Original Article

Higher Small Arterial Elasticity in Hypertensive Patients Treated with Angiotensin II Receptor Blockers

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Although evidence from basic research suggests the involvement of angiotensin II (Ang II) in the progression of arteriosclerosis, the clinical data are limited. In the present study, hypertensive outpatients who were well controlled with antihypertensive medication and had similar blood pressure levels were studied, and arterial elasticity was compared between those receiving Ang II receptor blockers (ARBs) and those treated with other antihypertensive agents. The effects of HMG-CoA reductase inhibitors (STs) on arterial elasticity were also evaluated. The study enrolled 298 outpatients who had been diagnosed with essential hypertension whose blood pressure was controlled to 150/95 or less by antihypertensive treatment (excluding angiotensin converting enzyme [ACE] inhibitors) for at least 2 months. The small artery elasticity index (SAEI) was determined for each patient from the radial artery pulse waves using a non-invasive pulse wave analysis system CR-2000. The mean of two blood pressure measurements taken from subjects lying in a recumbent position during SAEI analysis was used for the data analysis. The patients were grouped according to the use of ARBs and STs, and two-way analysis of variance (ANOVA) was used for statistical comparisons. A backward stepwise multiple regression analysis was carried out to identify factors contributing to the SAEI. Hypertensive patients receiving ARB treatment had a significantly higher SAEI compared to those not receiving ARBs, despite the similar blood pressure levels of both groups. No significant effects of ST treatment on the SAEI were observed (two-way ANOVA). A backward stepwise multiple regression analysis for the SAEI suggested that ARB treatment was an independent determinant of the SAEI after the adjusting of age, gender, total cholesterol, high density lipoprotein cholesterol, smoking and systolic blood pressure. Our results suggested that while providing blood pressure control similar to that of other antihypertensive agents, ARBs may also increase vascular elasticity and thereby delay the progression of arteriosclerosis. (*Hypertens Res* 2005; 28: 639–644)

***Key Words*: arterial elasticity, angiotensin II receptor blocker, statin, essential hypertension**

Introduction

The recent focus of antihypertensive therapy has shifted from simply lowering blood pressure to protect target organs, and hence one of the primary goals of antihypertensive therapy is to prevent the progression of arteriosclerosis. Reduced arterial elasticity is a common complication of hypertension and

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We reported the results of this study at the 26th Annual Meeting of the Japanese Society of Hypertension in 2003.

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Received October 21, 2004; Accepted in revised form June 10, 2005.

Table 1. Patients Characteristics

Age (years)	64.2±9.8
Gender (male/female)	189/109
DM (*n* [%])	94 (31.5)
HL (*n* [%])	163 (54.7)
Smoking (*n* [%])	90 (30.2)

n=298. DM, diabetes mellitus; HL, hyperlipidemia.

Table 2. Medication

ARB (*n*=61)	
Candesartan	45 (73.8%)
Losartan	14 (23.9%)
Valsartan	2 (3.3%)
Statin (*n*=94)	
Pravastatin	30 (31.9%)
Simvastatin	27 (28.7%)
Atorvastatin	23 (24.5%)
Serivastatin	12 (12.8%)
Fluvastatin	2 (2.1%)

ARB, angiotensin II receptor blocker.

has drawn recent attention as a non-invasive index of arteriosclerosis (*1*). Arterial elasticity has been shown to be impaired in the presence of risk factors (*2*) and is associated with cardiovascular events (*3*). Reduced arterial elasticity is observed in patients with congestive heart failure as well as in patients suffering from complications associated with diabetes, dyslipidemia, smoking, and other cardiovascular risk factors. Therefore, changes in arterial elasticity may serve as surrogate end points for the estimation of the status of the artery as well as for the estimation of effects of therapeutic intervention.

Angiotensin II (Ang II) is an important factor that contributes to the progression of arteriosclerosis (*4*, *5*). A number of clinical studies have indicated that Ang II receptor blockers (ARBs) or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (STs) independently inhibit the progression of arteriosclerosis. However, the effects on arterial elasticity of both types of drug have not yet been examined in the same population. In addition, recent reports have suggested that both drugs exhibit pleiotropic activities (*6*–*9*). Namely, ARBs are thought to posses therapeutic effects beyond lowering blood pressure, whereas STs may do more than simply reduce cholesterol level.

