EFFECTS OF CORONARY THROMBOLYSIS ON LEFT VENTRICULAR EJECTION FRACTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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Left ventriculograms were performed on 65 patients with acute myocardial infarction, once upon admission and again 3 months later. In 29 cases urokinase was injected intravenously and/or intracoronarily. The other 17 were treated without urokinase. In 8 out of 29 patients whose infarct-related coronary arteries remained completely occluded following urokinase therapy, the global ejection fraction was reduced from $54 \pm 3\%$ during the acute stage to $46 \pm 5\%$ during the chronic stage ($p < 0.001$). However, for the 21 patients whose coronary arteries were successfully recanalized, the 2 values were the same ($52 \pm 2\%$). The highest global ejection fractions were seen in 19 spontaneously recanalized patients (acute: $54 \pm 2\%$, chronic: $55 \pm 2\%$). For the 8 unsuccessful patients, the regional ejection fraction for the infarcted portion was reduced from $20 \pm 5\%$ during the acute stage to $18 \pm 6\%$ during the chronic stage. But for the successful patients there was an improvement from $22 \pm 2\%$ during the acute stage to $27 \pm 2\%$ during the chronic stage. Again, the regional ejection fraction was the highest for the spontaneously recanalized group, being $31 \pm 2\%$ and $36 \pm 3\%$ during the acute and chronic stages, respectively. These results indicate that if the coronary artery remains occluded during the acute stage the reduced left ventricular function continues to deteriorate even more during the chronic stage. Successful coronary thrombolysis, however, might salvage the infarcted myocardium as well as preserve the function of the left ventricle.

A number of reports indicate that successful coronary thrombolysis reduces mortality in patients with acute myocardial infarction,¹⁻³ but its effect on left ventricular function remains unclear.²⁻¹⁰ If the pathological changes occurring in the infarcted myocardium are truly irreversible, no improvement in myocardial function may be

expected even when subsequent coronary thrombolysis is successful. Macroscopic infarctions developed in experimental animals 40 min after coronary occlusion.¹¹ On the other hand, reperfusion within 2 hours after onset has been shown to be effective in reducing regional wall motion abnormalities.¹² Sheehan et al¹³ stated that salvage of the left ventricular function may not be expected unless reperfusion is achieved very early in the course of the infarction. Rentrop,¹⁴ in a review of 5 controlled clinical trials found only 1 in which there was any left

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Fig.1. Determination of five regional areas according to Gelberg et al.¹⁸

ventricular ejection fraction improvement. Since left ventricular function is a major determinant in prognosis for such patients,¹⁵ it is essential to elucidate these conflicts related to the effectiveness of coronary thrombolysis.

In this study, we analyzed left ventriculograms taken prior to and again 3 months following coronary thrombolysis. We found that the global ejection fraction deteriorated in patients whose infarct-related coronary arteries were still occluded following thrombolysis, but that there was no such deterioration if the coronary thrombolysis had been successful.

SUBJECTS AND METHODS

Of 212 patients admitted to Kinki University Hospital within 6 hours of onset of acute myocardial infarction, 65 (60 male and 5 female, age 57 ± 1 ($\pm$ SE)) were enrolled retrospectively in this study. Selection was based upon the availability of paired left ventriculograms, 1 obtained during the acute stage and the other 3 months later during the chronic stage. The ventriculograms had to be technically capable of permitting measurement of ejection fractions. Diagnoses of acute myocardial infarction were based upon such evidence as chest pains, and electrocardiographic and serum enzymatic results. Seventeen of the 65 patients were treated without urokinase [UK (-) group] and the other 29 were treated with urokinase [UK (+) group]. Cardiac catheterization was performed under informed consent. After left ventricular pressure record-

