Effect of the Initial Bolus Volume of Recombinant Tissue-Type Plasminogen Activator on Coronary Recanalization and Infarct Size in Japanese Acute Myocardial Infarction Patients

Hisao Ogawa, M.D., Hirofumi Yasue, M.D., Shuichi Oshima, M.D.
Yasuhiro Ogata, M.D., Yuichi Numata, M.D., Kinya Fujimoto, M.D.
Nobuya Imoto, M.D., Taro Saito, M.D., Youichi Hokamura, M.D.
Toru Takahashi, M.D., Hajime Watanabe, M.D., Hideaki Kodama, M.D.
Yasuhiro Morikami, M.D., Hiroo Miyagi, M.D., Kenji Obata, M.D.
Koshi Matsuyama, M.D., Naritsugu Sakaino, M.D.
Tomoki Nakamura, M.D. and Tomio Wakita, M.D.

for the Kumamoto University Myocardial Infarction Study (KUMIS) Group

Coronary recanalization rate and infarct size were compared between 2 different methods of intravenously administering recombinant tissue-type plasminogen activator (rt-PA) 41.4 mg; 1) an initial bolus dose of 30% followed by infusion of the remainder over 60 min (30% group), and an initial bolus dose of 10% followed by infusion of the remainder over 60 min (10% group). Thirty min after beginning rt-PA infusion, the coronary recanalization rate was higher in the 30% group than in the 10% group (82.9% (34/41) vs 53.7% (22/41), $p < 0.01$). The peak creatine kinase and peak creatine kinase-MB levels were lower in the 30% group than in the 10% group. We conclude that a higher initial bolus dose of rt-PA gives a higher rate of recanalization of the infarct-related artery at the very early phase, and probably leads to a smaller infarct size.

(*Jpn Circ J* 1995; **59**: 663–672)

ENZYMATIC recanalization of an occluded coronary artery with recombinant tissue-type plasminogen activator (rt-PA) or streptokinase has been shown to significantly reduce mortality in patients with acute myocardial infarction!^{–3} rt-PA therapy has been associated with a higher rate of early patency

than streptokinase therapy by the TIMI investigators¹ and the European Cooperative Study Group⁴. Accelerated or “front-loaded” regimens of rt-PA (Alteplase) have been shown to lead to increased angiographic patency rates in patients with acute myocardial infarction^{5,6}. Recently, the results of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) investigators⁷ and the GUSTO angiographic investigators⁸ have demonstrated that the administration of

Key words:

Recombinant tissue-type plasminogen activator
Acute myocardial infarction
Initial bolus volume
Coronary recanalization
Infarct size

(Received August 1, 1994; accepted January 19, 1995)

This study was supported in part by a Grant-in-Aid for Scientific Research (C07670794) from the Ministry of Education, and by a Smoking Research Foundation (Tokyo, Japan) Grant for Biomedical Research, and by a Grant from Japan Cardiovascular Research Foundation (Osaka, Japan). This material was presented in part at the 66th Scientific Sessions of the American Heart Association, Atlanta, GA, November 8–11, 1993

Mailing address: Hisao Ogawa, M.D., Division of Cardiology, Kumamoto University School of Medicine, 1-1-1 Honjo, Kumamoto City 860, Japan

rt-PA in an accelerated dosing schedule provides a survival benefit over previous standard thrombolytic regimens, and that more rapid and complete restoration of coronary flow through the infarct-related artery results in improved ventricular performance and lower mortality among patients with acute myocardial infarction. Furthermore, it has been shown that the administration of 100 mg of Alteplase in a double-bolus (50-mg each given 30 min apart) yields high early infarct-related coronary artery patency rates.⁹ In Japan, rt-PA (Alteplase) became commercially available in May, 1991. The present study was designed to examine the effect of a difference in the initial bolus volume of rt-PA on coronary recanalization and infarct size in Japanese acute myocardial infarction patients.

METHODS

Patient Population

Nineteen hospitals participated in this study from July 1, 1991 to August 31, 1993. Patients experiencing acute myocardial infarction and presenting at one of the participating hospitals were evaluated for inclusion in this study. Informed consent was obtained from each patient and/or his or her family before administration of rt-PA. The study protocol was approved by the institutional review board at each hospital.

The diagnosis of acute myocardial infarction was based on chest pain persisting for at least 30 min, ST-segment elevation of at least 0.1 mV in 2 or more contiguous limb leads, ST-segment elevation of at least 0.2 mV in 2 or more contiguous precordial leads, and elevation of serum creatine kinase and/or creatine kinase-MB isoenzyme (CK-MB) to more than twice the normal upper limit. All of the patients presented at a participating hospital and received the rt-PA alteplase (GRTPA, Tanabe Seiyaku Co, Ltd, or Activacin, Kyowa Hakko Kogyo Co, Ltd) less than 6 h after the onset of symptoms.

