system involvement and its interaction with adrenoreceptor-mediated cardiovascular functions, heart rate and blood pressure were measured and compared with plasma catecholamine concentrations in age-matched groups of normotensive and hypertensive subjects at rest and during exer-
exercise. Heart rate responsiveness was also measured by testing its sensitivity to isoproterenol.

Subjects and Methods

Patients and Controls

Thirty-six normal volunteers (20 men and 16 women; aged 21-68 years, mean 40 ± 3 SEM) with a casual seated blood pressure of below 140/90 mm Hg on three occasions and 26 patients with essential hypertension of World Health Organization (WHO) stages I and II (35 men and 21 women; aged 16-65 years, mean 41 ± 2 SEM) were studied after at least 6 weeks without any medication. Secondary forms of hypertension were ruled out by the addition of rapid sequence pyelography and the determination of vanillic mandelic acid in 24-hour urine collections to a standard hypertensive workup. Patients with a manifest heart or airway disease were excluded from the study. On chest x-ray, heart size and the cardiothoracic ratio were within normal limits; no differences were found between different age groups. The diastolic pressure of the seated patients was ≥ 100 mm Hg. Twenty normal and 24 hypertensive subjects were randomly selected for isoproterenol sensitivity measurements and exercise testing. Six of these 20 normal subjects and seven of the 24 hypertensive patients were aged less than 34 years; eight and nine respectively were aged 35 to 49 years; and six and eight respectively were aged over 50 years. Both subjects and patients gave their informed consent.

Methods

All experimental sessions were started at 8 a.m. to minimize diurnal variations. Subjects were allowed a light breakfast without coffee and asked to refrain from smoking. An indwelling cannula was placed in an antecubital vein. After the subjects had rested for 40 minutes in the recumbent position, blood pressure and heart rate were measured. Blood was drawn for catecholamine determination into vacutainer tubes containing heparin. The tubes were immediately placed on ice and centrifuged at 4°C (20 min at 2000 rpm). The plasma was then frozen at -70°C until assayed 4 to 6 weeks later.

Beta-Adrenergic Sensitivity Testing with Isoproterenol

Bolus injections of isoproterenol were made intravenously through a previously placed indwelling cannula, starting with a dose of 0.1 μg/m² body surface. The heart rate was measured by ECG after each dose. The dose was gradually increased to establish a dose/heart rate response curve.

From this curve the dose that increased the resting heart rate by 25 beats per minute, i.e., the chronotropic doseₙₐ (CDₙₐ), was derived. Placebo injections of isotonic salines were randomly interposed as a control. Tachyphylaxis does not occur with this isoproterenol bolus test, nor does the test interfere with neurotransmitter re-uptake. Expressing isoproterenol sensitivity as the CDₙₐ is a compromise between pharmacological desirability and safety, since the maximal chronotropic dose cannot be tested because of the risk of severe dysrythmias; on the other hand, baseline variability of a beat-to-beat heart rate measurement does not allow a reliable determination of the threshold dose.

Adrenergic Stimulation with Physical Exercise

For each subject a prestudy determination of the maximal physical work capacity (PWCmax) was done at least 24 hours before any further test. PWCmax was determined by stressing the patient to exhaustion on three increasing work loads within 14 to 16 minutes. PWCmax did not differ between normal and hypertensive subjects. On the day of the study, the subjects remained supine for 40 minutes after the isoproterenol test. They were subsequently placed on a bicycle ergometer for 5 minutes and then exercised for 5-minute periods with work loads adjusted to 25%, 50%, and 75% of their PWCmax. A 75% PWCmax represents a submaximal work load that can be performed under steady-state conditions.

At the end of each period, blood was drawn for catecholamine determination. Simultaneously, the heart rate was measured by ECG, the shortest R-R interval of three respiratory cycles being selected. The blood pressure was measured automatically using an infrasonic recorder (Physiometrics SR 1). Mean blood pressure was approximated by the calculation: diastolic pressure plus one-third of the pulse pressure.

