Intracoronary Urokinase in Acute Myocardial Infarction:
Prevalence of Total Coronary Occlusion During the Early Hours,
Effects on Myocardial Infarct Size and Left Ventricular Function,
and Outcome of Residual Coronary Stenosis

Takeshi Motomiya, M.D., Yoshiki Tokuyasu, M.D., Koji Watanabe, M.D.
Harumizu Sakurada, M.D., Nariaki Ejiri, M.D.
and Osamu Yanase, M.D.

The effects of intracoronary thrombolysis (ICT) were studied in 88 acute myocardial infarction patients. Total coronary occlusion was observed in 67 of the 88 patients (76.1%) who were evaluated within 6 hours of the onset of symptoms. Among these 67 patients 42 (62.7%) were successfully recanalized by intracoronary urokinase. The recanalization rate was higher in the lesion at the left anterior descending artery, in younger patients (49 years or less) and in patients with a shorter history of pre-infarction angina. Eight of 11 patients (72.7%) with subtotal coronary occlusion and 17 of 35 patients (48.6%) with recanalization after ICT showed spontaneous regression of the residual coronary stenosis at the chronic stage angiography. There was no re-o-cclusion in the subtotal occlusion group and only 6 cases of re-o-cclusion (17.1%) in the recanalization group. The majority of re-occlusions progressed from the lesion with 99% residual stenosis and delayed filling. Accordingly the true value of additional percutaneous transluminal coronary angioplasty would be limited to the latter cases. Reduction in infarct size and improvement in left ventricular function were limited to those patients with incomplete or subtotal coronary occlusion and were not seen in cases with total obstruction which was recanalized by ICT.

Both the demonstration by DeWood et al1 that thrombosis is frequently present in totally occluded coronary arteries in the hours immediately following transmural infarction and the report by Rentrop et al2 of intracoronary thrombolysis initiated widespread interest in the potential for thrombolysis as an effective method of salvaging acutely ischemic myocardium.

The purpose of the present study is to demonstrate the prevalence of total coronary occlusion in the early phases of acute myocardial infarction (AMI). The effects of intracoronary urokinase on the occluded coronary arteries, myocardial infarct size and left ventricular function are also examined, together with the outcome of residual stenosis of the infarct-related coronary artery.

MATERIALS AND METHODS

Study group
The study group consisted of 88 AMI patients who underwent acute coronary angiography within 6 hours (mean 4.1 ± 1.2 SD hours) of the

Key words:
Intracoronary thrombolysis
Urokinase
Acute myocardial infarction
Residual coronary stenosis

Department of Cardiology, Tokyo Metropolitan Hirono General Hospital, Tokyo, Japan
Mailing address: Takeshi Motomiya, M.D., Department of Cardiology, Tokyo Metropolitan Hirono General Hospital, 2-34 Ebisu, Shibuya-ku, Tokyo 150, Japan

702 Japanese Circulation Journal Vol. 52, July 1988
Fig. 1. Outcome of 88 patients with acute myocardial infarction who underwent emergency coronary angiography (Em CAG) and intracoronary thrombolysis (ICT) within 6 hours of the onset of symptoms.

Fig. 2. Prevalence of total coronary occlusion during the early hours of myocardial infarction and recanalization rate by intracoronary urokinase infusion in relation to A) infarct-related coronary branches, B) age of the patients and 3) history of preinfarction angina.

*Japanese Circulation Journal  Vol. 52, July 1988*
onset of chest pain. All patients had chest pain, which lasted more than 20 min, was not alleviated by sublingual nitroglycerin, and was presumed to be due to myocardial ischemia. The admission ECG showed changes compatible with acute myocardial infarction. The 88 patients consisted of 70 males and 18 females, aged between 29 and 76 years (57.6 ± 10.9 years). Eighty-three were cases of first myocardial infarction and 5 had a history of previous myocardial infarction.

Acute Angiography and Intracoronary Intervention

Informed consent for the procedure was obtained from the patient and/or a family member of the patient.

Intracoronary thrombolysis (ICT) was performed by selective injection of urokinase into the orifice of the infarct-related coronary artery. The dosage ranged from 480,000 to 960,000 IU at the rate of 240,000 IU per 10 min. The mean total dose of urokinase injected was 732,000 ± 183,000 IU. The urokinase injection was preceded by intravenous injection of a bolus of heparin (2,000 to 5,000 units) and a bolus of intracoronary nitroglycerin (0.2 mg). Intracoronary thrombolysis was followed by anticoagulation with intravenous heparin for 3 or 4 days and then oral warfarin for 3 months. An anti-platelet regimen of aspirin (ASA) 81 mg and dipyridamole 150 mg per day was also initiated on the 2nd hospital day in all cases.

Items Studied

1. The infarct-related coronary artery
   All patients were studied on 3 occasions; 1) at initial acute coronary angiography; 2) immediately after intracoronary thrombolysis; and 3) at chronic stage angiography (6.2 ± 1.7 weeks after the onset of AMI). The grading of stenosis was based on the American Heart Association (AHA) grading system which was modified by adding a grade of 99% with delayed filling.

