Original Article

Angiotensin II Type 1 Receptor Blockers Do Not Promote Coronary Collateral Circulation in Patients with Coronary Artery Disease

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We previously reported that angiotensin-converting enzyme inhibitors (ACE-Is) promote collateral circulation in patients with coronary artery disease (CAD). There have been many reports on the beneficial effects of angiotensin II type 1 receptor blockers (ARBs) on the cardiac microvasculature. Therefore, the following studies were performed to evaluate the association between treatment with an ARB and the enhancement of coronary collateral circulation as assessed by the Rentrop Score (RS) (Study 1) and to compare these results to those obtained with an ACE-I (Study 2). The subjects were 456 patients with angina who underwent coronary angiography. Study 1: Those who had one (1-V), two (2-V) or three significantly stenosed vessels (3-V) and who received only an ARB without any other anti-hypertensive medication were defined as the ARB group (*n*=81), and age-, sex- and body mass index–matched subjects (*n*=146) were selected as a comparative group. There were no significant differences in the percentage of patients with RS≥1 between the two groups. Study 2: Those who received an ACE-I as the only anti-hypertensive treatment were defined as the ACE-I group (*n*=67), which was matched to the ARB group in Study 1. The percentage of patients with RS≥1 in the ACE-I group was significantly higher than that in the ARB group as assessed by a Cochran-Mantel-Haenszel analysis. In addition, patients with 3-V disease who were treated with an ACE-I, but not an ARB, were most likely (odds ratio [confidence Interval]): 27.7 [4.8–161.0]) to show enhanced collateral circulation, as assessed by a multiple logistic regression analysis. These results suggest that treatment with an ACE-I, but not treatment with an ARB, was associated with the enhancement of collateral circulation in patients with CAD. (*Hypertens Res* 2006; 29: 135–141)

***Key Words*: angiotensin II type 1 receptor blockers, angiotensin-converting enzyme inhibitors, collateral circulation, stenosed vessels**

Introduction

Coronary artery disease (CAD) is the most important cause of death in the industrialized world. There are several ways to treat CAD, such as percutaneous transluminal angioplasty (PTCA), bypass surgery and medical therapy. However, despite these techniques the number of patients with CAD continues to increase.

After experimental myocardial infarction (MI), numerous dilated vessels appear in the border zone between the infarct and noninfarct areas (*1*). In response to this finding, several methods for replicating the vessel dilation have been investigated, including the administration of angiogenic growth fac-

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tors and the transplantation of bone marrow–derived angioblasts (*2*). These studies have suggested that the neovascularization after MI may be beneficial for the infarcted heart. Therefore, in patients with CAD, the development of collateral artery growth (arteriogenesis) or capillary network growth (angiogenesis) may be important.

There have been many reports on the beneficial effects of angiotensin II (Ang II) type 1 receptor blockers (ARBs) on the cardiac microvasculature (*3*). Ang II has been shown to exhibit pro-angiogenic activity that is mediated by the Ang II type 1 receptor (AT_1) (*4*). In mice which lack AT_{1a}, angiogenesis induced by hind-limb ischemia has been shown to be impaired compared to that in wild-type mice, and this effect was blood pressure-independent (*5*). An ARB, candesartan, also inhibited angiogenesis in wild-type mice after hind-limb ischemia at doses that did not affect the blood pressure level. On the other hand, de Boer *et al*. reported that the density of microvessels after MI was decreased in transgenic rats that overexpressed AT_1 receptor in the heart, and AT_1 receptor blockade by the ARB losartan restored the microvessel density (*6*).

Angiotensin-converting enzyme inhibitors (ACE-Is) have been reported to increase capillary density in rat limb muscles (*7*), sciatic nerves (*8*), and the coronary microvasculature (*9*–*11*). In addition, we previously reported that treatment with an ACE-I was associated with a progression of coronary collateral circulation in patients with CAD (*12*). These effects of ACE-Is may occur through bradykinin (BK) B2 receptor–induced nitric oxide (NO) synthesis (*13*, *14*).

Therefore, we here analyzed whether treatment with an ARB was associated with an enhancement of coronary collateral circulation, because there is no clear evidence to show that ARBs have beneficial effects in promoting collateral circulation in humans. In addition, the enhancement of such circulation might differ between ACE-Is and ARBs because of the BK B2 receptor–induced NO pathway. In the present study, we investigated coronary collateral circulation as assessed by the Rentrop Score (RS) in patients with CAD with or without ARB therapy (Study 1), and then compared the results by administration of an ARB to those by ACE-I administration (Study 2).

