Efficacy of Various Antihypertensive Agents as Evaluated by Indices of Vascular Stiffness in Elderly Hypertensive Patients

Takeshi TAKAMI and Minori SHIGEMASA

When observed in elderly hypertensive patients, increased pulse pressure (PP) and arterial stiffness are known to be independent risk factors for cardiovascular diseases. Increased systolic blood pressure (SBP) leads to left ventricular hypertrophy, while decreased diastolic blood pressure (DBP) results in decreased coronary circulation. It is known that increased arterial stiffness is the major cause of increased PP. Thus basic morbidity states of cardiac failure or ischemic heart diseases are more likely to develop in elderly hypertensive patients with increased PP and arterial stiffness, and there is need of antihypertensive drugs that decrease these effects in elderly hypertensives. In this study, we compared the effects of an angiotensin-receptor blocker (ARB: valsartan), an angiotensin-converting enzyme inhibitor (ACE-I: temocapril), and long-acting Ca antagonists (L- and N-type Ca channel blocker: cilnidipine; and L-type Ca channel blocker: nifedipine CR) on PP and arterial stiffness measured by pulse wave velocity in elderly hypertensive patients for 3 months. The ARB yielded the largest reductions in PP and brachial-ankle pulse wave velocity (baPWV), followed by the ACE-I and L- and N-type Ca channel blocker, while the L-type Ca channel blocker yielded no improvement. The effects on arterial stiffness and PP thus varied among the drug characteristics. Although ARB achieved the largest reduction in baPWV, this decrease was not associated with any reductions in PP, SBP, DBP, or mean blood pressure, as were the baPWV-decreases achieved by the other drugs, suggesting that ARB may further reduce the risk of arteriosclerosis in elderly hypertensive patients by decreasing arterial stiffness in addition to its antihypertensive effect. (Hypertens Res 2003; 26: 609–614)

Key Words: hypertension in the elderly, angiotensin-receptor blocker, arterial stiffness, brachial-ankle pulse wave velocity, pulse pressure

Introduction

The percentage of hypertensive patients who are also elderly is increasing. Hypertension in the elderly is characterized by systolic hypertension, with increased systolic blood pressure (SBP) as a risk factor rather than increased diastolic blood pressure (DBP), and increased pulse pressure (PP) is regarded as critical (1–7). Pulse pressure is regulated by stroke volume as well as the extensibility of elastic arteries, which are vulnerable to arterial stiffness. Increased arterial stiffness and PP are known to be independent risk factors for cardiovascular diseases (1–10). Increased SBP leads to left ventricular hypertrophy, while decreased DBP results in decreased coronary circulation. Left ventricular hypertrophy accelerates the progression of cardiovascular remodeling, decreases left ventricular diastolic function, increases left ventricular end-DBP, and promotes endocardial ischemia. Thus, hypertension in elderly patients is associated with basic conditions of cardiac failure or ischemic heart disease. Therefore, antihypertensive drugs that decrease not only blood pressure (BP) but also arterial stiffness and PP are required for the treatment of such patients. We compared the effects of an angiotensin-receptor blocker (ARB), an angiotensin-converting enzyme inhibitor (ACE-I), and long-acting Ca antagonists (L- and N-type Ca channel blocker: cilnidipine; and L-type Ca channel blocker: nifedipine CR) on PP and arterial stiffness measured by pulse wave velocity in elderly hypertensive patients for 3 months. The ARB yielded the largest reduction in PP and brachial-ankle pulse wave velocity (baPWV), followed by the ACE-I and L- and N-type Ca channel blocker, while the L-type Ca channel blocker yielded no improvement. The effects on arterial stiffness and PP thus varied among the drug characteristics. Although ARB achieved the largest reduction in baPWV, this decrease was not associated with any reductions in PP, SBP, DBP, or mean blood pressure, as were the baPWV-decreases achieved by the other drugs, suggesting that ARB may further reduce the risk of arteriosclerosis in elderly hypertensive patients by decreasing arterial stiffness in addition to its antihypertensive effect. (Hypertens Res 2003; 26: 609–614)
Table 1. Baseline Characteristics of Hypertensive Patients According to Treatment Assignment

<table>
<thead>
<tr>
<th></th>
<th>Valsartan (n = 20)</th>
<th>Temocapril (n = 20)</th>
<th>Cilnidipine (n = 20)</th>
<th>Nifedipine CR (n = 16)</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years old)</td>
<td>71.0 3.0</td>
<td>71.4 2.7</td>
<td>72.0 3.0</td>
<td>72.8 2.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/16</td>
<td>—</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>184.7 4.2</td>
<td>184.1 4.6</td>
<td>186.7 4.3</td>
<td>188.4 8.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>97.9 2.7</td>
<td>96.6 3.2</td>
<td>97.2 3.7</td>
<td>98.9 3.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>65.1 5.4</td>
<td>65.9 4.7</td>
<td>65.0 6.4</td>
<td>66.2 5.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>WHO criteria (stage I/II)</td>
<td>2/18</td>
<td>3/17</td>
<td>3/17</td>
<td>2/14</td>
<td>n.s.</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.8 1.5</td>
<td>22.9 1.7</td>
<td>22.7 1.7</td>
<td>23.2 1.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Smoking (n)</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; n.s., not significant.