Assay for Plasma Norepinephrine and Epinephrine

A radioenzymatic technique was employed. Interassay variability was ± 6% for plasma norepinephrine (PNE) and ± 14% for plasma epinephrine (PE). Evaluation of data was performed employing linear regression analysis and Student's t test for paired and unpaired data. Because the results of the isoproterenol sensitivity tests (CDₙₐ) were not normally distributed, Wilcoxon's nonparametric rank sum test was performed to compare groups of normotensive and hypertensive subjects. Profile analysis was used to test the significance of differences between repeated measurements in two groups.

Results

Norepinephrine in Normal and Hypertensive Subjects

In 36 resting recumbent normal subjects the PNE concentrations increased with age (fig. 1). This was not observed in the 56 hypertensives among whom some young patients displayed high PNE concentrations.
Age, Catecholamines, and Heart Rate

As summarized in table 1, PNE was doubled on standing. The increase upon standing of 242 ± 34 pg/ml in hypertensives was greater than the 155 ± 25 pg/ml observed in normal subjects (p < 0.05). On exercise (75% PWCmax), PNE reached fourfold normal resting levels. Under all grades of exercise, PNE was higher with increasing age. Except in response to high grades of exercise, PNE tended to be higher in hypertensive patients. The increment in PNE between rest and 75% PWCmax was significantly greater in the older patients when compared to the younger patients (p < 0.005). Measured at rest and during graded exercise, PNE revealed slightly, though not significantly, higher values in hypertensives.

Concentrations of PE showed a delayed rise in response to exercise but also increased three- to fourfold and tended to be lower with increasing age. Profile analysis of PE exhibited persistently and significantly higher values for hypertensives as compared with normal subjects (p < 0.05).

In response to equieffective exercise, the heart rate was consistently higher in both younger normotensive and hypertensive subjects (fig. 2). Exercise tachycardia and age were inversely related in normals (75% PWCmax, $r = -0.846$, $p < 0.001$ and PWCmax, $r = -0.739$, $p < 0.001$ respectively) and hypertensives (75% PWCmax, $r = -0.604$, $p < 0.01$ and PWCmax, $r = -0.734$, $p < 0.001$ respectively). For any given heart rate on exercise, PNE was higher in the old as compared with the young both in normal and hypertensive groups.

Age-related Increase in Plasma Norepinephrine and Decrease in Isoproterenol Sensitivity

The average dose of isoproterenol needed to stimulate the heart rate by 25 beats/minute (CDα) increased with age in normal ($r = 0.624$, $p < 0.01$) and hypertensive subjects ($r = 0.493$, $p < 0.05$). The isoproterenol CDα was higher in hypertensives when compared with that of normotensives (Wilcoxon's rank test, $p < 0.05$) (table 2).

The isoproterenol CDα correlated with PNE concentrations at 75% PWCmax in hypertensive patients ($r = 0.610$, $p < 0.01$) (fig. 3); hence, increasing PNE concentrations were associated with diminishing isoproterenol sensitivity. By contrast, the isoproterenol CDα was inversely correlated with maximal exercise tachycardia in normal ($r = -0.704$, $p < 0.001$) and hypertensive subjects ($r = -0.904$, $p < 0.001$) (fig. 4).
### TABLE 1. Plasma Norepinephrine and Epinephrine in 20 Normotensive and 24 Hypertensive Subjects at Rest and During Graded Exercise

