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Clinical Investigations

Long-Term Prognosis of Late Spontaneous Reperfusion after Failed Thrombolysis for Acute Myocardial Infarction

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Summary

Background: Early reperfusion improves left ventricular (LV) function and survival after acute myocardial infarction (MI). Thrombolytic therapy achieves early patency of the infarct artery in about two-thirds of patients. In nearly half of the remaining patients, in whom early reperfusion was not achieved with thrombolytic therapy, the infarct artery might reopen by the time of predischarge angiography. However, the impact of such late spontaneous reperfusion after failed thrombolytic therapy on LV function and long-term survival remained unclear.

Hypothesis: This study was undertaken to assess implication of late spontaneous reperfusion after failed thrombolytic therapy on LV function and long-term survival after acute MI.

Methods: The study consisted of 198 patients with anterior acute MI who underwent thrombolytic therapy and predischarge angiography: 160 patients with infarct artery patent early and late after therapy (persistent patency), 17 patients with infarct artery occluded early after therapy but patent at predischarge angiography (late spontaneous reperfusion), and 21 patients with infarct artery occluded early and late after therapy (persistent occlusion).

Results: Persistent patency was associated with enhanced improvement in LV ejection fraction (7.7 ± 11.8%) compared with late spontaneous reperfusion (0.0 ± 9.6%, $p = 0.03$) and persistent occlusion (−1.4 ± 9.7%, $p = 0.003$). Persistent patency was associated with better long-term survival than with late spontaneous reperfusion ($p < 0.001$) and persistent occlusion ($p < 0.001$). Multivariate analysis comparing persistent patency and late spontaneous reperfusion showed that early reperfusion was an independent predictor of long-term survival.

Conclusion: Late spontaneous reperfusion after failed thrombolytic therapy was associated with poor LV function and long-term survival, emphasizing the importance of early reperfusion.

Key words: angiography, survival, thrombolysis, ventricular function

Introduction

Early restoration of patency of the infarct-related artery (IRA) is an important determinant of improved left ventricular (LV) function and survival after acute myocardial infarction (MI).[1,2] Although thrombolytic therapy is widely used for patients with acute MI, coronary angiographic studies performed early after thrombolytic therapy have shown that the IRA remains occluded in about one-third of patients.[3–7] By the time of performance of chronic angiography, reperfusion may occur in nearly half of the patients in whom thrombolysis had failed.[3–5] However, it is still unclear whether such late spontaneous reperfusion after failed thrombolytic therapy is associated with favorable outcome. This study was undertaken to assess implication of late spontaneous reperfusion after failed thrombolytic therapy on LV function and long-term survival after acute MI.

Methods

Study Patients

The study consisted of 198 patients with anterior wall acute MI who underwent coronary angiography and thrombolytic

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therapy within 24 h after the onset of chest pain. All patients also underwent chronic angiography before discharge. The patients were divided to the following three groups: 160 patients in whom early reperfusion was achieved and persistent patency of the IRA was observed at predischarge angiography (persistent patency, Group 1), 17 patients in whom early reperfusion was not achieved but predischarge angiography found a patent IRA (late spontaneous reperfusion, Group 2), and 21 patients in whom the IRA was occluded both early after therapy and at predischarge angiography (persistent occlusion, Group 3). Patients with reocclusion of the IRA after early reperfusion were excluded from this study.

Cardiac Catheterization

Emergent cardiac catheterization was performed in a manner as previously reported.[8] Contrast left ventriculography was performed in the 30-degree right anterior oblique projection. Subsequent to diagnostic angiography, thrombolytic therapy was performed with urokinase. Usually, cumulative doses of urokinase were infused up to 96×10^4 IU until reperfusion was achieved. Adjunctive coronary angioplasty was performed in 94 (47%) patients. The allocation of adjunctive angioplasty was based on the physician's decision. Predischarge catheterization was performed at 25 ± 8 days after infarction.

Angiographic Analysis

The perfusion status of the left anterior descending artery was determined in accordance with Thrombolysis in Myocardial Infarction (TIMI) study classifications.[5] TIMI flow grade early after therapy was assessed on the final shot of the angiography after reperfusion therapy. Occluded IRA was defined as TIMI flow grade ≤ 1; patent IRA was defined as TIMI flow grade ≥ 2. Residual stenosis of the IRA was measured using hand-held calipers. Multivessel coronary disease was defined as ≥ 75% luminal narrowing in one or more vessels remote from the IRA. Collateral circulation was considered to be present when there was partial or complete filling of the epicardial segment of the IRA. The LV ejection fraction was calculated with the area-length method.

Data Analysis

Follow-up was achieved for 191 (96%) patients by mail or at clinical visits, determining the vital status of the patients. The primary endpoint was death of any cause. Statistical analysis was performed with the chi-square and *t*-test. Kaplan-Meier estimates were used to construct a long-term survival curve. Differences in long-term survival were assessed with the generalized Wilcoxon test. Cox's proportional hazards regression was used to identify independent predictors of long-term survival. Differences were considered significant if the p value was < 0.05. All group data are expressed as mean ± standard deviation (SD).

