Changes in Frequency of Orthostatic Hypotension in Elderly Hypertensive Patients Under Medications

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To evaluate changes in frequency of orthostatic blood pressure (BP) reduction (orthostatic hypotension; OH) in elderly hypertensive patients (HT) before and after treatment for hypertension, we measured BP after supine for 10 min and standing position for 2 min, before and after treatment for 2 years by five kinds of antihypertensive drugs in 50 elderly normotensive subjects (NT) and each of 50 HT in double-blind study. Orthostatic hypotension was defined as 10% or more decline of supine mean BP, and the frequency of OH was in 27% of HT following BP reduction by any kinds of antihypertensive drugs. In conclusion, the reducing or normalized BP by treatment for hypertension in elderly HT decreases the prevalence of orthostatic hypotension. Am J Hypertens 1996;9:263–268

KEY WORDS: Orthostatic hypotension, elderly hypertensive patients, norepinephrine, antihypertensive drugs.

Orthostatic blood pressure reduction or orthostatic hypotension (OH) has been widely investigated, but the precise mechanism and prevalence have not yet been clarified. However, the Systolic Hypertension in the Elderly (SHEP) study and Cardiovascular Health Study (CHS) Collaborative Research Groups have reported that OH is common in the elderly subjects, and increases with advancing age, with increasing mean systolic blood pressure (BP), and with decreasing mean body mass index. In addition, they reported the prevalence of OH was 18.2% in elderly subjects, 12.0% in systolic hypertensive patients and the other investigators reported that is 20% in the subjects over 65 years and 30% in the subjects over 75 years as OH was defined as a decline of 20 mm Hg or more in systolic BP or 10 mm Hg or more in diastolic BP. However, the prevalence of OH as a function of BP status is not clear, because the subjects in these reports were including normotensive (NT) and hypertensive (HT) subjects at various ratios. Furthermore, there are few studies about the prevalence of OH comparing before and after medications for hypertension. Sirogatz et al reported that some studies of the institutionalized elderly are more likely to include individuals with impairments or on medications that may cause postural hypotension, and that, therefore, tend to suggest a relatively high prevalence, and alternatively investigations designed to exclude those with hypertensive condition or on medications have found a low prevalence of postural hypotension. However, they classified antihypertensive medications into only...
two categories: diuretics or other antihypertensive medications. Furthermore, they gave no information concerning the duration of taking medications. In addition, their definition for postural hypotension was a reduction of 10 mm Hg or greater in systolic BP on going from sitting to standing while we defined OH as 10% or greater reduction of MBP from the supine to standing position.

The present study was conducted to evaluate the mechanism and the prevalence of OH before and after medications for hypertension, by calcium channel blocker, \( \beta \)-blocker, \( \alpha \)-blocker, angiotensin converting enzyme inhibitor, or diuretics, which are used commonly in Japan, in elderly established hypertensive patients.

**MATERIALS AND METHODS**

Fifty elderly (\( \geq 65 \) years old) normotensive, each group of 50 elderly established hypertensive subjects, who were treated for hypertension by calcium channel blocker, \( \beta \)-blocker, \( \alpha \)-blocker, angiotensin converting enzyme inhibitor, or diuretics, were age-, weight-, and body mass index-matched strictly (76±5, 73±6, 74±7, 75±7, 74±5, 78±8 years, 22.9±0.4, 22.7±0.5, 22.8±0.3, 22.9±0.4, 22.8±0.5, 22.8±0.5 kg/m\(^2\), mean±SD, respectively). Normotension was defined as \( < 140/90 \) mm Hg, and established hypertension was defined as \( > 160/95 \) mm Hg at three or more measurements. All subjects were untreated preceding this study and without severe cardiovascular complications except hypertension and without diabetes, I this study and without severe cardiovascular complications, their definition for postural hypotension was recognized in 22% of hypertensive and 4% of normotensive subjects.