Methods

Study Patients

The subjects consisted of 452 patients with angina who underwent coronary angiography, and included patients who had one (1-V), two (2-V) or three significantly stenosed coronary arteries (3-V) (>50% luminal narrowing) as defined by coronary angiography. Study 1: Those who did and did not receive ARB drugs as the only anti-hypertensive treatment were defined as the ARB group ($n=81$; female/male [F/M]: 23/58; age: 67±1 years) and an age-, sex- and body mass index (BMI)–matched comparative group ($n=146$; F/M: 42/104; age: 67±1 years), respectively. In the ARB group, 53 patients (66%) received losartan, 23 (28%) received candesartan, and 5 (6%) received valsartan. Patients who were receiving both an ARB and an ACE-I at the time of the initial coronary angiography were excluded. The duration of ARB treatment was 10±2 months. The ARB and comparative groups included 3 and 14 patients with bypass surgery, respectively, and this difference was not significant. Study 2: The duration of ARB treatment in Study 1 was significantly shorter than that of ACE-I treatment (30±4 months) that we reported previously (*12*). Therefore, we matched the duration of ACE-I treatment (11±2 months) to that of ARB treatment (10±2 months). Those who received ACE-I as the only anti-hypertensive treatment were defined as the ACE-I group ($n=67$; F/M: 19/48; age: 66±1 years), which was matched to the ARB group in Study 1. In the ACE-I group, 27 patients (40%) received temocapril, 15 (22%) received enalapril, 11 (16%) received lisinopril, 10 (15%) received imidapril, 2 (3%) received trandolapril, 1 (1%) received quinapril, and 1 (1%) received perindopril. Patients who were receiving both an ARB and an ACE-I at the time of the initial coronary angiography were excluded. The ACE-I and ARB groups included two and three patients with bypass surgery, respectively, and this difference was not significant.

The subjects were selected from among patients who underwent diagnostic coronary angiography for suspected or known coronary atherosclerosis or for other reasons (mostly atypical chest pain) at Fukuoka University Hospital from 1998 to 2002. The ethics committee of Fukuoka University Hospital approved this study and informed consent was obtained from each patient. Patients with acute MI (within 3 weeks after onset), heart failure, vascular disease (aortitis treated by prednisolone) or hepatic dysfunction (viral and nonviral, transaminases more than three times the normal value) were excluded from the study. Patients with total cholesterol (TC) >220 mg/dl or triglycerides (TG) >150 mg/dl were considered to have hyperlipidemia (HL). Patients with systolic or diastolic blood pressure ≥140 mmHg or ≥90 mmHg or who were under anti-hypertensive treatment were considered to have hypertension (HT). Patients who were treated for diabetes mellitus (DM) or who had symptoms of DM and a fasting glucose concentration=126 mg/dl were considered to have DM. Otherwise, the results of a 75-g oral glucose tolerance test were used to diagnose DM. None of the patients was receiving hormone replacement therapy.

Coronary Angiography

Coronary angiograms were recorded and divided into 15 segments according to the classification of the American Heart Association Grading Committee. The presence of stenosis was determined using a computer-assisted coronary angiography analysis system (Philips-H3000CCD; Philips, Eindhoven, Netherlands) after the direct intracoronary injection of isosorbide dinitrate. Arterial stenosis that produced more than

Table 1. Patients Characteristics in Comparative, ARB and ACE-I Groups in Study 1 and 2

	Study 1	Study 2	
	Comparative group (n=146)	ARB group (n=81)	ACE-I group (n=67)
Age (years)	67±1	67±1	66±1
Female (%)	29	29	29
BMI (kg/m^2)	24±0.2	23±0.3	24±0.4
HT (%)	54	76*	66
DM (%)	33	42	42
ACS (%)	9	15	23
OMI (%)	33	43	43
Smoking (%)	46	47	53
PTCA (%)	23	27	30
Serum lipid profile (mg/dl)			
TC	189±3	188±3	189±5
TG	143±8	138±9	139±10
HDL-C	47±1	49±2	50±3
LDL-C	115±3	111±3	109±4
Medication			
Statin	55	42	44
CCB	50	52	32$^{\#}$
β-Blockers	13	6	19$^{\#}$
Long-acting nitrates	3	4	3

Values are shown as mean±SEM. ARB, angiotensin II type 1 receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; ACS, acute coronary syndrome; OMI, old myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; CCB, calcium channel blocker. *$p<0.05$ *vs*. comaprative group. $^{\#}p<0.05$ *vs*. ARB group.