Methods

Subjects
We compared the brachial-ankle pulse wave velocity (baPWV)-reducing effects in 76 male hypertensive patients aged 65 years or older who visited the outpatient clinic of our hospital. All patients were devoid of complications such as diabetes mellitus, hyperlipidemia, hyperuricemia, and obstructive arteriosclerosis, and either had no history of antihypertensive treatment or had received no antihypertensive drugs for over 4 weeks. Patients diagnosed with moderate or more severe hypertension based on casual BP measurement were included, while patients with secondary hypertension were excluded. Diagnosis of hypertension was done to calculate the mean value of BP for three times. Subjects were randomly assigned to one of four groups for treatment with the following drugs: ARB (valsartan), ACE-I (temocapril), L- and N-type Ca-channel blocker (cilnidipine), or L-type Ca-channel blocker (nifedipine CR). As a rule, the subjects were treated with a single agent for 3 months. After the initial dose, serum biochemistry tests and urinalysis were regularly performed, and BP was regularly measured. As efficacy endpoints, baPWV and casual BP (sitting position) were measured and recorded at baseline and 3 months after initiation of treatment. An oral daily dose of 80 mg/day of valsartan (Novartis Pharma K.K., Tokyo, Japan), 2–4 mg/day of temocapril (Sankyo Co., Ltd., Tokyo, Japan), 10 mg/day of cilnidipine (Mochida Pharmaceutical Co., Ltd., Tokyo, Japan), or 20 mg/day of nifedipine CR (Bayer Yakuhin, Ltd., Osaka, Japan) was administered once a day in the morning. baPWV was determined from pulse waves measured on the right forearm and right ankle using form pulse wave velocity (PWV) (Colin Corp., Aichi, Japan). Two inspectors performed multiple measurements to validate the inter-observer and intra-observer reproducibility of baPWV.

Prior to the study, all patients provided their informed written consent after receiving an explanation of the contents of this study, the potential adverse reactions associated with each agent, and the policies of patient privacy of our institution. The study protocol was approved by the Institutional Ethical Committee.

Statistical Analysis
Data are expressed as the mean ± SD. Significant differences among the four groups were determined using one-way analysis of variance (ANOVA) combined with Scheffe’s post hoc test, and the ŋ² test where appropriate. Single linear regression analysis was used to evaluate the relation between change in baPWA and changes in BP (systolic, diastolic, mean and pulse). Repeated-measures of ANOVA were used to test for differences in BP and heart rate in each group. Differences of p < 0.05 were considered to indicate statistical significance.

Results

Subject Demographics
Subject baseline demographics are shown in Table 1. The numbers of patients assigned to the valsartan, temocapril, cilnidipine, and nifedipine CR groups were 20, 20, 20, and 16, respectively. The mean age was 71.0 ± 3.0 years for the valsartan group, 71.4 ± 2.7 years for the temocapril group, 72.0 ± 3.0 years for the cilnidipine group, and 72.8 ± 2.7 years for the nifedipine CR group. All subjects were male. There were no difference in these background or other factors such as baPWV, ambulatory BP, heart rate, stage of hypertension according to the WHO classification of BP level, body mass index (BMI), or smoking habit among the four treatment groups. None of the patients had any complications which may have affected the endpoints, including cerebral disease, renal dysfunction, diabetes mellitus, hyperlipidemia, hyperuricemia, obstructive arteriosclerosis, or secondary hypertension. The number of patients with left ventricular hypertrophy was the same as...
Ambulatory Blood Pressure and Pulse Pressure

SBP and DBP were significantly decreased in all four treatment groups. The differences between baseline ambulatory BP and ambulatory BP at 3 months after treatment are shown in Table 2. The reductions in SBP and DBP (ΔSBP and ΔDBP) in each treatment group were as follows: 46.3 ± 4.8 mmHg and 16.8 ± 5.4 mmHg in the valsartan group, 40.5 ± 6.6 mmHg and 14.8 ± 4.2 mmHg in the temocapril group, 46.8 ± 6.6 mmHg and 18.8 ± 4.2 mmHg in the cilnidipine group, and 50.5 ± 10.3 mmHg and 40.6 ± 11.6 mmHg in the nifedipine CR group. There was a significant difference in ΔSBP between the nifedipine CR group and the temocapril group (p < 0.05), while ΔDBP was significantly higher in the nifedipine CR group than in the other groups (p < 0.01).