In the present study, hypertensive patients who were well controlled with antihypertensive medication and had similar blood pressure levels were studied retrospectively, and the small arterial elasticity index (SAEI) was compared between those receiving ARBs and those treated with other antihypertensive agents. The arterial elasticity index is a non-invasive parameter for vascular assessment; here, we determined the SAEI from the radial artery pulse wave using a recently developed pulse wave analysis system, CR-2000 (*10*–*12*). As 31.5% (94 patients) of our subjects received STs, the effects of ST use on the SAEI was also evaluated. Various clinical factors affecting the SAEI were simultaneously determined and adjusted in order to examine the effects of ARBs and STs on the SAEI.

Methods

Subjects

The study enrolled 298 patients (mean age: 64.6±9.8 years; 189 males and 109 females) who were diagnosed with essential hypertension in the outpatient clinic at our hospital. This study was approved by the Ethics Committee of Fukuoka University Hospital, and informed consent was obtained from each patient. These patients received antihypertensive medication for at least 2 months, along with lifestyle treatment, and blood pressure was controlled to 150/95 or less. Patients prescribed an angiotensin converting enzyme (ACE) inhibitor were excluded from the study. The prevalence of hyperlipidemia, diabetes, and smoking and the prevalence of ARB and ST use among the subjects are listed in Tables 1 and 2, respectively.

Pulse Wave Analysis

Patients with severe valvular disease, arteriosclerosis obliterans, severe heart failure, or arrhythmic disorders such as chronic atrial fibrillation were excluded from the study due to the difficulty of obtaining appropriate data *via* the pulse wave analysis system. Small artery compliance was estimated by the new non-invasive pulse-wave contour analysis method developed and validated by the research group of Cohn *et al* (*10*). The computer-based Research CardioVascular Profiling system (CR-2000, Hypertension Diagnostics Inc., Eagan, USA) was used to perform the analysis. The SAEI was estimated from the diastolic decay portion of the cardiac cycle using an electrical analog model (*i.e.*, a modified Windkessel model) which considers the vasculature as consisting of an oscillatory or reflective compliance element.

Pulse wave analysis at the outpatient clinic was carried out according to a method previously described by our group (*13*). The patients rested in the recumbent position for at least 10 min, and blood pressure was measured in the left arm. The sensor was placed over the right radial artery at the point of maximum pulse amplitude, and the pulse waveform was monitored to ensure the acquisition of high-quality signals. The diastolic decay of the radial artery pressure waveform was then analyzed according to a modified Windkessel model in order to determine the SAEI (*10*, *13*). The reproducibility of this assay in our hospital was confirmed by repeated measurements of the same patient (*n*=11) on the same and on

Table 3. Patients Characteristics

	ARB	Non-ARB	*p*
Age (years)	62.4±9.5	65.2±9.8	0.0497
Gender (male/female)	46/15	143/94	0.0423
DM (%)	40.1	29.1	n.s.
HL (%)	45.9	57.0	n.s.
Smoking (%)	26.2	31.2	n.s.
TC (mg/dl)	193±32	191±37	n.s.
TG (mg/dl)	120 (99, 161)	114 (83, 159)	n.s.[#]
HDL-C (mg/dl)	51 (40, 64)	51 (42, 62)	n.s.[#]
LDL-C (mg/dl)	112±27	111±33	n.s.
Mean BP (mmHg)	100±12	97±13	n.s.
Systolic BP (mmHg)	134±16	132±18	n.s.
Diastolic BP (mmHg)	78±10	74±11	0.0223
Pulse pressure (mmHg)	56±12	58±14	n.s.

ARB, angiotensin II receptor blocker; DM, diabetes mellitus; HL, hyperlipidemia; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; BP, blood pressure; n.s., not significant. [#]Logarithmic distribution was used for the analysis.

Table 4. Patients Characteristics

	Statin	Non-statin	*p*
Age (years)	66.1±8.6	63.9±10.3	n.s.
Gender (male/female)	40/54	69/135	n.s.
DM (%)	26.6	33.8	n.s.
Smoking (%)	25.5	32.2	n.s.
TC (mg/dl)	190±32	192±35	n.s.
TG (mg/dl)	125 (88, 182)	113 (86, 154)	n.s.[#]
HDL-C (mg/dl)	50 (41, 62)	52 (41, 62)	n.s.[#]
LDL-C (mg/dl)	112±31	110±35	n.s.
Mean BP (mmHg)	96±13	98±13	n.s.
Systolic BP (mmHg)	130±19	133±17	n.s.
Diastolic BP (mmHg)	74±11	75±11	n.s.
Pulse pressure (mmHg)	56±13	58±14	n.s.

