Determinants of Left Ventricular Functional Recovery After Thrombolytic Therapy and/or Immediate Coronary Angioplasty in Acute Myocardial Infarction

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To determine the effect of thrombolytic therapy and/or immediate coronary angioplasty (PTCA) on left ventricular function, 129 patients with acute transmural myocardial infarction were retrospectively studied. Treatment strategies included thrombolytic therapy alone (n = 29), PTCA alone (n = 41), and combined thrombolytic therapy and PTCA (n = 59). Left ventricular ejection fraction (LVEF) and infarct zone regional wall motion (RWM) were determined from contrast ventriculography obtained acutely and at day 7–10. In the overall group, there was a 2 ± 9% increase in LVEF ($p < 0.02$) and a 0.7 ± 1.2 SD/chord increase in RWM ($p < 0.0001$) between day 1 and day 7–10. Patients with a patent infarct vessel at day 7–10 had a more significant change (Δ) in LVEF (3 ± 8 vs -5 ± 9%, $p = 0.0002$) and RWM (0.8 ± 1.2 vs 0.1 ± 1.0 SD/chord, $p < 0.02$) than patients with an occluded vessel. Patients with a residual stenosis < 70% at day 7–10 manifested a greater ΔLVEF (3 ± 8 vs -5 ± 9%, $p < 0.01$) and ΔRWN (0.9 ± 1.2 vs 0.1 ± 1.0 SD/chord, $p < 0.05$) than patients who were occluded. There was a negative correlation between residual stenosis and ΔRWM ($p < 0.04$). Patients treated < 3 hours after symptom onset demonstrated a more significant ΔRWM when compared to patients treated ≥3 hours (1.0 ± 1.3 vs 0.5 ± 1.1 SD/chord, $p < 0.04$). Patients treated with combined thrombolytic therapy and PTCA were observed to have a greater ΔRWM than patients treated with thrombolytic therapy alone (0.8 ± 1.2 vs 0.2 ± 0.9 SD/chord, $p < 0.05$). Patients with an LVEF > 40% demonstrated a more significant ΔLVEF than patients ≥ 40% (7 ± 8 vs 1 ± 8%, $p < 0.007$). A significant improvement in ΔLVEF was noted only in patients with an anterior infarction when compared to patients with an inferior infarction. Age, sex, presence of multivessel disease, history of prior myocardial infarction, initial patency of the infarct vessel, and presence of collaterals had no effect on left ventricular function. Stepwise multiple regression identified residual stenosis, time to treatment, and the degree of initial global impairment as the major joint predictors of ventricular functional recovery. (J Interven Cardiol 1988:1:3)

Introduction

Preservation of left venticular function is a major determinant of survival following myocardial infarction.[1–4] With experimental demonstration that restoration of blood flow after coronary occulsion reduces infarct size and improves regional function,[5,6] thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA) have found increasing application in patients with acute infarction.[7–10] Although previous studies have evaluated the efficacy of these treatment strategies in promoting functional recovery, their results have conflicted.[11–17]

This study was undertaken to assess the impact of thrombolytic therapy and/or immediate PTCA on left vetricular function during acute myocardial infarction and to determine variables which affect functional recovery.

Methods

Patient Selection. This report is a retrospective analysis of 184 consecutive patients with acute

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transmural myocardial infarction who were involved in various reperfusion therapy protocols at the University of Michigan Medical Center between January 1984 and February 1986. All patients underwent emergent cardiac catheterization within 7 hours of symptom onset.

In order to assess left ventricular function, only patients who underwent catheterization acutely and on repeat study at day 7–10 were studied. Of the 184 patients, 129 were included in the final analysis. Fifty-five were excluded because of technically inadequate ventriculograms (n = 44) or an inability to obtain repeat catheterization (n = 11). Based upon clinical characteristics, there was no selection bias between the included and excluded groups. Twenty-nine patients were treated with thrombolytic therapy alone [recombinant tissue plasminogen activator (rt-PA)], 41 patients with immediate PTCA alone, and 59 patients with combined thrombolytic therapy [rt-PA (n = 34) or streptokinase (n = 25)] and immediate PTCA. Informed consent was obtained prior to catheterization.

