Effects and Limitation of CCU
— Prevention of Evolving Myocardial Infarction —

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Emergency coronary angiography and intracoronary thrombolysis were performed on 47 patients who were hospitalized within 12 hours from onset of chest pain. It revealed either a severe stenosis (14 pts: stenosed group) or complete occlusion (33 pts) of infarct-related coronary artery. In 25 out of 33 patients (76%) with complete occlusion, reperfusion was achieved after 10 to 20 minutes of intracoronary urokinase (UK) infusion at a rate of 500 IU/kg/min (thrombolysed group). The failure to open coronary artery in remaining 8 patients may have been caused by the occlusion of atheroma itself (unsuccessful group). Left ventricular angiography was performed at one month after attack. In unsuccessful group, the mean age was younger and infarct-nonrelated vessel disease was lower frequency compared to other two groups. Ejection fraction in stenosed, thrombolysed and unsuccessful groups were 56.6 ± 12, 47.5 ± 14 and 44.3 ± 5.1%, respectively. Wall motion assessed by point-score system were 6.7, 5.9 and 3.6, respectively (p < 0.05 in each group). These facts suggest that early recanalization may result in greater reversal of cardiac function. The time to the peak CPK was shortened in stenosed and thrombolysed groups, but, the values of CPK was maximum in thrombolysed group. Rethrombosis was recognized in 2 patients during 1 to 30 months follow-up. No death and no remarkable complications were seen during this intervention, but 4 late deaths were recognized. Thus, early reperfusion by intracoronary UK infusion is effective therapy to improve cardiac function and reduction of death in AMI.

THROMBI are observed in high frequency in the coronary arteries of the patients who died immediately after the onset of transmural myocardial infarction. If we accept that thrombosis is the dominant mechanism of coronary occlusion in the patients with acute myocardial infarction, reopening the coronary artery by early lysis of the thrombus would seem a rational step to salvage the myocardium and reduce morbidity and mortality. And even if the thrombus is a formation of a secondary nature, the existence of the thrombus itself in the coronary artery is not desirable from the viewpoint of the blood-flow maintenance in coronary arteries. The present study was, therefore, designed to investigate whether human intracoronary thrombi could be lysed rapidly by intracoronary urokinase (UK) infusion and cardiac function could be improved after reperfusion.

SUBJECTS

From August 1980 to February 1983, emergency coronary angiography and intracoronary UK infusion were performed on 47 patients with acute transmural myocardial infarction who were hospitalized within 12 hours from

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Key Words:
Myocardial infarction
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Urokinase
Wall motion
Residual stenosis

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onset of symptoms. The age of the patients was 46 to 73 years old (average 60.2), 40 were male and 7 were female. The criteria for inclusion in this study were: 1) precisely defined time of onset of symptoms, 2) initial electrocardiogram (ECG) consistent with transmural myocardial infarction, 3) upper limit of the age was initially less than 70 years old, but, in recently, it was spreading a little bit more than 70 years old. Patients with cardiogenic shock regardless of infusion of catecholamines were excluded.

METHODS

All qualifying patients were catheterized without specific preoperative medication. After a bolus of 3000IU of heparin were injected by intravenously, coronary arteriography was performed by Judkins technique. If total or subtotal occlusion of the infarct-related coronary artery serving the electrocardiographically identified jeopardized myocardium persisted after 200 µg of intracoronary nitroglycerin or 2 mg of isosorbid-dinitrates, UK was infused by following technique. A small 3 french size injection catheter through Judkins catheter was inserted into the occluded coronary artery just proximal to the occlusion site. Afterwards, UK was infused at a rate of 500IU/kg/minute during 10 to 20 minutes. When the injection catheter was not superselectively inserted into the occluded artery such as left anterior descending coronary artery (LAD) or circumflex artery, and when right coronary artery was occluded at the proximal site, UK was administered from Judkins catheter itself. UK was dissolved in 50 ml of 5% glucose for injection 10 minutes. Completely occluded coronary artery was checked by angiographi-

![Fig.1. Subjects.](attachment://figure1.png)

cally every ten minutes.

