Original Article

Relationship between Myocardial Flow Reserve by Oxygen-15 Water Positron Emission Tomography in the Subacute Phase of Myocardial Infarction and Left Ventricular Remodeling in the Chronic Phase

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The purposes of this study were to examine the effects of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) on myocardial flow reserve in patients with acute myocardial infarction (AMI) in the subacute phase using oxygen-15 positron emission tomography (PET) and to elucidate the relationship between the myocardial flow reserve and remodeling in the chronic phase. Sixty patients who had been treated with coronary angioplasty within 12 h after the onset of AMI were enrolled. Patients were divided into an enalapril (ACEI) group and a candesartan (ARB) group. The myocardial flow reserve was measured by oxygen-15 water PET in the subacute phase from the 20th to the 30th day after the onset of AMI. Left ventriculography was performed to measure the left ventricular ejection fraction in the chronic phase about 6 months after the onset. Ten patients (33%) in the enalapril group and 4 patients (13%) in the candesartan group stopped taking their respective medications within a few days of starting, because of side effects such as cough or hypotension. Thus, the prevalence of medication intolerance was higher in the enalapril group. The myocardial flow reserve in the subacute phase and the left ventricular ejection fraction in the chronic phase were lower in the enalapril group (2.08 ± 0.30 and $42 \pm 6\%$) than in the candesartan group (2.25 ± 0.20 and $49 \pm 5\%$) ($p < 0.05$). The myocardial flow reserve significantly correlated with the left ventricular ejection fraction in all patients ($r = 0.45$, $p < 0.01$). The myocardial flow reserve assessed by PET in the subacute phase after AMI was found to be related to left ventricular remodeling in the chronic phase. (*Hypertens Res* 2008; 31: 1307–1313)

Key Words: myocardial flow reserve, positron emission tomography, acute myocardial infarction, remodeling

Introduction

Left ventricular remodeling after acute myocardial infarction (AMI) causes dysfunction of the ventricular wall from the early phase to the chronic phase (1–3), and is closely related to heart failure and cardiac death. The renin-angiotensin sys-

tem in the myocardium after AMI is excessively activated, leading to the remodeling of the left ventricular wall, which in turn causes left ventricular dilatation and expansion (4–7). Some randomized trials have shown that angiotensin-converting enzyme inhibitors (ACEI) improved survival and reduced major nonfatal cardiovascular events after AMI (4–7). Angiotensin receptor blockers (ARB) also have the same effect on

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Fig. 1. Myocardial blood flow images by ^{15}O -water PET using a 16-segment model at rest (left) and during hyperemia (middle), and a myocardial flow reserve image (right) in patients with acute anteroseptal myocardial infarction treated with direct stenting.

the remodeling after AMI (8–10). In addition, it has been reported that AMI causes impaired microcirculation and deterioration of the myocardial flow reserve in the infarcted region (11–13). However, there have been no studies using positron emission tomography (PET), which is superior to other imaging modalities in assessing myocardial flow reserve quantitatively in patients with AMI. Strictly speaking, the relationship between the myocardial flow reserve assessed by PET in the subacute phase and remodeling in the chronic phase has not been elucidated in patients with AMI. Moreover, the effects of ACEI or ARB on impaired myocardial flow reserve after AMI have not been reported. Therefore, the purposes of this study were to examine the effects of ACEI or ARB on myocardial flow reserve in the subacute phase in patients with AMI by oxygen-15 (^{15}O) PET and to elucidate the relationship between the myocardial flow reserve and remodeling in the chronic phase.

Methods

Subjects and Protocol

This study included 146 consecutive patients who suffered AMI and were treated with direct stenting at Kagawa University Hospital within 12 h after the onset of AMI between June 2002 and May 2005. The exclusion criteria were a history of myocardial infarction, the presence of obvious collateral flow in coronary angiography, significant residual stenosis (coronary stenosis $\geq 75\%$ in infarct-related or infarct-nonrelated arteries after coronary angioplasty), cardiogenic shock, mechanical support by intra-aortic balloon pumping or percutaneous cardiopulmonary support, and bronchial asthma. All 146 patients were alternately into two groups when they were hospitalized: an enalapril group, which was treated with 5 mg or 2.5 mg of enalapril daily; and a candesartan group, which was treated with 8 mg or 4 mg of candesartan daily. We started the treatment in the respective groups with 5 mg of enalapril or 8 mg of candesartan. When a patient's systolic