Results

Patient Characteristics

Baseline clinical and angiographic variables are shown in Table I. Mean age was higher in Group 3 than in Group 1. Diabetes was less frequent in Group 2 than in Group 1. There was no significant difference in gender, hypertension, previous infarction, Killip class on admission, time to emergent angiography, collateral circulation, multivessel disease, and time to predischarge angiography. At predischarge angiography, TIMI flow grade 2 was more frequent (29 vs. 8%, p = 0.04) and residual stenosis was more severe (63 ± 33% vs. 50 ± 28%, p = 0.02) in Group 2 than Group 1.

Left Ventricular Function

Acute LV ejection fraction was obtained in 173 patients. There was no significant difference in acute LV ejection fraction among the three groups: 48 ± 11% in Group 1, 44 ± 14% in Group 2, and 46 ± 11% in Group 3. Predischarge LV ejection fraction was obtained in 188 patients; it tended to be higher in Group 1 (55 ± 15%) than in Group 2 (48 ± 18%) and Group 3 (49 ± 13%), but the differences did not reach statistical significance. Serial ventriculograms were obtained in 157 patients. Changes in LV ejection fraction were significantly higher in Group 1 (7.7 ± 11.8%) than in Group 2 (0.0 ± 9.6%, p = 0.03) and Group 3 (− 1.4 ± 9.7%, p = 0.003). When only patients with predischarge TIMI flow grade 3 were compared, changes in LV ejection fraction were still significantly higher in Group 1 than in Group 2 (8.2 ± 11.7% vs. 4.1 ± 5.8%, p = 0.007).

Long-Term Survival

Five-year and 10-year survival were 90 and 75% in Group 1, 71 and 55% in Group 2, and 58 and 29% in Group 3, respectively (Fig. 1). Long-term survival was significantly better in

TABLE I Baseline clinical and initial angiographic findings

	Group 1 (n = 160)	Group 2 (n = 17)	Group 3 (n = 21)
Age (years)	57 ± 10	60 ± 16	63 ± 10[a]
Male gender (%)	139 (87)	12 (71)	18 (86)
Hypertension (%)	57 (36)	5 (29)	9 (43)
Diabetes (%)	31 (19)	0 (0)[a]	2 (10)
Previous infarction (%)	12 (8)	3 (18)	3 (14)
Killip class ≥ 2 (%)	17 (11)	3 (18)	4 (19)
Time to angiography (h)	5.2 ± 4.5	6.0 ± 3.5	6.6 ± 4.7
Collateral circulation before thrombolytic therapy (%)	66 (41)	8 (47)	9 (43)
Multivessel disease (%)	43 (27)	5 (29)	8 (38)
Follow-up achieved (%)	155 (96)	17 (100)	19 (90)

[a] $p < 0.05$ versus Group 1.

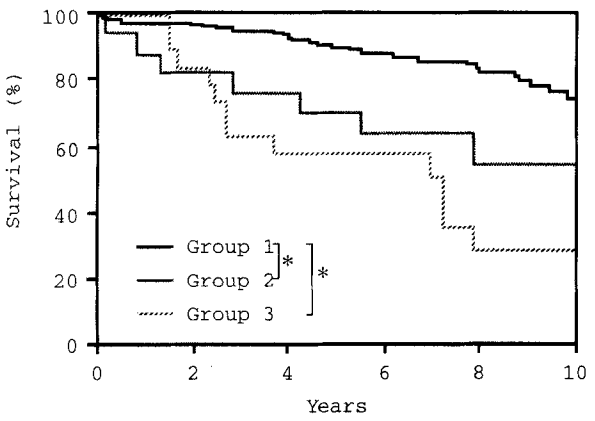

FIG. 1 Long-term prognosis after hospital discharge was compared among the three groups. Long-term survival was significantly better in Group 1 (persistent patency) than in Group 2 (late spontaneous reperfusion, *$p < 0.001$) and Group 3 (persistent occlusion, *$p < 0.001$). Because of the small sample size, there was no significant difference in survival between Groups 2 and 3 ($p = 0.41$).

TABLE II Predictrs of post-hospital mortality during 10 years of follow-up among patients with a patent IRA at predischarge angiography (Groups 1 and 2)

	Odds ratio (95%CI)	p Value
Group 1 vs. Group 2	0.28 (0.11–0.79)	0.02
Age per 10 years increase	2.07 (1.43–3.13)	<0.001
Male gender	1.53 (0.63–4.28)	0.38
Hypertension	2.32 (1.04–5.31)	0.04
Diabetes	1.13 (0.36–3.14)	0.83
Previous infarction	0.57 (0.16–1.81)	0.35
Killip class ≥2	1.46 (0.51–3.58)	0.45
Time to angiography ≥6 h	0.99 (0.40–2.29)	0.97
Collateral circulation	0.81 (0.33–1.89)	0.63
Multivessel disease	1.89 (0.79–4.40)	0.15
Predischarge LVEF per 5% increase	0.79 (0.68–0.92)	0.002

Abbreviations: CI = confidence interval, IRA = infarct-related artery, LVEF = left ventricular ejection fraction.

