Spontaneous Anterograde Flow of the Infarct Artery Preserves Myocardial Perfusion and Fatty Acid Metabolism in Patients With Anterior Acute Myocardial Infarction

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Background It remains unclear whether spontaneous anterograde flow preserves myocardial fatty acid metabolism in patients with acute myocardial infarction (AMI).

Methods and Results The present study comprised 129 patients with a first anterior AMI in whom Thrombolysis in Myocardial Infarction (TIMI) 3 flow was obtained on the final angiogram: 28 patients with spontaneous anterograde flow and 101 patients with total occlusion on the initial angiogram. Thallium-201 (^{201}Tl) and iodine-123- β -methyl-p-iodophenyl penta-decanoic acid (^{123}I -BMIPP) dual-isotope myocardial single-photon emission computed tomography (SPECT) was performed at 6.5 ± 4.2 days after onset. The SPECT image was divided into 17 segments, and each segment was graded with scores between 0 and 4 (0, normal uptake; 4, defective). The sum of each score was defined as the total defect score (TDS). TDS values for ^{201}Tl (9.0 ± 7.4 vs 16.8 ± 12.2 , $p < 0.01$) and ^{123}I -BMIPP (19.3 ± 11.6 vs 24.1 ± 10.4 , $p < 0.05$) were significantly lower in patients with spontaneous anterograde flow than in those with total occlusion.

Conclusions These results suggest that spontaneous anterograde flow of the infarct artery preserves not only myocardial perfusion but also fatty acid metabolism in patients with AMI. ^{123}I -BMIPP SPECT image may underestimate the area at risk especially in patients with spontaneous anterograde flow. (Circ J 2005; 69: 427–431)

Key Words: BMIPP; Reperfusion; Ventricular function

Previous studies demonstrated that spontaneous anterograde flow of the infarct artery was associated with better left ventricular function and more favorable outcome compared with total occlusion in patients with acute myocardial infarction (AMI).^{1–3} Although these beneficial effects of spontaneous anterograde flow are mainly because of reduced infarct size, it remains unclear how spontaneous anterograde flow affects myocardial metabolism in patients with AMI.

Iodine-123- β -methyl-p-iodophenyl penta-decanoic acid (^{123}I -BMIPP) is a tracer for the evaluation of coronary artery disease, and identifies altered fatty acid metabolism after reperfusion in AMI.^{4–6} In the present study we used thallium-201 (^{201}Tl) and ^{123}I -BMIPP to test the hypothesis that spontaneous anterograde flow could preserve not only myocardial perfusion but also fatty acid metabolism in patients with anterior AMI. We also compared the effect of spontaneous anterograde flow and very early reperfusion on myocardial perfusion and fatty acid metabolism.

Methods

Study Patients

The study group comprised 129 patients in Hiroshima City Hospital with a first anterior AMI in whom coronary angiography was performed within 12 h after the onset of chest pain, and in whom Thrombolysis in Myocardial Infarction (TIMI) 3 flow⁷ was obtained on the final angiogram. AMI was diagnosed by chest pain consistent with ongoing myocardial ischemia for >30 min and elevation of serum creatine kinase to more than twice the normal upper limit. To assess infarct size, serum creatine kinase was measured every 3 h for at least 24 h to obtain the peak value. Patients with signs of re-infarction were excluded. The study protocol was approved by the institutional ethics committee and written informed consent was obtained from all patients.

There were 28 patients with TIMI 2 or 3 flow of the infarct artery on the initial angiogram. The remaining 101 patients with TIMI 0 or 1 flow were divided into 2 groups: 42 patients in whom time to reperfusion was within 2 h (very early reperfusion) and 59 patients in whom time to reperfusion was more than 2 h (late reperfusion).³

Electrocardiogram

Electrocardiogram was obtained on admission routinely in all patients. ST elevation AMI or non-ST elevation AMI was diagnosed by the presence or the absence of ST elevation more than at least 2 mm in 2 or more contiguous leads.