<table>
<thead>
<tr>
<th>Age</th>
<th>Recumbent</th>
<th>Standing</th>
<th>25% of PWCmax</th>
<th>50% of PWCmax</th>
<th>75% of PWCmax</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NT, n = 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HT, n = 7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35 yr</td>
<td>166 ± 45</td>
<td>332 ± 47</td>
<td>432 ± 51</td>
<td>644 ± 68</td>
<td>1172 ± 142</td>
</tr>
<tr>
<td></td>
<td>218 ± 27</td>
<td>434 ± 69</td>
<td>457 ± 53</td>
<td>618 ± 95</td>
<td>1092 ± 129</td>
</tr>
<tr>
<td>35-49 yr</td>
<td>298 ± 49</td>
<td>433 ± 48</td>
<td>516 ± 54</td>
<td>652 ± 68</td>
<td>1188 ± 96</td>
</tr>
<tr>
<td></td>
<td>251 ± 23</td>
<td>405 ± 81</td>
<td>608 ± 78</td>
<td>746 ± 66</td>
<td>1326 ± 164</td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td>270 ± 51</td>
<td>443 ± 96</td>
<td>610 ± 137</td>
<td>810 ± 175</td>
<td>1211 ± 195</td>
</tr>
<tr>
<td></td>
<td>317 ± 42</td>
<td>584 ± 94</td>
<td>732 ± 152</td>
<td>946 ± 175</td>
<td>1731 ± 241</td>
</tr>
<tr>
<td>all NT, n = 20</td>
<td>250 ± 27</td>
<td>466 ± 35</td>
<td>519 ± 49</td>
<td>697 ± 60</td>
<td>1190 ± 76</td>
</tr>
<tr>
<td>all HT, n = 24</td>
<td>263 ± 20</td>
<td>505 ± 48</td>
<td>625 ± 64</td>
<td>824 ± 88</td>
<td>1383 ± 117</td>
</tr>
<tr>
<td></td>
<td>NT, n = 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HT, n = 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 35 yr</td>
<td>31 ± 7</td>
<td>48 ± 8</td>
<td>48 ± 6</td>
<td>73 ± 7</td>
<td>151 ± 33</td>
</tr>
<tr>
<td></td>
<td>65 ± 22</td>
<td>100 ± 29</td>
<td>93 ± 33</td>
<td>124 ± 38</td>
<td>197 ± 49</td>
</tr>
<tr>
<td>35-49 yr</td>
<td>31 ± 7</td>
<td>48 ± 8</td>
<td>48 ± 6</td>
<td>73 ± 7</td>
<td>151 ± 33</td>
</tr>
<tr>
<td></td>
<td>55 ± 12</td>
<td>100 ± 29</td>
<td>93 ± 33</td>
<td>124 ± 38</td>
<td>197 ± 49</td>
</tr>
<tr>
<td>≥ 50 yr</td>
<td>34 ± 7</td>
<td>47 ± 7</td>
<td>47 ± 7</td>
<td>73 ± 7</td>
<td>151 ± 33</td>
</tr>
<tr>
<td></td>
<td>44 ± 7</td>
<td>57 ± 3</td>
<td>57 ± 3</td>
<td>73 ± 7</td>
<td>151 ± 33</td>
</tr>
<tr>
<td>all NT, n = 20</td>
<td>35 ± 4</td>
<td>42 ± 4</td>
<td>48 ± 4</td>
<td>71 ± 5</td>
<td>132 ± 13</td>
</tr>
<tr>
<td>all HT, n = 24</td>
<td>54 ± 8</td>
<td>70 ± 10</td>
<td>75 ± 11</td>
<td>105 ± 13</td>
<td>172 ± 17</td>
</tr>
</tbody>
</table>

Abbreviations: PNE = plasma norepinephrine; PE = plasma epinephrine; NT = normotensive subjects; HT = hypertensive subjects. Results are given as mean values ± SEM; significance of intragroup differences between subsequent measurements is indicated as:

\*p < 0.05.
\p < 0.01.
\%p < 0.001.

A profile analysis of multiple intra-individual measurements indicated that PE concentrations in HT were significantly higher than in NT (p < 0.05).

