Systolic Left Ventricular Function After Reperfusion Therapy for Acute Myocardial Infarction
An Analysis of Determinants of Improvement

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Background. Contrast ventriculograms of 542 patients treated with intravenous thrombolytic agents for acute myocardial infarction were examined to define changes in left ventricular ejection fraction and regional wall motion that occur during the first week after reperfusion therapy for acute myocardial infarction and define clinical, acute angiographic and treatment variables related to improvement in global and regional left ventricular function.

Methods and Results. Intravenous tissue-type plasminogen activator and/or urokinase was administered to 885 patients during acute myocardial infarction. Mean time from symptom onset to thrombolytic therapy was 3 hours (22 patients received therapy within the first hour). Acute and 7-day catheterizations were performed. Paired left ventricular ejection fraction and centerline regional wall motion were available in 542 patients (67%). Stepwise, multivariable analysis of clinical, acute angiographic and treatment variables was used to develop two models: One related to improvement in left ventricular ejection fraction, and the second related to improvement in infarct zone regional function. Left ventricular ejection fraction did not change (51.2±11.1% for acute versus 51.9±11.0% for 1 week, p=0.19). Improvement in infarct zone regional function was modest (14%) at 1 week (−2.54±1.07 standard deviation per chord for acute versus −2.17±1.24 at 1 week, p<0.001). Subgroup analysis demonstrated modest improvement in ejection fraction (1.4±9.5%) and greater improvement in infarct zone function (19%) in patients with successful sustained reperfusion at 1 week. Depressed left ventricular ejection fraction and infarct zone regional wall motion at the acute study were strongly associated with improvement of these parameters at 1 week. Resolution of chest pain before acute catheterization, infarct-related artery flow at acute catheterization, and depressed regional wall motion in the noninfarct zone were associated with improvement in both ejection fraction and regional infarct zone function at 1 week. Notably, the time from the onset of symptoms to initiation of thrombolytic treatment was not related to subsequent improvement in ventricular function.

Conclusions. Dramatic improvement in left ventricular systolic function is not common after thrombolytic therapy for acute myocardial infarction. Improvement in global and regional systolic function is most closely related to acutely depressed ventricular function and successful acute coronary recanalization. Thus, patients with the most myocardium in jeopardy and successful coronary reperfusion demonstrate the greatest improvement in global and infarct zone ventricular function. Overall, the magnitude of this improvement is modest, suggesting that the benefits of coronary reperfusion are not solely related to improvement in systolic left ventricular function. (Circulation 1993;87:1531–1541)

Key Words • thrombosis • ejection fraction • centerline wall motion • angioplasty • clinical trials

Canine studies have established that coronary reperfusion after coronary occlusion salvages ischemic myocardium.1 The extent of myocardial salvage in these models has been shown to be critically dependent on the duration of coronary occlusion.1,2 In addition, recovery of left ventricular systolic function in these models has been shown to be delayed,
with the majority of improvement occurring within the first week after reperfusion.2-4 Thus, acute reperfusion therapy in humans has been built on the concept that left ventricular function would improve over time after thrombolysis and coronary reperfusion due to the salvage of “stunned” ischemic myocardium.

During the past several years, multiple clinical studies have been performed using aggressive coronary reperfusion strategies early in the course of acute myocardial infarction. The primary goals of these strategies, using intracoronary or intravenous thrombolytic agents with or without coronary angioplasty, have been to improve survival and salvage ischemic myocardium. Although the beneficial effects of these strategies on mortality have been established,5-7 their effect on left ventricular systolic function has been small and inconsistent, raising questions about whether other mechanisms may be responsible for the clinical benefit of thrombolytic therapy.8-14 One of the primary end points of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) studies was quantitative measurement of the change in regional and global left ventricular systolic function occurring during the first week after reperfusion therapy for acute myocardial infarction.

The purpose of this study was twofold. First, we sought to determine the changes that occur during the first week in global left ventricular ejection fraction and regional left ventricular wall motion in these studies involving thrombolysis and angioplasty therapy for acute myocardial infarction. Second, we sought to define the clinical, acute angiographic and treatment variables predictive of 7-day improvement in left ventricular ejection fraction and infarct zone regional wall motion in patients treated with these aggressive coronary reperfusion strategies.

### Methods

#### Patient Population

Of 805 patients prospectively enrolled in the TAMI trials (TAMI I, II, and III and urokinase studies), 542 had paired ventriculographic data (acutely and at 7 days), and they form the basis of this study. The details of the study designs have been described previously.15-18 Briefly, patients presenting within 6 hours of symptom onset of acute myocardial infarction were eligible. ECG ST segment elevation of 1 mm or more in two or more contiguous leads was required. Exclusion criteria included patient age of more than 75 years; history of recent stroke, trauma, surgery, or other predisposition to bleeding; previous coronary bypass grafting; or cardiogenic shock (defined as a systolic blood pressure of 80 mm Hg or less unresponsive to volume expansion). Patients who were entered received intravenous thrombolytic therapy consisting of tissue-type plasminogen activator (t-PA), urokinase, or both (Table 1).