Table 1. Clinical Characteristics and Angiographic Findings

	Enalapril (n=30)	Candesartan (n=30)	<i>p</i> value
Age (years)	66±12	65±11	n.s.
Men (n (%))	18 (63)	22 (73)	n.s.
Smoking (n (%))	23 (77)	21 (70)	n.s.
Hypertension (n (%))	18 (60)	17 (57)	n.s.
Hyperlipidemia (n (%))	9 (30)	10 (33)	n.s.
Diabetes (n (%))	14 (47)	12 (40)	n.s.
BMI	23.8±2.6	24.1±2.8	n.s.
Onset to admission (h)	5.4±2.9	5.3±3.5	n.s.
Anteroseptal (n (%))	15 (50)	15 (50)	n.s.
Lateral (n (%))	8 (27)	7 (23)	n.s.
Inferior (n (%))	7 (23)	8 (27)	n.s.
TIMI flow	0.52±0.77	0.50±0.80	n.s.
Stent size (mm)	3.48±0.59	3.51±0.61	n.s.
Slow flow (n (%))	2 (7)	2 (7)	n.s.

BMI, body mass index; TIMI, thrombolysis in myocardial infarction.

blood pressure was lower than 90 mmHg, we diminished the dose to 2.5 mg of enalapril or 4 mg of candesartan. This study analyzed the 60 patients who agreed to undergo ¹⁵O-water PET in the subacute phase from the 20th to the 30th day after the onset of AMI so the myocardial flow reserve at the infarcted area could be measured. Each group contained 30 patients initially. However, 6 patients in the enalapril group stopped taking the drug after developing a cough within a few days of starting the medication. Four patients in the enalapril group and 4 patients in the candesartan group stopped taking their respective medications because of hypotension. The left ventricular ejection fraction was measured by left ventriculography with contrast medium in the chronic phase about 6 months after the onset of AMI. The left ventricular ejection fraction was calculated by the area-length method using an off-line digital workstation (Digitex 2400; Shimadzu Corp., Tokyo, Japan). We compared the myocardial flow reserve in the subacute phase with the left ventricular ejection fraction in the chronic phase. We obtained informed consent from all participants after explaining to them the purposes of the study and the potential risks of their participation in it. The study was approved by the Ethics Committee of Kagawa University.

Myocardial Flow Reserve by ¹⁵O-Water PET

¹⁵O-water PET was performed at rest and during peak hyperemia induced by the infusion of adenosine triphosphate. The myocardial flow reserve was calculated as the ratio of myocardial blood flow at peak hyperemia to baseline myocardial blood flow. All subjects refrained from drinking caffeine-containing beverages and from consuming theophylline-containing drugs for at least 24 h before the PET examination.

Table 2. Short-Term Outcome and Medications

	Enalapril (n=30)	Candesartan (n=30)	<i>p</i> value
MACE (n (%))	0 (0)	0 (0)	n.s.
Max CPK	3,190±1,249	3,048±1,348	n.s.
Onset to PET (d)	25±4	25±5	n.s.
SBP (mmHg)	108±13	109±12	n.s.
DBP (mmHg)	74±8	70±9	n.s.
Heart rate (beats/min)	75±13	74±14	n.s.
β-Blockers (n (%))	6 (20)	8 (27)	n.s.
Statins (n (%))	24 (80)	23 (77)	n.s.
Spironolactone (n (%))	3 (10)	5 (17)	n.s.
Enalapril (n (%))			
5 mg	16 (53)		
2.5 mg	14 (47)		
Candesartan (n (%))			
8 mg		17 (57)	
4 mg		13 (43)	

MACE, major adverse cardiac events; CPK, creatinine phosphokinase; Onset to PET, time intervals between onset of acute myocardial infarction and PET examination; SBP, systolic blood pressure at PET examination; DBP, diastolic blood pressure at PET examination; PET, positron emission tomography.