50% luminal narrowing was considered significant. Coronary collateral circulation was graded according to RS (*15*) as follows: Grade 0, no filling of any collateral vessels; Grade 1, filling of side branches of the artery to be perfused by collateral vessels without visualization of the epicardial segment; Grade 2, partial filling of the epicardial artery by collateral vessels; Grade 3, complete filling of the epicardial artery by collateral vessels. The reproducibility of this grading system has been validated previously (*15*). The cardiac index was determined by left ventriculography.

Determination of Serum Lipid Concentrations

Blood was drawn in the morning after an overnight fast. Serum TC, TG, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were determined enzymatically, as described previously (*16*, *17*).

Transthoracic Echocardiography

An experienced sonographer, with the assistance of an experienced staff echocardiographer, obtained all echocardiographic data. Comprehensive examinations were performed on all of the study patients, including M-mode, ejection fraction, two-dimensional, conventional Doppler, and color Doppler echocardiography.

Statistical Analysis

Statistical analysis was performed using an SAS software package (Statistical Analysis System, version 6.12; SAS Institute Inc., Cary, USA) at Fukuoka University (Fukuoka, Japan). Categorical and continuous variables in the ARB, comparative and ACE-I groups were compared by a χ^2 analysis and an analysis of variance, respectively. RS values in the ACE-I and ARB groups in Study 2 were compared with a Cochran-Mantel-Haenszel analysis to adjust for the number of diseased vessels. The associations among RS, number of diseased vessels, and ACE-I and ARB status were examined by a logistic regression analysis (*18*). We calculated 95% confidence intervals (CI) for the odds ratios.

Results

Study 1

Patient Demographics

The clinical characteristics of the patients in the ARB and comparative groups are shown in Table 1. While there was a significant difference in HT between the two groups, there

Table 2. Stenosed Vessels, Rentrop Score and Cardiac Function in Comparative, ARB and ACE-I Groups in Study 1 and 2

	Study 1		Study 2
	Comparative group (n=146)	ARB group (n=81)	ACE-I group (n=67)
Stenosed vessels			
1-V/2-V/3-V (%)	36/35/28	52/26/22	43/41/16
Rentrop score			
0/1/2/3 (%)	61/12/17/9	71/11/13/5	51/7/31/10*
Cardiac function			
Cardiac index (l/min/m^2)	2.9±0.1	2.9±0.1	2.8±0.1
EF (%)	64±5	56±3	54±3

Values are shown as mean±SEM. ARB, angiotensin II type 1 receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; EF, ejection fraction. *$p<0.05$ *vs*. ARB group.

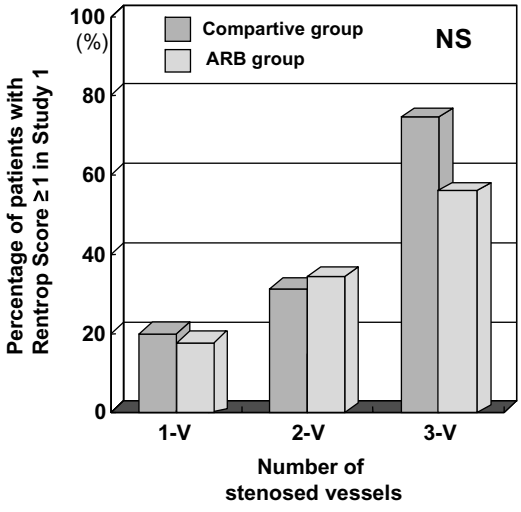

Fig. 1. *Relationship between the percentage of patients with Rentrop Score≥1 and the number of stenosed vessels in the comparative and ARB groups in Study 1. NS, not significant.*

were no differences with respect to age, sex, BMI, prevalence of DM or old MI (OMI). Baseline levels of TC, TG, HDL-C and LDL-C were similar between the groups.

All of the patients in both groups had at least one significantly stenosed vessel. Patients with OMI who had undergone PTCA during the acute phase of MI were re-evaluated by coronary angiography 6 months after the initial attack. There was no significant difference in the percentage of patients with acute coronary syndrome (ACS) between groups (comparative group 9% *vs*. ARB group 15%). The enhancement of collateral coronary circulation was associated with the strength and duration of angina.

