Does Coronary Artery Morphology Predict Favorable Results of Intracoronary Thrombolysis in Patients With Unstable Angina Pectoris?

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The efficacy of intracoronary thrombolysis (ICT) for unstable angina pectoris (UAP) has been limited, despite the similar pathogenesis between UAP and acute myocardial infarction. To ascertain the subset of UAP suitable for ICT, the clinical responses to ICT were assessed in patients with UAP. Eighty-two patients with medically refractory angina were divided into 2 groups according to the coronary artery morphology of the culprit lesion before ICT: (1) lesions with acute cut off and/or filling defects (AC) and (2) lesions with a tapered shape (TA). The TIMI flow grade was determined from coronary angiograms before and immediately after ICT. The diameter stenosis (%DS) and minimal lumen diameter (MLD) of the culprit lesion were determined using quantitative coronary angiographic analysis before and immediately after ICT. In addition, in-hospital cardiac event rates including urgent/emergency coronary angioplasty or bypass surgery, nonfatal myocardial infarction or cardiac death were compared between the 2 groups. Multivariate logistic regression analysis was performed using 13 clinical factors contributing to successful ICT. The results showed that all 3 coronary angiographic parameters (TIMI flow, %DS, and MLD) significantly improved in the AC group ($p < 0.01$, $p < 0.01$ and $p < 0.05$, respectively), whereas none of these parameters improved in the TA group. The in-hospital cardiac event rate after ICT was significantly higher in the TA group (76%) than in the AC group (48%; $p = 0.016$). Odds ratio predicting successful ICT was 7.09 ($p < 0.01$) for the AC lesion, and 2.54 ($p < 0.01$) for new angina. In conclusion the AC lesions are more commonly associated with coronary thrombosis that responds to ICT than are the TA lesions. Thus, the coronary angiographic morphology may be an important predictor for a successful ICT in patients with medically refractory UAP. (*Jpn Circ J* 1999; 63: 13–18)

Key Words: Coronary artery morphology; Intracoronary thrombolysis; Unstable angina pectoris

The most important mechanism in acute coronary syndrome is thought to be atheromatous plaque disruption, consequent platelet aggregation and nonobstructive thrombi.^{1–5} However, several large-scale, prospective, randomized clinical trials have shown that thrombolytic therapy for unstable angina pectoris (UAP) is not as efficacious as it is for acute myocardial infarction despite the similar pathogenesis between the 2 conditions.^{6–10} Recently, using coronary angiography, Mizuno et al¹¹ have reported that intracoronary thrombolysis (ICT) is effective in some patients with UAP with red thrombi. However, coronary angiography is not available routinely in clinical practice for patients with UAP.

Ambrose et al¹² and Rosch et al¹³ have classified coronary artery lesions into several types based on coronary angiographic findings. However, it has not been clarified in patients with UAP whether there is any difference in the response to thrombolytic therapy between the morphologic types of angiographic coronary lesion and what type of

coronary lesion is suitable for thrombolytic therapy. Accordingly, the aim of the present study was to use the coronary angiographic findings to ascertain the subset of UAP that is suitable for thrombolytic therapy. To this end, we retrospectively assessed the angiographic response of culprit lesions using quantitative coronary angiographic analysis and clinical outcome, including the results of coronary intervention after thrombolytic therapy, in patients with UAP.

Methods

Patients

The subjects consisted of 82 patients with medically refractory UAP out of 1,135 patients with UAP who were admitted to the Coronary Care Unit of the National Cardiovascular Center. Patients with medically refractory UAP were defined as having experienced recent (< 1 month) episodes of chest pain at rest and/or worsening with effort presumed to be ischemic in origin, lasting over 15 min (including postinfarction angina in hospital), which were refractory to medical treatment (including drip infusion of nitroglycerin or isosorbide dinitrate). An angina attack was defined as chest symptoms accompanied by transient ST elevation (≥ 0.1 mV) or depression (≥ 0.1 mV) or inverted T wave on ECG in at least 2 contiguous leads, and serum creatine kinase values after the chest symptoms limited to within twice the normal range.