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Fig 1. SPECT image of the left ventricle was divided into 17 segments for semiquantitative analysis. Short-axis slices were separated into 8 segments at the basal and mid-ventricular levels. The apical portion of one segment was evaluated on vertical long-axis slices. Each segment was graded visually with scores between 0 and 4 (0, normal uptake; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; 4, defective), and the sum of each score was defined as the total defect score.

Table 1 Baseline Characteristics of the Study Patients

	Spontaneous antegrade flow	Total occlusion	p-value
No. of patients	28	101	
Age (years)	64±14	60±11	NS
Male gender	18 (64%)	86 (85%)	<0.05
Diabetes	4 (14%)	20 (20%)	NS
Hypertension	11 (39%)	38 (38%)	NS
Current smoker	12 (43%)	62 (61%)	NS
Prodromal angina	12 (43%)	34 (34%)	NS
Electrocardiogram			NS
ST elevation AMI	20 (71%)	87 (86%)	
Non-ST elevation AMI	8 (29%)	14 (14%)	
Time to angiography (h)	4.3±3.1	3.2±2.0	<0.05
Culprit lesion location			NS
Proximal to first septal branch	18 (64%)	60 (59%)	
Distal to first septal branch	10 (36%)	41 (41%)	
Multivessel disease	11 (39%)	29 (29%)	NS
Collateral circulation	3 (11%)	40 (40%)	<0.01
Reperfusion therapy			NS
Thrombolysis only	1 (4%)	1 (1%)	
Coronary intervention	26 (92%)	100 (99%)	
Neither	1 (4%)	0 (0%)	
Peak creatine kinase (IU/L)	2,129±1,507	4,302±2,553	<0.01

Cardiac Catheterization

Emergency cardiac catheterization was performed via the right femoral artery or left brachial artery after heparin administration. Coronary angiography was performed in multiple projections before reperfusion therapy. Immediately after diagnostic angiography, reperfusion was performed with percutaneous coronary intervention or coronary thrombolysis, if indicated. The allocation of reperfusion therapy was not randomized and was based on the physician's decision.

Angiographic Analysis

All coronary angiograms were reviewed by 2 cardiologists unaware of the clinical data. Initial TIMI flow grade was assessed on the initial image, and final TIMI flow grade was assessed on the final coronary angiogram. Spontaneous antegrade flow was defined as TIMI 2 or 3 flow, and total occlusion was defined as TIMI 0 or 1 flow on the initial coronary angiogram. Multivessel coronary disease was defined as ≥75% stenosis remote from the infarct-related artery. Collateral circulation was considered present if partial or complete filling of the infarct artery distal to the culprit lesion was present. PredischARGE angiography was performed approximately 14 days later. Left ventricular ejection fraction (LVEF) was calculated by the area-length method.

²⁰¹Tl and ¹²³I-BMIPP Myocardial Single-Photon Emission Computed Tomography (SPECT)

Resting ²⁰¹Tl and ¹²³I-BMIPP dual-isotope myocardial

SPECT were performed approximately 6 days after the onset. After overnight fasting, an intravenous bolus injection of ²⁰¹Tl (111 MBq) and ¹²³I-BMIPP (111 MBq) was performed at rest and data acquisition was started 20 min later using a 3-headed SPECT system with low-energy, all-purpose parallel-hole collimators. A total of 60 projection images was obtained in a 128×128 matrix over 360 degrees, with 30 s/view. After reducing the matrix to 64×64, tomographic images along the vertical long, horizontal long and short axes were created with a Shepp and Logan filter. The SPECT image of the left ventricle was divided into 17 segments for semiquantitative analysis⁸. Short-axis slices were separated into 8 segments at the basal and mid-ventricular levels. The apical portion of one segment was evaluated on vertical long-axis slices (Fig 1). Each segment was graded visually with scores between 0 and 4 (0, normal uptake; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; 4, defective) in a blinded manner by the 2 experienced cardiologists. The sum of each score was defined as the total defect score (TDS), reflecting the severity of impaired myocardial perfusion or impaired fatty acid metabolism. The TDS values for ²⁰¹Tl and ¹²³I-BMIPP were compared, and the relation between ²⁰¹Tl and ¹²³I-BMIPP was defined as mismatch when the ¹²³I-BMIPP TDS exceeded that for ²⁰¹Tl by 10.