The study protocols included acute and 7-day cardiac catheterization. Left ventriculography at acute catheterization was performed as soon as arterial access was obtained. Coronary angiography was performed 90 minutes after the initiation of the thrombolytic infusion. Infarct-related artery patency and flow were graded according to the Thrombolysis in Myocardial Infarction (TIMI) classification.19

Patients were eligible to undergo coronary angioplasty or bypass grafting after receiving thrombolytic therapy. Patients with persistent occlusion of the infarct-related artery (TIMI flow 0 or 1) at 90 minutes were eligible for “rescue” angioplasty during the acute catheterization. During the TAMI I study, patients with patent vessels at 90 minutes (TIMI 2 or 3 flow) but 50% or greater residual diameter stenosis in the infarct-related artery were randomized to immediate (at that time) or deferred (7 days later) coronary angioplasty. Based on the results of TAMI I, patients in the TAMI II or III or the urokinase studies who had patent infarct vessels with TIMI 2 or 3 flow and residual coronary lesions (50% or greater diameter stenosis) did not undergo immediate angioplasty unless there was clinical evidence of ongoing ischemia. In these later studies, coronary angioplasty or bypass grafting was deferred in patients with residual lesions until after the 7-day follow-up catheterization, unless the patient developed clinical evidence of recurrent ischemia. If recurrent ischemia developed, emergency cardiac catheterization was performed. Revascularization with percutaneous transluminal coronary angioplasty or coronary artery bypass grafting was considered for these patients.

Aspirin and intravenous heparin were administered to all patients. Other cardiac medications, including nitrates and calcium channel blockers, were used as clinically indicated at the discretion of the patient’s attending physician. β-Blockers were avoided unless required for control of hypertension, arrhythmias, or

### Table 1. Summary of Thrombolytic Drugs Used in the TAMI I, II, and III and Urokinase Studies

<table>
<thead>
<tr>
<th></th>
<th>No. of patients enrolled</th>
<th>Thrombolytic agent</th>
<th>Patients with paired ventriculograms*</th>
<th>Infarct-related artery patency†</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAMI I</td>
<td>386</td>
<td>t-PA‡</td>
<td>266 (69%)</td>
<td>199 (75%)</td>
</tr>
<tr>
<td>TAMI II</td>
<td>146</td>
<td>t-PA+urokinase§</td>
<td>93 (64%)</td>
<td>62 (67%)</td>
</tr>
<tr>
<td>TAMI III</td>
<td>173</td>
<td>t-PA+heparin‖</td>
<td>116 (67%)</td>
<td>95 (82%)</td>
</tr>
<tr>
<td>Urokinase</td>
<td>100</td>
<td>Urokinase¶</td>
<td>67 (67%)</td>
<td>37 (55%)</td>
</tr>
<tr>
<td>Total</td>
<td>805</td>
<td></td>
<td>542 (67%)</td>
<td>393 (73%)</td>
</tr>
</tbody>
</table>

TAMI, Thrombolysis and Angioplasty in Myocardial Infarction; t-PA, tissue-type plasminogen activator.
*Percentages are of total number of patients in trial.
†Infarct-related artery patency (angiographic Thrombolysis in Myocardial Infarction II or III flow at 90 minutes) percentages are of patients with paired ventriculograms.
‡Intravenous t-PA (1.5 mg/kg/4 hr).
§Intravenous t-PA (1.5 mg/kg/4 hr) and intravenous urokinase (0.5-2.0 million units).
‖Intravenous t-PA (1.5 mg/kg/4 hr) and simultaneous fourth bolus heparin (10,000 units).
¶Intravenous urokinase (3 million units).
Table 2. Comparison of Patients With and Without Paired Ventriculograms