The exclusion criteria were a history of cerebrovascular accident or disease; uncontrolled hypertension (blood pressure >200 mmHg systolic or >120 mmHg diastolic); active internal bleeding; recent surgery; recent trauma (including prolonged cardio-

pulmonary resuscitation); known pregnancy; other serious illness or current oral anticoagulant therapy.

Treatment Strategies

All patients with acute myocardial infarction received intravenous morphine hydrochloride for pain relief, as well as sublingual nitroglycerin up to 0.6 mg and/or intravenous isosorbide dinitrate (Nitorol, Eisai Co, Ltd) up to 10 mg. Thereafter, all patients were treated using 2 different methods for administering rt-PA 41.4 mg. The patients were randomly assigned to either of the following administration protocols: 1) an initial bolus dose of 10% followed by infusion of the remainder over 60 min (10% group); or 2) an initial bolus dose of 30% followed by infusion of the remainder over 60 min (30% group).

A 5,000 U intravenous bolus of heparin (Heparin sodium, Shimizu-Takeda Co, Ltd) was administered to all patients before catheterization when emergent coronary angiography was performed or at the termination of rt-PA infusion when emergent coronary angiography was not performed. This was followed by the continuous infusion of about 500–1,000 U/h, adjusted as required to maintain the activated partial thromboplastin time at 1.5 to 2 times the control level for at least 48 h. All of the patients received 81 mg of oral aspirin (Banyu Co, Ltd or Lion Co, Ltd) after the rt-PA infusion and 81 mg/day while receiving heparin, and this was continued thereafter. Nitroglycerin (Millisrol, Nippon Kayaku Co, Ltd) 0.2–2.0 μ g/kg per min or isosorbide dinitrate 0.5–2.0 μ g/kg per min was administered intravenously in the acute phase, and oral long-acting isosorbide dinitrate (Nitorol R, Eisai Co, Ltd or Frandol, Toa Eiyo Co, Ltd) 80–160 mg per day was administered thereafter for patients without a contraindication to nitrates. Oral diltiazem (Herbesser, Tanabe Seiyaku Co, Ltd) was administered 120–240 mg per day for patients without a contraindication to diltiazem.

Angiographic Evaluation

Nitroglycerin 200 μ g or isosorbide dinitrate 0.5–4 mg was injected into the infarct-related coronary artery before rt-PA infusion in patients who underwent emergent coro-

TABLE I BASELINE CHARACTERISTICS IN THE 10% AND 30% GROUPS

Characteristic	10% group (n=93)	30% group (n=90)	p
Men/Women	63/30	64/26	NS
Age (yr)	65.7±10.5	64.2±10.5	NS
Body weight (kg)	59.2±10.6	58.8±11.0	NS
Location of infarction			
Anterior/lateral	41 (44.1%)	39 (43.3%)	NS
Inferior/posterior	52 (55.9%)	51 (56.7%)	NS
Previous infarction	5 (5.3%)	11 (12.2%)	NS
Time from onset to infusion			
0–3 h	53 (57.0%)	58 (64.4%)	NS
>3–≤6 h	40 (43.0%)	32 (35.6%)	NS
Mean (min)	192.2±88.2	180.9±90.9	NS
Killip class on admission			
1	80 (86.0%)	65 (72.2%)	NS
2	7 (7.5%)	17 (18.9%)	NS
3	4 (4.3%)	7 (7.8%)	NS
4	2 (2.2%)	1 (1.1%)	NS
Risk factor			
Hypertension history	36 (38.7%)	42 (46.6%)	NS
Diabetes	14 (15.1%)	18 (20.0%)	NS
Cigarette smoker	45 (48.4%)	49 (54.4%)	NS
Hyperlipidemia	24 (25.8%)	22 (24.4%)	NS
Obesity	29 (31.2%)	20 (22.2%)	NS

nary angiography. The study protocol called for angiographic assessment of the infarct-related coronary artery before rt-PA infusion, and at 30 and 60 min after initiation of rt-PA therapy. Mechanical interventions, such as angioplasty or bypass grafting, were not permitted before completion of the 60 min angiogram, but were performed later at the discretion of the investigator. Coronary angiography and contrast left ventriculography were also performed about 1 month after onset in patients in whom examination was possible. Standardized orthogonal views of the infarct-related coronary artery were recorded. Single-plane contrast left ventriculography was performed from the 30° right anterior oblique projection. Global wall-motion analysis was performed by an observer who had no knowledge of the clinical outcome or quantitative angiographic analysis at Division of Cardiology, Kumamoto University School of Medicine. Ventricular contours from selected non-postpremature end-diastolic and end-systolic cine frames were hand-drawn and digitized. Using a computer-assisted ventricular analysis program, global left ventricular ejection fraction was determined by the area-length method!¹⁰

Ventriculographic analysis was not performed if the only beats available were postpremature ventricular complexes, if inadequate contrast filling of the ventricular cavity occurred or if significant motion artifact was present during ventriculography.