ings had been completed, left ventriculograms were obtained at a right anterior oblique projection using 40 ml of 76% Urographin (Meglumine sodium amidotrizoates) injected at a rate of 15 ml/sec. Coronary angiograms were taken from multiple projections using the Judkins technique approximately 15 min after left ventriculogram. Cardiac output was determined by the dye-dilution technique. Urokinase was administered intravenously in 4 cases (IV group), intracoronarily in 17 cases (ICT group) and both intravenously and intracoronarily in 8 cases (IV + ICT group). For the IV group, 480,000 to 1,920,000 units of urokinase was injected within 15 min after establishing the diagnosis. For those patients whose initial coronary angiograms on admission indicated complete occlusion, the urokinase was injected at a rate of 200,000 units per 10 min, with the total amount for the ICT group ranging from 200,000 to 1,200,000 units. If the coronary angiogram taken after intravenous administration of urokinase still showed complete occlusion, additional urokinase was administered intracoronarily (IV + ICT group). In 19 patients, the initial angiograms before urokinase showed recanalization (spontaneously recanalized group: SR group). ICT was still performed in 15 of these 19 cases because the angiograms also indicated the presence of intracoronary thrombi. Left ventriculograms and coronary angiograms were repeated on all of the patients approximately 3 months later (chronic stage).

According to the American Heart Association's reporting system,¹⁶ the degrees of coronary stenosis were established as "no stenosis" or 75, 90, 99 or 100% occlusion. 99.9% stenosis was used to indicate 99% stenosis combined with a delay in the washout of the contrast material at the stenotic site. If coronary artery stenosis was 100% before administration of urokinase but 99.9% or less afterwards, the case was classified as "successful", otherwise it was considered "unsuccessful".

The area-length method¹⁷ was used to calculate global ejection fraction. The left ventricle was divided into 5 regions and regional ejection fractions were measured according to Gelberg et al.¹⁸ (Fig. 1). These measurements were made in duplicate, independently, by 2 doctors. A third measurement was taken in 12 cases because the values from the first 2 differed by more than 20%. In cases of anterior myocardial infarction, areas 2 (anterolateral) and 3 (apical) were

TABLE I PATIENT CHARACTERISTICS

Age	Sex	BSA	Forrester classifica- tion	Peak CPK	Time to LVG	No. of vessels involv- ed	UK dos- age	Left ventricular end- diastolic pressure	Mean pulmonary artery pressure	Cardiac index			
(yr)	Male/ Female	(m ²)		(IU/L)	(h)		(×10 ⁴ IU)	Acute Chr (mmHg)	Chr (mmHg)	Acute Chr (mmHg)	Chr (mmHg)	Acute (L/min/m ²)	Chr (L/min/m ²)
UK (+) group (29 cases)													
100% occlusion after Urokinase (unsuccessful group: 8 cases)													
57 ±4	8/0	1.65 ±0.06	1.1 ±0.1	3129 ±706	7.3 ±1.1	1.8 ±0.3	92.0 ±22.6	13 ±2	11 ±2	22 ±1	13** ±1	3.55 ±0.32	2.83 ±0.31
99% occlusion with delay (99.9% occlusion) after Urokinase (5 cases)													
55 ±3	4/1	1.69 ±0.08	1.4 ±0.4	3486 ±602	5.8 ±0.9	2.0 ±0.3	130.8 ±28.2	10 ±2	9 ±1	19 ±2	13 ±1	2.58 ±0.27	2.86 ±0.13
99% occlusion after Urokinase (6 cases)													
56 ±4	6/0	1.70 ±0.04	1.3 ±0.2	4142 ±659	5.9 ±0.8	1.5 ±0.2	141.0 ±43.9	15 ±2	12 ±2	19 ±2	14 ±1	3.08 ±0.23	2.50 ±0.19
90% occlusion after Urokinase (8 cases)													
58 ±3	8/0	1.68 ±0.03	1.1 ±0.1	4107 ±955	4.9 ±0.8	1.6 ±0.3	103.0 ±33.7	16 ±1	11 ±2	16 ±2	15 ±1	3.09 ±0.30	2.47 ±0.24
75% occlusion after Urokinase (2 cases)													
53	2/0	1.71	1.0	3093	4.8	2.0	78.0	14	7	18	11	2.81	2.73
99.9, 99, 90, 75% occlusion after Urokinase (Total of recanalized cases: successful group: 21 cases)													
56 ±2	20/1	1.68 ±0.02	1.2 ±0.1	3872 ±437	5.4 ±0.4	1.7 ±0.2	118.1 ±18.7	14 ±1	10** ±1	18 ±1	14** ±1	2.94 ±0.15	2.60 ±0.11
SR group (spontaneously recanalized group: 19 cases)													
55 ±2	15/4	1.61 ±0.03	1.1 ±0.1	2678 ±531	5.7 ±0.7	1.8 ±0.2	54.0 ±9.0	15 ±1	11 ±1	17 ±1	13 ±1	2.99 ±0.15	3.12 ±0.25
UK (−) group (17 cases)													
53 ±2	17/0	1.69 ±0.03	1.0 ±0.0			1.6 ±0.2		11 ±1	15 ±2	13 ±1		3.19 ±0.18	3.11 ±0.22
Normal (10 cases)													
54 ±3	7/3	1.53 ±0.07						8 ±1		13 ±1			3.32 ±0.34

