Clinical Studies

Cardiovascular Regulatory Functions in Elderly Patients With Hypertension

Akiko Kawamoto, Kazuyuki Shimada, Kozo Matsubayashi, Taishiro Chikamori, Osamu Kuzume, Hisakazu Ogura, and Toshio Ozawa

To dissociate the effects of an elevated blood pressure on the cardiovascular regulatory functions from those of aging in the hypertensive elderly individual, resting hemodynamic measurements and circulatory autonomic functions in 30 elderly (mean age, 66 years) hypertensive (World Health Organization stages I and II) patients were compared with those in 30 healthy elderly (mean age, 65 years) normotensive volunteers. The elderly hypertensive group showed a significantly lower cardiac index and higher total peripheral resistance. β-Receptor sensitivity, as determined by chronotropic dose of infused isoproterenol, and baroreceptor reflex sensitivity index, derived from phase II, but not phase IV, of Valsalva's maneuver, were only slightly but significantly reduced in the hypertensive group. The variability of heart rate at rest as an index of parasympathetic control of heart was similar between these two groups. Plasma norepinephrine level was significantly inversely related to resting mean blood pressure ($r = -0.31, p < 0.05$) when analyzed as a whole group. Plasma renin activity, but not plasma aldosterone, was significantly decreased in the hypertensive group. To define the effects of age itself, these parameters in normotensive elderly subjects were also compared with those in 12 young normotensive subjects (mean age, 23 years). Although resting hemodynamic measurements did not differ, various circulatory autonomic functions were significantly different between these two age groups. The variability of heart rate in 24-hour ambulatory monitoring, β-receptor responsiveness, resting vagal cardiac activity, and baroreceptor reflex sensitivity derived from phase IV of Valsalva's maneuver were significantly depressed in the elderly. Resting plasma norepinephrine level was elevated and renin-aldosterone system decreased in the elderly. Thus, the hemodynamic pattern of elderly hypertensive patients with mild essential hypertension is of the low-output, high peripheral resistance type. Neither the sympathetic nervous nor the renin-angiotensin system is likely to be responsible for this increase in peripheral resistance. Furthermore, in contrast to the currently prevailing belief, high blood pressure, although an important modulating factor in the younger patients, has very limited, if any, influence on the cardiovascular regulatory functions in older subjects whose autonomic functions have already been substantially altered by advancing age. *(Hypertension 1989;13:401–407)*

There is relatively little information about the pathophysiological state of the cardiovascular system in hypertension of the elderly, whose cardiovascular autonomic regulatory functions would have been altered by both advancing age and high arterial blood pressure.1 Age is well-known to be associated with a progressive reduction in β-adrenergic receptor responsiveness,2 baroreceptor reflex sensitivity,3 and parasympathetic control of heart rate4 in normotensive subjects. The inhibitory effects of hypertension on these autonomic functions have also been described in middle-aged or younger patients.2–4 These findings have led to the generally believed, but not yet confirmed, concept that cardiovascular autonomic functions are affected by hypertension even in the aged patient. However, studies that have examined the effects of hypertension on the cardiovascular regulatory functions in the elderly have been inadequate. In fact, although Gribbin et al5 showed that baroreceptor reflex sensitivity was reduced independently by increasing age and arterial pressure, there was only one subject who was over 60 years old in their study population, which con...
sisted of 81 normotensive and hypertensive subjects aged 19–66 years. Other investigators also showed that parasympathetic control of heart rate, evaluated by the heart rate variability, was reduced by age and hypertension.4 Again, of the 46 study subjects aged 20–74 years, only five subjects were over 60 years old. Thus, little is known about how an elevated blood pressure per se affects the cardiovascular system in the elderly, which has already been altered by another important modulating factor, “age”. The present study was undertaken to answer this question by comparing hemodynamic and cardiovascular autonomic parameters in elderly hypertensive patients with those in normotensive elderly subjects who had undergone extensive health-screening tests. Furthermore, to define the effects of age itself on these functions, comparisons were also made between normotensive young and elderly subjects. We found that, in contrast to the commonly accepted view, high blood pressure had only a limited, if any, influence on the various cardiovascular regulatory functions in the elderly.