The failure to open coronary artery was decided after 20 minutes infusion of UK. Patients displaying recanalization at follow-up were discharged on a regimen of warfarin, usually with dipyridamole, 150 mg three times a day.

**Control Population**

A control population was retrospectively enrolled within the limitations of private referral and recognition of the need for studies additional to the conventional therapy of myocardial infarction. All 17 such patients did not receive intracoronary UK because of case finding beyond 12 hours of the onset of symptoms. All the 17 patients were catheterized usually at 48.1 ± 15 days after attack of myocardial infarction to compare ventricular function with that in the intracoronary UK treated group.

**Myocardial Function**

Left ventriculography was performed at 30 days after attack of myocardial infarction, and was not performed at acute stage because of apprehension of troublesome complications such as ventricular fibrillation and flutter.

Ejection fraction was calculated by contrast ventriculography using Dodge’s formula. Anterior wall motion in anterior infarction caused by LAD occlusion was also assessed qualitatively using point-score system employed by the American Heart Association’s classification, when the wall motion of each segment of anterobasal, anterolateral and apex showed normal contraction, point 3 was given in each segment, and when the contraction of each segment was dyskinesis or aneurysm, point 3
TABLE I PATIENT'S BACKGROUND

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (mean ± SD)</th>
<th>Time from attack to CAG</th>
<th>Other vessel disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenosed (n = 14)</td>
<td>61.9 ± 7.4</td>
<td>6.6 ± 2.6 hrs</td>
<td>7 cases (50.0%)</td>
</tr>
<tr>
<td>Thrombolysed (n = 25)</td>
<td>63.2 ± 6.6</td>
<td>6.2 ± 3.5 hrs</td>
<td>18 cases (72.0%)</td>
</tr>
<tr>
<td>Unsuccessful (n = 8)</td>
<td>51.3 ± 6.1 *</td>
<td>5.9 ± 4.0 hrs</td>
<td>1 case *(12.5%)</td>
</tr>
<tr>
<td>Conservative therapy (n = 17)</td>
<td>61.3 ± 10.3</td>
<td>48.1 ± 15 days</td>
<td>7 cases (41.2%)</td>
</tr>
</tbody>
</table>

* = p < 0.05; Significant difference compared to other groups.

was diminished, akinesis, point 2 asynsisis, point 1, where higher scores indicated a normal or hyperfunctioning myocardium and lower scores, dyskinesis or aneurysm. Theses scores could range from 0 to 9. The score of wall motion was judged from three different cardiologists, afterwards, the average score was calculated.

RESULTS
Thrombotic complete obstruction were found in 33 of 47 patients (70%) and severe stenosis, in 14 patients (30%). Infarct-related coronary arteries were followed. Left main trunk 2 cases (2), left anterior descending coronary artery 31 cases (9), circumflex artery 4 cases (1), right coronary artery 10 cases (2). The number of parenthesis showed cases who had severe stenosis in infarct-related vessel. In 25 out of 33 patients (76%) with complete occlusion, reperfusion was achieved after 10 to 20 minutes of intracoronary UK infusion at a rate of 500IU/kg/min (thrombolysed group). In the remaining 8 patients, this procedure was unsuccessful (unsuccessful group). In 14 patients with severe stenosis, intracoronary UK was also applied to expecting magnification of a stenotic part (stenosed group). In this study, all the 47 patients with intracoronary UK infusion were classified these three groups. And, 17 patients with conservative therapy also were investigated (Fig. 1). Average years of these four groups were similar to each group except unsuccessful group that was 10 years or more younger than other three groups. Time from onset of chest pain to coronary angiography was not significant in three groups of intracoronary UK infusion. Coronary angiography was not performed on acute stage in conservative group. It was done at 48.1 ± 15 days after infarction. Other vessel disease where infarct-nonrelated coronary artery were recognized high frequency in thrombolysed, stenosed and conservative groups compared to unsuccessful group. (Table I)

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The Findings of Coronary Artery in Acute Myocardial Infarction:

Coronary blood flow was visualized at initial angiography in 14 of 47 patients as described previously (stenosed group). The degree of narrowing on the infarct-related vessel was 86.3 ± 5.3% in early phase, no remarkable changes in immediately after UK infusion and 76.7 ± 6.6% in angiography after one month. In thrombolysed group, early angiography revealed complete occlusion, immediately after urokinase infusion 90.7 ± 3.4% and the examination after one month, 82.5 ± 5.6%. In contrast, complete occlusions in unsuccessful group were still persisted after UK infusion and until one month, only one out of 8 patients had spontaneous recanalization at an examination of one month after attack, it was subtotal occlusion. In this patient, UK was infused by Judkins catheter because of inability advance an infusion catheter. On the other hand, it was 94.2 ± 2.1% in conservative group which catheterized at averaged 48 days after attack. (Fig. 2).
Ejection Fraction (FE) at one Month After Attack.

Global ventricular function was assessed in UK treated patients and conservative patients. EF in stenosed group was significantly higher than it in unsuccessful group (p < 0.05) EF in thrombolysed group was located mid point of both two groups. From the viewpoint of average ages and frequency of other vessel disease, higher EF in thrombolysed group than that in unsuccessful group could be significant. Average EF in all UK-treated patients were tend to higher it in conservative group. (Fig. 3)

Regional Wall Motion:

Anterior wall motion in anterior infarction was assessed, because of many numbers of anterior infarction were in this study. The
score in stenosed group was the highest in UK treated group. The order of score in UK treated patients was followed stenosed thrombolysed and unsuccessful group. There were significant difference among these three groups. (p < 0.05 in each group). And tend to difference between thrombolysed group and conservative group was recognized (p = 0.057) (Fig. 4).

Serum CPK Levels:
Most patients displayed an increase in serum enzymes. In a few patients, prior to the administration of UK, they had CPK values higher than the upper limit of normal (173 mIU). Peak CPK values in thrombolysed group were the highest in UK-treated groups, and the time from onset of symptoms to peak CPK was 12 hours. In contrast, peak CPK values in unsuccessful group was less than thrombolysed group, and the time interval to peak CPK was delayed. The enzymatic effluent from infarcted muscle was great in recanalized patients as a result of wash out (Fig. 5).

However, peak CPK values in stenosed group was less than thrombolysed group and the time interval to peak CPK was shortened than thrombolysed group.

EKG Changes:
Although, it is not common to use summation of ST segment elevation in the leads V1 through V6, SST was applied to this study, because of precordial mappings in all patients with anterior infarction caused by LAD occlusion were not fully recorded at hourly and daily. Significant reductions in SST segment elevation were seen immediately after UK infusion and hourly. Reductions in SST until 48 hours after UK infusion in stenosed and thrombolysed group, were significant compared to unsuccessful group (Fig. 6).

Medical Treatment After Acute Stage:
Medical treatment after acute stage was mainly warfarin and dipyridamole, to prevent rethrombi. The former dose was 2.7 ± 1.1 mg per day, the later was 125 ± 50 mg per day. The duration of follow-up period was 1 to 30 months, averaged 16.2 ± 9 months. Rethrombosis were recognized in 2 patients during this follow-up period.

Mortality:
There was no death during this procedure and early stage in UK treated groups. A late death occurred at 45 days from infarction in stenosed group. He was died from cardiogenic shock. A second death occurred at 7 days after infarction, this patient displayed extensive anterior infarction at autopsy. A third patient in thrombolysed group was died during rehabilitation stage at 31 days from infarction. He had also extensive anterior infarction at autopsy. The coronary arteries of both of these patients had recanalized. A fourth patients in stenosed group died from cardiogenic shock at 10 days from infarction. Recanalization of right coronary artery had failed to open in this patient. Moreover, he had an anomaly of circumflex artery (Hypoplasia), and also extensive posterior infarction at autopsy. Thus, the mortality rate in UK-treated groups was 8.5%.

