Original Article

Angiotensin Receptor Blocker Improves Coronary Flow Velocity Reserve in Hypertensive Patients: Comparison with Calcium Channel Blocker

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Large-scale clinical studies have indicated that angiotensin receptor blockers (ARBs) have beneficial effects against cardiovascular diseases. We designed this study to compare the effects of an ARB and a calcium channel blocker (CCB) on coronary flow velocity reserve (CFVR), a predictor of cardiovascular events, as estimated using transthoracic Doppler echocardiography. Sixteen hypertensive patients (63.1 ± 9.6 years old; 10 males) were randomly allocated in a double-blind fashion to valsartan ($n=8$, 40–80 mg/day) or nifedipine ($n=8$, 20–40 mg/day) groups. Age- and gender-matched subjects without hypertension were enrolled as a control group ($n=12$). CFVR was calculated by dividing the adenosine triphosphate-induced hyperemic flow velocity by the basal flow velocity in the left anterior descending coronary artery. Baseline characteristics and reduction in systolic and diastolic blood pressure after 6 months were similar in both groups. CFVR in the valsartan group increased from 2.34 ± 0.38 to 3.10 ± 0.84 at 2 months ($p < 0.05$), and to 3.04 ± 1.09 at 6 months ($p < 0.01$). Both values became comparable to that in the control group (2.81 ± 0.60). CFVR in the valsartan group was significantly higher ($p < 0.001$) than that in the nifedipine group, which was little changed at 6 months. This discrepancy was derived from the significant increase of hyperemic velocity in the valsartan group, from 36.6 ± 17.3 cm/s to 41.1 ± 12.7 cm/s at 2 months, and to 48.1 ± 20.2 cm/s at 6 months. We concluded that the ARB valsartan not only reduced high blood pressure but improved CFVR in hypertensive patients. However, these effects were not seen with the CCB nifedipine. (*Hypertens Res* 2007; 30: 699–706)

Key Words: angiotensin receptor blocker, calcium channel blocker, coronary flow velocity reserve, transthoracic Doppler echocardiography

Introduction

The renin-angiotensin system (RAS) regulates blood pressure (BP) and is linked with many cardiovascular diseases. Angiotensin II is the principal substance of the RAS and through its action on angiotensin II receptors plays a central role in main-

taining BP and in altering coronary hemodynamics. Although angiotensin II binds to both type 1 (AT₁) and type 2 (AT₂) receptor subtypes, the AT₁ receptor mediates most of the cardiovascular effects of angiotensin II. Angiotensin receptor blockers (ARBs), which have recently gained widespread acceptance as initial medications for managing hypertension, act by blocking the AT₁ receptors with concomitant stimula-

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Table 1. Baseline Characteristics of Study Patients

	Valsartan (<i>n</i> =8)	Nifedipine (<i>n</i> =8)	Control (<i>n</i> =12)	<i>p</i> value
Age (years)	64.4±8.5	61.6±11.3	62.8±8.8	n.s.
Gender (male/female, <i>n</i>)	6/2	4/4	9/3	n.s.
Body mass index (kg/m ²)	24.2±3.1	26.5±4.1	24.3±3.0	n.s.
Systolic blood pressure (mmHg)	155.5±18.7*	151.3±9.9*	122.0±14.0	<0.01
Diastolic blood pressure (mmHg)	94.3±14.9*	87.5±8.9*	64.0±5.0	<0.01
Heart rate (beats/min)	71±7	69±6	65±7	n.s.
RPP (systolic, mmHg × beats/min)	11,022±1,550*	10,357±1,043*	8,009±1,693	<0.01
Coronary risk factor				
Diabetes mellitus (<i>n</i> (%))	1 (13)	2 (25)	5 (42)	n.s.
Hypercholesterolemia (<i>n</i> (%))	7 (88)	4 (50)	9 (75)	n.s.
Cigarette smoking (<i>n</i> (%))	2 (25)	1 (13)	4 (33)	n.s.
Blood biochemical data				
Fasting glucose (mg/dL)	109±42	107±22	129±39	n.s.
Total cholesterol (mg/dL)	204±35	214±20	233±28	n.s.
Triglyceride (mg/dL)	134±62 [#]	131±30 [#]	199±76	<0.05
HDL cholesterol (mg/dL)	59±18	47±7	50±21	n.s.
Echocardiographic data				
Ejection fraction (%)	67.5±12.8	71.4±6.7	69.6±8.0	n.s.
Left ventricular mass (g)	220.3±81.9	190.8±41.4	199.4±66.9	n.s.
Left ventricular mass index (g/m ²)	129.7±52.3	110.5±24.5	120.0±34.5	n.s.