<table>
<thead>
<tr>
<th></th>
<th>Paired ventriculographic data (n=542)</th>
<th>No paired ventriculographic data (n=263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55±10</td>
<td>58±10</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>447 (82%)</td>
<td>199 (76%)</td>
</tr>
<tr>
<td>Patients on β-blockers</td>
<td>53 (10%)</td>
<td>29 (11%)</td>
</tr>
<tr>
<td>Patients on calcium blockers</td>
<td>141 (26%)</td>
<td>64 (24%)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>207 (38%)</td>
<td>130 (49%)</td>
</tr>
<tr>
<td>History of prior myocardial infarction*</td>
<td>27 (10%)</td>
<td>28 (20%)</td>
</tr>
<tr>
<td>Time to thrombolytic treatment (minutes)</td>
<td>177±68</td>
<td>175±66</td>
</tr>
<tr>
<td>Myocardial infarction location†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>215 (40%)</td>
<td>114 (44%)</td>
</tr>
<tr>
<td>Inferior</td>
<td>327 (60%)</td>
<td>145 (56%)</td>
</tr>
<tr>
<td>Location of infarct-related artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main</td>
<td>0</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>208 (39%)</td>
<td>99 (40%)</td>
</tr>
<tr>
<td>Right coronary</td>
<td>266 (49%)</td>
<td>107 (43%)</td>
</tr>
<tr>
<td>Circumflex</td>
<td>64 (12%)</td>
<td>40 (16%)</td>
</tr>
<tr>
<td>Infarct-related artery patency at 90 minutes‡</td>
<td>393 (73%)</td>
<td>172 (70%)</td>
</tr>
<tr>
<td>No. of diseased vessels§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>28 (5%)</td>
<td>20 (8%)</td>
</tr>
<tr>
<td>One</td>
<td>291 (54%)</td>
<td>91 (35%)</td>
</tr>
<tr>
<td>Two</td>
<td>144 (27%)</td>
<td>81 (31%)</td>
</tr>
<tr>
<td>Three</td>
<td>76 (14%)</td>
<td>67 (26%)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction—acute study (%)</td>
<td>51.2±11.1</td>
<td>48.5±12.5</td>
</tr>
<tr>
<td>Baseline regional wall motion (SD/CHD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct zone</td>
<td>-2.54±1.07</td>
<td>-2.60±1.15</td>
</tr>
<tr>
<td>Noninfarct zone</td>
<td>0.38±1.61</td>
<td>-0.09±1.75</td>
</tr>
<tr>
<td>Emergency angioplasty</td>
<td>40 (7%)</td>
<td>22 (8%)</td>
</tr>
<tr>
<td>Emergency bypass grafting</td>
<td>23 (4%)</td>
<td>21 (8%)</td>
</tr>
<tr>
<td>Urgent bypass grafting</td>
<td>22 (4%)</td>
<td>26 (10%)</td>
</tr>
<tr>
<td>Elective bypass grafting</td>
<td>48 (9%)</td>
<td>37 (14%)</td>
</tr>
<tr>
<td>Death before hospital discharge</td>
<td>4 (0.7%)</td>
<td>50 (19%)</td>
</tr>
</tbody>
</table>

*These data not available for Thrombolysis in Acute Myocardial Infarction I.
†Defined by ECG ST segment elevation.
‡Patency defined as Thrombolysis in Myocardial Infarction 2 or 3 flow.
§Defined angiographically as more than 50% diameter stenosis.
||Data from 156 patients with acute ventriculographic data.

severe angina because of their possible effect on the left ventricular function end point (Table 2).

Acute and 7-Day Left Ventriculography

Single-plane left ventriculograms were analyzed at the University of Michigan Core Laboratory. The end-diastolic and end-systolic contours from the 30° right anterior oblique view were traced by a single observer who was blinded to patient identity, time of study, and type of therapy received. Global left ventricular ejection fraction was determined using the area–length method.20 The centerline method was used to quantitate regional left ventricular wall motion.21 Within the region of interest, the mean wall motion of one half of the most abnormally contracting contiguous chords was determined to yield the wall motion index of that region. This result was expressed in standard deviations (from normal) per chord (SD/CHD); hypokinesis was indicated by negative values. Intraobserver variability in blinded repetitions of 50 consecutive studies was less than 1.5 ejection fraction points and 5% for regional wall motion measurements.

Of the 805 patients enrolled in these studies, 542 had paired ventriculographic data for analysis. Reasons that ventriculographic data were not available from the time of the acute catheterization included hemodynamic instability in eight patients and technically inadequate studies in 99 patients (technically inadequate ventriculograms were those with incomplete opacification of the ventricle or excessive ventricular ectopy). Seven-day ventriculographic data were not available in 217 patients. This was due to death within the first week in 48 patients, patient refusal of repeat catheterization in 81 patients, and technically inadequate ventriculograms in 88 patients.

The 542 patients with paired ventriculographic data are compared with the 263 patients lacking paired
TABLE 3. Variables Analyzed by Multivariable Regression

Baseline clinical variables
- Age
- Sex
- Heart rate
- Systolic blood pressure
- Diastolic blood pressure
- Time from symptom onset to administration of thrombotic agent
- Resolution of chest pain before catheterization
- Location of infarction
- History of hypertension
- History of diabetes mellitus
- History of angina before infarction
- History of β-blocker use

Catheterization variables (acute study)
- Left ventricular ejection fraction
- Regional wall motion in the infarct zone
- Regional wall motion in the noninfarct zone
- Infarct-related artery flow (Thrombolysis in Myocardial Infarction grade at 90 minutes)
- Residual stenosis in infarct-related artery
- Number of diseased vessels
- Location of infarct-related artery