For the production of ¹⁵O compounds, a low-energy deuterium accelerator was used. ¹⁵O-labeled water was produced with a dialysis technique in a continuously working water module. Sterility and pyrogen tests were performed daily to verify the purity of the product. Gas chromatography analysis was performed to verify the purity of the product before each study. PET was performed using a whole-body scanner equipped with germanium-68 (⁶⁸Ge)/gallium-68 (⁶⁸Ga) retractable line sources for transmission scans. All emissions and transmissions were reconstructed using a filtered back-projection. The full-width at half-maximum was 4.7 mm at the center of the field of view. The optimal imaging position was determined by a 5-min rectilinear scan after exposure to an external ⁶⁸Ge ring source. A 6-mm transmission scan was then acquired in order to correct the attenuation of all subsequent emission scans.

Blood volume images were produced in the following manner: The subject's nostrils were closed and the subject inhaled ¹⁵O-carbon monoxide for 1 min (0.14% CO mixed with room air). After the patient inhaled the tracer, the CO was allowed to combine with hemoglobin for 3 min before a 15-min static scan was started. During the 5-min rectilinear scan period, venous blood samples were drawn every 2 min and radioactivity in the whole blood was measured with an automatic gamma counter. The inhaled dose in the CO examination was 2,000 MBq.

¹⁵O radioactivity returned to the background level 15 min after the blood volume scan. Then ¹⁵O-water was infused into an antecubital vein as a slow (2 min) infusion. ¹⁵O-labeled

Fig. 2. Myocardial blood flow at rest as determined by ^{15}O -water PET.

water was administered twice in the entire study. The administered dose of ^{15}O -water was 500 MBq/min. A 20-frame dynamic PET scan was performed for 6 min (6×5 s, 6×15 s, and 8×30 s).

PET images were analyzed as described previously (14–16). The myocardial blood flow of the whole left ventricle was measured using ^{15}O -water as the flow tracer and employing the previously validated ^{15}O -water slow infusion technique. Measurement was performed at rest and during hyperemia produced by ATP infusion. We allowed the subject to rest for approximately 15 min after the measurement to allow for decay of the ^{15}O radioactivity. We repeated the second measurement of myocardial blood flow during ATP-induced hyperemia. ATP was infused for 9 min at 0.16 mg/kg/min, according to the standard protocol (17). PET acquisition was started 3 min after the beginning of ATP infusion. Blood pressure was recorded at 1-min intervals, and an electrocardiogram was monitored continuously throughout the procedure at baseline and at every minute during hyperemia administration. Myocardial blood flow was measured at each segment according to the 16-segment model (Fig. 1). As shown in Fig. 1, we assigned the area of AMI according to the 16-segment model uniformly in every case using the bull's-eye maps. The segments perfused by the infarct-related coronary artery were used for measuring the myocardial blood flow and myocardial flow reserve.

Statistical Analysis

Statistical analysis was performed using the SPSS software package (SPSS, Chicago, USA). Continuous variables are expressed as means $\pm$ SD. Dichotomous data are presented as frequencies. Categorical variables were compared by the χ^2 test. For the comparison of mean values between the two groups, Student's *t*-test was used. Linear regression analysis evaluated the association between the myocardial flow reserve and left ventricular ejection fraction. *p* values less than 0.05 were considered statistically significant.

Fig. 3. Hyperemic myocardial blood flow during adenosine triphosphate infusion as determined by ^{15}O -water PET.

Results

Patient Characteristics

Clinical characteristics and angiographic findings are listed in Table 1. There were no significant differences between the two groups with regard to age, gender, and the prevalence of risk factors such as smoking, hypertension, diabetes mellitus, and hyperlipidemia. Angiographic findings did not differ between the two groups. The mean times from the onset of AMI to admission to the cardiac catheterization room were similar (5.4 h in the enalapril group and 5.3 h in the candesartan group). The prevalence (7%) of slow flow during percutaneous coronary intervention was the same for both groups.

Short-term outcomes and medications are listed in Table 2, and these variables also did not differ between the two groups. The maximum level of creatinine phosphokinase was $3,190 \pm 1,249$ in the enalapril group and $3,048 \pm 1,348$ in the candesartan group. There were no major adverse cardiac events in any of the subjects. The mean times from admission to PET examination were similar (25 ± 4 d in the enalapril group and 25 ± 5 d in the candesartan group). The use of β -blockers was kept to a minimum in both groups in order to enable the use of ACEI or ARB without excessive lowering of blood pressure. Neither oral nitrates nor calcium channel blockers were used for any patient.