All data are expressed as the mean±SD. *n*, patient number; RPP, rate-pressure product; HDL, high-density lipoprotein; n.s., not significant. [#]*p*<0.05, **p*<0.01 vs. control subjects.

tion of AT₂ receptors. ARBs can exert several clinical effects: clinical studies have demonstrated that they prevent diabetes mellitus (1) and provide better end-organ protection of the heart (2), blood vessels (3), kidney (4) and brain (5) when compared with other antihypertensive agents.

In hypertensive patients, the coronary flow reserve (CFR) is impaired because of functional and structural alterations of the coronary microcirculation and left ventricular hypertrophy. In addition to hypertension, it has been reported that CFR decreases with various coronary risk factors, such as hypercholesterolemia, diabetes mellitus and aging (6, 7). Assessment of CFR can provide crucial information, both as a diagnostic and prognostic tool for patients at risk for coronary artery disease as well as for the detection of coronary stenosis. Decreased CFR reflects coronary endothelial dysfunction and is associated with a significantly higher incidence of cardiovascular events during long-term follow-up (8, 9). However, an important drawback is that CFR is usually measured by intracoronary Doppler flow wire, an invasive technique not suitable for repetitive measurements. CFR can be noninvasively evaluated by positron emission tomography, but this requires a large-scale and expensive facility. Because of advancements in echo-technologies, recent studies have reported that coronary flow velocity (CFV) and coronary flow velocity reserve (CFVR) in the left anterior descending (LAD) coronary artery can be measured by transthoracic Doppler echocardiography (TTDE), which is both noninvasive and widely used in clinical settings (10). The

results of noninvasive measurement of CFV and CFVR using TTDE have been shown to be in agreement with those by the invasive measurement of CFV and CFVR using an intracoronary Doppler flow wire (11). To our knowledge, it has not been determined whether ARBs, in addition to their BP-lowering effects, may also be able to recover the diminished CFVR. Since TTDE can be repetitively used for measuring CFVR, in the present study we attempted to compare the short and middle-term effects of valsartan (an ARB) and long-acting nifedipine (a calcium channel blocker; CCB) on CFVR in hypertensive patients.

Methods

This open-label randomized crossover trial was performed in a single center, and was designed and monitored in accordance with the ethics and principles of good clinical practice and the Declaration of Helsinki. An institutional review board approved the protocol before the trial started and all participants gave written informed consent to participate.

Subjects and Study Protocol

Between October and December 2002, the study subjects, who had never been treated with any kind of depressor, visited the Hospital of the University of Occupational and Environmental Health as outpatients for diagnosis and treatment of essential hypertension. Essential hypertension was deter-

mined by the following criteria: 1) high blood pressure on more than two occasions (systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg) and 2) no symptoms and/or signs of secondary hypertension. All patients provided their medical histories, and were examined by physical examination, electrocardiography, echocardiography, chest X-ray, and ordinary blood sampling. All patients were also confirmed to be free of coronary artery disease by the absence of angina and abnormal responses on exercise stress electrocardiography. All patients were also confirmed to be free of coronary artery disease, hypertrophic cardiomyopathy, congestive heart failure, atrial fibrillation, 2nd degree atrioventricular block and obstructive lung disease. Sixteen consecutive patients (63.1 ± 9.6 years old; 10 males) were then enrolled in the study. Subjects were randomized into either a group taking valsartan ($n=8$, 40–80 mg/day valsartan) or a group taking nifedipine ($n=8$, 20–40 mg/day long-acting nifedipine). Each medicine was administered after a meal in the morning and was increased when effects were thought to be short lived. CFVR was examined before the study, at 2 months and 6 months after the start of taking the medicine.