Furthermore, orthostatic hypotension after 1 year of medication for hypertension was recognized in 22% and 4% of NT, and 4% and 1% of HT by the definition of 10% or more, and by the definition of 20/10 mm Hg, respectively. However, there were no significant differences in the frequency of OH between NT and HT by either definition of OH (premedications: NT \( \geq 0.146 \) by the definition of 10% or more, and \( P = 0.159 \) by the definition of 20/10 mm Hg; post-medication: \( P = 0.069 \) by the definition of 10% or more, \( P = 0.466 \) by the definition of 20/10 mm Hg, by \( \chi^2 \) test). On the other hand, frequency of OH in HT after 1 year of medication decreased significantly by both definitions. Furthermore, after medications of any antihypertensive drugs, the incidence of OH decreased significantly. In particular, metoprolol, enalapril and nifedipine made the incidence of OH to decrease significantly; metoprolol: 26% (before medication), 16% (1 month), 10% (3 months), 2% (1 year), 0% (2 years), enalapril: 28%, 8%, 8%, 0%, 0%, nifedipine: 26%, 16%, 6%, 4%, 4%, thiazide: 26%, 20%, 16%, 14%, 10%, prazosin: 28%, 28%, 26%, 21%, 19%, as a definition of OH as a decline of 10% or more in supine mean BP. The incidence of OH by definition of OH as a decline of 20/10 mm Hg or more was as follows: NT: 4%, 6%, 4%, 4%, nifedipine: 22%, 8%, 4%, 0%, 0%, metoprolol: 20%, 10%, 0%, 0%, 0%; enalapril: 18%, 6%, 6%, 0%, 0%; prazosin: 18%, 12%, 12%, 10%, 10%; thiazide: 22%, 6%, 10%, 8%, 6%. The reduction of frequency of OH was noted as the number of subjects increased, whose systolic BP was less than 140 mm Hg and those with BP still higher than 140 mm Hg continued to have OH (Figures 2 and 3). Even prazosin, which is well known for the side effect of OH, decreased the incidence of OH.

In all subjects, supine systolic BP correlated significantly with systolic BP, diastolic BP and mean BP before and after medication (premedications: \( r = 0.40, P = 0.001 \), \( r = 0.46, P = 0.001 \), \( r = 0.48, P = 0.001 \); postmedications (at 1 year): \( r = 0.44, P = 0.001 \), \( r = 0.30, P = 0.008 \), \( r = 0.41, P = 0.001 \), respectively). In the present study, none of the subjects who showed OH were symptomatic such as dizziness, fainting, etc. both before and after medications, even in the case of prazosin.

Supine plasma NE before medications was slightly

* indicates \( P < .05 \), t indicates \( P < .01 \) compared with the basal incidence.

**RESULTS**

Age and body mass index in each group were not different and the stages of hypertension in each group were not different. The incidence of OH by definition of OH as a decline of 10% or more in supine mean BP is shown in Figure 1. According to our definition of orthostatic hypotension as a decline of 10% or more in the supine mean BP, OH was recognized in 27% of hypertensive patients and 22% of normotensive subjects, while we used the definition of OH as a decline of 20/10 mm Hg or more, OH was also recognized in 20% of hypertensive and 4% of normotensive subjects before medication. Orthostatic hypotension after 1 year of medication for hypertension was recognized in 22% and 4% of NT, and 4% and 1% of HT by the definition of 10% or more, and by the definition of 20/10 mm Hg, respectively. However, there were no significant differences in the frequency of OH between NT and HT by either definition of OH (premedications: NT \( \geq 0.146 \) by the definition of 10% or more, and \( P = 0.159 \) by the definition of 20/10 mm Hg; post-medication: \( P = 0.069 \) by the definition of 10% or more, \( P = 0.466 \) by the definition of 20/10 mm Hg, by \( \chi^2 \) test). On the other hand, frequency of OH in HT after 1 year of medication decreased significantly by both definitions. Furthermore, after medications of any antihypertensive drugs, the incidence of OH decreased significantly. In particular, metoprolol, enalapril and nifedipine made the incidence of OH to decrease significantly; metoprolol: 26% (before medication), 16% (1 month), 10% (3 months), 2% (1 year), 0% (2 years), enalapril: 28%, 8%, 8%, 0%, nifedipine: 26%, 16%, 6%, 4%, 4%, thiazide: 26%, 20%, 16%, 14%, 10%, prazosin: 28%, 28%, 26%, 21%, 19%, as a definition of OH as a decline of 10% or more in supine mean BP. The incidence of OH by definition of OH as a decline of 20/10 mm Hg or more was as follows: NT: 4%, 6%, 4%, 4%, nifedipine: 22%, 8%, 4%, 0%, 0%, metoprolol: 20%, 10%, 0%, 0%, 0%; enalapril: 18%, 6%, 6%, 0%, 0%; prazosin: 18%, 12%, 12%, 10%, 10%; thiazide: 22%, 6%, 10%, 8%, 6%. The reduction of frequency of OH was noted as the number of subjects increased, whose systolic BP was less than 140 mm Hg and those with BP still higher than 140 mm Hg continued to have OH (Figures 2 and 3). Even prazosin, which is well known for the side effect of OH, decreased the incidence of OH.