DM, diabetes mellitus; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; BP, blood pressure; n.s., not significant. [#]Logarithmic distribution was used for the analysis.

another day. The Peason's correlation coefficients were 0.96 and 0.93, respectively.

General Clinical Examination

Blood pressure and pulse were measured with subject in the recumbent position during pulse wave analysis, and the mean of two blood pressure measurements was used for the data analysis. Fasting blood samples were collected from patients prior to pulse wave analysis, and fasting blood glucose, total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) were measured. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald formula.

Coronary Risk Factors

Hyperlipidemia was defined as either verified hyperlipidemia on oral medication or a fasting lipid profile of TC≥220 mg/dl or TG≥150 mg/dl. Diabetes was defined as either verified diabetes treated with oral medications or insulin, or a fasting blood glucose level of ≥126 mg/dl. A history of smoking was defined as either a current smoking habit or a history of smoking within the past 10 years.

Statistical Analysis

Values were expressed as follows: as mean±SD for continuous normally distributed variables, as the median (first quartile, third quartile) for continuous non-normally distributed data, and as percentages for categorical data. Since the distributions of the TG, HDL-C, SAEI were not normal, the logarithmic distribution of these values was used for the analysis. Statistical comparisons among groups were performed using two-way analysis of variance (ANOVA) to examine the effects of both ARBs and STs. Categorical variables (such as gender) were compared between ARB and non-ARB groups and also between ST and non-ST groups by χ^2 test. Continuous variables were compared between groups by Student's *t*-test. A backward stepwise multiple regression analysis was carried out to identify significant predictive variables for the SAEI. In addition to ARB and ST treatment, the following factors were included in a backward stepwise multiple regression analysis with the SAEI as a dependent variable: age; gender; TC; TG; HDL-C; LDL-C; history of hypertension; hyperlipidemia; smoking; diabetes mellitus; and systolic, diastolic, and mean blood pressure. To examine the effects of ARB or ST treatment on the SAEI, multiple regression analysis was performed with the adjustment of parameters selected as independent variables. Statistical analysis was performed using the SAS Software Package (Release 8.2, Statistical Analysis System, SAS Institute Inc., Cary, USA) at Kyushu University Hospital. *p* values of less than 5% were considered to be significant.

Results

Table 3 summarizes the results of the comparison of various factors between ARB and non-ARB groups, the average age was slightly but significantly younger in the ARB group. The male-to-female ratio and diastolic blood pressure were significantly higher in the ARB group.

There were no significant differences with respect to various parameters between the STs and non-STs groups (Table 4).

Two-way ANOVA for ARB treatment and ST treatment

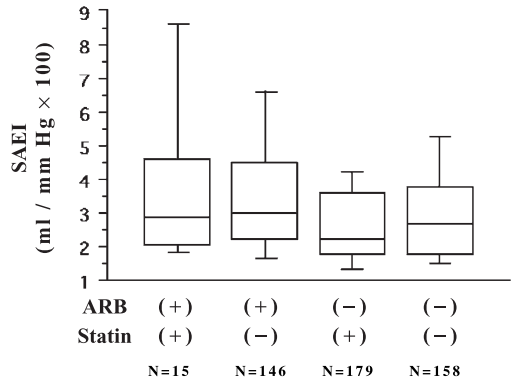

Fig. 1. *Comparison of SAEI between the groups with or without ARB or statin treatment. ARB: patients treated with angiotensin II receptor blockers. SAEI, small artery elasticity index.*

with the SAEI as a dependent variable showed that the SAEI in the ARB group was significantly higher ($F(1,295)=8.31$, $p=0.0042$; Fig. 1) than that without the ARB treatment (Table 5). However, the SAEI in the ST group was not significant ($F(1,295)=2.55$, $p=0.1117$). A backward stepwise multiple regression analysis for the SAEI as a dependent variable indicated that the determinants of the SAEI were age, gender, TC, HDL-C, smoking, systolic blood pressure, and ARB treatment. Multiple regression analysis adjusted for these parameters indicated that ARB, but not ST, treatment significantly contributed to the higher SAEI (Table 6).