Patency of the infarct-related coronary artery was assessed at each clinical site according to the Thrombolysis in Myocardial Infarction (TIMI) flow grade classification: grade 0=no perfusion beyond the point of occlusion; grade 1=penetration of contrast material past the area of obstruction with incomplete opacification of the distal coronary bed; grade 2=complete perfusion of the distal bed at a slower rate than that of an uninvolved coronary artery; and grade 3=complete perfusion at a rate comparable to that of an uninvolved artery!¹¹ Angiograms were subsequently reviewed and graded by 2 investigators who had no knowledge of the patient characteristics and treatment assignments. Angiographic films in which it was difficult to grade the flow were brought to the Division of Cardiology, Kumamoto University School of Medicine, and reevaluated by 2 senior angiographers who had no knowledge of the patient characteristics and

TABLE II ANGIOGRAPHIC DATA OF 101 AMI PATIENTS IN CORONARY ANGIOGRAPHY BEFORE, 30 MIN AND 60 MIN AFTER THE START OF rt-PA

Angiographic data	10% group (n=49)	30% group (n=52)	p
Time from onset to rt-PA infusion			
0–3 h	25 (51.0%)	33 (63.5%)	NS
>3–≤6 h	24 (49.0%)	19 (36.5%)	NS
Mean (min)	199.5±88.8	182.3±91.6	NS
Coronary patency			
before rt-PA infusion	8 (16.3%)	11 (21.2%)	NS
Coronary recanalization			
30 min after rt-PA infusion	22/41 (53.7%)	34/41 (82.9%)	p<0.01
Coronary recanalization			
60 min after rt-PA infusion	28/41 (68.3%)	35/41 (85.4%)	NS

Fig. 1. A schematic summary of rt-PA therapy in 183 consecutive patients with acute myocardial infarction, consisting of 93 patients in the 10% group and 90 patients in the 30% group. Coronary angiography before, 30 min after and 60 min after the start of rt-PA infusion was performed in 49 patients in the 10% group and 52 patients in the 30% group. AMI=acute myocardial infarction.

treatment assignments. Any discrepancies between the evaluations at the study sites and those at the Division of Cardiology, Kumamoto University School of Medicine were resolved by consensus.

Clinical and Laboratory Data

Information was collected regarding the patients' clinical courses during their hospital stay. Serum creatine kinase and creatine kinase-MB were analysed at 4-h intervals until 24 h, and at 8-h intervals between 24 h and 48 h.

Statistical Analysis

Angiographic status of TIMI grades 2 or 3 was considered "patent" and TIMI grades 0 or 1 were considered "occluded". Clinical data and events were tabulated according to treatment groups. A *t* test was used to compare mean numeric data and a chi-square test was used to evaluate ordinal data. Data are expressed as mean values±SD unless otherwise indicated. Percentages are followed by their 95% confidence intervals (CI). Statistical significance was defined as $p<0.05$.

RESULTS

Patient Characteristics (Table I)

One hundred ninety three consecutive patients were treated. Ten patients were excluded from the analysis: Eight patients (4 patients each in 10% and 30% groups) were treated >6 h after the onset of symptoms; and 2 patients (1 patient in each group) were treated after prolonged and traumatic cardiopulmonary resuscitation. Thus, a total of 183 consecutive patients were enrolled in this study; 93 and 90 patients were randomly assigned to the 10% and 30% groups, respectively. There were no statistically significant differences between the 10% group and 30% group in terms of demographic or baseline characteristics, including location of infarction, previous infarction, Killip class and risk factors. Time from onset of symptoms to rt-PA infusion was similar between the 10% and 30% groups (10% group 192.2±88.2 min, 30% group 180.9±90.9 min).

Fig. 2. The recanalization rate 30 min and 60 min after the start of rt-PA infusion in the 10% and 30% groups.

Fig. 3. The patency rate 60 min and 1 month after the start of rt-PA infusion in the 10% and 30% groups. The patency rate at 1 month without PTCA is also shown.