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greater in hypertensive patients than in normotensive subjects (normotensives: 220 ± 40 pg/mL, hypertensives: 280 ± 50 pg/mL), and in both normotensive and hypertensive subjects with OH were significantly greater than in the subjects without OH (normotensives with OH: 250 ± 40 pg/mL, normotensives without OH: 210 ± 30 pg/mL, \( P < .05 \)), hypertensives with OH: 330 ± 40 pg/mL, hypertensives without OH: 260 ± 40 pg/mL \( (P < .05) \), mean ± SD). Supine and standing plasma NE levels after medications were slightly greater in hypertensive patients and significantly greater in the subjects with OH also than in normotensive subjects and the subjects without OH as well as the plasma NE status before medications. Standing NE before medication were also greater in hypertensive patients than in normotensive subjects (normotensives: 470 ± 50 pg/mL, hypertensives: 520 ± 80 pg/mL, \( P < .05 \)) and in both normotensive and hypertensive subjects with OH were greater than those in the subjects without OH (NT with OH: 510 ± 50 pg/mL, NT without OH: 460 ± 40 pg/mL \( (P < .05) \), HT with OH: 530 ± 40 pg/mL, HT without OH: 510 ± 40 pg/mL (NS)). After 1 year of medication: supine NE: normotensives: 230 ± 40 pg/mL, hypertensives: 300 ± 60 pg/mL; NT with OH: 250 ± 40 pg/mL, NT without OH: 220 ± 30 pg/mL, HT with OH: 400 ± 50 pg/mL, HT without OH: 300 ± 40 pg/mL; standing NE: normotensives: 480 ± 50 pg/mL, hypertensives: 560 ± 50 pg/mL; NT with OH: 540 ± 40 pg/mL, NT without OH: 510 ± 30 pg/mL, HT with OH: 580 ± 70 pg/mL, HT without OH: 560 ± 50 pg/mL.

Furthermore, the ratio of standing NE/supine NE in the subjects with OH regardless of BP status or any kind of medications was less than in the subjects without OH. Ratio of standing NE/supine NE before treatment were 2.2 ± 0.4 in NT with OH, 2.4 ± 0.3 in NT without OH, 1.6 ± 0.3 in HT with OH, and 2.0 ± 0.2 in HT without OH, and after treatment 2.1 ± 0.2 in NT with OH, 2.3 ± 0.2 in NT without OH, 1.5 ± 0.3 in HT with OH and 1.9 ± 0.4 in HT without OH.

**DISCUSSION**

In this study, we tried to examine the prevalence and mechanism in orthostatic BP reduction in particular relation to BP status and to sympathetic nerve activity. Our results indicate that in elderly subjects OH was
common and increased with advancing age and BP levels, and these results were in good accordance with those in SHEP study, the CHS Collaborative Research Group, and our previous study. Some investigators reported that the incidence of OH was also negatively correlated with body mass index. However, we could not verify this phenomenon, because in the present study, body mass index was matched strictly. Furthermore, we recognized that in elderly hypertensives patients, the prevalence of OH decreased with reducing BP levels by medications and that the changes in BPs from supine to standing position correlated significantly to supine BP. These results support the concept that factors significantly associated with the presence of OH were higher mean systolic BP and elevated sitting BP.