Brachial-Antkle Pulse Wave Velocity (baPWV)

BaPWV was significantly decreased in the valsartan, temocapril, and cilnidipine groups (p < 0.01), but remained unchanged in the nifedipine CR group. The reductions in baPWV (ΔbaPWV) were significantly smaller in the nifedipine group than in the other groups (p < 0.01).

Correlation between ΔbaPWV and Changes in Blood Pressure (ΔPP, ΔSBP, ΔDBP, ΔMBP)

ΔbaPWV and ΔPP were significantly correlated in all 76 patients (r = 0.62, p < 0.001), suggesting that reduction in PP contributes to improvement of arterial stiffness. As shown in Table 3, however, the examination of individual groups revealed varying results, i.e., ΔbaPWV and ΔPP were not

Table 3. Correlation Coefficient (β): Correlations between Change in baPWV and Various Blood Pressure Parameters

<table>
<thead>
<tr>
<th></th>
<th>Valsartan</th>
<th>Temocapril</th>
<th>Cilnidipine</th>
<th>Nifedipine CR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔSBP</td>
<td>0.236</td>
<td>0.517*</td>
<td>-0.017</td>
<td>0.608**</td>
<td>0.084</td>
</tr>
<tr>
<td>ΔDBP</td>
<td>-0.092</td>
<td>0.052</td>
<td>0.458*</td>
<td>-0.809**</td>
<td>-0.616**</td>
</tr>
<tr>
<td>ΔMBP</td>
<td>-0.011</td>
<td>0.305</td>
<td>0.362</td>
<td>-0.622**</td>
<td>-0.528**</td>
</tr>
<tr>
<td>ΔPP</td>
<td>0.252</td>
<td>0.509*</td>
<td>-0.252</td>
<td>0.821**</td>
<td>0.620**</td>
</tr>
</tbody>
</table>

PWV, pulse wave velocity; Δ, difference between 3 months after treatment; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure. *p < 0.05, **p < 0.01: one-way analysis of variance with Scheffe’s test.

the number of patients with WHO criteria stage II hypertension.
correlated in the valsartan group ($r = 0.25$, not significant (NS)), significantly correlated in the temocapril group ($r = 0.51$, $p < 0.05$), not correlated in the cilnidipine group ($r = -0.25$, NS), and significantly correlated in the nifedipine CR group ($r = 0.82$, $p < 0.01$). In the groups given temocapril, cilnidipine, or nifedipine CR, ΔbaPWV exhibited a significant correlation with at least one of the parameters of BP change (ΔPP, ΔSBP, ΔDBP, ΔMBP), whereas in the valsartan group no such correlation was noted between ΔbaPWV and any of ΔPP, ΔSBP, ΔDBP, and ΔMBP.

**Discussion**

Arteriosclerosis is associated with morphological alterations such as hypertrophy and stenosis as well as functional alterations such as loss of arterial wall elasticity or sclerosis, which are regarded as arterial stiffness and thus are distinguished from arteriosclerosis. In recent years, however, arterial PWV has been shown to be a good marker of arterial stiffness (8, 9, 11) and to be an excellent predictor of the prognosis of hypertension (12, 13). It has been reported that the risk of cardiovascular disease increases as PWV increases, and that PWV can therefore be an excellent predictor of fatal cardiovascular disease (13). Arteriosclerosis due to aging, and increased arterial stiffness in particular, decreases the Windkessel function responsible for buffering BP increase, thereby increasing SBP and decreasing DBP. Moreover, an increase in PWV associated with arteriosclerosis leads to elevation of SBP mediated by reflex waves. As a result, PP may also be elevated in elderly hypertensive patients. The authors of a follow-up investigation of the Framingham heart study (1) reported that, among subjects with similar DBP, those with higher SBP showed a higher risk of coronary diseases, while among subjects with similar SBP, those with lower DBP showed a higher risk of coronary diseases. Based on these findings, they concluded that increased PP may be an even greater risk factor for coronary disease than increased SBP and DBP. The Survival and Ventricular Enlargement trial (SAVE) and Studies of Left Ventricular Dysfunction (SOLVD) series also reported that increased PP was an independent risk factor for all-cause deaths and cardiovascular mortality (4, 5). A meta-analysis of the data from large-scale clinical studies in elderly hypertensive patients found that increased PP was a critical risk factor for deaths and cardiovascular events (3). Based on the above, we hypothesized that an improvement of the arterial stiffness and a decrease in PP could reduce the risk of cardiovascular events in hypertensive patients. We therefore investigated the effects of various antihypertensive agents on PWV and PP in elderly hypertensive patients.