Data Analysis

Statistical analysis was performed with the chi-square test for categorical variables. The unpaired Student's t-test was used for continuous variables. Differences were con-

Table 2 Baseline Characteristics of the Patients With Total Occlusion

	Very early reperfusion	Late reperfusion	p-value
No. of patients	42	59	
Age (years)	57±11	62±11	<0.01
Male gender	39 (93%)	47 (80%)	NS
Diabetes	8 (19%)	12 (20%)	NS
Hypertension	14 (33%)	24 (41%)	NS
Current smoker	26 (62%)	36 (61%)	NS
Prodromal angina	7 (17%)	27 (46%)	<0.01
Electrocardiogram			NS
ST elevation AMI	37 (88%)	50 (85%)	
Non-ST elevation AMI	5 (12%)	9 (15%)	
Time to angiography (h)	1.7±0.4	4.2±2.0	<0.01
Culprit lesion location			<0.05
Proximal to first septal branch	30 (71%)	30 (51%)	
Distal to first septal branch	12 (29%)	29 (49%)	
Multivessel disease	9 (21%)	20 (34%)	NS
Collateral circulation	19 (45%)	21 (36%)	NS
Reperfusion therapy			NS
Thrombolysis only	1 (2%)	0 (0%)	
Coronary intervention	41 (98%)	59 (100%)	
Neither	0 (0%)	0 (0%)	
Peak creatine kinase (IU/L)	4,249±2,198	4,340±2,791	NS

Fig2. Representative resting ^{201}Tl (Left) and ^{123}I -BMIPP (Right) myocardial SPECT images in patients with spontaneous anterograde flow and total occlusion who underwent reperfusion therapy. In a patient with spontaneous anterograde flow, the myocardial uptake of ^{123}I -BMIPP was moderately reduced in the apical and anteroseptal segments, whereas that of ^{201}Tl was only mildly reduced. In a patient with total occlusion, the myocardial uptake of ^{123}I -BMIPP was severely reduced in the apical and anteroseptal segments, whereas that of ^{201}Tl was moderately reduced.

sidered significant if the p-value was <0.05. All data are expressed mean ± SD.

Results

Baseline Characteristics

There were no significant differences in the baseline characteristics between patients with spontaneous anterograde flow and those with total occlusion, except for more males, longer time to angiography and less collateral circulation in those with spontaneous anterograde flow (Table 1). The baseline characteristics of the patients with very early reperfusion and those with late reperfusion are

shown in Table 2.

Infarct Size

The peak creatine kinase value was obtained in all patients and it was significantly lower in patients with spontaneous anterograde flow than in those with total occlusion ($2,129 \pm 1,507$ vs $4,302 \pm 2,553$ IU/L, $p < 0.01$), even when compared with only those with very early reperfusion ($2,129 \pm 1,507$ vs $4,249 \pm 2,198$ IU/L, $p < 0.01$).

SPECT (Fig 2, Table 3)

The TDS value for ^{201}Tl was significantly lower in patients with spontaneous anterograde flow than in those with

Table 3 SPECT Findings

	Spontaneous anterograde flow	Total occlusion	p-value
TDS value for ^{201}Tl	9.0 $\pm$ 7.4	16.8 $\pm$ 12.2	<0.01
TDS value for ^{123}I -BMIPP	19.3 $\pm$ 11.6	24.1 $\pm$ 10.4	<0.05
Mismatch between ^{201}Tl and ^{123}I -BMIPP	19 (68%)	42 (42%)	<0.05

total occlusion (9.0 $\pm$ 7.4 vs 16.8 $\pm$ 12.2, p <0.01), even when compared with only those with very early reperfusion (9.0 $\pm$ 7.4 vs 16.6 $\pm$ 12.5, p <0.01). The TDS value for ^{123}I -BMIPP was significantly lower in patients with spontaneous anterograde flow than in those with total occlusion (19.3 $\pm$ 11.6 vs 24.1 $\pm$ 10.4, p <0.05). There was a trend to lower TDS values for ^{123}I -BMIPP in patients with spontaneous anterograde flow, even when compared to only those with very early reperfusion (19.3 $\pm$ 11.6 vs 24.1 $\pm$ 11.3, p =0.10). Mismatch between ^{201}Tl and ^{123}I -BMIPP was observed more frequently in patients with spontaneous anterograde flow than in those with total occlusion (68% vs 42%, p <0.05), even when compared to only those with very early reperfusion (68% vs 40%, p <0.05).