Treatment variables
- Use of coronary angioplasty
- Emergency coronary angioplasty during hospitalization
- Emergency coronary bypass grafting
- Urgent coronary bypass grafting
- Congestive heart failure during hospitalization

ventriculographic data in Table 2. The patients with paired ventriculographic data were similar to those without paired data with respect to the time from onset of symptoms until infusion of intravenous thrombolytic therapy. These groups also were similar with respect to the location of myocardial infarction, location of the infarct-related artery, patency of the infarct-related artery at 90 minutes, infarct zone regional wall motion measured acutely, and use of emergency coronary angioplasty. However, the group without paired ventriculographic data was older, included more women, and had a higher incidence of hypertension and previous myocardial infarction. The group without paired ventriculographic data had more multivessel coronary artery disease, lower acute left ventricular ejection fraction, more depressed acute regional wall motion in the noninfarct zone, increased incidence of coronary artery bypass grafting, and higher incidence of in-hospital death.

Statistical Analysis

Descriptive data are presented as mean±1 SD for continuous variables and as percentages for discrete variables. Stepwise multiple linear regression analysis was used to develop and validate two models predictive of 7-day improvement in left ventricular systolic function. The outcome variables were the change in left ventricular ejection fraction at 7 days and the change in infarct zone regional wall motion during the same time frame. In both models, a set of 24 preselected predictors were examined (Table 3).

The same process of model development was used for each of the two outcomes. This process involved a unique stepwise approach that allowed for model development in a clinically relevant fashion. First, clinical variables available to the physician at patient presentation were studied. With a backward selection technique, a subset of significant baseline clinical variables was derived (p<0.1). After adjusting for these clinical characteristics, a backward selection technique again was used to determine the significant acute angiographic variables. Finally, the treatment end point variables were added to the significant clinical and angiographic factors, and the backward selection technique again was used, resulting in a combined clinical, angiographic and treatment end point model.

To provide internal validation, the technique of bootstrapping was used.22 A random sample of two thirds of the population was drawn with replacement from the original sample. Backward elimination with linear regression modeling then was used on the “bootstrapped” sample. This step was repeated 40 times for each model, and the number of times each variable reached statistical significance (p<0.1) was calculated. An arbitrary threshold for replication was set at 75% (or 30 of 40 model validations).

Subgroup analysis also was performed comparing the left ventricular function of patients with successful acute reperfusion and no coronary reocclusion to the subgroup with unsuccessful acute reperfusion or infarct-related artery reocclusion. Analysis of adjuvant coronary revascularization treatments on left ventricular function also was performed. The ventricular function of patients undergoing emergency angioplasty or coronary artery bypass grafting before the 7-day repeat catheterization was compared with the ventricular function of patients without these interventions. The angioplasty subgroup contained patients undergoing acute rescue angioplasty or emergency angioplasty for recurrent ischemia.

Results

Acute and 1-Week Ventricular Function

The mean left ventricular ejection fraction was 51.2±11.1% during the acute study and was 51.9±11.0% at the 7-day study (p=0.19). Although no overall change in ejection fraction was demonstrated, a significant amount of interpatient variability was seen (Figure 1). More than 25% of patients had an improvement of more than 5%, and more than 25% had a deterioration of ejection fraction of more than 5%.

Regional wall motion in the infarct zone improved from −2.54±1.07 SD/CHD at acute catheterization to −2.17±1.24 SD/CHD at the 7-day evaluation (p<0.001). Figure 1 also demonstrates substantial variability in regional function with many patients improving and many patients deteriorating. Thus, on average, modest improvement in the severity of hypokinesis within the infarct zone occurred during the first week after myocardial infarction.

The regional wall motion in the noninfarct zone regressed slightly from 0.38±1.61 SD/CHD acutely to 0.30±1.45 SD/CHD at 7 days (p=0.035). Again, many
patients changed by more than 1 SD/CHD in either direction.

Multivariable Analysis

Predictors of improvement in left ventricular ejection fraction. Analysis of clinical variables yielded only a few that were associated with improvement in global left ventricular systolic function at 1 week. Resolution of chest pain before acute catheterization and a history of hypertension were significantly associated with improvement in left ventricular ejection fraction over the first week. Even before considering the acute angiographic variables, only a statistically insignificant trend \( (p=0.13) \) was observed between shorter time to treat-ment and improvement left ventricular ejection fraction (Figure 2).

When the acute angiographic findings were added to the analysis, reduced acute ejection fraction emerged as the most important predictor of improvement in left ventricular ejection fraction at 1 week. Reduced acute noninfarct zone regional wall motion and acute TIMI grade 3 coronary flow in the infarct vessel also were independently associated with improvement in left ventricular ejection fraction at 1 week. The number of diseased coronary vessels, location of myocardial infarction, and residual stenosis in the infarct vessel did not add independent information. Similarly, the treatment variables, including angioplasty and coronary artery bypass grafting, were not independently predictive of improvement in global left ventricular systolic function.