Thrombolytic Therapy. Thrombolytic therapy was administered to 88 patients prior to catheterization. Twenty-five patients were treated with streptokinase and 63 with rt-PA. The dose of streptokinase was 1.5 million U intravenously over 30 minutes. The dose of rt-PA was 1.25 mg/kg intravenously over 3 hours (n = 29) or 150 mg over 6 hours (n = 34). The clinical exclusion criteria for thrombolytic therapy included: (1) recent surgery, trauma, or cardiopulmonary resuscitation; (2) previous cerebrovascular accident; (3) active bleeding; (4) bleeding diathesis; (5) malignant hypertension; (6) age > 75 years; and (7) cardiogenic shock.

Catheterization Technique. All 129 patients underwent immediate catheterization upon arrival at the University of Michigan Medical Center. Following vascular sheath insertion, heparin 5000 U was administered intravenously. Selective coronary arteriography was performed in multiple projections. Contrast left ventriculography was performed in the 30° right anterior oblique position using a power injection of contrast through a pigtail catheter. After catheterization, patients received heparin in a continuous intravenous infusion for 7–10 days to maintain the activated partial thromboplastin time at 2 to 2.5 times control. In addition, aspirin 325 mg per day, dipryidamole 75 mg three times per day, and diltiazem 30 – 90 mg four times per day were administered. Repeat angiography was performed at day 7–10.

PTCA Procedure. One hundred patients underwent immediate PTCA. Following an additional dose of heparin 5000 U, a steerable balloon catheter system was used. The balloon was inflated serially until there was at least a 50% reduction in the initial infarct vessel stenosis. The angiographic exclusion criteria for PTCA included: (1) left main coronary stenosis >50%; (2) "left main equivalency": ≥70% stenosis in both the proximal left anterior descending and proximal left circumflex coronary arteries; (3) diffuse, multivessel disease not amenable to PTCA; (4) an unidentifiable infarct vessel; and (5) an infarct vessel stenosis <50%.

Assessment of Left Ventricular Function and Coronary Arteriography. Left ventricular function was determined from contrast ventriculography obtained acutely and on repeat study at day 7–10. The end-diastolic and end-systolic endocardial contours of the right anterior oblique ventriculogram were traced manually and digitized into a digital radiographic computer (ADAC Laboratories, DPS 4100C) for processing. All studies were blinded to patient identity, time of study, type of intervention, and coronary anatomy. Technically inadequate ventriculograms due either to poor opacification of the chamber or an inability to generate at least one sinus beat were not included in the analysis. Left ventricular ejection fraction (LVEF) and infarct zone regional wall motion (RWM) were determined from the area length[18] and center-line chord [expressed in units of standard deviation (SD) per chord][19] methods, respectively.

Percent diameter stenosis of the infarct-related artery at day 7–10 was determined by a blinded observer using caliper measurement. The projection in which the lesion appeared the most severe was selected for analysis. In addition, patency was assessed using TIMI flow grade.[20] For the purpose of this study, occlusion was defined as TIMI flow 0/1 and patency as TIMI flow 2/3.

Statistical Analysis. All results were given as mean ± standard deviation. Univariate analysis was performed with Student's *t*-test, paired *t*-test, Chi-square test, analysis of variance, analysis of covariance, and pairwise multiple comparisons. Linear regression analysis was used to determine

the effect of residual stenosis on left ventricular function. The joint predictive importance of variables for left ventricular functional improvement was examined using stepwise multiple regression in conjunction with all possible subsets (APS) regression. A probability of less than 0.05 was considered significant.

Results

Of the 129 patients, 82% were males. The mean age was 54 ± 10 years. Forty-one percent had an anterior myocardial infarction. Thirteen percent had a history of prior myocardial infarction. Forty percent had multivessel disease (≥70% stenosis in a noninfarct vessel) on coronary angiography. The time to treatment was 3.6 ± 1.6 hours.