We selected a control group from among 228 consecutive patients who underwent CFVR study by TTDE and coronary angiography. After excluding patients with hypertension and those whose coronary arteries were not normal on coronary angiography, 12 subjects (63.5 ± 9.2 years old; 9 males) remained and were enrolled as controls.

Concomitant Drugs, and Exercise and Dietary Therapies

Other than the prescribed ARB and CCB, subjects were not allowed to take any new drugs that might affect BP at any time during the study. The dosage and administration of drugs already taken for other purposes could not be changed during the study regardless of whether or not they would affect blood pressure. As well, no alterations to exercise and dietary therapy regimens were allowed.

Echocardiographic Studies

Echocardiography was performed with a Philips Sonos 5500 echocardiography unit (Andover, USA). As reported previously (12, 13), we first looked for an anterograde flow pattern at the distal site of the LAD with a 12 MHz probe. For CFVR measurements, we initially recorded baseline spectral Doppler signals in the distal portion of the LAD. Next, ATP (Kowa Co. Ltd., Nagoya, Japan) was administered (160 $\mu\text{g}/\text{kg}/\text{min}$) for 3 min to record spectral Doppler signals during hyperemia. ATP is immediately converted to adenosine and affects resistance vessels *via* both endothelium-dependent and -independent mechanisms (14, 15). The electrocardiogram and heart rate were monitored continuously during the examination. BP was recorded at baseline and every min after intravenous administration of ATP. When coronary flow was

Fig. 1. Changes in systolic and diastolic blood pressure (SBP and DBP) in patients treated by valsartan or long-acting nifedipine. There were no significant differences between the two groups. Each point and bar is presented as the mean $\pm$ SD. * $p < 0.05$ compared to the values at baseline in each group (paired *t*-test).

not imaged clearly, a flow enhancing agent, galactose-palmitic acid compound (Schering, Berlin, Germany), was administered by bolus infusion (1 mL of a 300 mg/mL solution), 1 min before recording baseline or hyperemic flow images. Two experienced investigators, blinded to the patient groups, independently analyzed the echocardiograms, and, when the results were not in accordance, a third investigator made the final decision. Measurements were performed off-line by tracing the contour of the spectral Doppler signal using a computer incorporated in the ultrasound system. The average diastolic mean velocity (ADMV) was measured at baseline (ADMV-basal) and peak hyperemia (ADMV-hyp). Average measurements were obtained from three cardiac cycles. CFVR was defined as the ratio of ADMV-hyp to ADMV-basal, as described previously (12, 13). Reproducibility ($(\Sigma \text{mean}/\text{SD})/n \times 100$) for ADMV-basal, ADMV-hyp and CFVR between before and 4 h after placebo loading in this study was 7.51%, 9.00% and 6.42%, respectively. Left ventricular mass index (LVMI) was estimated according to the standards of the American Society of Echocardiography (16).

Statistical Analysis

Quantitative data are presented as the mean $\pm$ SD. Differences between groups were compared by repeated-measures ANOVA. Changes within the same group were analyzed by paired Student's *t*-test. Correlation was analyzed by Pearson's correlation coefficient. Statistical significance was estab-

Fig. 2. Changes in heart rate (A) and rate-pressure product (B) in patients treated by valsartan or long-acting nifedipine. There were no significant differences in either parameter either within or between groups. Each point and bar is presented as the mean $\pm$ SD.