Relation between Coronary Collateral Circulation and the Number of Stenosed Vessels

Although there was no difference in the number of stenosed vessels, RS or cardiac function between the ARB and comparative groups (Table 2), coronary collateral circulation can develop in the advanced stages of coronary atherosclerosis (*19*). Therefore, we assessed coronary collateral circulation according to the percentage of patients with RS≥1 among those with 1-V, 2-V or 3-V. As shown in Fig. 1, there were no significant differences in the percentage of patients with RS≥1 between the ARB and comparative groups. In addition, there was no difference in RS between subjects with and without HT (data not shown).

Study 2

Patient Demographics

Among the 148 patients, 67 (45%) received treatment with an ACE-I and the remaining 81 (55%) received treatment with an ARB (Table 1). There was no difference between the ACE-I and ARB groups with respect to age, sex, BMI, prevalence of HT, HL, DM, smoking, OMI, PTCA or cardiac function. In addition, there was no difference between the two groups in the percentage of patients treated with statin and long-acting nitrates (Table 1). All patients in both groups had at least one significantly stenosed vessel. There was no significant difference in the percentage of patients with ACS between the groups (ACE-I group 23% *vs*. ARB group 15%). However, the ACE-I group had a higher percentage of patients treated with a calcium channel blocker (CCB) and a smaller percentage of patients treated with a β-blocker than the ARB group. Therefore, we next evaluated the effects of CCBs and β-blockers on collateral circulation. There were no significant differences in the enhancement of collateral circulation between patients who were treated with a CCB or a β-blocker and those who did not receive such treatment (data not shown). Hence, we confirmed that treatment with CCBs and β-blockers did not influence the enhancement of collateral circulation.

Effects of ACE-I and ARB Treatment on Coronary Collateral Circulation

Although there was no difference in the number of stenosed

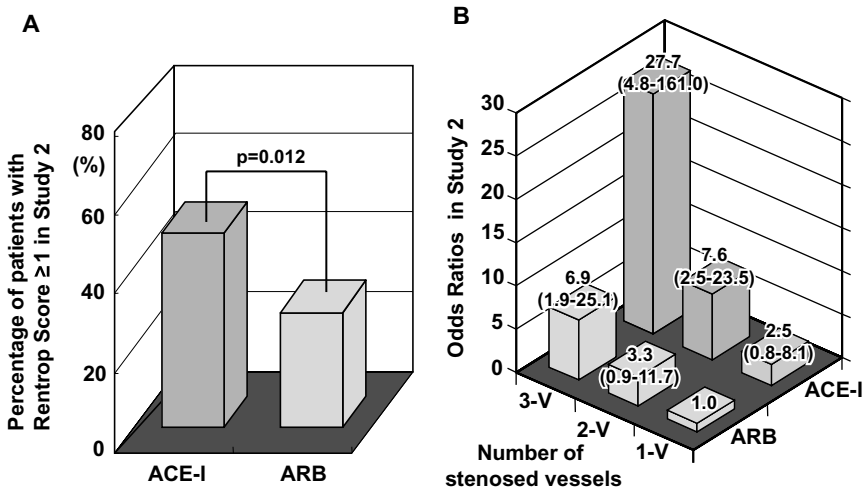

Fig. 2. *Percentage of patients with Rentrop Score≥1 in the ACE-I and ARB groups as assessed by a Cochran-Mantel-Haenszel analysis (A). Odds ratios for the association of each combination of stratum (1-V, 2-V or 3-V) and status (ACE-I group or ARB group) with collateral development as assessed by a multiple logistic regression analysis (B). Odds ratios and 95% confidence intervals are shown.*

vessels, the ACE-I group included a higher percentage of patients with RS≥1 than the ARB group. Therefore, we assessed the percentage of patients with RS≥1 while adjusting for the number of stenosed vessels. As shown in Fig. 2A, the ACE-I group had a significantly higher percentage of patients with RS≥1 than the ARB group. In addition, Fig. 2B shows the odds ratio for each combination of ACE-I and ARB treatment and the number of stenosed vessels (1-V, 2-V and 3-V). As shown, patients with 3-V disease who were treated with an ACE-I, but not those treated with an ARB, were most likely (odds ratio [CI]: 27.7 [4.8–161.0]) to show enhanced collateral circulation. These results suggest that treatment with an ACE-I, but not treatment with an ARB, is useful for promoting the enhancement of collateral circulation in patients with CAD.