The final model (Table 4) included the variables of acute global left ventricular ejection fraction, acute noninfarct zone regional wall motion, TIMI grade 3 coronary flow in the infarct-related artery, resolution of chest pain before acute catheterization, and history of hypertension. Acute ejection fraction was dramatically the most significant variable \( (F=68.2, p<0.001) \), and the angiographic variables were much more powerful than the clinical variables. Acute left ventricular ejection fraction, acute noninfarct zone wall motion, and acute TIMI grade 3 flow in the infarct vessel contained 87% of the information predictive of improvement in ejection fraction. Depressed left ventricular ejection fraction at the acute study remained the strongest predictor of improvement in ejection fraction when patients with prior myocardial infarctions were excluded from the analysis \( (p<0.001) \). The model had an \( R^2 \) of 0.23 \((p<0.001)\), demonstrating that the variability was not completely explained by the model, although the overall relation was highly statistically significant.

Predictors of improvement in infarct zone regional function. The findings with respect to 7-day improvement in infarct zone regional function were similar, but not identical, to the analysis for global ventricular function (Table 4). Among the clinical variables, resolution of chest pain before acute catheterization again was related to improvement in infarct zone regional wall motion at 7 days. Unlike the global function analysis, history of hypertension was not associated with infarct zone regional improvement \( (p=0.70) \). In addition, inferior infarction was marginally related to improvement in infarct zone regional wall motion. Like the global function analysis, no relation was found between the duration of symptoms before administration of thrombolytic therapy and improvement in regional infarct zone function \( (p=0.597, \text{Figure 3}) \).

When the angiographic and treatment variables were added into the analysis, acutely depressed infarct zone regional wall motion was the strongest predictor of subsequent improvement. This again was true when patients with prior infarctions were excluded from the analysis. Impaired regional wall motion in the noninfarct zone at the acute study also was associated with greater subsequent improvement in the infarct zone. In contrast to the findings for global left ventricular function, the absence of TIMI grade 0 flow rather than the presence of TIMI grade 3 flow as observed for global function was a more powerful predictor of improvement in infarct zone regional wall motion. Finally, emergency

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**Figure 1.** Box-and-whisker plot illustrating the change in left ventricular ejection fraction (EF) and regional wall motion occurring from the acute catheterization to the 7-day study. Box illustrates the 25th and 75th percentiles of the data with the median drawn in the center. Whiskers represent 2 SDs from the mean of the data. No overall change in EF (Δ EF) occurred from the acute to the 7-day study. There was, however, significant interpatient variability in the data. There was modest overall improvement in the regional wall motion in the infarct zone (Δ infarct zone) from the acute to the 7-day study \((p<0.001)\). Again, there was significant interpatient variability. There was a slight decrease in the regional wall motion in the noninfarct zone (Δ noninfarct zone) from the acute to the 7-day study \((p=0.035)\).

**Figure 2.** Scatterplot of change in left ventricular ejection fraction (from the acute to 7-day catheterization) versus the time from onset of symptoms to the administration of intravenous thrombolytic therapy. No relation was observed between change in left ventricular ejection fraction and time to administration of thrombolytic therapy \((p=0.13)\). Note that the majority of patients were treated within 3 hours of symptom onset and 128 patients (24%) received thrombolytic therapy within 2 hours of the onset of symptoms of myocardial infarction.
coronary artery bypass grafting was found to be a marginal predictor of infarct zone regional wall motion improvement.

Model Validation

The results of the bootstrapping validation revealed that the time from the onset of chest pain to initiation of treatment with thrombolytics was significantly related to improvement in ejection fraction in 30 of 40 iterations and to infarct zone regional improvement in 22 of 40 iterations. In the global function analysis, acute ejection fraction, acute noninfarct zone function, history of hypertension, TIMI grade 3 infarct-related artery flow, and relief of chest pain before acute angiography were significantly related to improvement in at least 30 of 40 iterations. Thus, all parameters defined from the multivariable analysis met the validation criteria by bootstrapping. In the regional function analysis, acute infarct zone function, chest pain relief before angiography, acute noninfarct zone function, and inferior myocardial infarction were significantly related to improvement in more than 30 of 40 iterations, whereas absence of acute TIMI grade 0 coronary flow was significant in 29 and emergency bypass surgery in 27 of 40 iterations and thus just failed to meet criteria for validation by bootstrapping. Other than the relation of time to treatment with improvement in global ejection fraction, no new factors were identified by bootstrapping.