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Fig 1. Coronary angiogram of a representative patient in the AC group. A lesion with acute cut-off and a filling defect is seen at the distal portion of the right coronary artery.

Fig 2. Coronary angiogram of a representative patient in the TA group. A lesion with a tapered shape is seen at the proximal portion of the left anterior descending artery.

Exclusion Criteria

We defined the contraindications for thrombolytic therapy as recent major surgery, active peptic ulcer, gastrointestinal bleeding or genitourinary tract bleeding less than 3 months before admission, any cerebrovascular accident (thrombotic, embolic or hemorrhagic), uncontrolled hypertension, recent trauma, bleeding diathesis, diabetic retinopathy, pregnancy and menstruation. Cases of multivessel disease with undefined culprit lesions were excluded.

Emergency Coronary Angiography

A heparin bolus of 5,000 IU was injected at the start of the emergency angiography. Coronary angiography was performed by the Judkins' method⁴ and the diseased vessels were defined as $\geq 70\%$ stenotic change using quantitative coronary angiographic analysis (NixdorfTM, Siemens Inc, Germany) as follows.

Criteria of Coronary Lesion Morphology Patients were divided into 2 groups according to the coronary artery morphology of the culprit lesion before intracoronary thrombolysis (ICT): (1) lesions with an acute cut-off shape and/or filling defects (AC) and (2) lesions with a tapered shape (TA) without acute cut-off or filling defects. Fig 1 and 2 show representative cases of the AC and TA lesions, respectively.

Quantitative Coronary Angiographic Analysis Coronary angiograms were analyzed using quantitative coronary angiography of the edge detection method (Nixdorf) to determine the percentage diameter stenosis (%DS) and minimal lumen diameter (MLD) of the culprit lesion after intracoronary injection of nitroglycerin. The diameter of a 5 French or 6 French Judkins' coronary catheter was used as the reference length.

Coronary Perfusion Grade

Coronary perfusion status was classified according to the system used in the Thrombolysis in Myocardial Infarction (TIMI) trial:¹⁵ Grade 0, no perfusion (no antegrade flow beyond the point of occlusion); Grade 1, penetration without perfusion (contrast material passes beyond the area of obstruction but fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence); Grade 2, partial perfusion (contrast material passes across the obstruction and opaci-

fies the coronary artery distal to the obstruction with time delay in entry or clearance); and Grade 3, complete perfusion (antegrade flow into the bed distal to the obstruction occurs without delay).

Intracoronary Thrombolysis

After informed consent was obtained, all patients received ICT because their UAP could not be stabilized with medical therapy. After intracoronary administration of 0.5 mg of nitroglycerin, 1,600,000 IU of tissue type plasminogen activator (maximum 6,400,000 IU) or 240,000 IU of urokinase (maximum 960,000 IU) was injected into the ischemia-related coronary artery every 10 min until the maximal dose was reached. ICT was considered to be successful when TIMI grade 3 flow and relief of chest pain were obtained.

Inhospital Cardiac Events

We investigated in-hospital cardiac events including urgent coronary interventions (angioplasty or bypass surgery), nonfatal myocardial infarction and cardiac death. Urgent coronary interventions, which included angioplasty or bypass surgery for patients with unsuccessful ICT ($\leq$ TIMI grade 2 flow or unresolved chest pain) or with recurrence of medically refractory angina pectoris after ICT, were defined as those being performed for suboptimal results after ICT (not in the cases that obtained TIMI grade 3 flow and relief of chest pain).

Multivariate Logistic Regression Analysis

Multivariate logistic regression analysis (forward step method) was performed using 13 clinical and angiographic factors contributing to successful ICT. These factors included age, diabetes mellitus, history of smoking, ST-shift during anginal attacks, new angina, Braunwald classification (IIIB and IIIC), number of diseased coronary arteries, type AC/TA lesion, lesion haziness, lesion irregularity, lesion length, MLD and %DS.