Subjects and Methods

Subjects

The study population consisted of 30 hypertensive patients (21 men and nine women) aged 36–76 years, 30 male normotensive subjects aged 58–77 years, and 12 young healthy male volunteers aged 16–28 years, eight of whom were college students. All hypertensive patients had diastolic blood pressure of more than 90 mm Hg or systolic blood pressure of more than 160 mm Hg on two different visits to the clinic, when medication had been discontinued for at least 4 weeks before the study, and were at World Health Organization stages I and II. Secondary hypertension was ruled out after a typical workup. All normotensive subjects (blood pressure <140/90 mm Hg) consisted of volunteers recruited from the community who maintained moderate levels of daily physical activity. They had no history of cardiovascular (including blood pressure), respiratory, endocrine, or other major diseases. The results of physical and laboratory examinations that included blood and urine tests, chest x-ray, electrocardiograms at rest, and spiromgrams were normal. Furthermore, maximal exercise tests showed neither electrocardiographic ischemic changes nor impaired functional aerobic capacity in any subject. Informed consent was given by every participant.

Study Protocols

The following examinations were performed on an ambulatory basis:

1) Twenty-four-hour blood pressure monitoring. Indirect ambulatory blood pressure was recorded at 10-minute intervals for 24 hours by using a finger volume-oscillometric device BP-100 (ME-Commercial, Tokyo, Japan). This oscillometric device is equipped with a transmittance infrared photoelectric plethysmograph that can analyze the characteristic change in amplitude of arterial volume pulsations in the human finger and was validated, as previously reported.5,6 Readings that showed an inconsistent change in systolic or mean blood pressure and those with pulse pressure less than 10 mm Hg were not considered in the analysis.6 More than 85% of the total number of readings during the 24-hour period passed the deletion criteria in any record.

2) Urinary sodium concentration. A 24-hour urine sample was collected to determine sodium excretion rate under the usual diet. Urinary creatinine level was also measured by the method of Jaffe.7

3) Hemodynamic and autonomic function tests. The subjects came to the laboratory in the morning after an overnight fast. The subjects lay supine, a 20-gauge needle was inserted into one antecubital vein, and after a 30-minute rest period, blood pressure was measured with a standard cuff method. Blood samples (16 ml) were then collected in prechilled tubes containing EDTA for the determination of plasma norepinephrine level, plasma renin activity, and plasma aldosterone. Norepinephrine concentrations were assayed by high-performance liquid chromatography with fluorometric detection as described previously.8 Aldosterone and renin activity were measured by radioimmunoassay.

The brachial artery was then cannulated percutaneously. A polygraph recorded intra-arterial blood pressure and electrocardiogram (lead V5). Cardiac index was measured by cuvette dye dilution methods.

Coefficient variation of the RR intervals in the electrocardiogram was obtained as a measure of cardiac parasympathetic activity and defined as the standard deviation divided by the mean of RR intervals obtained from 100 heart beats at rest.9,10 Instantaneous RR interval was derived by use of an Autonomic R100 (ME-Commercial). Periods with ectopic cardiac rhythm were excluded. Subjects breathed easily and did not perform the Valsalva maneuver in the supine position.

Baroreceptor reflex sensitivity was measured by the change in RR intervals per unit change in systolic blood pressure during phase II and IV of the Valsalva maneuver as previously described.8,11 Isoproterenol hydrochloride sensitivity was measured from dose–response curves to rapid intravenous injection as the dose required to increase the heart rate by 25 beats/min (chronotropic dose25 or CD25) according to the methods described by Cleaveland et al.12 The heart rate was calculated every 4 seconds throughout the test. Routinely, 0.1 µg was used as the initial dose. If no response was obtained, 0.5 µg was given, and the dose thereafter doubled (1.0 µg, 2.0 µg, 4.0 µg, 8.0 µg) until an increase in heart rate of more than 30 beats/min resulted.

Statistical Analysis

Statistical analysis was performed with Biomedical Programs (BMDP) statistical software (Univer-
TABLE 1. Characteristics of Three Different Age and Blood Pressure Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young (n=12)</th>
<th>Elderly (n=30)</th>
<th>Elderly HT (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>23.2±0.9*</td>
<td>65.3±0.9*</td>
<td>66.0±1.1</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>170.2±3.9t</td>
<td>162.6±1.0</td>
<td>159.5±1.7</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>66.1±6.5</td>
<td>62.3±1.5</td>
<td>62.1±2.0</td>
</tr>
<tr>
<td>Body surface (m²)</td>
<td>1.76±0.08t</td>
<td>1.66±0.02</td>
<td>1.63±0.03</td>
</tr>
</tbody>
</table>

*p<0.001, tp<0.01, tp<0.05, significant difference between normotensive young (Young) and elderly (Elderly) subjects. Differences between elderly normotensive and hypertensive (Elderly HT) groups are not significant for all of the measurements.