Discussion

The ultimate goal of antihypertensive therapy is not to lower blood pressure, but rather to prevent cardiovascular events by reducing the progression of arteriosclerosis. The present study investigated the use of ARBs and STs on small arterial elasticity, known to be an important index of arterial functional as well as structural changes associated with arteriosclerosis. In the present study, the SAEI was significantly higher in the ARB group than in the non-ARB group. Among various clinical parameters, significantly younger age and a higher male ratio were also observed in the ARB group. A multiple regression analysis indicated that ARB treatment was an independent determinant for a higher SAEI. This result suggested that treatment with ARBs, but not with STs, contributed to greater small artery elasticity. Since the blood pressure levels of the ARB and non-ARB groups were equivalent, the contributing effect of ARB treatment on the higher SAEI was considered to be independent of the blood pressure-lowering effect of ARBs.

Several basic research and clinical reports have implicated that Ang II is involved in the development of arterial stiffness. Chronic infusion of Ang II in apolipoprotein E knock-out (apoE-KO) mice *via* an osmotic mini-pump for 1 month

Table 5. Two Way ANOVA

	F value	DF	*p* value
ARB	8.31	1,295	0.0042
Statin	2.55	1,295	0.1117

ANOVA, analysis of variance; ARB, angiotensin II receptor blocker; DF, degree of freedom.

accelerated the development of atherosclerosis fivefold in the carotid arteries, and significantly increased aortic stiffness, as measured *in vivo* by pulse wave velocity (PWV) and *in vitro* by elastography (*14*). The administration of Ang II also increased the PWV of wild-type mice to a magnitude similar to that observed in apoE-KO mice. Consistent with these findings, Ang II has been reported to decrease arterial compliance *ex vivo* (*15*) and *in vivo* (*16*).

The exact mechanism for Ang II-induced vascular stiffening remains unclear at present. However, this process has been correlated with morphological changes (breaks in the internal elastic lamina and inflammatory cell infiltration) and biochemical changes (increases in collagen content and decreases in elastin content) in the aortic wall (*14*). The molecular mechanisms for Ang II-induced vascular pathology involve the activation of NF-κB-dependent proinflammatory mediator such as interleukin-6, intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin, monocyte chemoattractant protein-1, *etc*. and the down-regulation of anti-inflammatory mediators such as peroxisome proliferator-activated receptors (PPARs), which are members of the nuclear receptor superfamily of transcription factors that control the expression of a large array of genes, in the aortic wall (*17*). The activation of proinflammatory mediators promotes monocyte/macrophage infiltration into the vascular wall. These inflammatory cells are a major source of urokinase-type plasminogen activator (uPA) and other proteolytic enzymes, including matrix metalloproteinases (MMPs). uPA hydrolyzes plasminogen to form plasmin, a trypsin-like proteolytic enzyme capable of directly degrading the components of the extracellular matrix, as well as activating MMPs. Indeed, the expression of uPA and MMP2 and 9 is significantly up-regulated in the aortas from mice treated with Ang II (*18*). These proteolytic enzymes degrade certain components of the extracellular matrix (*19*, *20*), including elastin in the aortic wall, thus contributing to aortic stiffening. The PPAR is the central regulator of insulin and glucose metabolism and thereby improves insulin sensitivity. Schupp *et al*. demonstrated that a subset of ARBs (telmisartan and irbesartan) stimulate PPARγ activity independent of their Ang II receptor subtype 1 blocking actions (*7*). These results indicate that ARBs improve glucose metabolism, which in turn reduces the onset of diabetes mellitus and subsequent arteriosclerosis. These basic data, taken together, suggest that Ang II promotes arterial stiffening.