Discussion

Based on recent studies which indicate that ARB can restore myocardial capillary density (*20*, *21*), we studied whether ARB treatment is associated with the enhancement of coronary collateral circulation in humans, and then compared the effects of ARB treatment with those of ACE-I treatment. Our study is the first to demonstrate that ACE-Is, but not ARBs, are associated with the enhancement of coronary collateral circulation in patients with CAD.

Numerous studies have demonstrated that the renin-angiotensin system (RAS) is involved in the enhancement of cardiovascular disease and the remodeling process. Ang II has been reported to induce angiogenesis through the upregulation of vascular endothelial growth factor (VEGF) (*4*, *22–24*) and VEGF-induced endothelial progenitor cell proliferation (*25*). In other studies, although ACE-I blocked Ang II–induced signaling by inhibiting Ang II production, hypoxia in the ischemic limb was sufficiently potent to upregulate VEGF expression independent of Ang II levels (*26*, *27*). The ACE-I quinaprilat was shown to induce angiogenesis comparable to VEGF in a hind-limb ischemia model (*28*). Although the ARB candesartan reduced ACE activity about 50% (*29*), ACE-I almost blocked the activity. The difference may be also important for BK production. In addition, chronic B2 receptor blockade was shown to prevent the ACE-I–induced increase in cardiac capillary density in hypertensive rats (*11*). Similarly, the ACE-I perindopril enhanced reparative angiogenesis induced by hind-limb ischemia (*14*). In addition, we previously reported that in an *in vitro* model of human coronary artery endothelial cell tube formation, stimulation of the B2 receptor by BK led to the transactivation of KDR/Flk-1, a VEGF receptor which induced angiogenesis (*13*). Taken together, our findings support these experimental studies in humans. The difference between the effects of treatment with an ACE-I and an ARB on the enhancement of collateral circulation may be due to BK/VEGF signaling.

There is an ongoing dispute in regard to the effect of the RAS and ARBs on microvessel growth. Based on our results, we suggest that treatment with an ARB was not associated with the enhancement of coronary collateral circulation in humans. However, these results differ from the findings of previous studies with ARB, in which the AT_1 receptor seemed to confer pro-angiogenic effects, and ARB inhibited angiogenesis. In the well-described ischemic hind-limb model, ARB impairs reparative angiogenesis (*5*, *30*). ARB hampered Ang II–induced microvessel growth in the cremaster muscle (*31*). On the other hand, ARB treatment did not enhance the

coronary collateral circulation in our study. Since an adaptation to chronic coronary stenosis can proceed either *via* an arteriogenic pathway or *via* a predominantly angiogenic pathway, which indicates that multiple occlusions may give rise to a mixed arteriogenic/angiogenic type of adaptation (*32*), our study is inconsistent with a previous study which showed that ARB induced an angiogenic effect. Moreover, Schieffer *et al*. (*20*) found that both ACE inhibition and AT_1 receptor blockade (partially) restored myocardial capillary density. They also reported that ARB restored capillary density post-MI. This discrepancy in the role of ARB may be related to the fact that the degree of angiogenic effect is strongly dependent on the model used.

In our previous study (*12*), patients with 1-V disease who were treated with an ACE-I showed a significantly higher degree of collateral circulation than patients with 1-V disease who were not treated with an ACE-I. However, in this study, patients with 3-V disease who were treated with an ACE-I showed significantly higher degree of collateral circulation than patients with 3-V disease who were treated with an ARB. This difference may be due to the difference in the duration of treatment. In the previous study the duration of ACE-I treatment was 30±4 months, while in this study the duration of ARB treatment was 10±2 months and that of ACE-I treatment was 11±2 months. The duration of treatment may correlate with the duration of the disease. Therefore, we assume that the duration of the disease in our previous study was longer than that in this study. Since the enhancement of collateral coronary circulation is associated with the strength and duration of ischemia, in the previous report, coronary collateral circulation may have enhanced in members of the control group (*12*), who were not treated with an ACE-I, especially among 3-V patients who had severe ischemia. Hence, the difference between patients with and without ACE-I treatment may disappear.

Study Limitation

Our study was a nonrandomized, retrospective, observational study. We simply examined the association between treatment with an ACE-I or ARB and coronary collateral circulation. A large randomized controlled trial of ACE-I or ARB treatment in patients with CAD is warranted to evaluate the potential benefits of these agents.

Conclusion

In conclusion, our study provides initial observational evidence to suggest that treatment with an ACE-I is associated with a significant promotion of coronary collateral circulation in patients with CAD. The results suggest that the effects of ACE-Is may help prevent myocardial ischemia.

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