LVG = Left ventriculogram; Chr = chronic

All values are expressed as mean $\pm$ standard errorDifference between acute and chronic: ** $p < 0.01$

assumed to be the infarcted portion; while for inferior infarction, area 4 (diaphragmatic) was assumed to be the infarcted portion. Ten patients with chest pain syndrome served as controls.

The statistical significances of the differences between any 2 groups were tested using the unpaired t-test, it was considered significant if the p value was less than 5%.

RESULTS

Among the UK (+), SR or UK (-) groups (Table I), there were no significant differences in

age, in clinical severity of infarction according to Forrester's classification,¹⁹ in serum creatine phosphokinase (CPK) peak activity, the time from onset to left ventriculogram or coronary angiograms, or in the number of coronary vessels involved. Also, there was no such difference between successful and unsuccessful groups. In both the unsuccessful and the successful groups, left ventricular end-diastolic pressures and mean pulmonary artery pressures were lower in the chronic stage. Neither the cardiac indexes, the left ventricular end-diastolic volumes or the end-systolic volumes for all 3 groups (Tables I & II)

TABLE II LEFT VENTRICULAR EJECTION FRACTION

Left ventricular volume				Global ejection fraction		Regional ejection fraction			
End-diastole		End-systole				Infarcted portion		Non-infarcted portion	
Acute	Chr	Acute	Chr	Acute	Chr	Acute	Chr	Acute	Chr
(ml/m ²)		(ml/m ²)		(%)		(%)		(%)	
UK (+) group (29 cases)									
100% occlusion after Urokinase (unsuccessful group: 8 cases)									
75 ±12	105 ±10	34 ±6	56 ±8	54 ±3	46*** ±5	20 ±5	18 ±6	49 ±4	38* ±3
99% occlusion with delay (99.9% occlusion) after Urokinase (5 cases)									
72 ±4	87 ±4	33 ±4	48 ±3	57 ±2	50 ±5	25 ±5	26 ±3	47 ±4	38 ±4
99% occlusion after Urokinase (6 cases)									
97 ±7	101 ±7	44 ±0.3	45 ±6	50 ±4	55 ±4	21 ±3	29 ±4	43 ±3	42 ±3
90% occlusion after Urokinase (8 cases)									
92 ±12	119 ±15	47 ±8	56 ±11	48 ±2	51 ±3	16 ±3	26 ±4	40 ±4	39 ±3
75% occlusion after Urokinase (2 cases)									
91	99	50	46	54	56	29	24	43	44
99.9, 99, 90, 75% occlusion after Urokinase (Total of recanalized cases: successful group: 21 cases)									
88 ±6	106 ±7	43 ±4	50 ±5	52 ±2	52 ±2	22 ±2	27 ±2	43 ±2	40 ±2
SR group (spontaneously recanalized group: 19 cases)									
103 ±12	107 ±4	45 ±6	49 ±4	54 ±2	55 ±2	31 ±2	36 ±3	44 ±2	42 ±2
UK (-) group (17 cases)									
	104 ±5		48 ±5		54 ±3		28 ±3		44 ±2
Normal (10 cases)									
	92 ±4		29 ±2		69 ±2				53 ±2

Chr = chronic

All values are expressed as mean ± standard error

Difference between acute and chronic: * $p < 0.05$; *** $p < 0.001$

showed any changes between the acute and the chronic stages. Among 8 unsuccessful patients, 2 remained complete occlusion, 3 showed 99% stenosis, 3 showed 90% stenosis or less at chronic stage. Among 5 patients who showed 99.9% stenosis at acute stage, only 1 showed 99.9% stenosis and 4 showed 90% stenosis or less at chronic stage. Among 16 patients who showed 99% stenosis or less at acute stage, only 2 showed 99% stenosis at chronic stage and other 14 patients showed 90% stenosis or less.