Table 2. Changes of Average Diastolic Mean Velocity before and after Antihypertensive Treatment

	Valsartan (n=8)	Nifedipine (n=8)	Control (n=12)	p value
ADMV-basal (cm/s)				
Baseline	14.6 $\pm$ 2.2	18.1 $\pm$ 6.4	13.8 $\pm$ 2.9	n.s.
2 months	13.1 $\pm$ 1.7	21.4 $\pm$ 5.7*	—	
6 months	14.8 $\pm$ 2.4	21.5 $\pm$ 8.7*	—	
ADMV-hyp (cm/s)				
Baseline	36.6 $\pm$ 17.3	49.7 $\pm$ 20.0	47.7 $\pm$ 10.6	n.s.
2 months	41.2 $\pm$ 12.7	48.7 $\pm$ 12.3	—	
6 months	48.0 $\pm$ 20.2 [#]	52.0 $\pm$ 20.2	—	

All data are expressed as the mean $\pm$ SD. ADMV, average diastolic mean velocity; -basal, measured at baseline; -hyp, measured at hyperemia; n.s., not significant. * $p < 0.01$ vs. control subjects. [#] $p < 0.05$ compared to the values at baseline in each groups (paired *t*-test).

lished at the $p < 0.05$ level. Statistical analysis was performed using Statview J 5.0 (SAS, Cary, USA).

Results

Subject Characteristics and Changes in BP

The baseline characteristics of the study patients are shown in Table 1. No significant difference was found in terms of clinical and demographic characteristics between the valsartan and nifedipine groups. The baseline BP values were comparable: 155.5 $\pm$ 18.7/94.3 $\pm$ 14.9 mmHg in the valsartan group and 151.3 $\pm$ 9.9/87.5 $\pm$ 8.9 mmHg in the nifedipine group. Four patients had previously taken an hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor and maintained the same dose during the study. The distribution of these medicines was similar between the two groups. BP was well reduced by both valsartan (mean dosage 50.0 $\pm$ 18.5 mg) and nifedipine

(27.5 $\pm$ 10.4 mg), to 140.0 $\pm$ 12.1/80.0 $\pm$ 8.8 mmHg and 138 $\pm$ 10.0/78.9 $\pm$ 7.5 mmHg, respectively. The reductions by both medicines were statistically equal (Fig. 1). In contrast, heart rate and the rate-pressure product were not changed between before and either 2 or 6 months after treatment in either group (Fig. 2). No patient dropped out of the study and none suffered drug-induced side effects such as renal insufficiency, skin eruptions or impaired sense of taste by valsartan, or leg edema by nifedipine.

Measurements of CFVR by TTDE

All images were clear enough for the calculation of ADMV at baseline and under hyperemic conditions in all 16 patients. Moreover, flushing, chest discomfort and other adverse reactions induced by ATP were endurable and all 16 patients attended their scheduled CFVR examinations.

The mean ADMV-basal value was not significantly differ-

Fig. 3. Changes in coronary flow velocity reserve (CFVR) in patients treated by valsartan or long-acting nifedipine. CFVR in the valsartan group improved at 2 months through to 6 months after, reaching a similar level to that of the control group. Contrarily, CFVR in the nifedipine group did not indicate any significant changes. * $p < 0.05$ and ** $p < 0.01$ compared to the values at baseline in each group (paired t -test); # $p < 0.01$ compared the two treatment groups by repeated-measures ANOVA.

ent between the two groups, and there were no significant differences between the ADMV-basal values and the ADMV values measured at 2 and 6 months after administration in either group. All these values were comparable to those of the control group ($n = 12$, 16.1 ± 5.2 cm/s). With respect to hyperemia, in the valsartan group, repeated-measures ANOVA revealed significant increases in ADMV-hyp (48.0 ± 20.2 cm/s) at 6 months compared to the values before therapy (36.6 ± 17.3 cm/s, $p < 0.05$) (Table 2). Consequently, as shown in Fig. 3, CFVR in the valsartan group increased significantly from 2.34 ± 0.38 to 3.10 ± 0.84 at 2 months ($p < 0.05$) and 3.04 ± 1.09 at 6 months ($p < 0.01$). Similarly, these two values after valsartan administration became comparable to those in the control group (2.81 ± 0.60). On the other hand, CFVR in the nifedipine group did not undergo any significant changes (2.72 ± 0.22 at baseline, 2.29 ± 0.26 at 2 months, and 2.41 ± 0.40 at 6 months). Comparing the two depressors by repeated-measures ANOVA, valsartan induced a significantly greater increase in CFVR than nifedipine ($p < 0.001$).

