Borderline Hypertension: Relationship Between Age, Hemodynamics and Circulating Catecholamines

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SUMMARY The relationships between age, systemic and renal hemodynamics, circulating catecholamines (norepinephrine, epinephrine and dopamine) and intravascular volumes were studied in 38 normotensive subjects and in 77 patients with borderline essential hypertension. Borderline hypertensive patients had a higher cardiac index \((p < 0.02)\) and renal blood flow \((p < 0.05)\) than normotensive subjects if they were younger than 30 years of age, whereas in older patients no difference was observed. In contrast, total peripheral resistance was normal in young borderline hypertensive patients, but significantly increased \((p < 0.02)\) in patients older than age 40 years. Cardiac output \((r = -0.28, p < 0.01)\) and renal blood flow \((r = -0.47, p < 0.001)\) correlated inversely with age in the entire population and in both subgroups. Cardiac output also correlated closely with renal blood flow in all subjects \((r = 0.45, p < 0.001)\). Circulating norepinephrine levels increased with age \((r = 0.25, p < 0.05)\), whereas epinephrine concentration tended to decrease. Plasma and total blood volume correlated directly with cardiac output \((r = 0.39, p < 0.001)\) and inversely with peripheral resistance \((r = -0.34, p < 0.001)\). These data indicate that the hyperdynamic circulation (high cardiac output and renal blood flow) of borderline hypertension is found predominantly in patients younger than age 30 years. Older patients are characterized by an elevated total peripheral resistance and normal cardiac output. The age-dependent increase in circulating norepinephrine and decrease in epinephrine levels may participate in the shift of the hemodynamic profile from high-cardiac-output hypertension in the young to a high-arteriolar-resistance hypertension in the older patient.

WIDIMSKY and co-workers demonstrated more than 2 decades ago that cardiac output was significantly elevated in a group of young patients said to have “juvenile hypertension.” Other investigators have confirmed the observation that patients with borderline hypertension have a significantly higher cardiac output than sex- and age-matched normotensive subjects. Because the elevation of the cardiac output could be abolished with \(\beta\)-adrenergic-receptor blockade and vagal tone was found to be reduced, it seemed to be mediated to some extent by a net increase in adrenergic activity. Moreover, renal blood flow has been reported to be increased in these borderline hypertensive patients as well as in their offspring. These observations led Bianchi et al. to suggest a primary renal abnormality as cause of essential hypertension.

Borderline hypertension has been defined as a state found in relatively young patients in whom diastolic blood pressure fluctuates around 90 mm Hg. This clinical entity has been associated with pathophysiologic alterations involving the autonomic nervous system, systemic hemodynamics, and the renin-angiotensin system. However, older patients may also exhibit borderline high values of arterial pressure, but no information on other cardiovascular or endocrine characteristics is available. The present cross-sectional study was designed to evaluate the effects of age on systemic and renal hemodynamics, circulating catecholamines, and intravascular volume in patients with borderline hypertension and age- and sex-matched normotensive subjects.

Methods

One hundred fifteen subjects, 38 normotensive and 77 with borderline hypertension, were included in the study. For this study we defined borderline hypertension in the same terms as in most previous instances: patients who had diastolic pressures greater than 90 mm Hg on several outpatient visits, but normal pressures at other times. Each patient had a complete clinical evaluation to exclude any secondary form of hypertension. Most of the patients had never been treated for hypertension; in the few patients who had been, antihypertensive drugs were discontinued at least 4 weeks before the study. No patient had electrocardiographic or radiographic evidence of left ventricular hypertrophy, hypertensive retinopathy changes, or renal involvement. The study was explained to all patients and signed, informed consent was obtained. The protocol was approved by our Clinical Investigation Committee. Hemodynamic assessment was performed as previously reported. Renal blood flow was determined concomitantly by a single injection of \(^{131}\)I-para-aminohippuric acid. The disappearance curve was resolved into two linear components and the renal blood flow was calculated as proposed by Sapirstein et al.