We recorded PP waveforms in the right forearm and right ankle simultaneously using a simple, non-invasive oscillometric method and determined baPWV as an index of arterial stiffness to examine the effects of various antihypertensive agents in hypertensive patients. Studies have reported that baPWV exhibits a strong correlation with carotid-femoral PWV determined by the tonometric method (14, 15). Because a large-scale investigation trial using PWV as an endpoint reported that perindopril (ACE-I) significantly reduced PWV (16), we selected an ACE-I, temocapril (17, 18), as a control drug. Other antihypertensive agents selected for the study were an ARB (valsartan) (19, 20) and two Ca-channel blockers. One of the Ca-channel blockers was an L-type Ca-channel blocker (nifedipine CR), which blocks only L-type Ca-channels present in vascular smooth muscle, and the other was an L- and N-type Ca-channel blocker (cilnidipine), which blocks L-type Ca-channels as well as N-type Ca-channels present in sympathetic nerve endings and also has a sympatholytic effect (21–23).

Valsartan, temocapril, cilnidipine, and nifedipine CR each significantly decreased SBP and DBP. However, ΔDBP was significantly greater in the nifedipine CR group than in the other three treatment groups ($p < 0.01$). As a result, PP remained unchanged after treatment in the nifedipine CR group, but was significantly decreased in the other three treatment groups. Although a significant difference was found in ΔSBP between the temocapril group and nifedipine CR group, small ΔDBP resulted in a decrease in PP in the temocapril group.

Similar to PP, baPWV was significantly decreased in the valsartan, temocapril, and cilnidipine groups, but exhibited little change in the nifedipine CR group. Furthermore, while baPWV was improved in each of the valsartan, temocapril, and cilnidipine groups, the baPWV increase in the valsartan group was significantly higher than that in the other two groups. Wilkinson et al. (24) reported that intravenous administration of angiotensin II and norepinephrine increased...
arterial wall stiffness and that norepinephrine increased PP. Another study reported that AT1 receptor genotypes were involved in an age-related increase in aortic stiffness in hypertensive patients (25). A further study reported that although alteration in arterial structure may be important in improving arterial stiffness, ARBs inhibited collagen accumulation in the aorta in an experimental model (26). These findings may explain the present findings that ARB, ACE-I, and an L- and N-type Ca-channel blocker, all of which inhibit the release of norepinephrine, improved both PWV and PP.

It has been found that nitric oxide (NO) donors such as sinitrodil decrease arterial stiffness and PP without much effect on vascular resistance and DBP (27, 28), and another study reported that doxazosin, an α-blocker, promotes NO production, thereby contributing to improvement of arterial stiffness (29). Thus, the enhancement of NO production by valsartan (30), temocapril (31), cilnidipine (32), and nifedipine (33), may have contributed to the results observed in this study. However, the beneficial effect of valsartan on ∆baPWV might have been due not only to NO production, but also to enhancement of AT1 receptor blockade (30).

The present study found the largest baPWV-reducing effect in the ARB group. Concerning the mechanism of reduction of baPWV, since a significant correlation was found between ∆baPWV and at least one of ∆PP, ∆SBP, ∆DBP, and ∆MBP with ACE-I and two Ca-channel blockers, changes in BP may nonetheless be associated with improvement of atherosclerosis. However, ∆baPWV did not correlate with any one of ∆PP, ∆SBP, ∆DBP, and ∆MBP with ARB, suggesting the importance of blockade of angiotensin receptors in addition to antihypertensive effect in improving arterial stiffness.

In conclusion, since it has been demonstrated that arterial stiffness and increased PP are risk factors for the onset of cardiovascular diseases, it is necessary to take these factors into consideration in the treatment of hypertension. In the present study, the effects of antihypertensive agents on PP and arterial stiffness in elderly hypertensive patients varied among drug classes. These results suggested that PWV is regulated not only by BP but also by changes in the nature of the arterial wall resulting from continuous hypertension (34), and that ACE-I reduces arterial collagen (26) by a mechanism of action not involving bradykinin but blockade of angiotensin receptors instead. The results of the present study suggest that although ARBs, ACE-I, and L- and N-type Ca-channel blockers reduce the risk of atherosclerosis by decreasing arterial stiffness in addition to exerting an antihypertensive effect, ARB may further reduce the risk of atherosclerosis in elderly hypertensive patients.

References