Subgroup Analysis

Patients with acute reperfusion and sustained patency. Patients with successful, acute reperfusion at 90 minutes and sustained infarct-related artery patency at 7 days demonstrated better infarct zone regional function acutely and greater 7-day improvement in ejection fraction and infarct zone regional function compared with patients with unsuccessful acute reperfusion or infarct-related artery reocclusion (Table 5). The trend toward greater acute ejection fraction in patients with successful sustained reperfusion did not reach statistical significance (*p=0.14). Modest 7-day improvement in ejection fraction (1.4±9.5%) occurred in patients with successful reperfusion and sustained patency compared with a modest decrease in ejection fraction in patients with unsuccessful acute reperfusion or coronary reocclusion. Infarct zone regional function demonstrated less hypokinesis acutely as well as greater 7-day improvement in patients with successful, sustained reperfusion. Noninfarct zone regional function was not different in patients with successful, sustained reperfusion, and the 7-day change in noninfarct zone function was similar to that of patients with unsuccessful reperfusion or reocclusion.

Adjuvant revascularization treatments: angioplasty or bypass grafting. Patients who underwent coronary bypass grafting had lower ejection fractions at the acute study and reduced noninfarct zone regional function compared with patients who underwent angioplasty or who underwent neither angioplasty nor bypass grafting (Table 6). Patients undergoing angioplasty or bypass surgery had more severe hypokinesis in the infarct zone at the acute study than patients undergoing neither treatment. Patients undergoing bypass grafting demonstrated 7-day improvement in ejection fraction (3.6±10.3%) compared with no change in ejection fraction in the angioplasty and neither-therapy groups. The magnitude of the infarct zone regional wall motion improvement also was greater in the bypass subgroup. In the bypass subgroup, noninfarct zone regional function improved at 7 days compared with slight regression of noninfarct zone function in the other two subgroups.

Discussion

The present study, which describes the largest population of patients with serial acute and follow-up angiographic evaluation after thrombolytic therapy, demon-
strates that the magnitude of improvement in left ventricular systolic function is small within the first week after myocardial infarction. Contrary to the belief that "stunned" myocardium may recover and dramatically improve left ventricular function, on average no overall change in global ejection fraction and only modest improvement in regional infarct zone function were demonstrated during the first week after thrombolytic therapy. Despite the absence of large group changes, the individual improvement is most closely related to the amount of initial myocardial damage as reflected by acute global and regional systolic function. Other consistent findings were that coronary reperfusion as measured by TIMI grade flow at acute angiography and relief of chest pain before acute angiography were associated with subsequent improvement in left ventricular global and infarct zone regional systolic function. This is further supported by the subgroup analysis demonstrating modest 7-day improvement in ejection fraction and greater improvement in infarct zone regional function in those with successful acute and sustained reperfusion.

Essentially, we could identify no factors that would enable a clinician at the bedside to identify patients with a high likelihood of improvement in systolic left ventricular function. In addition, despite the large number of patients in this study, only a marginal relation (by bootstrapping only) between time to thrombolytic treatment and improvement in global systolic function could be demonstrated. No relation between time to treatment and recovery of regional infarct zone function was demonstrated. These findings can be considered highly reliable because they were internally validated and are consistent with previous smaller studies.

**Comparison With Prior Studies**

The lack of sizeable change in global function is consistent with previous reports. The TIMI I study group has produced the largest previous report with serial angiography, and the change over the duration of

### TABLE 5. Effect of Success of Reperfusion on Left Ventricular Function

<table>
<thead>
<tr>
<th></th>
<th>Successful reperfusion (n=355)</th>
<th>Unsuccessful reperfusion (n=182)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>51.7±11.3</td>
<td>50.4±10.9</td>
<td>0.15</td>
</tr>
<tr>
<td>7-Day</td>
<td>53.1±11.2</td>
<td>49.7±10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change</td>
<td>1.4±9.5</td>
<td>−0.6±8.2</td>
<td>0.028</td>
</tr>
<tr>
<td>Infarct zone regional wall motion (SD per chord)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>−2.45±1.13</td>
<td>−2.72±0.92</td>
<td>0.014</td>
</tr>
<tr>
<td>7-Day</td>
<td>−1.98±1.29</td>
<td>−2.53±1.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change</td>
<td>0.47±1.10</td>
<td>0.19±0.89</td>
<td>0.019</td>
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<tr>
<td>Noninfarct zone regional wall motion (SD per chord)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>0.45±1.63</td>
<td>0.29±1.57</td>
<td>0.276</td>
</tr>
<tr>
<td>7-Day</td>
<td>0.38±1.47</td>
<td>0.17±1.43</td>
<td>0.189</td>
</tr>
<tr>
<td>Change</td>
<td>−0.08±1.25</td>
<td>−0.12±1.06</td>
<td>0.902</td>
</tr>
</tbody>
</table>

Successful reperfusion, infarct-related artery Thrombolysis in Myocardial Infarction flow ≥2 at 90 minutes and 7 days; unsuccessful reperfusion, infarct-related artery Thrombolysis in Myocardial Infarction flow ≤1 at 90 minutes or 7 days.