Group 1 than in Groups 2 and 3 ($p < 0.001$). Long-term survival in Group 2 was superior to that in Group 3, although there was no significant difference ($p = 0.41$). When only 160 patients with predischarge TIMI flow grade 3 were compared, there was still a tendency toward better long-term survival in Group 1 than in Group 2 ($p = 0.05$).

To assess whether only persistent patency of the IRA obtained early after infarction improves long-term survival or whether late spontaneous reperfusion after failed thrombolytic therapy also had a beneficial effect, a multivariate analysis was performed comparing Groups 1 and 2 (Table II). Among patients with a patent IRA at predischarge angiography, Group 1 compared with Group 2 was independently related to survival during 10 years of follow-up after hospital discharge, suggesting that only early reperfusion with persistent patency of the IRA was necessary to improve long-term survival. When LV ejection fraction, which was missing in six patients in Group 1 and in two patients in Group 2, was excluded from the analysis, inclusion in Group 1 was still an independent predictor of long-term survival (odds ratio 0.28, 95% confidence interval 0.11–0.78, $p = 0.02$).

Discussion

Thrombolytic therapy improves LV function and improves survival after acute MI through reperfusion of the IRA.[6, 7, 9] Patency of the IRA, as a predictor of survival after infarction, has been assessed both early and late after thrombolytic therapy. However, early after thrombolytic therapy, the IRA remains occluded in about one-third of the patients. Nearly half of the occluded IRAs early after thrombolytic therapy spontaneously reopen by the time of performance of chronic angiography.

It has been demonstrated that persistent patency is associated with a favorable outcome, but persistent occlusion and reocclusion are not. However, it has been unclear whether or not late spontaneous reperfusion represents mostly successful reperfusion. The current study showed that late spontaneous reperfusion after failed thrombolytic therapy was associated with poor predischarge LV function and long-term survival as well as with persistent occlusion. Late spontaneous reperfusion did not represent successful reperfusion, and only early reperfusion with persistent patency was associated with favorable outcome after infarction.

Although most trials in acute MI demonstrating efficiency of thrombolytic therapy limited patient entry to the first 3–6 h after symptom onset, several studies have shown that reperfusion beyond this time window might have benefit.[10, 11] The Late Assessment of Thrombolytic Efficacy (LATE) study group has claimed that the time window for thrombolytic therapy should be extended to at least 12 h, or in some patients to 24 h after onset of acute MI.[10] In the current study, we reviewed angiograms only at two points: about 60 min after initiation of thrombolytic therapy and about 3 weeks after infarction. Although it was unknown when late spontaneous reperfusion after failed thrombolytic therapy was achieved, it seemed to be too late to improve outcome after infarction.

Several kinds of thrombolytic agents are currently available, including fibrin nonspecific agents, streptokinase and urokinase, and fibrin-specific agents, tissue plasminogen activator, and prourokinase.[3–9] Although fibrin-specific agents achieve a higher early patency rate, the late patency rate after fibrin-nonspecific agents has shown to be as high as that with fibrin-specific agents.[3, 4] Patency after fibrin nonspecific agents does "catch up" with specific agents by a mechanism of late spontaneous reperfusion. Our data suggest that late patency through a mechanism of "catch up" is not sufficient to improve outcome after acute MI and again emphasize the importance of early reperfusion. Fibrin-specific agents, especially the new generation of tissue plasminogen activator that

achieve rapid reperfusion, seem to be preferable to nonspecific agents.[12] Furthermore, primary angioplasty, which achieves more rapid and more efficient reperfusion, may have an advantage on long-term survival over thrombolytic therapy.[13,14]

In this study, TIMI flow grade 2 at predischarge angiography was more frequent in patients with late spontaneous reperfusion than in those with persistent patency. This might have influenced the poor prognosis in patients with late spontaneous reperfusion.[15] However, it is noteworthy that, even in patients with predischarge TIMI flow grade 3, late spontaneous reperfusion is associated with poor chronic LV function and survival. Also, chronic residual stenosis was more severe in patients with late spontaneous reperfusion. With severe residual stenosis, adequate blood flow might not be restored.[11] Because elective angioplasty of the IRA was not performed in these study patients, it was not discussed whether elective angioplasty for severe residual stenosis after late spontaneous reperfusion might improve outcome. Recent studies have reported that elective coronary angioplasty of the occluded IRA late after infarction prevents LV remodeling.[16] Without measurements of LV volume in the current study, the influence of late spontaneous reperfusion on LV remodeling was not discussed.

This study is not a randomized but a retrospective study and suffers from the limitations of all nonrandomized, data-based analyses. Moreover, the small sample size is a major limitation of this study, and no difference in outcomes between Groups 2 and 3 was demonstrated. A large study should be performed to confirm the findings of this study.

Conclusion

Failure of reperfusion after thrombolytic therapy was associated with poor LV function and long-term survival even if late spontaneously reperfusion was obtained by the time of predischarge angiography. Our data emphasize the importance of early reperfusion in acute myocardial infarction.

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