Predischarge angiography was performed in 100 patients (78%) at 12 $\pm$ 4 days after the onset. All patients had a patent infarct artery. Both acute and predischarge left ventriculograms were obtained in 85 patients (66%). The change in LVEF was significantly higher in patients with spontaneous anterograde flow than in those with total occlusion (13 $\pm$ 9% vs 3 $\pm$ 16%, p <0.05). There was a trend to a higher LVEF in patients with spontaneous anterograde flow, even when compared to only those with very early reperfusion (13 $\pm$ 9% vs 6 $\pm$ 17%, p =0.16). Predischarge LVEF significantly correlated with the TDS values for ^{201}Tl (r^2 =0.27, p <0.01, n =100) and ^{123}I -BMIPP (r^2 =0.28, p <0.01, n =100).

Discussion

Present Study

By using ^{201}Tl and ^{123}I -BMIPP dual-isotope myocardial SPECT, this study demonstrated that (1) spontaneous anterograde flow of the infarct artery preserved not only myocardial perfusion, but also fatty acid metabolism in patients with anterior AMI, and (2) these beneficial effects of spontaneous anterograde flow was superior even to those of very early reperfusion.

Previous Studies

Previous studies demonstrated the association between spontaneous anterograde flow and left ventricular function in AMI.¹⁻³ Stone et al reported that patients with initial TIMI 3 flow before reperfusion therapy had better acute LVEF than those without.¹ We also demonstrated that initial TIMI 3 flow was associated with better acute LVEF, but the acute LVEF of patients with initial TIMI 2 flow was similar to that of patients with initial TIMI 0 or 1 flow. On the other hand, compared with patients with TIMI 0 or 1 flow, the predischarge LVEF was significantly better not only in patients with initial TIMI 3 flow but also in patients with initial TIMI 2 flow.³ Thus, spontaneous anterograde flow seemed to preserve left ventricular function during the early phase of AMI. In the current study, we demonstrated that the TDS value for ^{201}Tl and peak creatine kinase value were significantly lower in patients with spontaneous anterograde flow than in those with total occlusion, suggesting

that the beneficial effects of spontaneous anterograde flow resulted from a reduction in the infarct size.

Myocardial Metabolism

The major component of ^{123}I -BMIPP in the myocardium is the triglyceride pool, and ^{123}I -BMIPP is partially metabolized first by α -oxidation, then by β -oxidation. Because the myocardial accumulation of ^{123}I -BMIPP is associated with triglyceride synthesis, which in part reflects fatty acid utilization, ^{123}I -BMIPP is used as a tracer for myocardial fatty acid metabolism. Matsunari et al reported that segments with reduced uptake of ^{123}I -BMIPP showed ^{201}Tl redistribution on exercise redistribution ^{201}Tl imaging.⁹ Kawamoto et al reported that myocardial ischemia in which the uptake of ^{123}I -BMIPP was more reduced than that of ^{201}Tl showed increased uptake of fluorodeoxyglucose.¹⁰ Those results indicate that reduced uptake of ^{123}I -BMIPP represents myocardial ischemia. Moreover, previous studies showed that the degree of reduced uptake of ^{123}I -BMIPP correlated with either the severity of coronary artery stenosis or the severity of ischemic attack in patients with angina pectoris.^{11,12}

In the current study, we demonstrated that the TDS value for ^{123}I -BMIPP was significantly lower in patients with spontaneous anterograde flow than in those with total occlusion, suggesting beneficial effects of spontaneous anterograde flow on preserving myocardial fatty acid metabolism in patients with AMI. This effect of spontaneous anterograde flow also may contribute to the preservation of left ventricular function during the early phase of AMI.