Plasma volume was determined during the hemodynamic studies with \(^{125}\)I human serum albumin. The volume of red cells was measured simultaneously with \(^{51}\)Cr-labeled red blood cells. Levels of circulating epinephrine, norepinephrine and dopamine were deter-
mined from arterial blood during the same hemodynamic study. At least 1 hour was allowed to elapse between insertion of the catheters and drawing of blood for catecholamine determinations.

Patients were subdivided according to their age into groups younger than 20 years, 20-29 years, 30-39 years, 40-49 years and older than 50 years of age. Grossly obese subjects whose weight exceeded 125% of ideal weight (weight standards of the Metropolitan Insurance Company) were excluded and body surface area was not significantly different between the groups. Comparisons between borderline and normotensive subjects were made by t test. Linear regression analysis was performed between age and various hemodynamic values, circulating catecholamines and intravascular volumes.

Results

Among subjects younger than 30 years of age, cardiac index was higher ($p < 0.02$) in borderline hypertensives than in normotensive subjects (table 1). However, among patients who were more than 30 years old, cardiac index was identical in both groups. Moreover, cardiac index (or output) decreased with age and a negative correlation with a shallow slope was found between age and cardiac index in normal subjects ($r = -0.32$, $p < 0.05$), with a somewhat steeper slope in borderline hypertensives ($r = -0.32$, $p < 0.01$), and in the entire study population ($r = -0.28$, $p < 0.01$) (fig. 1). Although total peripheral resistance was quantitatively similar in normotensive subjects and borderline hypertensive patients younger than 30 years of age, it was increased in the older borderline hypertensive patients ($p < 0.02$ for all patients older than 40 years of age). As a result, peripheral resistance weakly correlated with age only in the borderline hypertensive patients ($r = 0.24$, $p < 0.05$). Similarly, renal blood flow was increased in borderline hypertensive patients of the younger age group ($p < 0.05$), whereas in patients over the age of 30 years, no difference was observed between the two groups. Thus, renal blood flow correlated inversely with age in both groups and in the whole study population ($r = -0.47$, $p < 0.001$) (fig. 2). Renal blood flow also correlated with cardiac output in both subgroups and the entire study population in all subjects ($r = 0.47$, $p < 0.001$) (fig. 3).

Levels of circulating norepinephrine showed an increase with age in borderline essential hypertensive patients ($r = 0.36$, $p < 0.01$) and in the entire study population ($r = 0.25$, $p < 0.05$) (fig. 4), but not in normal subjects ($r = 0.1$). Norepinephrine weakly correlated with total peripheral resistance in patients with borderline hypertension ($r = 0.32$, $p < 0.05$). In contrast, plasma epinephrine levels tended to decrease with age in both groups, whereas dopamine showed no age-dependent pattern. Plasma and total blood volumes were similar in borderline hypertensive patients and normotensive subjects, and no trend was observed with increasing age (table 1). Nevertheless, an inverse correlation was found between total blood volume (or plasma) and peripheral resistance ($r = -0.34$, $p < 0.001$) in all subjects. Cardiac output correlated with plasma or total blood volume ($r = 0.39$, $p < 0.001$) in the whole study population.

Discussion

Three main findings evolved from the present study: First, the elevation of cardiac output in borderline hypertension was found only in subjects younger than 30 years of age and disappeared in patients older than 30 years. Second, renal blood flow closely paralleled the changes in cardiac output, being highest in the young patients and decreasing to normal values in patients older than age 30 years. Third, circulating norepinephrine levels increased with age, more so in borderline hypertensives than in normotensive subjects, whereas epinephrine levels tended to decrease.

Several investigators have shown that patients with borderline hypertension have at least twice as high a risk of developing established hypertension than nor-

![Figure 1](https://example.com/figure1.png)  
**Figure 1.** Progressive decrease of cardiac output with age in patients with borderline hypertension (solid line, open circles, $r = -0.32$, $p < 0.01$), normotensive subjects (dashed line, filled circles, $r = -0.32$, $p < 0.05$), and all subjects ($r = -0.28$, $p < 0.01$).