Results

Clinical Findings

Although body height and calculated body surface area of the normotensive elderly subjects were significantly less than those of the normotensive young subjects, body profiles as well as age were similar in both elderly groups (Table 1). As shown in Table 2, although blood pressures and heart rate were not significantly different between normotensive young and elderly groups, the standard deviation of heart rate in 24-hour ambulatory monitoring was significantly less in the elderly than in the young. The hypertensive elderly subjects showed significantly higher blood pressure levels than the normotensive elderly subjects not only at the clinic but also, though somewhat to a lesser degree, after supine rest for 30 minutes. The mean of blood pressure measured at 10-minute intervals during 24-hour ambulatory monitoring was also significantly different. Heart rate was significantly higher in the elderly hypertensive group than the elderly normotensive group after supine rest, but not in other occasions. The standard deviations of blood pressure and heart rate in the ambulatory recording were similar in these two groups of elderly subjects.

Autonomic Functions

The results of autonomic function tests are illustrated in Figure 2. As compared with normotensive young subjects, normotensive elderly subjects showed higher plasma norepinephrine level and higher chro-

TABLE 2. Blood Pressure and Heart Rate in Three Different Age and Blood Pressure Groups

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Young (n=12)</th>
<th>Elderly (n=30)</th>
<th>Elderly HT (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP (mm Hg)</td>
<td>DBP (mm Hg)</td>
<td>HR (beats/min)</td>
</tr>
<tr>
<td>Casual</td>
<td>117.1±2.1</td>
<td>67.8±2.7</td>
<td>63.8±2.6</td>
</tr>
<tr>
<td></td>
<td>126.1±2.1</td>
<td>79.5±1.4</td>
<td>64.1±1.4</td>
</tr>
<tr>
<td></td>
<td>118.3±3.4</td>
<td>67.9±3.3</td>
<td>65.0±3.0</td>
</tr>
<tr>
<td></td>
<td>121.2±1.7</td>
<td>72.8±1.4</td>
<td>57.4±1.2</td>
</tr>
<tr>
<td>Ambulatory</td>
<td>118.2±2.6</td>
<td>75.4±1.9</td>
<td>70.3±1.9</td>
</tr>
<tr>
<td></td>
<td>115.6±2.2</td>
<td>74.8±1.8</td>
<td>64.8±1.6</td>
</tr>
<tr>
<td></td>
<td>15.2±0.8$</td>
<td>10.6±0.6</td>
<td>15.2±0.8$</td>
</tr>
</tbody>
</table>

Systolic (SBP) and diastolic (DBP) blood pressure and heart rate (HR) were measured at clinics in the sitting position (Casual), at laboratory after supine rest for 30 minutes (Resting), and at 10-minute intervals for 24-hour period with ambulatory monitoring device (Ambulatory). Means and standard deviations (SD) of each measurement were obtained from the ambulatory recording.

*p<0.001, tp<0.01 significantly different between elderly normotensive and hypertensive (Elderly HT) subjects. $p<0.001 significantly different between normotensive young (Young) and elderly (Elderly) subjects.
nototropic dose of isoproterenol (CD25/BS), which suggests the age-related decrease in β-adrenergic receptor sensitivity. Variability of resting heart rate and baroreceptor reflex sensitivity index derived from phase IV (BRSI-IV), but not phase II (BRSI-II), of the Valsalva maneuver, were significantly lower in the normotensive elderly than in the normotensive young subjects.

On the other hand, CD25/BS was slightly larger and BRSI-II was slightly less in the elderly hypertensive group than each was in the normotensive elderly group. These differences were significant by the nonparametric Mann-Whitney test but did not attain statistical significance when tested by the less sensitive parametric Student's t-test. Variability of resting heart rate and BRSI-IV were not significantly different between the two elderly groups (by either nonparametric or parametric comparisons). Furthermore, the difference in plasma norepinephrine level between these two elderly groups did not reach statistical significance. Plasma norepinephrine level was, however, significantly inversely related to resting mean blood pressure as shown in Figure 3. Other autonomic parameters were not significantly correlated with blood pressure.

Renin-Aldosterone System

Plasma renin activity and aldosterone levels were significantly lower in the normotensive elderly than in the young subjects (Figure 4). Normotensive
elderly subjects excreted significantly less urinary sodium during a 24-hour period than the young subjects. The difference in sodium intake might be responsible for the observed age-related differences in autonomic functions. Accordingly, comparisons were made between the young and elderly subjects who had levels of urinary sodium excretion exceeding the lowest in the young group (i.e., 123 meq/day). There were still significant differences in each autonomic function between these subgroups of similar sodium intake levels (data not shown).

On the other hand, plasma renin activity was significantly lower in the elderly hypertensive group than that in the normotensive elderly group, whereas plasma aldosterone was similar in these two groups.