2. Effects of ICT on infarct size and left ventricular function.

Infarct size was estimated by determination of total creatine kinase released (ΣCK) following the method of Norris et al and ECG QRS score following the method of Wagner et al in 83 patients. Cardiac function at the late period was evaluated by determination of left ventricular ejection fraction (LVEF) following the method of Dodge in 68 patients.

Data are presented as mean ± SD. Differences between mean values were assessed by means of the Student t test. The chi square test and the Fisher’s exact test were also used for statistical analysis.

*Japanese Circulation Journal Vol. 32, July 1988*
RESULTS

1. The infarct-related coronary artery

Initial acute coronary angiography: Among 88 patients who underwent coronary angiography within 6 hours of the onset of AMI, 21 (23.9%) revealed incomplete (subtotal) obstruction of the infarct-related coronary artery and 67 (76.1%) demonstrated complete (total) obstruction (Fig. 1).

The infarct-related coronary lesion was demonstrated in the left anterior descending artery (LAD) in 56 cases out of 88 (63.6%), in the left circumflex artery (LCX) in 10 cases (11.4%) and in the right coronary artery (RCA) in 22 cases (25.0%) (Fig. 2). Incomplete obstruction was seen more frequently in LAD than RCA (32.1% vs. 4.5%, p < 0.01). Incomplete obstruction was seen in 5 out of 22 patients (22.7%) above 65 years of age, in 15 out of 46 patients (32.6%) between the ages of 50 and 64 years and 1 out of 20 patients (5%) under 49 years of age. The difference between the second and third age groups was statistically significant (p < 0.02).

Intracoronary thrombolysis (ICT): Intracoronary thrombolysis was performed in all cases regardless of whether obstruction of the infarct-related coronary artery was total or subtotal. Among 67 patients with complete obstruction, 34 (50.7%) demonstrated recanalization after ICT and 33 (49.3%) did not. Eight patients who were recanalized with 99% residual stenosis and delayed filling were classified as 'no recanalization' in this study. If these 8 patients were classified as being recanalized, 42 patients (62.7%) were recanalized and 25 (37.3%) were not (Fig. 1).

The recanalization rate varied between the different coronary branches, and was highest in the LAD followed by the LCX and the RCA respectively (Fig. 2). The difference in recanalization rate between the LAD (60.5%) and RCA (33.3%) was statistically significant (p < 0.05). The group of patients under 49 years of age demonstrated the highest rate of recanalization, followed by those aged 50–64 years and, finally, the patients over 65 years of age (78.9% vs 51.6% vs 17.6%, p < 0.05). The group of patients with a history of pre-infarction angina for a period of 20 days or less demonstrated a higher rate of recanalization than those patients having pre-infarction angina for 21 days or more (61.7% vs 25.0%, p < 0.01).

Chronic stage coronary angiography: Fig. 3 shows the changes in the stenosis diameter in the infarct-related coronary artery from the initial acute coronary angiography to post-ICT and to the chronic stage coronary angiography. Among 11 patients who demonstrated incomplete obstruction, 6 (54.5%) showed an improvement in stenosis, diameter of more than 1 grade, 5 (45.5%) showed no change and none had wors-
ened after ICT. At the chronic stage 8 patients (72.7%) demonstrated improvement, 2 (18.2%) showed no change and 1 (9.1%) had worsened as compared with the findings after ICT.

Among 42 patients who demonstrated recanalization, 35 had chronic stage angiography, when 17 (48.6%) showed an improvement in the stenosis, 10 (28.6%) showed no change and 8 (22.8%) had worsened, including 6 with re-occlusion (17.1%). In the latter 6 patients re-occlusion developed from coronary stenosis of 99% with delayed filling in 4 and from 90% in 2. One of the 2 patients with 90% stenosis had a coronary arterio-venous fistula to the pulmonary artery immediately proximal to the lesion. Among 25 patients with no recanalization, 21 underwent a chronic stage coronary angiography; 11 (52.4%) of these demonstrated recanalization and 10 (47.6%) remained 100% obstructed.

2. Effects of ICT on infarct size and left ventricular function

ΣCK: Mean ΣCK was 6137 ± 4863 IU/l in 19 patients with incomplete obstruction, 8036 ± 5932 IU/l in 34 patients with recanalization and 5751 ± 4277 IU/l in 30 patients with no recanalization (Fig. 4A left panel). There were no significant differences between the 3 groups. Comparing only those patients with an initial QRS score of 4 or less, no history of previous myocardial infarction and lesion located in segment 6 or 7 of the LAD, LVEF was 56.5 ± 9.1% in the first group, 50.5 ± 8.8% in the second group and 45.0 ± 9.9% in the third group, respectively. The first group, with incomplete obstruction, exhibited a significantly higher LVEF as compared with the third group, with no recanalization (p < 0.05) (Fig. 4B right panel).

LVEF in 13 patients with an initial QRS score of 5 or more was 35.5 ± 6.7%, which was lower than any of the former 3 groups (p < 0.01 each).