TABLE III PEAK CREATINE KINASE (CK) AND PEAK CREATINE KINASE-MB (CK-MB) AND EJECTION FRACTION IN THE 10% AND 30% GROUPS

	10% group	30% group	p
Peak creatine kinase (CK) (IU/L)	2590 ± 1606 (n=89)	2031 ± 1516 (n=89)	p < 0.05
Peak creatine kinase-MB (CK-MB) (IU/L)	280 ± 160 (n=55)	196 ± 163 (n=61)	p < 0.01
Ejection fraction in left ventriculography at 1 month (%)	54.4 ± 11.8 (n=77)	55.1 ± 13.2 (n=78)	NS
Ejection fraction in left ventriculography without previous infarction at 1 month (%)	54.5 ± 11.6 (n=72)	55.1 ± 12.4 (n=70)	NS

Coronary Angiographic Evaluation (Table II and Figs. 1–3)

Forty-nine patients in the 10% group and 52 patients in the 30% group underwent coronary angiography before, 30 min after and 60 min after the start of rt-PA infusion. The mean time from the onset of symptoms to emergent coronary angiography was similar between the 10% and 30% groups (199.5 ± 88.8 min in the 10% group and 182.3 ± 91.6 min in the 30% group). Patency of the infarct-related coronary artery was observed before rt-PA infusion in 8 of 49 patients (16.3%; 95% CI=2.0% to 22.4%) in the 10% group and in 11 of 52 patients (21.2%; 95% CI=3.2% to 23.7%) in the 30% group, with no significant differences between the 2 groups. Recanalization of the infarct-related coronary artery 30 min after rt-PA infusion was observed in 22 of 41 patients (53.7%; 95% CI=37.2% to 70.1%) in

the 10% group and in 34 of 41 patients (82.9%; 95% CI=70.2% to 95.7%) in the 30% group. This recanalization rate was significantly higher ($p < 0.01$) in the 30% group than in the 10% group. However, there was no significant difference in recanalization 60 min after rt-PA infusion between the 10% group and the 30% group, although the rate tended to be higher in the 30% group (35 of 41, 85.4%; 95% CI=73.3% to 97.4%) than in the 10% group (28 of 41, 68.3%; 95% CI=52.8% to 83.8%). Four patients in the 10% group and 4 patients in the 30% group only underwent coronary angiography 60 min after the start of rt-PA infusion. Seventy-two patients in the 10% group and 76 patients in the 30% group underwent coronary angiography 1 month after the onset. Angiograms obtained 60 min and 1 month after beginning rt-PA infusion showed no significant differences in patency

Fig. 4. Peak creatine kinase (CK) levels (IU/L) in the 10% and 30% groups.

Fig. 5. Peak creatine kinase-MB (CK-MB) levels (IU/L) in the 10% and 30% groups.

TABLE IV CLINICAL EVENTS DURING HOSPITALIZATION IN THE 10% AND 30% GROUPS

	10% group (n=93)	30% group (n=90)	p
Percutaneous transluminal coronary angioplasty (PTCA)	22 (23.7%)	26 (28.9%)	NS
Rescue/Immediate	14	15	NS
Deferred/Elective	8	11	NS
Failure	2/22 (9.1%)	3/26 (11.5%)	NS
Coronary artery bypass graft surgery (CABG)	1 (1.1%)	1 (1.1%)	NS
Coronary patency at 1 month	63/72 (87.5%)	65/76 (85.5%)	NS
Bleeding			
Overall	20 (21.5%)	14 (15.6%)	NS
Puncture site	11 (11.8%)	8 (8.9%)	NS
Blood transfusion	1 (1.1%)	0 (0%)	NS
Cerebral	2 (2.2%)	0 (0%)	NS
Reinfarction	5 (5.4%)	6 (6.7%)	NS
Postinfarction angina	3 (3.2%)	8 (8.9%)	NS
In-hospital mortality	6 (6.5%)	4 (4.4%)	NS
Cardiogenic shock	3	3	NS
Cardiogenic shock due to reinfarction	1	1	NS
Cardiac rupture	1	0	NS
Cerebral bleeding	1	0	NS

between the 2 groups. Coronary angiograms both 60 min and 1 month after beginning rt-PA infusion were available from 42 patients in the 10% group and from 45 patients in the 30% group. None of these patients in the 10% group showed reocclusion, while 3 patients in the 30% group showed reocclusion. Although none of these 3 patients with reocclusion had any clinical signs of reinfarction,

2 were treated successfully with percutaneous transluminal coronary angioplasty (PTCA) for early reocclusion after rt-PA infusion. The patency rate at 1 month among patients without PTCA was similar between the 2 groups.