### TABLE 6. Effect of Adjuvant Revascularization Treatments on Left Ventricular Function

<table>
<thead>
<tr>
<th></th>
<th>Bypass surgery (n=56)</th>
<th>Angioplasty (n=142)</th>
<th>Neither (n=344)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>46.5±11.0</td>
<td>49.1±10.5</td>
<td>52.8±11.1</td>
</tr>
<tr>
<td>7-Day</td>
<td>50.2±11.9</td>
<td>49.2±10.7</td>
<td>53.3±10.8</td>
</tr>
<tr>
<td>Change</td>
<td>3.6±10.3</td>
<td>0.10±8.13</td>
<td>0.49±9.28</td>
</tr>
<tr>
<td>Infarct zone regional wall motion (SD per chord)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>−2.68±0.91</td>
<td>−2.73±0.97</td>
<td>−2.44±1.12</td>
</tr>
<tr>
<td>7-Day</td>
<td>−1.95±1.32</td>
<td>−2.54±0.99</td>
<td>−2.05±1.29</td>
</tr>
<tr>
<td>Change</td>
<td>0.73±1.17</td>
<td>0.20±0.95</td>
<td>0.39±1.03</td>
</tr>
<tr>
<td>Noninfarct zone regional wall motion (SD per chord)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>−0.26±1.92</td>
<td>0.27±1.53</td>
<td>0.54±1.56</td>
</tr>
<tr>
<td>7-Day</td>
<td>0.19±1.87</td>
<td>0.21±1.45</td>
<td>0.36±1.38</td>
</tr>
<tr>
<td>Change</td>
<td>0.45±1.22</td>
<td>−0.07±1.01</td>
<td>−0.18±1.23</td>
</tr>
</tbody>
</table>

Bypass surgery, coronary artery bypass surgery before follow-up (7-day) recatheterization; angioplasty, rescue or emergency angioplasty before follow-up catheterization; neither, patients not undergoing angioplasty or bypass surgery before follow-up catheterization.

All p<0.05 (for bypass surgery versus angioplasty or neither) except 7-day noninfarct zone regional wall motion.
the initial hospitalization was minimal after treatment with both t-PA and streptokinase.14,19 The change in left ventricular systolic function in previous studies using serial, paired ventriculographic data after intravenous thrombolytic therapy is summarized in Table 7.10,19,23-25 The data in these smaller studies are consistent with the present study. The lack of ejection fraction change in aggregate in our study is even more impressive considering that patients who died and thus were unable to have repeat 7-day ventriculography were the patients likely to have the least improvement in left ventricular function.

The regional changes observed in left ventricular function are within the realm of previous studies19,24-26 and similar to the original report of regional infarct zone improvement after successful reperfusion with intracoronary streptokinase.27 The units of measurement (SD/CHD) of regional infarct zone function are not intuitive, but the magnitude of overall change demonstrated in this study is small. Nevertheless, documentation of this degree of improvement provides further evidence for salvage of myocardium by reperfusion therapy.

Mechanism of Modest Functional Recovery

Previous canine studies may help to explain the modest overall change in regional left ventricular function in the infarct zone observed in the present study. Coronary occlusion produces myocardial necrosis proceeding in a "wave front" fashion from the endocardium to the epicardium.1 The extent of necrosis has been shown to be critically dependent on the duration of coronary occlusion. A 3-hour occlusion, for example, produces about 60% necrosis of the canine left ventricular wall beginning at the endocardium.1 The majority of the systolic function of the left ventricle is provided by these endocardial layers. Thus, preservation of left ventricular systolic function, rather than ventricular mass, may be even more critically dependent on rapid coronary reperfusion. In fact, when 60% transmural necrosis occurs in the dog, only 20% of baseline systolic wall thickening returns.2 Thus, even in these TAMI studies, using aggressive coronary reperfusion strategies during acute myocardial infarction (mean time of 3 hours to thrombolytic therapy administration), dramatic improvement in infarct zone ventricular function theoretically is unlikely. Conversely, these experimental data suggest that reperfusion in this time frame may preserve important, viable myocardium in the epicardial layers that is not detectable even by sensitive measures of regional systolic ventricular function. In this light, discrepancies between the size of thallium defects and infarct zone regional function after reperfusion therapy have been suggested.28,29 Future studies comparing other measures of infarct size such as thallium or isonitrile with systolic left ventricular function will be necessary to resolve this issue.