Comparing the 3 groups with normals, the left

ventricular global ejection fraction at acute and chronic stages decreased significantly (Fig. 2, $p < 0.01-0.001$). The lowest chronic stage values ($46 \pm 5\%$) were found in patients whose coronary arteries remained occluded. The decrease in global ejection fraction between the acute and the chronic stages for these patients was significant, but for the other (successful and spontaneously recanalized) groups there were no such decreases in global ejection fraction.

Changes in regional ejection fraction at the infarcted portion paralleled those in the global

Fig.2. Changes in global and regional left ventricular ejection fractions between the acute and chronic stages.

ejection fraction. The regional ejection fraction at the infarcted portion for those whose coronary arteries remained occluded after coronary thrombolysis decreased from acute to chronic stage (from $20 \pm 5\%$ to $18 \pm 6\%$), while these figures for the other 2 groups improved during the same period (Fig. 2). Among the infarcted groups, this value during the chronic stage was highest for the spontaneously recanalized group ($36 \pm 3\%$). During the acute stage, the non-infarcted portion for the unsuccessful group evidenced the highest regional ejection fractions but this hyperkinetic motion disappeared in the chronic stage. Left ventriculogram at acute stage was performed within 4 hrs after onset in 10 patients. There was no difference in the change of global or regional ejection fraction from acute to chronic stage in regard to reperfusion time.

DISCUSSION

Our study shows that if we failed to recanalize the coronary artery the regional ejection fraction at the infarcted portion, already being markedly impaired, continued to deteriorate even further. On the other hand, if the coronary artery was successfully recanalized the wall motions in these

same regions showed no aggravation 3 months after infarction. During the chronic stage the highest value in the regional ejection fraction was observed in the spontaneously recanalized group; the second highest value being for the successfully thrombolized group. Although our study was based on a relatively small number of cases, these results suggest that early recanalization will improve left ventricular function at the infarction.

The establishment of flow to 99.9% stenosis (99% with delay) by thrombolysis may be less effective to salvage the myocardium. In our study, the change of the regional ejection fraction over chronic stage in patients with 99.9% stenosis showed the intermediate values between 100% occlusion and 99% stenosis. Thus, these patients were grouped as the successful group. The changes of regional ejection fraction over chronic stage were similar between the successful group and the spontaneously recanalized group.

Many studies have indicated that coronary thrombolysis improved left ventricular wall motion²⁻⁷ but a similar number of reports have shown that no such improvement exists^{8-10,20,21} Serruys et al³ recently reviewed 7 randomized

trials and came to the conclusion that the results did indeed conflict with each other. This can be attributed to several factors. In the Western Washington trial,⁹ the global ejection fraction was measured by use of contrast ventriculography or gated blood-pool scan. The authors reported a nearly threefold reduction in 30-day mortality but no improvement in the global ejection fraction. Since myocardial infarction involves only a limited portion of the left ventricle and the non-infarcted portion often evidences hyperkinesia during the acute stage,²² any conclusions based upon the global ejection fraction^{8,9,20} might be misleading. In order to circumvent this possibility, we calculated regional ejection fractions according to Gelberg et al.¹⁸ Collateral circulation during complete occlusion may play an important role in improvement following recanalization. Rogers et al.²³ found that subsequent improvement in left ventricular function frequently occurs in patients with significant collateral flow. The interval between onset and reperfusion might also be a crucially important determinant.¹²⁻¹⁴ Zaret and Wackers²⁴ pointed out that measured ejection fraction may vary greatly in response to altered pre- or afterloads. This indicates that delayed studies made at patient discharge must be carried out after completing resolution of myocardial stunning. Differences in patients backgrounds together with the methods employed might be responsible for the differences in results among these various studies on coronary thrombolysis.