In the overall group, there was a 2 ± 9% increase in LVEF (51 ± 11 to 53± 12%, $p < 0.02$) and a 0.7 ± 1.2 SD/chord increase in RWM (-2.7 ± 1.0 to -2.0 ± 1.4 SD/chord, $p < 0.0001$) between day 1 and day 7–10.

Determinants of Myocardial Recovery (Univariate Analysis)

Patency. The effect of patency on left ventricular function is shown in Table I. There was no difference between patients with a patent infarct-related artery and those with an occluded artery in LVEF or RWM at acute catheterization (day 1). At repeat catheterization (day 7–10), patients who demonstrated sustained patency of the infarct-related artery manifested greater improvement in LVEF and RWM than patients who had an occluded artery.

Residual Stenosis at Day 7–10. Subset analysis revealed 96 patients with a residual stenosis < 70% at day 7–10, 15 patients 70%–99%, and 18 patients 100% (Table II). Patients with a residual stenosis < 70% had more significant improvement in LVEF and RWM than patients with an occluded artery. There was no difference in left ventricular function between patients with a 70%–99% residual stenosis and patients with an occluded artery.

For patients who manifested sustained patency of the infarct-related artery at day 7–10, regression analysis demonstrated an inverse association between residual stenosis and the change (Δ) in RWM ($p < 0.04$) between day 1 and day 7–10 and a trend towards significance in ΔLVEF ($p < 0.06$).

Time to Treatment. There were 48 patients treated < 3 hours and 81 patients ≥ 3 hours after symptom onset (Table III). Patients treated < 3 hours had more significant improvement in RWM than patients treated ≥ 3 hours. There was no difference in LVEF between the two groups.

Type of Therapy. The effect of type of therapy on left ventricular function is depicted in Table IV. Patients treated with combined thrombolytic therapy and PTCA demonstrated a more significant ΔRWM than patients treated with thrombolytic therapy alone. Patients undergoing PTCA alone demonstrated a trend towards a more significant ΔRWM when compared to the thrombolytic therapy alone group. The PTCA alone and the combined thrombolytic therapy and PTCA groups were observed to have greater numbers of patients with a residual stenosis <70% than the thrombolytic therapy alone group. Patency at day 7–10 was similar in the three groups. Initiation of treatment was significantly longer in the PTCA alone group than in the other two groups.

Initial Global EF. One hundred nine patients were observed to have a LVEF ≥ 40% (mean 54 ± 9%) and 20 patients an LVEF < 40% (mean 34 ± 4%) at day 1. The latter group demonstrated a

Table I. Effect of Patency on Left Ventricular Function

Patency at Acute (Day 1) Catheterization

	Patent (n = 69)	Occluded (n = 59)	p value
EF (%)			
Day 1	52 ± 12	50 ± 10	NS
Day 7–10	54 ± 12	52 ± 12	NS
Change	2 ± 9	2 ± 8	NS
RWM (SD/chord)			
Day 1	−2.6 ± 1.1	−2.9 ± 1.0	NS
Day 7–10	−2.0 ± 1.4	−2.2 ± 1.3	NS
Change	0.6 ± 1.2	0.7 ± 1.2	NS

Patency at Repeat (Day 7–10) Catheterization

	Patent (n = 111)	Occluded (n = 18)	p value
EF (%)			
Day 1	51 ± 11	52 ± 8	NS
Day 7–10	54 ± 12	47 ± 11	<0.04
Change	3 ± 8	−5 ± 9	0.0002
RWM (SD/chord)			
Day 1	−2.7 ± 1.1	−2.9 ± 0.7	NS
Day 7–10	−1.9 ± 1.4	−2.8 ± 0.9	0.008
Change	0.8 ± 1.2	0.1 ± 1.0	<0.02