Infarct Size (Table III and Figs. 4, 5)

Peak creatine kinase (CK) levels were

available in 89 patients of the 10% group and in 89 patients of the 30% group. Peak creatine kinase-MB (CK-MB) levels were available in 55 patients of the 10% group and in 61 patients of the 30% group. Peak CK was $2,590 \pm 1,606$ IU/L in the 10% group and $2,031 \pm 1,516$ IU/L in the 30% group. Peak CK-MB was 280 ± 160 IU/L in the 10% group and 196 ± 163 IU/L in the 30% group. Both peak CK and peak CK-MB were significantly lower in the 30% group than in the 10% group. On the other hand, the mean global ejection fraction measured 1 month after the onset of symptoms was similar between the 2 groups ($54.4 \pm 11.8\%$ in 77 patients of the 10% group and $55.1 \pm 13.2\%$ in 78 patients of the 30% group). The mean global ejection fraction without previous myocardial infarction 1 month after the onset was also similar between the 2 groups.

Clinical Events (Table IV)

Nitrates were administered to 77 patients (82.8%) in the 10% group and 84 patients (93.3%) in the 30% group. Diltiazem was prescribed to 70 patients (75.3%) in the 10% group and to 70 patients (77.8%) in the 30% group. Reinfarction occurred in 5 patients (5.4%) in the 10% group and in 6 patients (6.7%) in the 30% group during the hospital stay. Postinfarction angina was seen in 3 patients (3.2%) in the 10% group and in 8 patients (8.9%) in the 30% group. PTCA was performed within 1 month in 22 patients (23.7%) in the 10% group and in 26 patients (28.9%) in the 30% group. Coronary artery bypass graft surgery (CABG) was performed within 1 month in 1 patient in each group. Bleeding complications occurred with almost equal frequency in the 2 treatment groups. Two cerebral bleedings occurred in this trial, both in the 10% group. There were 6 (6.5%) in-hospital deaths in the 10% group and 4 (4.4%) in the 30% group. There were no significant differences in these clinical events and complications between the 2 groups.

DISCUSSION

The present study shows that the recanalization rate 30 min after the start of rt-PA infusion was higher in the 30% group than in the 10% group. The results also show that

the infarct size^{12,13} estimated by peak creatine kinase levels and creatine kinase-MB levels was smaller in the 30% group than in the 10% group. The RAAMI Study Investigators⁶ showed that an accelerated 90 min regimen of rt-PA 100 mg (15 mg bolus followed by 50 mg over 30 min, then 35 mg over 60 min) achieved more rapid reperfusion rates without an apparent change in the safety profile than the standard regimen of rt-PA 100 mg (an initial 10 mg bolus followed by 50 mg for the 1st h, then 20 mg/h for 2 h). The GUSTO angiographic substudy⁸ has demonstrated that the rate of the infarct-related coronary artery at 90 min was higher in patients given accelerated-dose rt-PA (81%) than in those given combination therapy (73%), in which 1.0×10^6 U of streptokinase was given over a 60 min period concomitantly with t-PA (1.0 mg/kg, with 10% of the total dose given as a bolus, for a total dose of ≤ 90 mg). Our study supports these previous results in that higher patency rates for the infarct-related coronary artery depended on the volume of the initial bolus. These 2 studies, as well as most other studies, compared the patency rates among the various treatment strategies for reperfusion. However, in the present study, we examined the recanalization rates in the 2 treatment groups after coronary angiography before rt-PA infusion.

The RAAMI Study Investigators⁶ reported that angiographic patency rates were significantly higher in the accelerated-regimen group (76%) than in the standard-regimen group (63%) at 60 min after initiation of rt-PA infusion, while the rates were similar at 90 min (81% vs 77%). The GUSTO angiographic substudy⁸ also demonstrated that the patency rates 180 min after the start of therapy were essentially equal among the group given accelerated-dose rt-PA, the group given combination therapy, and the group given streptokinase. They believed that this phenomenon (catching-up phenomenon) occurs too late to result in an equally favorable clinical outcome with regard to ventricular function and mortality. Our results showed a similar catching-up phenomenon, in that the recanalization rate at 30 min after the start of rt-PA infusion was higher in the 30% group than in the 10% group, while there was no significant

difference in the recanalization rate between the two groups at 60 min. In the present study, the infarct size^{12,13} estimated by peak CK and CK-MB was smaller in the 30% group than in the 10% group despite this catching-up phenomenon. Patency of the infarct-related coronary artery was observed before rt-PA infusion in 16.3% in the 10% group and 21.2% in the 30% group, with no significant difference between the 2 groups. Our results were similar to those of recent studies^{14–16} in which approximately 20 to 30% of the infarct-related coronary arteries were patent before thrombolytic therapy, even in the early phase of acute transmural myocardial infarction.