### Figure 2.
Responses of plasma norepinephrine and heart rate to graded exercise in three age groups of hypertensive patients as compared with those observed in age-matched normotensive subjects. Significance of differences between different age groups is indicated by asterisks.
### Table 2. Chronotropic Dose of Isoproterenol in ng/m² in Three Age Groups of Normotensive and Hypertensive Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>All subjects</th>
<th>&lt; 34 years</th>
<th>35–49 years</th>
<th>≥ 50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>1.36 ± 0.10</td>
<td>0.97 ± 0.15</td>
<td>1.31 ± 0.30*</td>
<td>1.82 ± 0.12†</td>
</tr>
<tr>
<td></td>
<td>n = 20</td>
<td>n = 6</td>
<td>n = 8</td>
<td>n = 6</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>3.50 ± 1.61</td>
<td>1.20 ± 0.18§</td>
<td>2.42 ± 0.30¶</td>
<td>6.73 ± 2.44*¶</td>
</tr>
<tr>
<td></td>
<td>n = 24</td>
<td>n = 7</td>
<td>n = 9</td>
<td>n = 8</td>
</tr>
</tbody>
</table>

Data are mean values ± SEM.

Comparison among age groups of normotensive and hypertensive subjects:

* p < 0.05.
† p < 0.01.
§ p < 0.005.

Comparison between normotensive and hypertensive groups of similar age:

¶ p < 0.05.
¶ p < 0.005.

Comparison between normotensive and hypertensive groups using Wilcoxon’s rank sum test: p < 0.05.

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**Increase in Pressure Response to Exercise and Reduced Isoproterenol Sensitivity**

In the 24 hypertensive patients, positive correlation was found between PNE concentrations and systolic (r = 0.57, p < 0.01), diastolic (r = 0.53, p < 0.01), and mean blood pressure (r = 0.63, p < 0.01) as measured in a recumbent position. For a given PNE concentration, the corresponding exercise-stimulated pressure was found to be higher in both the older normotensive and older hypertensive groups (fig. 5). Higher blood pressures at 75% PWCmax were also associated with a reduced isoproterenol sensitivity in normal (r = 0.781, p < 0.001) and hypertensive subjects (r = 0.576, p < 0.01) (fig. 6).
Discussion

In patients with essential hypertension, PE was consistently higher at rest, upon standing, and during exercise when compared with age- and sex-matched normal subjects. Hypertensive patients also exhibited a greater increase in PNE after assumption of the upright position. If under these circumstances the plasma concentrations of PNE and PE indeed reflect sympathetic activity, patients with essential hypertension tend to have an elevated sympathetic tone. That elevated sympathetic activity contributes to the hypertensive process is also supported by the correlation between PNE and blood pressure that was found in hypertensive patients but not in normal subjects. These findings are in agreement with some but not with other studies. The considerable overlap between the PNE levels of hypertensive and normal subjects can be reduced by taking the age-related increase of PNE — also described by others — into account in the analysis. Thus, in agreement with the results of other investigators, we found supranormal values of resting PNE in approximately one-third of the patients below the age of 45 years. Conversely, we found that PE concentrations tended to fall with increasing age, although on the average they were
FIGURE 5. Responses of plasma norepinephrine and pressure to graded exercise in three age-matched groups of normotensive and hypertensive subjects.

FIGURE 6. Comparison of exercise-stimulated blood pressure and isoproterenol sensitivity in normotensive and hypertensive subjects. PWCmax = maximal physical work capacity.
significantly higher in the hypertensive patients, which is in accord with a recent study. 18

There are several possible explanations for our observations. The higher PNE responses upon standing might reflect not only an increased neural release consequent upon higher sympathetic nervous activity, but also enhanced delivery into the circulation or a reduction in neuronal or extraneuronal reuptake. Also, the increase in both transmitters might theoretically be due to an equal reduction in metabolism. This seems unlikely, however, since clearance of norepinephrine from plasma was not found to be different in normal and hypertensive subjects. 17 Consequently, the relative increase in PNE and PE most likely reflects a (perhaps only slightly) elevated sympathetic tone. 1 Elevated sympathetic activity may be the result of different factors. Thus in young hypertensives, central or perhaps psychodynamic mechanisms may prevail. 18 Moreover, the sympathetic system activates the β-adrenoreceptor-mediated renin-angiotensin system, which may exert a positive feedback on the central nervous system, 18 thereby sustaining or further stimulating sympathetic activity. With the development of hypertension and with increasing age, factors such as a reduction in baroreflex sensitivity 20 may maintain or further increase sympathetic tone.