Table II. Effect of Residual Stenosis (Day 7–10) on Left Ventricular Function

	I <70% (n = 96)	II 70–99% (n = 15)	III 100% (n = 18)	p value[a]
EF (%)				
Day 1	51 ± 12	50 ± 11	52 ± 8	NS
Day 7–10*	54 ± 12	51 ± 10	47 ± 11	<0.08
Change**	3 ± 8	1 ± 9	−5 ± 9	0.0007
RWM (SD/chord)				
Day 1	−2.8 ± 1.1	−2.4 ± 0.9	−2.9 ± 0.2	NS
Day 7–10[ψ]	−1.9 ± 1.4	−2.2 ± 1.1	−2.8 ± 0.9	<0.02
Change[ψψ]	0.9 ± 1.2	0.2 ± 0.8	0.1 ± 1.0	0.006
Time to treatment (hrs)	3.6 ± 1.7	3.5 ± 1.2	3.7 ± 1.2	NS

Pairwise multiple comparisons: Groups I, II, III

*I vs II	p = NS	**I vs II	p = NS
I vs III	p < 0.1	I vs III	p < 0.01
II vs III	p = NS	II vs III	p = NS
[ψ]I vs II	p = NS	[ψψ]I vs II	p = NS
I vs III	p < 0.05	I vs III	p < 0.05
II vs III	p = NS	II vs III	p =NS

[a] Analysis of variance: Groups I, II, III.

more significant ΔLVEF than the former (7 ± 8 vs 1 ± 8%, p < 0.007).

Infarct Location. Fifty-three patients had an anterior and 76 patients an inferior myocardial infarction (Table V). A significant improvement in LVEF was noted only in patients with an anterior infarction. Both groups manifested comparable RWM recovery.

Clinical Characteristics. Age, sex, history of prior myocardial infarction, multivessel coronary artery disease, and presence of angiographically visible collaterals had no effect on left ventricular function (Table VI).

Table III. Effect of Time to Treatment on Left Ventricular Function

	<3 hours (n = 48)	≥3 hours (n = 81)	p value
EF (%)			
Day 1	50 ± 11	52 ± 11	NS
Day 7–10	53 ± 13	53 ± 12	NS
Change	3 ± 12	1 ± 12	NS
RWM (SD/chord)			
Day 1	−2.7 ± 1.1	−2.8 ± 1.0	NS
Day 7–10	−1.7 ± 1.5	−2.3 ± 1.3	<0.03
Change	1.0 ± 1.3	0.5 ± 1.1	<0.04

Determinants of Myocardial Recovery (Stepwise Multiple Regression). Stepwise multiple regression demonstrated that residual stenosis at day 7–10 (p = 0.0001), time to treatment (p < 0.04), and initial global EF < 40% (p < 0.01) were the significant joint predictors of global and regional functional improvement.

Discussion

The results of this study suggest that the efficacy of emergent coronary intervention in promoting left ventricular functional recovery in patients with acute myocardial infarction is dependent upon infarct vessel patency and residual stenosis at day 7–10, time and type of treatment, the degree of initial global impairment, and infarct location. Stepwise multiple regression, furthermore, identified residual stenosis, time to treatment, and initial global impairment as the key joint predictors of myocardial functional improvement.

The role of residual stenosis in left ventricular functional recovery has previously been described by Sheehan et al.[21] Our study in contrast assessed residual stenosis at day 7–10, not acutely. Determination of residual stenosis at a later date may be more accurate since the severity of the lesion following successful reperfusion tends to be overesti-

Table IV. Effect of Type of Treatment on Left Ventricular Function

	I PTCA (n = 41)	II Thrombolytic Therapy (n = 29)	III Thrombolytic Therapy + PTCA (n = 59)	p value[a]
EF (%)				
Day 1	51 ± 10	51 ± 12	51 ± 12	NS
Day 7–10	54 ± 10	51 ± 12	53 ± 14	NS
Change	3 ± 8	0 ± 9	2 ± 9	NS
RWM (SD/chord)				
Day 1	−2.8 ± 0.8	−2.5 ± 1.2	−2.8 ± 1.1	NS
Day 7–10	−2.0 ± 1.2	−2.3 ± 1.2	−2.0 ± 1.6	NS
Change*	0.8 ± 1.2	0.2 ± 0.9	0.8 ± 1.3	<0.04
Residual stenosis at day 7–10: % patients				
<70%Ψ	85	52	78	<0.01
70–99%ΨΨ	3	38	5	<0.01
100%	12	10	17	NS
Time to treatment (hrs)†	5.1 ± 2.3	3.4 ± 1.1	3.0 ± 1.4	<0.0001