Reocclusion of recanalized coronary arteries limits the efficacy of recanalization.^{1,17} Adjunctive therapy with currently available antiplatelet (aspirin)¹⁸ and anticoagulant (heparin)¹⁹ agents has been shown to be beneficial in overcoming this problem. In the present study, all of the patients received intravenous heparin and aspirin. It has been shown that prolonged low-dose nitroglycerin infusion gives several benefits versus a placebo: smaller CK infarct size, better global ejection fraction, and less infarct expansion and thinning.²⁰ We prescribed nitroglycerin and isosorbide dinitrate for 82.8% of the patients in the 10% group and 93.3% of those in the 30% group. Furthermore, the Diltiazem Reinfarction Study Group²¹ reported that diltiazem was effective in preventing early reinfarction and recurrent angina in patients with non-Q wave infarction. Although diltiazem does not have a beneficial effect on Q wave infarction,²² it does affect postinfarction angina caused by coronary spasm.²³ Furthermore, it has been shown that the Japanese population has a higher incidence of coronary spasm than those in other countries.²⁴ Therefore, we administered diltiazem orally from the acute phase to 75.3% of the patients in the 10% group and to 77.8% of those in the 30% group. In our study, the incidence of reinfarction was similar to those in other reports^{6,7,25} but the incidence of postinfarction angina (3.2% in the 10% group and 8.9% in the 30% group) was lower than that of the RAAMI Study Group (22% in the standard-regimen group and 16% in the accelerated-regimen group).⁶

This difference may be due to the effect of diltiazem prescribed from the acute phase in the present study.

In Japan, the intracoronary administration of urokinase 960,000 IU resulted in recanalization rates of approximately 70% in a previous study.²⁶ In the present study, the total dose of alteplase was 41.4 mg intravenously, and the coronary recanalization rate was 63.8% in the 10% group and 85.4% in the 30% group 60 min after initiation of alteplase infusion. These recanalization rates were almost the same as that with the intracoronary administration of urokinase²⁶ and that in the TIMI trial, phase 1! The patency rate was 71.7% in the 10% group and 87.5% in the 30% group 60 min after initiation of alteplase infusion in the present study, and these rates were almost the same as that with an accelerated 100 mg dose of alteplase in the RAAMI Study⁶ and the GUSTO angiographic substudy.⁸ The doses of alteplase in our study were smaller than those in these previous studies, however, there were also differences in body weight. It is known that Blacks are more sensitive to rt-PA, as manifested by an increased thrombolytic efficacy, than Caucasians.²⁷ The difference in the doses of rt-PA between our study and the RAAMI Study⁶ and the GUSTO angiographic substudy⁸ may be due to a difference in sensitivity to rt-PA between a Japanese population and Western populations.

Recent clinical studies^{28–30} have reported that patients with complete reperfusion (TIMI grade 3) show a greater clinical benefit, such as a lower mortality and a greater global ejection fraction, than those with partial reperfusion (TIMI grade 2). In the present study, we defined TIMI grades 2 or 3 as “patent” and TIMI grades 0 or 1 as “occluded”. Therefore, further studies are required in larger populations of the differences in clinical features between the 10% and 30% groups, with patients with coronary patency divided into those with TIMI grade 2 and those with grade 3.

In conclusion, a higher initial bolus dose of rt-PA gives a higher rate of recanalization of the infarct-related coronary artery at the very early phase, and probably leads to a smaller infarct size.

APPENDIX

The Kumamoto University Myocardial Infarction Study (KUMIS) Group

Kumamoto University Hospital, Kumamoto.
Principal Investigator: Hirofumi Yasue, M.D., Coinvestigator: Hisao Ogawa, M.D.

Fukuoka Tokushukai Hospital, Fukuoka.
Principal Investigator: Shuichi Oshima, M.D.

Japanese Red Cross Kumamoto Hospital, Kumamoto. Principal Investigator: Yasuhiro Ogata, M.D., Coinvestigator: Yuichi Numata, M.D.

Haibara General Hospital, Shizuoka. Principal Investigator: Kinya Fujimoto, M.D.

Yatsushiro General Hospital, Kumamoto. Principal Investigator: Nobuya Imoto, M.D.

Kumamoto Central Hospital, Kumamoto. Principal Investigator: Taro Saito, M.D.

Kumamoto City Hospital, Kumamoto. Principal Investigator: Youichi Hokamura, M.D.

Tamana Central Hospital, Kumamoto. Principal Investigator: Toru Takahashi, M.D.

Kumamoto Rohsai Hospital, Kumamoto. Principal Investigator: Hajime Watanabe, M.D.

Kenritsu Nobeoka Hospital, Miyazaki. Principal Investigator: Hideaki Kodama, M.D.

Kumamoto National Hospital, Kumamoto. Principal Investigator: Hiroo Miyagi, M.D.

Arao City Hospital, Kumamoto. Principal Investigator: Yasuhiro Morikami, M.D.