The area at risk and the salvaged myocardium can be estimated accurately by myocardial perfusion imaging performed before and after reperfusion therapy.^{13,14} Because this examination requires tracer administration on admission and imaging shortly after reperfusion therapy, it is unpopular and frequently avoided under serious conditions. Previous studies demonstrated that the uptake of ^{123}I -BMIPP at 1 week was similar to the uptake of technetium-99m tetrofosmin before reperfusion therapy, and ^{123}I -BMIPP has been used to identify the area at risk in the subacute phase of AMI.¹⁵ In the current study, there was no significant difference in the culprit lesion location between patients with spontaneous anterograde flow and those with total occlusion. However, the TDS value for ^{123}I -BMIPP was significantly lower in patients with spontaneous anterograde flow than in those with total occlusion, suggesting that the ^{123}I -BMIPP SPECT image might underestimate the area at risk especially in patients with spontaneous anterograde flow.

Spontaneous Anterograde Flow vs Very Early Reperfusion

Brodie et al previously reported that time to reperfusion, up to 2 h, was an important determinant of survival and recovery of left ventricular function, and that after 2 h, recovery of left ventricular function was modest and survival was relatively independent of the time to reperfusion.¹⁶ From this point of view, it is important to assess whether or not the beneficial effects of spontaneous anterograde flow

were merely related to very early reperfusion.

In the current study, we demonstrated that the TDS values for ^{201}Tl and ^{123}I -BMIPP, which reflected myocardial perfusion and fatty acid metabolism respectively, were lower in patients with spontaneous anterograde flow than in those with very early reperfusion. In addition, we have previously reported that acute and predischARGE LVEF are significantly better in patients with spontaneous anterograde flow than in those with very early reperfusion.³ Our current results suggest that the beneficial effects of spontaneous anterograde flow are related not only very early reperfusion but also to other mechanisms such as intermittent occlusion. On the other hand, in spontaneous anterograde flow, angiography was performed 4.3 ± 3.1 h after the onset. Even in spontaneous anterograde flow, the TDS value for ^{201}Tl was significantly lower in the 19 patients in whom time to reperfusion was within 4 h than in the 9 patients in whom time to reperfusion was more than 4 h, although the TDS value for ^{123}I -BMIPP was similar for the 2 groups (data not shown). These results suggest that it is important for myocardial salvage to obtain persistent TIMI 3 flow with reperfusion therapy as early as possible even in patients with spontaneous anterograde flow.

Study Limitations

First, the allocation of reperfusion therapy was based on the physician's decision, but there was no significant difference in the choice of reperfusion therapy between patients with spontaneous anterograde flow and those with total occlusion, and final TIMI 3 flow was obtained in all patients. Second, the ^{123}I -BMIPP SPECT image was obtained only once approximately 6 days after onset. In patients with spontaneous anterograde flow, especially fatty acid utilization may improve, to a certain degree, in the first few days after the onset of AMI. Although it is certain that spontaneous anterograde flow preserves myocardial fatty acid metabolism during the early phase of AMI, further studies are necessary to clarify the temporal process of myocardial fatty acid metabolism in patients with spontaneous anterograde flow or total occlusion. Third, this study could not demonstrate a significant difference in the TDS values for ^{201}Tl and ^{123}I -BMIPP between patients with very early reperfusion and those with late reperfusion. Possible reasons are that patients with very early reperfusion had less prodromal angina¹⁷ and had the culprit lesion proximal to the first septal branch significantly more often than those with late reperfusion. Finally, predischARGE angiography was performed in only 78% of the patients. It remains unclear whether the remaining patients had a patent infarct artery at the time of SPECT, but it should be noted that patients with signs of re-infarction were excluded from this study.

Conclusion

Spontaneous anterograde flow of the infarct artery preserved not only myocardial perfusion but also fatty acid metabolism in patients with anterior AMI. These beneficial effects of spontaneous anterograde flow are related not only to very early reperfusion but also to other mechanisms such as intermittent occlusion. ^{123}I -BMIPP SPECT image may underestimate the area at risk, especially in patients

with spontaneous anterograde flow.

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