Pairwise multiple comparisons: Groups I, II, III

*I vs II	p = 0.01	ΨI vs II	p < 0.05
I vs III	p = NS	I vs III	p = NS
II vs III	p < 0.05	II vs III	p < 0.05
ΨΨI vs II	p < 0.05	†I vs II	p < 0.01
I vs III	p = NS	I vs III	p < 0.01
II vs III	p < 0.05	II vs III	p = NS

[a] Analysis of variance: Groups I, II, III.

mated at acute catheterization given the presence of residual thrombus.[22] The effect of residual stenosis on left ventricular function might be explained by the fact that (1) infarct size directly correlates with the severity of the residual stenosis[23] and (2) following successful thrombolysis, patients often have a high grade residual stenosis which predisposes them to recurrent ischemia, reinfarction,[24–26] and presumably poorer left ventricular function.

Table V. Effect of Infarct Location on Left Ventricular Function

	EF%			
	Day 1	Day 7–10	Change	p value
Anterior MI (n = 53)	46 ± 12	49 ± 12	3 ± 10	<0.04
Inferior MI (n = 76)	55 ± 9	56 ± 11	1 ± 8	NS
	RWM (SD/chord)			
Anterior MI (n = 53)	−2.7 ± 1.2	−2.1 ± 1.3	0.6 ± 1.3	NS
Inferior MI (n = 76)	−2.7 ± 0.9	−2.1 ± 1.4	0.6 ± 1.2	NS

Patients who were treated with combined thrombolytic therapy and immediate PTCA or immediate PTCA alone demonstrated significant improvement in regional function when compared to patients treated with thrombolytic therapy alone. The fact that the PTCA-treated groups manifested less residual stenosis at day 7–10 might explain this difference. The effect of immediate PTCA on myocardial recovery has been confirmed by previous studies. O'Neill and colleagues found that PTCA, given its ability to more effectively reduce residual stenosis, led to greater functional recovery than intracoronary streptokinase.[17] Topol et al. demonstrated more significant regional recovery in patients treated with combined rt-PA and

Table VI. Effect of Clinical and Angiographic Variables on Left Ventricular Function

	EF (%)			RWM (SD/chord)		
	Day 1	Day 7–10	Change	Day 1	Day 7–10	Change
Age (years)						
<60 (n = 85)	52 ± 11	54 ± 12	2 ± 8	−2.6 ± 1.1	−2.0 ± 1.4	0.6 ± 1.2
≥60 (n = 44)	49 ± 10	52 ± 12	3 ± 9	−2.9 ± 0.9	−2.1 ± 13	0.8 ± 1.2
p value	NS	NS	NS	NS	NS	NS
Sex						
male (n = 106)	51 ± 11	53 ± 12	2 ± 8	−2.7 ± 0.9	−2.0 ± 1.3	0.7 ± 1.2
female (n = 23)	53 ± 12	54 ± 13	1 ± 9	−2.7 ± 1.5	−2.2 ± 16	0.5 ± 1.2
p value	NS	NS	NS	NS	NS	NS
Prior infarction						
yes (n = 17)	52 ± 11	54 ± 12	2 ± 9	−2.6 ± 1.1	−2.0 ± 1.4	0.6 ± 1.2
no (n = 112)	48 ± 11	49 ± 12	1 ± 7	−3.1 ± 0.6	−2.4 ± 1.2	0.7 ± 1.2
p value	NS	NS	NS	NS	NS	NS
Multivessel disease						
yes (n = 50)	52 ± 12	53 ± 13	1 ± 8	−2.7 ± 1.1	−2.1 ± 1.3	0.6 ± 1.2
no (n = 79)	50 ± 10	53 ± 11	3 ± 10	−2.8 ± 10	−2.0 ± 1.5	0.8 ± 1.2
p value	NS	NS	NS	NS	NS	NS
Collaterals						
yes (n = 42)	52 ± 11	53 ± 12	1 ± 9	−2.7 ± 1.0	−2.0 ± 1.4	0.7 ± 1.1
no (n = 87)	52 ± 10	54 ± 12	2 ± 7	−2.9 ± 0.7	−2.4 ± 1.3	0.5 ± 1.1
p value	NS	NS	NS	NS	NS	NS