Bleeding Complication

Major bleeding was defined as intracranial hemorrhage or overt bleeding associated with a decrease in hemoglobin of more than 5 g/dl.

Table 1 Clinical Characteristics of the Study Patients

	Type AC (n=31)	Type TA (n=51)	p value
Age (years)	65	66	NS
Male/female ratio	23/8	37/14	NS
Previous MI	13	25	NS
Hyperlipidemia	14	17	NS
Diabetes	11	22	NS
Current smoking	22	33	NS
Hypertension	18	29	NS
New angina/Worsening/post-MI angina	17/4/10	24/15/12	NS
Braunwald IIIB/IIIC/etc	17/7/7	36/6/9	NS
Attack with ST elevation/without ST elevation	21/10	37/14	NS
Diseased coronary artery			
Single vessel	14	19	NS
Double vessel	6	14	
Triple vessel	11	15	
Left main trunk	0	3	
Lesion length (Rosch class a/b/c/undefined)	12/16/0/3	30/19/1/1	NS
Thrombolytic agent			
UK/t-PA	28/3	50/1	NS
UK dose (10^3 IU)	600 $\pm$ 220	580 $\pm$ 220	NS
t-PA dose (10^3 IU)	3,200 $\pm$ 1,530	3,200	

AP, angina pectoris; MI, myocardial infarction; t-PA, tissue-plasminogen activator; UK, urokinase; NS, not significant.

Table 2 Comparison of Angiographic Outcome

	Type AC (n=31)			Type TA (n=51)		
	Before ICT	After ICT	p value	Before ICT	After ICT	p value
%DS (%)	85.3 $\pm$ 13.9	72.7 $\pm$ 17.1	$p<0.01$	81.2 $\pm$ 10.2	78.3 $\pm$ 10.2	$p=NS$
MLD (mm)	0.44 $\pm$ 0.57	0.77 $\pm$ 0.66	$p<0.05$	0.50 $\pm$ 0.20	0.58 $\pm$ 0.23	$p=NS$
TIMI flow						
0	10	3	$p<0.01$	1	2	$p=NS$
1	0	1		3	0	
2	8	1		13	8	
3	13	26		34	41	

Eight cases from TIMI 2–TIMI 3, one from TIMI 0–TIMI 3, and five from TIMI 0–TIMI 3 improved in AC group. Seven from TIMI 2–TIMI 3, one from TIMI 1–TIMI 2, and two from TIMI 1–TIMI 3 improved in TA group.

%DS, % diameter stenosis; ICT, intracoronary thrombolysis; MLD, minimal lumen diameter; TIMI, Thrombolysis In Myocardial Infarction.

Statistical Analysis

Data are presented as mean $\pm$ SD (standard deviation). Paired data including %DS and MLD before and after ICT were compared by the paired t-test. Statistical comparisons of the differences in TIMI flow and in-hospital cardiac events were performed by the Chi-square contingency test. Differences were considered statistically significant when $p<0.05$. Odds ratios for the 13 clinical and angiographic factors were calculated using multivariate logistic regression analysis (SPSS 6.1 J for the Macintosh).

Results

Baseline Clinical and Angiographic Characteristics

Comparison of the baseline clinical and angiographic characteristics between the AC and TA groups is shown in Table 1. There were no significant differences between the 2 groups.