Both groups excreted similar amounts of urinary sodium during a 24-hour period (Figure 4). There was no significant difference between elderly hypertensive and normotensive groups in either urinary creatinine excretion (1.0 ± 0.07 vs. 1.1 ± 0.05 g/day, respectively, NS) or sodium creatinine ratio (9.1 ± 0.8 vs. 8.0 ± 0.7 g/g, respectively, NS), but the hypertensive group had a larger urine volume than the normotensive group (1.49 ± 0.1 vs. 1.18 ± 0.08 l/day, respectively, p < 0.05).

Discussion

Not as many investigations have been carried out in elderly patients as in middle-aged or younger patients. To our knowledge, there is only a single study by Terasawa et al,13 who reported hemodynamic data comparing elderly normotensive and hypertensive subjects. They reported in 1972 that cardiac index was lower by 13% in hypertensive than in normotensive subjects, whereas total peripheral resistance was higher in hypertensive subjects by 50%. Our results are consistent with their findings, which indicate the hemodynamic pattern of elderly hypertensive subjects with mild essential hypertension without heart failure is of the low-output, high peripheral resistance type. The rise in total peripheral vascular resistance could lead to the decline in cardiac output due to the resistance to left ventricular emptying. Several structural and functional mechanisms could contribute to the rise in total peripheral resistance in elderly patients with essential hypertension; these include thickening and rigidity of large as well as small vessels and enhanced vasoconstrictor or reduced vasodepressor mechanisms.14,15 In this context, it should be noted that plasma norepinephrine and renin activity tended to be depressed in hypertensive compared with normo-
motensive subjects under similar sodium intakes, which indicates that neither the sympathetic nervous nor the renin-angiotensin system is responsible for the increased peripheral resistance in the elderly hypertensive patient. Apparently other unknown factors may be involved in this alteration of the hemodynamic profile.

In normotensive subjects, neither resting cardiac output nor peripheral resistance was different between each age group. It has recently been shown that these basic hemodynamic parameters are not influenced by age itself when the age-associated modifying factors, which include occult coronary artery disease or sedentary lifestyle, are excluded from the study population by extensive screening procedures,\textsuperscript{16} which we did in the present study. Thus, we could probably define changes almost purely related to aging itself. It should be noted that even in these carefully screened subjects, the participant represents an ordinary community-dwelling healthy elderly individual, and not an atypical, highly conditioned subgroup.

Although advancing age is associated with an increase in plasma norepinephrine level\textsuperscript{17} and a decrease in plasma renin activity\textsuperscript{18} in normotensive subjects, as was shown in the present study even after the subjects were equally matched in sodium intake levels, there is relatively little direct information about the state of these parameters in hypertension in the elderly. The inverse relation between plasma norepinephrine and blood pressure levels was found in elderly subjects by Stern et al.\textsuperscript{19} The same group also reported that plasma renin activity was lower in hypertensive elderly than in normotensive elderly subjects, while plasma aldosterone was similar between the two groups.\textsuperscript{19} Thus our data have confirmed their observations.

Age-related alterations in various elements of cardiovascular autonomic functions were observed in our normotensive elderly population, in agreement with earlier studies.\textsuperscript{2-4} Thus, $\beta$-adrenergic receptor responsiveness, resting vagal cardiac activity, and baroreceptor reflex sensitivity (particularly during baroreceptor stimulation in phase IV of Valsalva's maneuver) were attenuated in the elderly subjects. These changes also may account for the reduced heart rate variability during ambulatory monitoring in the elderly. In contrast, the results of circulatory autonomic function measurements in the elderly hypertensive subjects are rather unexpected ones. Our data showed that isoproterenol sensitivity in the elderly hypertensive group was slightly, but significantly reduced compared with the elderly normotensive group. Less sensitive analysis by parametric testing failed to show this difference. This finding emphasizes the subtlety of changes in $\beta$-receptor sensitivity in the elderly patients with essential hypertension in comparison with the elderly normotensive group. This was also the case with baroreceptor reflex sensitivity. Baroreceptor reflex sensitivity index, derived from phase II of the Valsalva maneuver, was slightly but significantly reduced only by nonparametric testing in the hypertensive patients, whereas that derived from phase IV of the maneuver did not differ between the two groups. This indicates that hypertension has a marginal, if any, influence on the baroreceptor reflex sensitivity in elderly subjects. Furthermore, the variability of heart rate at rest, an index of parasympathetic control of the heart, was similar between normotensive and hypertensive elderly subjects.

Taken together with these data, we conclude that, in contrast to the common belief, high blood pressure, although an important modulating factor in the younger subjects, has very limited, if any, influence on the cardiovascular regulatory functions in the older subjects whose autonomic functions have already been substantially altered by advancing age.

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