DISCUSSION
For intracoronary thrombolysis, coronary angiography and local application of UK were performed on 47 patients who had attacks of acute myocardial infarction within 12 hours. In one-third of these 47 patients, coronary blood flow in infarct-related artery was already visualized at initial angiography. Visualization of coronary blood flow at initial angiography which were explained as a stenosed group in present study suggests that the mechanism of onset of myocardial infarction might be thrombus formation, coronary spasm, severe stenosis itself and these combinations. Namely, spontaneous thrombolysis, relief of spasm or both of them may have been occurred before coronary angiography in stenosed group. The mean time from the onset of symptoms with chest pain to coronary angiography had been completed and coronary thrombolysis identified was 6 hours 12 minutes for the 25 patients in successful group (Table I). Time difference from symptoms to coronary angiography among these three groups were not significant. The effective dose of UK to lyse thrombus was indicated from our experimental studies which 2 hours-age thrombi were lysed by intracoronary infusion of UK at a rate of 500 IU/kg/min during 20 minutes.1,2 The dose of UK less than 500 IU/kg/min such as 100 to 300 IU/kg/min during 20 minutes was not enough to rapidly lyse thrombi produced by copper wire technique. Although a few intracoronary thrombi was lysed by infusion of UK 500 IU/kg/min during

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10 minutes, approximately, 10,000 IU/kg of UK were needed for thrombolysis to get angiographically beautiful coronary blood flow. No patients with complete occlusion was fully recanalized by infusion of nitroglycerin or isosorbid e dinitrates. The narrowing parts of infarct-related arteries in both of stenosed and thrombolysed groups were improved at the examination of angiography after one month. This fact shows that thrombolysis is still continuing for a few hours after infusion of UK. The achievement of early recanalization in 76% of complete occlusion and in 70% of patients in follow-up period is comparable to the results of other institutions. Rethrombosis was found in 2 of 25 initially recanalized patients (8%) at one month follow-up period. In contrast, spontaneous recanalization was found in 1 of 8 initially unsuccessful patients. Finally, recanalization was found in 24 of 33 initially occluded coronary arteries (73%) at follow-up period. No rethrombosis was found in all 14 patients who were explained as stenosed group. Therefore, recanalization at follow-up period was found in 38 of 47 patients (81%) who had this procedure. Late rethrombosis under the treatment of mainly warfarin and dipyridamole was not found at angiographic or electrocardiographic follow-up of mean 16.2 months. Previous studies used Streptokinase have shown that EF was improved in discharge than in acute stage. Moreover, Timmis et al have shown, a significant improvement was noted in those who entry EF was less than 50%. EF in this study was not examined at acute stage as discribed previously. The results of EF at one month after myocardial infarction was the greatest in stenosed group which was recanalized from earlier stage than other two groups (thrombolysed and unsuccessful groups). Thrombolysed group was followed on stenosed group. Unsuccessful group showed the lowest EF regardless of younger age and low frequency of complication with other vessel disease. This fact suggests that early recanalization may result in greater reversal of cardiac function.

We attempted to exclude circumflex or right coronary-related vessels on changing wall motion by confirming our study of wall motion to patients with LAD-related vessel. Our study showed great score of wall motion in thrombolysed patients with LAD occlusion than in unsuccessful group with LAD occlusion. This fact suggests that early recanalization may also have salutary changes in wall motion.

Complication and Prognosis:
Reperfusion arrhythmias have been observed frequently after recanalization. No serious arrhythmias such as ventricular fibrillation, flutter, or tachycardia were not observed in our study. Two reason were considerable. Firstly, gradual reperfusion was occurred to remaining residual stenosis. Secondly, the mean time from onset of symptoms to reperfusion was prolonged to comparable with other reports. It was 6 hours 12 minutes in our study, but even if early reperfusion like less than 3 hours, no serious arrhythmia was not observed.

Although ventricular premature contractions occurred in a few cases, it resulted in no lasting clinical problems. The doses of UK were higher than those of studies in other institutions! When UK 10,000IU/kg during 20 minutes was administered, no major or minor bleeding was observed in puncture site. Only a patient, who had 15,000IU/kg of UK during 30 minutes, because of resistance to lyse thrombus, had a long time to stop bleeding from puncture site, it took over 30 minutes. Residual stenosis was lasting after recanalization, therefore aortic corona bypass operation or PTCA were considered.

REFERENCES
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