Angiographic Outcomes

The summary of coronary angiographic findings is shown in Table 2. In the AC group, the %DS of the culprit lesion was significantly reduced ($p<0.01$) and the MLD significantly increased after ICT ($p<0.05$), whereas these

Cardiac event rate after ICT

Fig 3. In-hospital cardiac event rates after ICT. The in-hospital cardiac event rate after ICT was significantly higher in the TA group than in the AC group.

values did not change significantly in the TA group. Also, the TIMI flow grade significantly improved after ICT in 14 of the 31 patients (45%) in the AC group, whereas it

Table 3 Comparison of Urgent PTCA Outcome

	Type AC (n=15)	Type TA (n=26)	p value
Initial success rate of urgent PTCA (%)	67%	69%	NS
Acute occlusion during PTCA	4	8	NS
Major complication after PTCA			
MI	1	4	
CABS	0	0	NS
Cardiac death	0	0	

CABS, coronary artery bypass surgery; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

Table 4 Multivariable Correlates of Successful ICT

Variable	Odds Ratio	95% CI	p value
Type AC lesion	7.09	2.09–23.9	0.0015
New angina	2.54	1.29–4.98	0.0067

CI, confidence interval; ICT, intracoronary thrombolysis.

improved in only 10 of the 51 patients (20%) in the TA group ($p<0.05$).

Clinical Outcomes

As a result, 13 patients (42%) were successfully treated with ICT alone in the AC group, whereas in the TA group only 9 patients (18%) were able to be treated with ICT alone ($p<0.02$). The in-hospital cardiac event rate (urgent coronary interventions, nonfatal myocardial infarction or cardiac death) after ICT was significantly higher in the TA group (76%) than in the AC group (48%; $p=0.016$; Fig 3).

Outcomes of Urgent Angioplasty

In the patients who underwent urgent angioplasty (15 patients in AC group, 26 patients in TA group), the initial success rate and complication rate were similar between the 2 groups (Table 3).

Factors Contributing to Successful ICT

Multivariate logistic regression analysis confirmed that the lesion type AC and new angina were independently associated with successful ICT. Odds ratio predicting successful ICT was 7.09 ($p=0.0015$) for the type AC lesion, and 2.53 ($p=0.0067$) for new angina (Table 4).

Bleeding Complication

There were no cases of intracranial hemorrhage after the procedure in either group. However, 2 in the TA group required blood transfusion after the procedure because of bleeding at their puncture site.

Discussion

Previous Studies and Our Results

Ambrose et al have studied the morphological features of culprit lesions in patients with acute coronary syndrome and reported that the incidence of eccentric and/or irregular lesions is higher in patients with UAP than in patients with stable angina pectoris.¹² However, they did not mention the efficacy of treatment for these lesions. Some trials have reported that ICT was effective for improving culprit lesion stenosis, but did not improve clinical outcome in patients with thrombus shadows on their coronary angiograms.⁶ However, there has not been a report comparing the responses to thrombolytic agents between lesions with

different coronary angiographic morphologies in patients with medically refractory angina. The present study has demonstrated more favorable effects of ICT on stenosis visible on coronary angiography and on the in-hospital cardiac event rate in patients with type AC lesions compared with patients with TA lesions. Namely, the efficacy of ICT in patients with UAP is influenced by the coronary artery morphology, and ICT for UAP is more efficacious in patients with type AC lesions than with type TA lesions.

Pathologic studies in patients with acute coronary syndrome have revealed that lipid-rich coronary plaques with a thin, fibrous cap are prone to rupture and are superimposed by thrombosis.⁵ Despite the similar pathogenesis between UAP and acute myocardial infarction, thrombolytic therapy for UAP has not been established. One of the reasons for the ineffectiveness of ICT for patients with UAP in previous studies may be that patients with transient ST elevation at the time of an ischemic attack were excluded.^{9–10} In relation to this, Haze et al reported that ST elevation at the time of an ischemic attack relates to new angina, single vessel disease, and intracoronary thrombus formation, while ST depression relates to worsening angina, multivessel disease, and complex coronary morphology.¹⁶ White et al reported that streptokinase treatment in acute coronary syndrome with ST depression does not seem to be beneficial.¹⁷ However, in the present study, the incidence of attacks with ST elevation was not significantly different between the AC and TA groups. Further studies are necessary to clarify the relation between ST elevation and the angiographic findings as well as the efficacy of thrombolytic therapy in patients with UAP.