PTCA than those patients treated with rt-PA alone.[27] The former group had less residual stenosis and a decreased incidence of recurrent ischemic events. The results of our study, nevertheless, differ with those of the TAMI Trial[28] and the European Cooperative Study[29] where immediate PTCA was found not to improve LVEF following thrombolytic therapy. Residual stenosis, however, was not assessed in these trials. Of interest, the PTCA alone group, despite being treated at a later time interval, demonstrated more significant improvement in regional function than the thrombolytic therapy alone group. This finding might be due to the ability of PTCA to more definitively reduce the underlying atherosclerotic lesion. The degree of residual stenosis may therefore be a more powerful predictor of left ventricular functional recovery than time to treatment.

Sustained patency at day 7–10 appeared to be a more important predictor of myocardial recovery than initial patency. Loss of patency at day 7–10, moreover, was associated with a decline in global function.

Left ventricular function was influenced by time to treatment. Patients treated < 3 hours after symptom onset demonstrated more significant improvement in RWM than patients treated ≥ 3 hours. There was no difference, however, in LVEF between the two groups. Several clinical studies have reported that the critical window for global recovery by coronary intervention occurs within 2 hours.[30,31] Koren et al., moreover, found that streptokinase administered later than 1.5 hours after symptom onset resulted in little gain in LVEF.[32] The lack of global improvement in our study may therefore be attributable to the fact that few patients were treated within 2 hours.

Previous reports have suggested that the magnitude of myocardial recovery following thrombolytic therapy appears dependent upon the degree of initial impairment or infarct location.[33–36] Patients with severely depressed left ventricular function derive more benefit from reperfusion owing to the greater potential for improvement. In our study, patients with an initial LVEF < 40% and those with an anterior myocardial infarction manifested the greatest recovery in global function. In contrast, patients with well-preserved baseline function demonstrated minimal improvement.

The importance of angiographic visible collaterals remains unclear. Although several studies have noted functional improvement with collateral presence,[37,38] we found no such association. In addition, sex, age, presence of multivessel disease, and history of prior myocardial infarction had no effect on left ventricular function.

Limitations. Because LVEF is a measure of the ischemically impaired infarct zone and the hyperdynamic noninfarct zone, it may be an insensitive means of assessing myocardial preservation. With regression of the compensatory hyperkinesia which often occurs before infarct zone recovery,[39] LVEF in the early postinfarct period may remain unchanged or even decrease. Furthermore, maximum improvement in global and regional function may not be seen for 6 months.[40] Our study in evaluating ventricular function at day 7–10 may therefore have underestimated the degree of recovery.

Conclusions and Future Directions

Early restoration of coronary blood flow and definitive recanalization to reduce the underlying residual stenosis appears critical in promoting myocardial recovery. The efficacy of thrombolytic therapy in preserving left ventricular function may be limited by an inability to re-establish anterograde flow in a significant proportion of patients[9,41–43] and by the persistence of a high grade residual stenosis. In contrast, PTCA, despite addressing the underlying atherosclerotic lesion, is an involved procedure limited to institutions with a cardiac catheterization laboratory and skilled personnel. Combined thrombolytic therapy and PTCA may therefore be a more practical alternative. Intravenous thrombolytic therapy can be initiated rapidly and safely in most health care facilities and PTCA subsequently performed in an appropriate hospital setting. The optimal timing for PTCA remains unclear and is the focus of several ongoing randomized trials. The results of this study suggest that an aggressive approach to acute myocardial infarction be aimed at patients who have a high grade residual stenosis, present early after symptom onset, and manifest extensive myocardial insult.

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