To elucidate the mechanism by which valsartan improved CFVR, heart rate or LVMI was compared with CFVR before and after taking the depressors. Before administration of the depressor, CFVR indicated a significant inverse-correlation with heart rate or LVMI ($n = 15$; $r = -0.545$, $p < 0.05$ or $r = -0.612$, $p < 0.05$, respectively). Since heart rate at 2

months tended to increase in the nifedipine group (Fig. 2A), the reduced CFVR at 2 months in the nifedipine group might have been due to this increase. However, no significant correlations were detected between CFVR and either the changes of heart rate or LVMI in either of the treatment groups (data not shown).

Discussion

The present study revealed that impaired CFVR in hypertension was improved by valsartan, an angiotensin receptor blocker. By contrast, although blood pressure was reduced by both depressors to statistically similar levels, CFVR was not changed by long-acting nifedipine, a CCB. Therefore, valsartan's increased effect on CFVR might have been achieved by effects independent of its BP-lowering action.

CFVR Estimated by TTDE

Although CFVR measurement by TTDE has become a useful technique in clinical settings (10, 11), the success rate for obtaining clear coronary flow is low (16, 17). Recently, LAD flow has been more clearly detectable by color mapping and the use of a flow enhancer. Therefore, adequate flow images were obtained in all patients in this study. We used adenosine, converted from ATP, to induce hyperemia in the coronary artery. This hyperemic reaction has been considered to be mediated in an endothelium-independent manner; however, it has also been shown that hyperemic flow increases shear stress resulting in the augmentation of nitric oxide from the endothelium. Therefore, it is now accepted that adenosine increases coronary flow by both endothelium-independent and dependent mechanisms (14, 15). In the present study, the changes in ATP-induced coronary flow from the use of depressors could represent the integrated effects of both medial smooth muscle and endothelial cells.

Changes of CFVR in Hypertension

Reduced CFR is thought to be one of the abnormalities in the early stages of coronary artery disease (18). CFR is impaired by coronary risk factors, such as hypertension, hypercholesterolemia, diabetes mellitus and aging. In particular, a reduction in hypertension is related to two factors; one is a structural and functional change in coronary resistance vessels, and the other left ventricular hypertrophy (19). As structural changes in coronary resistance vessels are characterized by eutrophic remodeling, the wall-to-lumen ratio increases without reduction of the internal diameter and without changes of the wall mass. Recently, it was demonstrated over a 10-year period of follow up that increased wall-to-lumen ratio is associated with increased cardiovascular events (20). In hypertension, these structural and functional changes cause a reduction in hyperemic flow velocity. In clinical research, reductions in CFR are reported in patients with hypertension

with (21, 22) or without (23, 24) left ventricular hypertrophy. In this study, it was also confirmed that patients with hypertension had decreased CFVR compared to the control group. As for the mechanism of reduced CFVR, heart rate or LVMI was compared with CFVR before and after taking the depressors. Although LVMI was not significantly greater in either hypertension group than in the control group (Table 1), CFVR was inversely correlated with LVMI before administration of the depressors (data not shown). Park *et al.* (25) has reported that whereas structural remodeling of the small arteries is found in all hypertensive patients, left ventricular hypertrophy is found in 45% of patients with mild essential hypertension. This suggests that structural remodeling may precede left ventricular hypertension in hypertensive patients. This study likewise suggests that the improvement of CFVR following treatment with valsartan may be attributable to the reversal of structural remodeling in the early phase of hypertension.

Changes of CFVR by ARB

Large-scale clinical trials have suggested that the selective inhibition of angiotensin II by ARBs could prevent end-organ damage such as cardiovascular diseases and atherosclerosis (1–5). The selective inhibition of angiotensin II can exert beneficial effects independent of lowering BP. In this study, there were no changes in heart rate or the rate-pressure product, which may influence CFVR, in those treated with valsartan or long-acting nifedipine. Since valsartan and long-acting nifedipine exerted statistically similar BP-lowering effects, the mechanism for the improvement of CFVR by valsartan might be independent of its BP-lowering effects. This valsartan-induced CFVR improvement was derived from an increase in ADMV-hyp.