DISCUSSION

Prevalence of Total Occlusion

The severity of reduction in blood flow during the early phase of AMI had not been investigated comprehensively until 1980 when DeWood et al reported that the early period (up to 4 hours) of transmural infarction in human beings was characterized by the complete absence of blood flow in the diseased coronary artery in the majority (87.3%) of cases. Furthermore, there was also a high incidence of total occlusion (85.3%) if patients were studied during the first 4 to 6 hours after the onset of chest pain. This proportion decreased significantly to 65% when patients were studied 12 to 24 hours after the onset of symptoms.

In the present study, 76.1% of cases had complete obstruction of the infarct-related coronary artery in the early period of AMI (up to 6 hours) and the remaining 23.9% had incomplete obstruction.

In the DeWood series, the decreasing frequency of total occlusion over the course of time suggests that multiple factors may operate in the early hours of transmural infarction. Possible factors are coronary spasm or platelet aggregation or thrombosis with subsequent lysis; but the clinical importance of each factor is still unclear. Recent evidence12,13 however, suggests that there may be a dynamic interaction between coronary spasm, platelet aggregation, and atherosclerotic plaque that leads to coronary occlusion.

Intracoronary Thrombolysis

Rapid recanalization of a totally occluded coronary artery during intracoronary urokinase infusion implies that fresh thrombotic material was present at the site of obstruction in 42 of 67 cases (62.7%). This recanalization rate is similar to the result (66.8%) of a multicenter coronary

Japanese Circulation Journal Vol. 52, July 1988
thrombolysis survey in Japan but lower than the American or European reports (64–87%)\textsuperscript{15} In our patients, the narrowing that remained after intracoronary lysis had improved at the chronic stage angiography in 33 (62.3%) of 53 cases. This fact provides evidence for the concept that thrombosis is one of the mechanisms of residual coronary stenosis. Coronary stenosis still present at repeat angiography in the chronic stage of infarction was most likely to be due to atherosclerosis.

The present study revealed that patients obtaining reperfusion within 6 hours of onset of symptoms showed a tendency toward a lower CK and higher LVEF compared to those with no recanalization. However, there was no statistically significant difference between the 2 groups.

However, the reduction in infarct size and the improvement in left ventricular function seems to be limited to patients with evolving myocardial infarction (QRS score of 4 or less in this study) with incomplete obstruction at the initial acute angiography or who underwent spontaneous re-canalization. Though good recanalization was obtained, no benefits were shown in patients with a QRS score of 5 or more; that is, those completing infarction. These data are compatible with those from the randomized trial of Rentrop et al\textsuperscript{16} in which patients with initial subtotal obstruction had improved left ventricular function and a trend toward a lower mortality in comparison to those with initial complete obstruction. These studies seem to emphasize the value of much earlier reperfusion.

Despite these rather discouraging results of ICT, some encouraging trends are discernible from both randomized and uncontrolled studies. Comparisons of regional and overall left ventricular function strongly suggest that effective thrombolysis with intracoronary streptokinase therapy results in a higher ejection fraction, an improvement in regional wall motion, and a reduction in enzymatic and electrocardiographic estimates of infarct size, particularly in patients undergoing reperfusion within 4 hours of onset of symptoms\textsuperscript{12,13}

**Follow-up after ICT in Relation to Residual Stenosis**

After successful coronary recanalization, high-degree residual stenosis of the infarct-related vessel persists in many patients. Whether percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft surgery, or only medical treatment should be employed to prevent reocclusion is still controversial. An incidence of more than 20% of reinfarction and late reocclusion after successful intracoronary streptokinase treatment has been reported\textsuperscript{14,15}. Harrison et al\textsuperscript{16} reported that rethrombosis occurred in 29% of successfully reperfused patients as a whole and in 54% of reperfused patients with residual stenosis of 90% or more. However, the observation that the extent of residual stenosis may decrease spontaneously and that the early reocclusion rate after PTCA may be as high as 30%\textsuperscript{17} emphasizes that the true value of additional PTCA remains to be assessed. Völker et al\textsuperscript{18} also reported spontaneous regression of critical stenosis in 56% of recanalized vessels and recommended a cautious attitude to further intervention.

In the present study 8 patients (72.7%) with subtotal obstruction and 25 patients (59.5%) with total obstruction which was recanalized by ICT showed spontaneous regression from the acute to the chronic stage. There was no re-thrombosis in the subtotal obstruction group and only 6 cases of re-occlusion (14.2%) in the recanalized patients. The majority of re-occlusions progressed from the lesions with 99% residual stenosis associated with delayed filling. The results suggest that the indication for emergency invasive interventions, such as PTCA or bypass surgery following ICT, would be limited to cases with 99% residual coronary stenosis with delayed filling. The decision for further invasive treatment should depend on the clinical follow-up.

**Acknowledgement**

The authors wish to thank Miss Rosemarie Rowley for her assistance in preparing the manuscript.

**REFERENCES**


4. NORRIS RM, WHITELock RM, BARRATT-BOYES C, SMALL CW: Clinical measurement of


Japanese Circulation Journal Vol. 52, July 1988