We defined orthostatic BP reduction in two different levels as a decline of 10% or more in supine mean BP and 20/10 mm Hg or more in supine BP. Although there are mainly reports in which OH was defined as a decline of 20/10 mm Hg or more in sitting BP or supine BP, we thought that an absolute value of 20/10 mm Hg may be inappropriate because the basal BPs between normotensives and hypertensives are significantly different. Therefore, we used the percentage decline of BP to compare the incidence of OH between normotensive and hypertensive subjects. Furthermore, we used the BP and plasma NE levels after standing position for 2 min, rather than 1 or 3 min, because we have reported that the maximum changes in plasma NE from supine to standing position were recognized at 2 min after standing position in young hypertensive patients.

It is known that plasma NE, as an index of sympa-
thetic nerve activity, increases with aging\textsuperscript{8} and that plasma NE responses to a change in position are increased in normotensive healthy elderly subjects, although cardiac responsiveness to sympathetic stimulation is diminished.\textsuperscript{9} On the other hand, in elderly hypertensive patients, plasma NE does not increase in association with aging, and our previous findings indicate that plasma NE response to upright posture is blunted.\textsuperscript{7,8} Recently, Esler et al and Mark et al reported that NE spillover\textsuperscript{10,11,12} or muscle sympathetic nerve activity\textsuperscript{13} is better than plasma NE concentration to indicate an index of sympathetic nerve activity, and that head-up tilting typically reduced the rate of norepinephrine clearance from plasma.\textsuperscript{10} However, they also reported that the spillover of NE was different in each organ, and that plasma NE concentration showed partly the sympathetic nerve activity in whole body. Anderson et al\textsuperscript{13} reported also that the muscle sympathetic nerve activity and blood flow were different between arm and leg muscle during mental stress. For this reason, in this study we used plasma NE concentration as an index of sympathetic nerve activity, and also because plasma NE concentrations are convenient to measure in many subjects on numerous occasions.

In the present study, basal supine plasma NE is greater in hypertensive patients and in subjects with OH, and plasma NE response to upright posture is blunted in elderly hypertensive patients and in subjects with OH regardless of hypertension medications. These results agree with our previous study\textsuperscript{6} and the NE spillover study for postural change by Esler et al.\textsuperscript{11}

In the present study, metoprolol, enalapril and nifedipine had stronger effects in reducing OH inci-

\begin{figure}[h]
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\caption{The percentage of incidence of orthostatic blood pressure reduction, defined as a decline of 10\% or more in supine mean BP, before and after treatment in all subjects by level of supine systolic blood pressure. * indicates 0\%.}
\end{figure}
ence after long-term (more than 3 months) medication use than did thiazide or prazosin, particularly after 1 year of medication. These differences might be caused by the differences in the mechanisms of BP reduction, especially due to the effects on sympathetic nerve activity, because in the acute medicated phase, \(\beta\)-blockers and angiotensin converting enzyme (ACE) inhibitors have suppressive effects on the sympathetic nerve activity, and diuretics stimulate sympathetic nerve activity. However, these effects may exist only in the acute phase but not in the chronic phase. Therefore other mechanisms, such as the effects of blood pressure reduction itself on the central control of circulation, should be considered. On the other hand, prazosin may affect baroreceptor reflex mechanism by its own peripheral sympathetic blocking action resulting in the persistent postural blood pressure reduction.

Our findings that the incidence of OH decreased followed by decreasing BP and normalizing BP by antihypertensive drugs (especially \(\beta\)-blockers, calcium antagonists, and ACE inhibitors) in elderly hypertensive patients may indicate that some of hypertension-associated blunted mechanism of BP regulation predisposes orthostatic BP reduction in elderly hypertensive patients. Some investigators reported also that OH may result from age-related physiological change, age-associated disease or impaired homeostatic mechanisms of blood pressure regulation,\(^4\) impaired hemodynamic mechanisms or blunted \(\beta\)-adrenergic vascular reactivity and\(^5\) a predominance of \(\alpha\)-adrenergic vascular reactivity.\(^6\)

In conclusion, hypertension and the blunted sympathetic nerve activity may play some important roles in the development of frequent orthostatic hypotension in the elderly hypertensives.

REFERENCES