Hitoyoshi General Hospital, Kumamoto. Principal Investigator: Kenji Obata, M.D.

Mitsui-Ohmuta Hospital, Kumamoto. Principal Investigator: Koshi Matsuyama, M.D.

Amakusa Regional Medical Center, Kumamoto. Principal Investigator: Naritsugu Sakaino, M.D.

Ushibuka City Hospital, Kumamoto. Principal Investigator: Tomoki Nakamura, M.D.

Koritsu Taragi Hospital, Kumamoto. Principal Investigator: Tomio Wakita, M.D.

Juzen Hospital, Kumamoto. Principal Inves-

tigator: Naritsugu Sakaino, M.D.

Kumamoto Regional Medical Center, Kumamoto. Principal Investigator: Kazuo Goto, M.D.

REFERENCES

1. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, Ludbrook P, Markis JE, Mueller H, Passamani ER, Powers ER, Rao AK, Robertson T, Ross A, Ryan TJ, Sobel BE, Willerson J, Williams DO, Zaret BL, Braunwald E: Thrombolysis in Myocardial Infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase: clinical findings through hospital discharge. *Circulation* 1987; **76**: 142–154
2. Gruppo Italiano per lo Studio Della Streptochinasi Nell'infarto Miocardico (GISSI): Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. *Lancet* 1987; **2**: 871–874
3. White HD, Rivers JT, Maslowski AH, Ormiston JA, Takayama M, Hart HH, Sharpe DN, Whitelock RML, Norris RM: Effect of intravenous streptokinase as compared with that of tissue plasminogen activator on left ventricular function after first myocardial infarction. *N Engl J Med* 1989; **320**: 817–821
4. Verstraete M, Bernard R, Bory M, Brower RW, Collen D, de Bono DP, Erbel R, Huhmann W, Lennane RJ, Lubsen J, Mathey D, Meyer J, Michels HR, Rutsch W, Scharlt M, Schmidt W, Uebis R, von Essen R: Randomised trial of intravenous recombinant tissue-type plasminogen activator versus intravenous streptokinase in acute myocardial infarction: report from the European Cooperative Study Group for Recombinant Tissue-type Plasminogen Activator. *Lancet* 1985; **1**: 842–847
5. Neuhaus K-L, Feuerer W, Jeep-Tebbe S, Niederer W, Vogt A, Tebbe U: Improved thrombolysis with a modified dose regimen of recombinant tissue-type plasminogen activator. *J Am Coll Cardiol* 1989; **14**: 1566–1569
6. Carney RJ, Murphy GA, Brandt TR, Daley PJ, Pickering E, White HJ, McDonough TJ, Vermilya SK, Teichman SL, for the RAAMI Study Investigators: Randomized angiographic trial of recombinant tissue-type plasminogen activator (alteplase) in myocardial infarction. *J Am Coll Cardiol* 1992; **20**: 17–23
7. The GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993; **329**: 673–682
8. The GUSTO Angiographic Investigators: The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med* 1993; **329**: 1615–1622
9. Purvis JA, McNeill AJ, Siddiqui RA, Roberts