![Figure 2](https://example.com/figure2.png)  
**Figure 2.** Progressive decrease of renal blood flow with age in patients with borderline hypertension (solid line, open circles, $r = -0.51$, $p < 0.001$), normotensive subjects (dashed line, filled circles, $r = -0.52$, $p < 0.01$), and all subjects ($r = -0.47$, $p < 0.001$).
motensive subjects. A faster resting heart rate and elevated cardiac output have been indicated as predictors of the future development of hypertension. The present data, however, indicate that borderline hypertensive patients older than 30 years of age have a normal cardiac index. Julius and Esler showed that the increased cardiac output in young borderline hypertensive patients can be abolished by β-adrenergic receptor blockade. Further, atropine administration results in a smaller increase in heart rate in patients with borderline hypertension than in comparable normotensive subjects. Therefore, in young patients with borderline hypertension, there is evidence of a net increase in adrenergic input to the cardiovascular system. By the same token, peripheral vasoconstriction may shift the intravascular volume toward the central circulation, which further increases cardiac output without significant change in total blood volume. The hyperdynamic circulation in young borderline hypertensive patients seems merely to reflect an increased adrenergic drive. Our finding of a normal cardiac output in borderline hypertensive patients older than 30 years of age suggests that established hypertension may develop directly from an increase in vascular resistance. Hence, the high cardiac output seems not to be a sine qua non in the pathogenesis of established essential hypertension, and the term cardiogenic hypertension should not be used in this context. Conceivably, however, some older patients with borderline hypertension may have had borderline elevated blood pressure values throughout their life and their "normal" cardiac output could be the result of their longstanding subtle hemodynamic changes.

As age progresses, cardiac output returns to normal values and total peripheral resistance becomes elevated, more so in patients with established hypertension than in the few who remain borderline throughout their lives. However, total peripheral resistance becomes significantly higher in patients with borderline hypertension than in age-matched normotensive subjects. That these changes suggest a modified adrenergic input to the cardiovascular system is indicated by the corresponding increase in circulating norepinephrine and the decrease in epinephrine levels. The progressive decrease in cardiac output with age has been observed previously. In our cross-sectional study, borderline hypertensive patients showed a somewhat steeper decline than normotensive subjects, possibly as a result of increased afterload.

Several investigators have found increased renal blood flow in patients with borderline hypertension or in children of hypertensive parents. Our data showing a close correlation between cardiac output and renal blood flow support those findings. However, Tuck et al. found cardiac output to be normal in the presence of an increased renal blood flow. Nonetheless, our findings confirm previous data indicating that renal blood flow closely parallels the changes in cardiac output, and no redistribution was observed with regard to the renal (or splanchnic) circulation in borderline or established hypertension. Our data are also consistent with our findings in spontaneously hypertensive rats. The fact that renal blood flow is elevated in patients younger than age 30 years and in normal in older subjects with borderline hypertension (with the same normal distribution of systemic flow to the kidneys) argues against a primary renal abnormality as a possible cause of essential hypertension.

An age-dependent increase of circulating norepinephrine in hypertensive and normotensive subjects has already been reported by other laboratories. However, the present data indicate a steeper increase with age in borderline hypertension than in normotensive subjects. Conversely, plasma epinephrine concentration tended to decrease with age, which confirms recent data of Bertel et al., who also showed that aging seemed to be associated with a progressive reduction in β-receptor sensitivity or reactivity. Such a defective β-receptor-mediated responsiveness could induce a compensatory increase in sympathetic outflow. Moreover, the reduction in baroreflex sen-