In this study, further deterioration of regional ejection fraction at the infarcted portions were demonstrated in patients whose coronary arteries remained occluded during the acute stage. It has been shown that if the coronary artery has been occluded, the subendocardial myocardium in the center of the risk area initially becomes necrotic, is surrounded by jeopardized but still viable myocardium, and irreversible injury continues to progress as if it were riding a wavefront.¹¹ Provided that successful coronary thrombolysis is completed early and while this wavefront is still moving, the myocardium surrounding the necrotic area is kept viable even if the myocardium has been confronted with necrosis. In other words, if the coronary artery is not recanalized during the acute stage, the jeopardized myocardium will progress into necrosis, the infarction will continue to extend, and the ejection fraction will deteriorate further.

At the same time, however, there is still a

considerable quantity of viable muscle within the acutely infarcted area.²⁵ The amount of viable myocardium remaining depends upon the amount of coronary flow from the infarct-related artery and/or collateral circulation. In cases wherein no antegrade arterial flow has been established, the jeopardized myocardium will become infarcted and the regional ejection fraction will deteriorate. The differences between this phenomenon and any suppression of an extension in the wavefront must be kept very clear because the former is a worsening of the wall motion at the point of infarction and not simply an increase in the size of the infarction itself.

Emphasis must be placed upon the role of hyperkinesia²² as one cause for ejection fraction to continue to deteriorate during the chronic stage. In 8 occluded patients in the present study, a slight decline in the ejection fraction at the infarcted portion was accompanied by an even greater fall in the global ejection fraction during the chronic stage. This is related to significant reductions in the regional ejection fraction in non-infarcted areas, thereby suggesting that hyperkinesia is present during the acute stage. If increased circulation of catecholamine elicits hyperkinesia during the acute stage,²⁶ it might also enhance remnant muscle contractions at the point of infarction.

McKay et al.²⁷ stressed the importance of left ventricular remodeling and postulated that, in a group of patients who had achieved a 20% increase in left ventricular end-diastolic volume 2 weeks after the infarction, there was a 13% increase in infarcted and a 19% increase in non-infarcted endocardial perimeter size; in other words, the non-infarcted portion showed the greater increase. Klein et al.²⁸ postulated that if the infarcted portion exceeds 20 to 25% of the total left ventricle, then the normal myocardium will no longer be able to compensate and the entire left ventricle will be dilated. As a consequence, the global ejection fraction during the chronic stage is reduced. Pre- and afterload reduction therapies undertaken during the acute stage might result in apparently high ejection fraction, this might also obscure the effect of coronary thrombolysis on ejection fraction.

Despite the existence of these various mechanisms in the recanalized groups, the regional ejection fraction in the infarcted portion improves rather than drops during the chronic stage. These values are highest for the spontaneously

recanalized group. Leiboff et al²⁰ stated that over a period of 2 weeks, in contrast to the streptokinase (STK) or intracoronary nitroglycerin groups, those patients with a subtotal occlusion at baseline angiography demonstrated a significant level of spontaneous improvement in the ejection fraction. Rogers et al²³ came to a conclusion similar to ours by stating that in a spontaneously recanalized group improvements in the ejection fraction were excellent but that in an occluded group the ejection fraction deteriorated. This indicates that coronary thrombolysis is effective in preventing an extension of the wavefront of the jeopardized myocardium within the infarcted portion.

Several other mechanisms may also contribute to a masking of deterioration over the chronic stage. It is known that in acute myocardial infarction the infarcted heart muscle loses its compliancy and becomes rather stiff. Accordingly, the normal myocardium adjacent to this stiff tissue may not be able to contract normally and the area wherein the wall motion has been impaired is overestimated (the tethering effect)²⁹. But, during the chronic stage, the adjacent myocardium is able to contract normally and ejection fraction values improve²⁹. This effect, however, accounts for only 5% of the infarcted portion²⁹ and therefore cannot be too important. However, there are also transient myocardial swellings³⁰ and hemorrhages³¹ occurring during myocardial infarction. These pathological changes, becoming prominent after reperfusion during the acute stage, might be responsible for a temporary reduction in wall motion around the infarcted portion. However, in this study, since the left ventriculograms were performed before recanalization these pathological changes may not represent a major or important mechanism related to the masking of deterioration during the chronic stage.

It is our conclusion that, in patients with acute myocardial infarction, left ventricular function will worsen if the coronary artery remains occluded, and that early recanalization is important in salvaging the jeopardized myocardium and maintaining normal left ventricular function. Thus, we conclude that coronary thrombolysis is useful for the treatment of acute myocardial infarction.

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