- MJD, McClements BM, Mceneaney D, Campbell NPS, Khan MM, Webb SW, Wilson CM, Adgey AAJ: Efficacy of 100 mg of double-bolus alteplase in achieving complete perfusion in the treatment of acute myocardial infarction. *J Am Coll Cardiol* 1994; **23**: 6–10
10. Kennedy JW, Trenholme SE, Kasser IA: Left ventricular volume and mass from single-plane cineangiogram: a comparison of anteroposterior and right anterior oblique methods. *Am Heart J* 1970; **80**: 343–352
11. The TIMI Study Group: The thrombolysis in Myocardial Infarction (TIMI) trial. Phase 1 findings. *N Engl J Med* 1985; **312**: 932–936
12. Sobel BE, Bresnahan GF, Shell WE, Yoder RD: Estimation of infarct size in man and its relation to prognosis. *Circulation* 1972; **46**: 640–648
13. Rogers WJ, Mcdaniel HG, Smith MA, Mantle JA, Russel RO, Rackley CE: Correlation of angiographic estimates of myocardial infarct size and accumulated release of creatine kinase MB isoenzyme in man. *Circulation* 1977; **56**: 199–205
14. DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS, Lang HT: Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980; **303**: 897–902
15. Khaja F, Walton JA, Brymer JF, Lo E, Osterberger L, O'Neill WW, Colfer HT, Weiss R, Lee T, Kurian T, Goldberg AD, Pitt B, Goldstein S: Intracoronary fibrinolytic therapy in acute myocardial infarction: report of a prospective randomized trial. *N Engl J Med* 1983; **308**: 1305–1311
16. Rentrop KP, Feit F, Blanke H, Stecy P, Schneider R, Rey M, Horowitz S, Goldman M, Karsch K, Meilman H, Cohen M, Siegel S, Sanger J, Slater J, Gorlin R, Fox A, Fagerstrom R, Calhoun WF: Effects of intracoronary streptokinase and intracoronary nitroglycerin infusion on coronary angiographic patterns and mortality in patients with acute myocardial infarction. *N Engl J Med* 1984; **311**: 1457–1463
17. Ohman EM, Califf RM, Topol EJ, Candela R, Abbottsmith C, Ellis S, Sigmon KN, Kereiakes D, George B, Stack R, and the TAMI Study Group: Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. *Circulation* 1990; **82**: 781–791
18. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group: Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17187 cases of suspected acute myocardial infarction.: ISIS-2. *Lancet* 1988; **2**: 349–360
19. Hsia J, Hamilton WP, Kleiman N, Roberts R, Chaitman BR, Ross AM, for the Heparin-Aspirin Reperfusion Trial (HART) Investigators: A comparison between heparin and low-dose aspirin as adjunctive therapy with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 1990; **323**: 1433–1437
20. Jugdutt BI, Warnica JW: Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion, and complications. Effect of timing, dosage, and infarct location. *Circulation* 1988; **78**: 906–919
21. Gibson RS, Boden WE, Theroux P, Strauss HD, Pratt CM, Gheorghide M, Capone RJ, Crawford MH, Schlant RC, Kleiger RE, Young PM, Schechtman K, Perryman B, Roberts R, and the Diltiazem Reinfarction Study Group: Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction: results of a double-blind, randomized, multicenter trial. *N Engl J Med* 1986; **315**: 423–429
22. The Multicenter Diltiazem Postinfarction Trial Research Group: The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988; **319**: 385–392
23. Nakamura M, Koiwaya Y: Effect of diltiazem on recurrent spontaneous angina after acute myocardial infarction. *Circ Res* 1983; **52**(Suppl 1): 158–162
24. Yasue H, Takizawa A, Nagao M, Nishida S, Horie M, Kubota J, Fujii H: Pathogenesis of angina pectoris in patients with one-vessel disease: possible role of dynamic coronary obstruction. *Am Heart J* 1986; **112**: 263–272
25. Neuhaus K-L, von Essen R, Tebbe U, Vogt A, Roth M, Riess M, Niederer W, Forycki F, Wirtzfeld A, Maeurer W, Limbourg P, Merx W, Haerten K: Improved thrombolysis in acute myocardial infarction with front-loaded administration of alteplase: results of the rt-PA-APSAC patency study (TAPS). *J Am Coll Cardiol* 1992; **19**: 885–891
26. Kambara H, Kawai C, Kammatsuse K, Sato H, Nobuyoshi M, Chino M, Miwa H, Uchida Y, Kodama K, Mitsudo K, Hayashi T, Kajiwarra N, Sekiguchi M, Yasue H: Coronary thrombolysis with urokinase infusion in acute myocardial infarction: Multicenter study in Japan. *Cathet Cardiovasc Diagn* 1985; **11**: 349–360
27. Sane DC, Stump DC, Topol EJ, Sigmon KN, Clair WK, Kereiakes DJ, George BS, Stoddard MF, Bates ER, Stack RS, Califf RM, and the Thrombolysis and Angioplasty in Myocardial Infarction Study Group: Racial differences in response to thrombolytic therapy with recombinant tissue-type plasminogen activator. Increased fibrin (ogen)olysis in Blacks. *Circulation* 1991; **83**: 170–175
28. Karagounis L, Sorensen SG, Menlove RL, Moreno F, Anderson JL, for the TEAM-2 Investigators: Does thrombolysis in myocardial infarction (TIMI) perfusion grade 2 represent a mostly patent artery or a mostly occluded artery? Enzymatic and electrocardiographic evidence from the TEAM-2 study. *J Am Coll Cardiol* 1992; **19**: 1–10
29. Vogt A, von Essen R, Tebbe U, Feuerer W, Appel K-F, Neuhaus K-L: Impact of early perfusion status of the infarct-related artery on short-term mortality after thrombolysis for acute myocardial infarction: retrospective analysis of four German multicenter studies. *J Am Coll Cardiol* 1993; **21**: 1391–1395
30. Anderson JL, Karagounis LA, Becker LC, Sorensen SG, Menlove RL, for the TEAM-3 Investigators: TIMI perfusion grade 3 but not grade 2 results in improved outcome after thrombolysis for myocardial infarction. Ventriculographic, enzymatic, and electrocardiographic evidence from the TEAM-3 Study. *Circulation* 1993; **87**: 1829–1839