Response of the Intracoronary Thrombus to Thrombolytic Therapy

The different therapeutic response to thrombolytic agents between the 2 types of lesions may be attributable to the difference between red thrombi and white thrombi. According to studies using coronary angiography, ICT may be more effective for red thrombi, which are composed of erythrocytes, leukocytes, platelets and fibrin, than for white thrombi, which are composed of platelets, fibrin or both.^{18–20} Mizuno et al reported that a red thrombus was detected in all patients with acute myocardial infarction, whereas it was detected in only 22% of patients with UAP and a white thrombus was frequently detected in 78% with UAP.²⁰ Thus, we would speculate that the type AC lesions in the present study may be associated with red-dominant thrombi, which would better respond to ICT than the type TA lesions. In contrast, the type TA lesions may be associated with an organic stenosis with white-dominant thrombi, which may be resistant to ICT. In relation to this, it has been reported that thrombolytic agent may provoke platelet

activation.²² We previously reported that a high plasma value of P-selectin, which is one of the selectin family adhesion molecules and appears on the platelet surface after thrombin activation, relates to ST depression attacks and acute cardiac events.²³ These findings suggest that an effective antiplatelet regimen is necessary in addition to, or rather than, thrombolytic therapy for patients with UAP.

Inhospital Cardiac Events

The in-hospital cardiac event rates were very high for both groups (48% in the AC group, 76% in the TA group) in the present study. However, this was because most patients included in this study had medically refractory, severe angina and because urgent angioplasty was counted as an cardiac event even when it was successful. If successful urgent angioplasty was excluded from cardiac events, the event rates were 3% (1/31) for the AC group and 31% (16/51) for the TA group ($p < 0.01$).

Clinical Implications

Meyrer et al reported that the initial success rate was lower and the complication and restenosis rates were higher in patients with urgent angioplasty than in patients with elective angioplasty.²⁴ The rate of unsuccessful angioplasty due to complications has been reported to be especially high in patients with UAP with complex lesions.²⁵ These findings, together with the present results, suggest that thrombolytic therapy may be the first choice of treatment in patients with type AC lesions to improve coronary flow through the culprit lesion and reduce the in-hospital cardiac event rate. On the other hand, the present results demonstrate that ICT is not beneficial in patient with type TA lesions because of the urgent bypass surgery that has to be performed after unsuccessful ICT. Therefore, we have to avoid ICT in patients with type TA lesions because of the need to decrease bleeding complication during urgent coronary artery bypass surgery. Moreover, the present results suggest that direct coronary angioplasty may be more beneficial and necessary for patients with type TA lesions.

At present, it is difficult to judge the difference in coronary artery morphology from clinical characteristics without coronary angiography. In the present study, the clinical characteristics of the 2 groups did not show any difference in the incidence of 'new angina', 'ST elevation at the time of anginal attack' or 'Braunwald type IIIB/IIIC' by univariate analysis, which was contrary to our expectation. However, multivariate logistic regression analysis confirmed that 'lesion type' and 'new angina' were independently associated with successful ICT. These results suggest that ICT is suitable for type AC lesions with new angina.

Study Limitations

There are several limitations in this study. First, the present study was a retrospective study in a relatively small group of patients in a single medical center. To confirm the present results, prospective, randomized study in a larger patient group will be necessary. Second, we did not compare the efficacy of ICT with that of primary angioplasty without ICT, because the purpose of this study was to find the patient group suitable for ICT. However, because the primary success rate of angioplasty without any complication has been increasing in recent years thanks to the improvements in devices (the success rate of urgent angioplasty in this present study is low, because

new devices were not used during this period), primary angioplasty might be another choice of treatment for patients with medically refractory unstable angina. Further studies are necessary to clarify this point.

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