A possible hypothesis is that angiotensin II increases intracellular superoxide anions, which inactivate nitric oxide, by binding AT₁ receptors and thereby reducing ADMV-hyp (26). Thus, the blockade of AT₁ receptors by the ARB improved endothelium-dependent vasodilation. It has also been reported that an ARB reduced vascular microinflammation in essential hypertension (27). However, a CCB was shown to increase basal coronary flow but not hyperemic coronary flow and resulted in reduced CFVR (28). Thus, these previous findings suggest that ARBs and CCBs have quite different effects on CFVR, in agreement with the present study.

Another hypothesis is that angiotensin II plays an important role in vascular structural abnormalities, including that of perivascular fibrosis, and endothelial dysfunction in hypertensive patients. Stimulation of AT₁ receptors leads to increased reactive oxygen species in part *via* activation of nonreceptor tyrosine kinases, and of protein kinase C (PKC) and phospholipase D, thereby contributing to endothelial dysfunction by inactivating nitric oxide (29). As well, chronic treatment with an ARB has been proven to reduce perivascu-

lar fibrosis in increased reactive oxygen species (30) and to increase transforming growth factor- β expression (31). Schiffrin *et al.* (32) demonstrated that the ARB losartan normalized the structure of the small arteries and the endothelial dysfunction, whereas the β -blocker atenolol caused no change. Rizzoni *et al.* (33) also demonstrated that the structure of small arteries dissected from gluteal subcutaneous tissue correlates with coronary flow. Thus, one possible hypothesis is that treatment with ARBs, but not CCBs, improves ADMV-hyp as a result of the correction of the vascular structure, including perivascular fibrosis, and the endothelial dysfunction.

The present study demonstrates the possibility that ARBs might differ from CCBs in that the former exert effects on CFVR that are independent of their BP-lowering effects. As another clinical implication, the favorable effects on microvascular coronary flow caused by ARBs might be applicable to microvascular angina, for which a β -blocker or CCB (34) is now the first choice. To our knowledge, no clinical study has examined the effects of ARBs on microvascular angina. However, it has been reported that valsartan or ramipril, an angiotensin-converting enzyme inhibitor, reduced coronary microvessel inflammation in unstable angina (35). It was also reported that AT₁ receptor blockade restored microvessel density in the non-infarcted myocardium of rats (36). Considering these results together with those of the present study, it is reasonable to conclude that ARBs are new therapeutic candidates for the treatment of microvascular angina. Further study is needed to elucidate this point.

Moreover, a previous study in Japanese hypertensive patients (37) supports the hypothesis that renin-angiotensin blockade confers protection against cardiovascular events that is independent of its BP-lowering effect. ARBs may indeed be indicated as a candidate for first-line therapy in patients with mild essential hypertension if the BP-lowering effect is similar to those of other antihypertensive drugs (19).

Study Limitations

There are some limitations to this study. The first is that it has not been established whether TTDE can measure coronary flow velocity at the LAD distal site with the same precision as an intracoronary flow wire. Although we did not compare data between TTDE and a flow wire, it has been reported that CFR by a flow wire was well correlated with CFVR by TTDE (11). The second limitation is that this study enrolled patients without significant atherosclerosis in LAD. Thus, it is not clear whether an ARB also could improve CFVR in hypertensive patients with significant atherosclerosis. The last limitation comes from the small scale of the present study. Although the number of patients was too small to examine the effects of other ARBs or CCBs, we provided some evidence of a significant outcome regarding the effects of valsartan on CFVR. To confirm the class effects from ARBs or CCBs, a larger population study is needed.

Conclusions

Although the number of subjects in this study was limited—indeed it was more along the lines of a pilot study—the results and conclusions have important implications in terms of drug treatments for patients with hypertension and impaired CFVR. This study showed that an ARB, valsartan, improved impaired CFVR, perhaps by an effect that was separate from its acknowledged BP-lowering one. It was also suggested that this effect of the ARB mainly depended on the beneficial effect that the improved hyperemia had on the coronary flow. Moreover, this study showed that TTDE is feasible for ascertaining changes in CFVR in a clinical setting.

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