Myocardial Flow Reserve in the Subacute Phase and Left Ventricular Ejection Fraction in the Chronic Phase

The baseline myocardial blood flow in the infarct-related area at rest using PET was 0.92 ± 0.17 mL/min/g in the enalapril group and 0.90 ± 0.18 mL/min/g in the candesartan group (Fig. 2). There were no significant differences between the two groups. The hyperemic myocardial blood flow during ATP infusion was 1.91 ± 0.29 mL/min/g in the enalapril group

Fig. 4. Myocardial flow reserve as determined by ^{15}O -water PET.

and 2.03 ± 0.32 mL/min/g in the candesartan group (Fig. 3). The hyperemic myocardial blood flow was significantly lower in the enalapril group than in the candesartan group ($p < 0.05$), and the myocardial flow reserve was 2.08 ± 0.30 in the enalapril group and 2.25 ± 0.20 in the candesartan group (Fig. 4). The myocardial flow reserve was significantly lower in the enalapril group than in the candesartan group ($p < 0.05$). All patients underwent follow-up catheterization in the chronic phase. The mean time from the onset of AMI to follow-up left ventriculography was 195 ± 18 d. The left ventricular ejection fraction was $42 \pm 6\%$ in the enalapril group and $49 \pm 5\%$ in the candesartan group (Fig. 5). The left ventricular ejection fraction was significantly lower in the enalapril group than in the candesartan group ($p < 0.05$).

Relationship between Myocardial Flow Reserve and Left Ventricular Ejection Fraction

Figure 6 shows that there was a significant correlation ($r = 0.447$, $p = 0.00132$) between the myocardial flow reserve in the subacute phase and the left ventricular ejection fraction in the chronic phase in all patients.

Discussion

Previous studies using Doppler guidewire and contrast echocardiography have revealed that the degree of impaired coronary flow reserve after reperfusion for AMI was correlated with remodeling and prognosis in the chronic phase (12, 13). Shimada *et al.* (11) reported that the coronary flow reserve measured by Doppler guidewire at 3 weeks after anterior AMI was related with later ventricular function. In that study, 17 patients who showed a normal coronary flow reserve (≥ 2.0) had better left ventricular function in the chronic phase than 17 patients who showed abnormal coronary flow reserve (< 2.0). Ueno *et al.* (12) also reported that the coronary flow velocity reserve as measured by transthoracic Doppler echocardiography at 24 h after revasculariza-

Fig. 5. Left ventricular ejection fraction in the chronic phase.

Fig. 6. Relationship between myocardial flow reserve in the subacute phase and left ventricular ejection fraction in the chronic phase in all patients.

tion of anterior AMI was related with the recovery of left ventricular wall motion at discharge. Although PET is thought to be the most accurate modality for measuring myocardial blood flow, compared to other imaging modalities such as Doppler guidewire and transthoracic Doppler echocardiography, there are no reports regarding the relationship between myocardial flow reserve as strictly measured by PET and remodeling. Moreover, the effects of ACEI and ARB on impaired myocardial flow reserve after AMI have not been reported. We examined these relationships using ^{15}O -water PET, which is superior to other examination methods used in the quantitative analysis of myocardial blood flow.

Both ACEI and ARB reduce hypertrophy by lowering blood pressure. Moreover, they inhibit the renin-angiotensin-aldosterone system. This results in reductions in hypertrophy and fibrosis in the myocardium after AMI (18). Myocardial blood flow depends on stenosis of the coronary artery, arterial pressure, left ventricular pressure, lumen integrity, vasomotor control, microcirculation, and extravascular forces related to