The response of the target organ depends not only on sympathetic nervous activity and the transmitters but also on the reactivity of the receptors, e.g., as reflected in the β-adrenoreceptor-mediated exercise tachycardia or isoproterenol sensitivity. The blunting of these responses observed with increasing age and hypertension supports the concept of an age- and perhaps pressure-linked decrease in β-adrenoreceptor sensitivity and is in accord with similar findings of an age-related decrease in exercise tachycardia, a reduced heart rate response to acute β-adrenoreceptor blockade. 21 Although our experimental design allowed direct testing of cardiac β-adrenoreceptors only, there is evidence that other β-adrenoreceptor-mediated functions behave alike. Thus, with older age a low and hyperactive renin secretion, 22 blunted production of cAMP, 23 and a decrease of the β-adrenoreceptor binding capacity of lymphocytes 26 have been observed. These changes may be interpreted as a defect of the β-adrenoreceptors secondary to age. However, the more pronounced reduction of isoproterenol sensitivity observed in hypertensive patients points at additional mechanisms. In view of a slightly elevated neurogenic tone in hypertensive patients, the more pronounced decrease in β-adrenoreceptor sensitivity could well be the consequence of β-adrenoreceptor overstimulation.

It is therefore tempting to speculate that hypertension could be initiated by elevated sympathetic nervous activity coupled with an initially elevated cardiac output 24 and an activated renin-angiotensin system. 22 Chronic stimulation of this kind, possibly resulting in impaired β-adrenoreceptor-dependent functions, may help to maintain the high blood pressure, since an imbalance between β vasodilatation (reduced) and α vasoconstriction (enhanced) would be the consequence. A desensitization of β-adrenoreceptors has been shown experimentally 26, 27 and is also seen in patients with bronchial asthma after long-term therapy with β-sympathomimetic agents. 28 Furthermore, in the latter patients, an enhanced vasoconstrictor response to phenylephrine was observed, which demonstrates the possibility of an imbalance between decreased β- and increased α-adrenoreceptor-mediated effects in this disorder. 29

The enhanced pressure responses found in our older patients on exercise are in keeping with this view. Furthermore, a predominance of α-vasoconstrictor forces may be due not only to the lack of β-dilator effects but also to age-related absolute increases in α-adrenoreceptor effects as has been shown, for example, in the case of α-adrenoreceptor-mediated platelet aggregation. 30

Some information of enforced α-adrenoreceptor-mediated responses may be derived from infusion studies with norepinephrine. Despite the belief that the pressure response to norepinephrine is α-adrenoreceptor-mediated, it has to be remembered that exogenous norepinephrine is not selective for postsynaptic α- or β-adrenoreceptors. 31 In addition, norepinephrine, via pressure-induced baroreflex activation, leads at the same time to an increase in vagal and decrease in sympathetic tone. Bearing these provisos in mind, we re-analyzed the data published by Gombos et al. 24 and found that for a 25 mm Hg rise in mean pressure, decreasing doses of norepinephrine were needed with increasing age (n = 20, r = -0.615, p < 0.01). A similar age trend can be calculated from two other studies. 26, 32 In this context, structural arteriolar changes secondary to hypertension may be important. If this were the case, increased pressure responses to different pressor hormones would be found. In a recent study, however, an enhanced pressure response to norepinephrine only — and not to angiotensin II — was observed, 33 which lends support to the view of an imbalance between arteriolar β- and α-adrenoreceptor-mediated effects.

Our hypothesis regarding the development of essential hypertension is consistent with the finding that young hypertensive patients display a relatively higher cardiac output that decreases later with an attendant rise in arteriolar resistance. 34 A change in adrenoreceptor sensitivity and/or reactivity may contribute to the transition from a high cardiac output-high renin state to a high peripheral resistance form of hypertension in which structural changes in the peripheral and renal vasculature 26, 40 become more important, perhaps as a result of pressure and age.

Acknowledgments

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