**Figure 3.** Positive correlation between renal blood flow and cardiac output in the entire study population.

**Figure 4.** Progressive increase of norepinephrine with age in borderline hypertensive patients (solid line, open circles, \( r = 0.36, p < 0.01 \)), normotensive subjects (dashed line, filled circles, \( r = 0.1, \text{NS} \)) and all subjects (\( r = 0.25, p < 0.05 \)).
TABLE 1. Effects of Age on Systemic and Renal Hemodynamics and Circulating Catecholamines in Normotensive (NT) and Borderline (BH) Subjects

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>&lt;20 years</th>
<th>20-29 years</th>
<th>30-39 years</th>
<th>40-49 years</th>
<th>&gt; 50 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT</td>
<td>0</td>
<td>10</td>
<td>13</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>BH</td>
<td>5</td>
<td>19</td>
<td>27</td>
<td>16</td>
<td>5</td>
</tr>
</tbody>
</table>

Mean arterial pressure (mm Hg)

| NT       | 85 ± 1.7 | 89 ± 1.7 | 84 ± 4.7 | 87 ± 7 |
| BH       | 92 ± 0.7 | 93 ± 2.6 | 95 ± 1.8 | 94 ± 1.9 |

Heart rate (beats/min)

| NT       | 67 ± 3   | 67 ± 2   | 68 ± 4   |
| BH       | 76 ± 3   | 71 ± 3   | 65 ± 2   |

Cardiac index (l/min/m²)

| NT       | 3.01 ± 0.2 | 3.08 ± 0.2 | 3.26 ± 0.7 |
| BH       | 3.57 ± 0.6* | 3.39 ± 0.1* | 3.13 ± 0.2 |

Total peripheral resistance (units)

| NT       | 30.1 ± 3.1 | 28.4 ± 1.3 | 27.7 ± 2.5 |
| BH       | 28.4 ± 0.4 | 29.8 ± 1.4 | 30.6 ± 1.5† |

Renal blood flow (ml/min/m²)

| NT       | 648 ± 62  | 561 ± 37  | 606 ± 69 |
| BH       | 719 ± 58† | 708 ± 35† | 620 ± 34 |

Total blood volume (l)

| NT       | 5.06 ± 0.3 | 4.89 ± 0.2 | 5.02 ± 0.3 |
| BH       | 5.45 ± 0.5 | 5.26 ± 0.2 | 5.33 ± 0.2 |

Plasma volume (ml/cm)

| NT       | 18 ± 1.0  | 18 ± 0.6  | 17 ± 1.0  | 15 ± 0.4 |
| BH       | 16 ± 0.6  | 18 ± 0.6  | 17 ± 0.4  | 19 ± 0.6 |

Norepinephrine (pg/ml)

| NT       | 286 ± 70  | 278 ± 51  | 295 ± 49  | 312 ± 12 |
| BH       | 211 ± 21  | 224 ± 47  | 249 ± 57  | 371 ± 62 |

Epinephrine (pg/ml)

| NT       | 88 ± 22   | 89 ± 33   | 73 ± 25   |
| BH       | 117 ± 21  | 102 ± 39  | 81 ± 34   |

Dopamine (pg/ml)

| NT       | 64 ± 29   | 48 ± 19   | 77 ± 34   |
| BH       | 78 ± 49   | 12 ± 74   | 91 ± 27   |

Values are mean ± SEM.

*p < 0.02, patients younger than 30 years vs normotensive subjects.
†p < 0.05, patients younger than 30 years vs normotensive subjects.
‡p < 0.02, patients older than 40 years vs normotensive subjects.

Abbreviations: NT = normotensive; BH = borderline hypertensive.

sitivity observed with aging may further stimulate norepinephrine production.6 Indeed, the present findings of an age-dependent increase in norepinephrine and a decrease in epinephrine levels may explain the hemodynamic findings of a high cardiac output in the young borderline hypertensive patient and increased total vascular and renal resistance as hypertensive disease progresses.

References

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F H Messerli, E D Frohlich, D H Suarez, E Reisin, G R Dreslinski, F G Dunn and F E Cole

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