There is a substantial amount of evidence demonstrating

Table 6. Multivariable Regression Analysis for SAEI

	Parameter estimate	SEM	*p* value
Age	−0.0189	0.0026	<0.0001
Gender	0.2300	0.0592	0.0001
TC	0.0022	0.0008	0.0051
log (HDL-C)	−0.2258	0.0907	0.0135
Smoking	−0.1349	0.0599	0.0252
Systolic BP	−0.0104	0.0014	<0.0001
ARB	0.1593	0.0656	0.0148
Statin	−0.0780	0.0536	0.1468

SAEI, small artery elasticity index; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; BP, blood pressure; ARB, angiotensin II receptor blocker; n.s., not significant.

that ARBs or ACE inhibitors reduce vascular stiffness *via* both structural and functional changes. Lage and colleagues reported that treatment with an ACE inhibitor improves arterial compliance in patients with congestive heart failure (*21*). In elderly hypertensive patients with left ventricular hypertrophy, administration of the ARB valsartan was found to be the most effective treatment in terms of reducing the PWV among four different anti-hypertensive medications (the others were: ACE inhibitors, and short- and long-acting Ca antagonists) (*22*). By comparing the effects of an ARB, losartan, to those of a general diuretic, hydrochlorothiazide, in hypertensive patients, Mahmud and Feely reported that losartan induces a blood pressure-independent decrease in both aortic stiffness and arterial wave reflection (*23*). Shargorodsky *et al*. also reported that a 3-month period of antihypertensive treatment with valsartan led to improved small and large artery compliance (*24*). These clinical results indicate that treatment with an ARB appears to contribute not only to blood pressure reduction, but also to a reduction in arterial stiffness; these findings are in agreement with the present results.

Unlike ACE inhibitors, ARBs, by selectively blocking the Ang II type 1 receptor, can inhibit the effects of Ang II produced by a non-ACE enzyme chymase and can also activate the Ang II type 2 receptor; thus, ARBs are expected to provide the advantage of inhibiting the progression of arteriosclerosis. Indeed, the increased local synthesis of Ang II by chymase in the human vasculature has also been reported in patients with conditions such as aortic atherosclerosis and aneurysm (*25*). It has also been reported that chymase inhibitor administered to a high cholesterol-fed hamster model decreased aortic arteriosclerosis (*26*), indicating that chymase-mediated Ang II formation also contribute to the development of arteriosclerosis. Thus, it appears that ARBs can inhibit the deleterious effects of chymase-dependent Ang II formation.

Previous reports have shown that the SAEI reflects subtle vascular alterations due to aging (*12*), hypertension (*5*), and type I diabetes (*27*). It has been reported that the SAEI is lower in postmenopausal women with symptomatic coronary artery disease than in those without these disease (*10*). In subjects with high-normal blood pressure, the SAEI is inversely related to the intima-media thickness of the common carotid artery (*28*). Another recent paper by Syeda *et al*. has indicated that a low SAEI is associated with diffuse coronary artery disease (*29*). Our recent observations also indicated that a low SAEI is of strong diagnostic value in male hypertensive patients with coronary artery disease (*13*). Thus, the SAEI appears to be a useful tool for the clinical non-invasive screening of individuals who are predisposed to arteriosclerotic diseases, especially coronary artery disease. Our present results strongly suggest that treatment with ARBs is an independent predictor of a higher SAEI in hypertensive patients. Therefore, ARB treatment is recommended for hypertensive patients. Since the present report described a cross-sectional retrospective study, additional prospective clinical studies are warranted to confirm the effects of ARB on small artery elasticity.

The anti-inflammatory and anti-arteriosclerotic actions of STs have been the focus of recent attention, and STs have been shown to relieve vascular inflammation (*30*), stabilize plaques (*9*), and improve the function of vascular endothelial cells (*31*). In the present study, no significant differences in the SAEI were observed between the ST and non-ST groups. As there were no significant differences in the lipid parameters between the two groups, we assume that the patients in the ST group had more severe hyperlipidemia than those in the non-ST group. Possible differences in the duration of ST therapy among patients may have affected the analysis of our results. Hence, carefully controlled prospective studies are still needed to assess the association of ST treatment with arterial elasticity.

In conclusion, the present study assessed the respective effects of ARBs and STs on small arterial elasticity in patients with essential hypertension, the blood pressure of whom was well-controlled with antihypertensive agents. A significantly higher SAEI was observed in patients who receive ARB treatment than in patients who did not receive ARB treatment. This finding suggests that ARBs, while providing blood pressure control similar to that of other antihypertensive agents, may also increase vascular elasticity and thereby delay the progression of arteriosclerosis. Hence, for the selection of the optimum antihypertensive agent, the anti-arteriosclerotic effects of the drug as well its capacity to lower blood pressure should be considered.

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