intramyocardial pressure or wall stress (19, 20). Because myocardial oxygen consumption increases up to 6- or 7-fold during exercise, the normal heart has the ability to increase myocardial blood flow up to 3- or 4-fold (21). AMI decreases the capacity of the myocardial blood vessels, decreases coronary pressure, and disturbs the endothelium. These changes result in a decrease in the myocardial flow reserve. In an animal study, ACEI and ARB reduced the deterioration of the myocardial flow reserve after myocardial infarction by decreasing hypertrophy and fibrosis in the myocardium (22). In our study, both the myocardial flow reserve and the left ventricular ejection fraction were significantly lower in the ACEI group (2.08 ± 0.30 and $42 \pm 6\%$) than in the ARB group (2.25 ± 0.20 and $49 \pm 5\%$). However, the prevalence of medication intolerance tended to be higher in the ACEI group (33%) than in the ARB group (13%), although the difference did not achieve statistical significance ($p=0.06$). Moreover, the myocardial flow reserve in the subacute phase after AMI was related with the left ventricular ejection fraction in the chronic phase. Therefore, we considered that although ACEI and ARB might reduce the damage to the myocardial flow reserve after AMI to the same degree, the relatively high prevalence of medication intolerance in the ACEI group might have produced the differences in myocardial flow reserve and left ventricular ejection fraction between the two groups in the present study. At present, it is controversial as to whether ACEI or ARB should be used as the first choice. In the present study, a cough as a side effect was more frequent in the ACEI group. We compared the patients who were tolerant ($n=46$) vs. those who were intolerant ($n=14$) to ACEI or ARB in the present study. The myocardial flow reserve was significantly higher in the medication-tolerant patients (2.30 ± 0.10) than in the medication-intolerant patients (1.70 ± 0.18) ($p<0.01$), and the left ventricular ejection fraction was significantly higher in the medication-tolerant patients ($48 \pm 5\%$) than in the medication-intolerant patients ($38 \pm 6\%$) ($p<0.05$). The present study also demonstrated that interrupting the administration of these medicines resulted in worse remodeling. If the administration of ACEI is interrupted due to a cough, ARB should be administered as soon as possible.

This study has several limitations. First, we did not set a control untreated group. However, randomized trials have shown that inhibition of the renin-angiotensin-aldosterone system reduces left ventricular damage after AMI (4–10). Therefore, we compared the ACEI and ARB groups in terms of the effects of post-AMI myocardial flow reserve assessed by PET on left ventricular remodeling. Second, when we measured the myocardial flow reserve using ^{15}O -water PET, we assigned the AMI area according to the 16-segment model uniformly in every case, as shown in Fig. 1. Because the culprit lesion of the coronary artery differed in each case, the myocardial blood flow and reserve might be more accurately determined by changing the size of the regions of interest (ROI) on a case-by-case basis. However, because the maxi-

mum level of creatinine phosphokinase did not differ between the two groups, the size of the infarcted area was thought to be similar in both groups. Third, we did not perform coronary angiography before the PET examination to assess residual coronary stenosis, which can affect the myocardial flow reserve. However, all patients underwent direct stenting, and no adverse events occurred before the PET examination. Therefore, we believe there were no acute thromboses after stenting in these patients. When we performed coronary angiography in the chronic phase, 27% of the patients showed coronary restenosis $\geq 75\%$. However, no patients showed severe stenosis $\geq 90\%$. Therefore, it seems that coronary restenosis did not influence the left ventricular ejection fraction in the chronic phase. Fourth, we have no data regarding left ventricular filling pressure at the time of the PET examination, which might have influenced the myocardial flow reserve. Fifth, we cannot determine the precise mechanism by which left ventricular remodeling was prevented in the ACEI and ARB groups. Not only the preserved myocardial flow reserve but also the inhibition of structural remodeling by ACEI or ARB may have contributed to the prevention of left ventricular remodeling. Because the myocardial flow reserve correlated with the left ventricular ejection fraction ($r=0.447$, $p=0.00132$) (Fig. 6), the preserved myocardial flow reserve may have contributed, at least in part, to the prevention of left ventricular remodeling. Sixth, we did not examine the dose-response relationship in the ACEI and ARB groups. However, neither the myocardial flow reserve nor the left ventricular ejection fraction demonstrated any differences between the patients receiving a full dose and those receiving a half dose in either the ACEI or the ARB group. Finally, our study was limited by the small number of patients. However, we used PET to measure the myocardial flow reserve and found statistical differences between the two patient groups. Because PET is superior to other methods of examination in the quantitative analysis of myocardial blood flow and in terms of diagnostic accuracy, we believe this study has important clinical implications.

In conclusion, the myocardial flow reserve as assessed by PET in the subacute phase after AMI was demonstrated to be related to the recovery of left ventricular dysfunction in the chronic phase.

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