Multivariable Analysis

Although no overall change in left ventricular function was observed before discharge, the lack of overall change resulted from substantial improvement in some patients and substantial deterioration in others. Regardless of whether improvement in global or regional function was the end point, the degree of acute impairment was the factor most closely associated with improvement in function; those patients with the worst function acutely were most likely to improve. This also held true when only patients with first myocardial infarctions were analyzed. Although this finding may be related in part to the statistical phenomenon of regression to the mean,30 it also suggests that patients with the greatest extent of jeopardized myocardium benefit the most from coronary reperfusion. Our results with respect to predischarge change in ejection fraction are consistent with the smaller study reported by Marzoll and colleagues,31 both in the direction and the magnitude of the effect. Others also have reported that acute function is a critical predictor of subsequent improvement, although these reports have not provided rigorous quantitative analysis in large numbers of patients.19,32-34

Multivariable analysis in this study also demonstrated that coronary perfusion at acute catheterization was associated significantly with left ventricular function improvement, although the magnitude of this effect was less than the effect of acute systolic function. Both the clinical variable of resolution of chest pain at the time of acute catheterization and infarct vessel patency defined by acute angiography were univariately significant, although the latter predominated in multivariable analysis. The presence of TIMI grade 3 flow was the most important factor in the global function analysis, whereas the absence of TIMI grade 0 flow was the critical measure in the regional function analysis. The most reasonable interpretation of this difference is that the degree of flow is important but the overall effect is so
small that graded effects are difficult to measure. Marzoll and colleagues\textsuperscript{31} found similar results with respect to acute infarct vessel perfusion and subsequent improvement in left ventricular ejection fraction.

The impact of noninfarct zone regional function on global and infarct zone systolic function is intriguing. Patients with greater impairment of noninfarct zone function at acute catheterization had greater improvement in both infarct zone regional function and global ventricular function at 1 week. The phenomenon of “ischemia at a distance” may explain in part this observation. In patients with multivessel coronary disease, the acutely occluded artery may have supplied collateral blood flow to the noninfarct zone before infarction. In such patients, reperfusion and restoration of flow in the infarct-related artery may improve flow to both the infarct and noninfarct territories and may result in subsequent improvement of both regional and global left ventricular function.

History of hypertension was identified as a weak predictor of improvement in global but not regional function. The presence of left ventricular hypertrophy, with increased left ventricular mass, may allow for greater recovery of overall left ventricular function after reperfusion. Hypertrophied ventricles also may be less prone to thinning and dilation and thus allow preservation of global left ventricular systolic function.

Effect of Successful, Sustained Reperfusion

The modest preservation of global and regional function in patients with successful angiographic reperfusion and no reocclusion provides further support for salvage of myocardium with aggressive reperfusion strategies. This observation is in distinction to the slight deterioration in global function over the first week observed in patients with unsuccessful reperfusion or reocclusion. This analysis is consistent with previous placebo-controlled trials demonstrating modest improvement in ventricular function in patients treated with thrombolytic therapy and deterioration in ventricular function in those receiving placebo.\textsuperscript{10,23–26,35}

Effect of Bypass Surgery and Angioplasty

The beneficial effect of coronary bypass surgery (performed 4.4±9.9 days after myocardial infarction) on both global and regional ventricular function is consistent with previous data.\textsuperscript{36} Patients undergoing rescue or emergency angioplasty had more severe infarct zone dysfunction acutely (similar to the group undergoing bypass) than patients treated with thrombolytic therapy alone. The 7-day improvement in infarct zone function in the angioplasty group was similar to the improvement observed in patients given thrombolytic therapy alone and was not as great as the infarct zone improvement seen after bypass surgery. This observation suggests that recovery of ventricular function is more complex than the animal models would predict, perhaps requiring more global revascularization to improve even regional infarct zone function. Possibly, ischemic areas in the peri-infarct zone recover only when the noninfarct region also is revascularized. Alternatively, the improvement in noninfarct zone function may mechanically influence (“tether”) and improve the regional wall motion in the infarct zone.

Time to Treatment and Recovery of Function

Perhaps the most striking finding in this study is the lack of relation between time to treatment and subsequent improvement in left ventricular function. This finding exists despite the large number of patients and the careful measurement of both global and regional ventricular function in this study. Marzoll and colleagues also found no effect of time to treatment, whereas the TIMI investigators reported a weak relation.\textsuperscript{19,33} This finding again suggests that variables related to subsequent improvement in left ventricular systolic function after coronary reperfusion in humans may be different and more complex than predicted by the canine models. One factor that was not measured in our study that is important in both the canine model and clinical studies is coronary collateral blood flow.\textsuperscript{37} Collateral flow to the distal bed of the infarct vessel may preserve some jeopardized myocardium, which may recover after thrombolysis and anterograde coronary reperfusion. In addition, infarct vessel patency and flow during acute myocardial infarction constitute a dynamic process, as demonstrated by the frequent occurrence of multiple changes in the level of ST segment elevation, which may affect the severity of myocardial ischemia and infarction.\textsuperscript{38} Despite these caveats, the consistency of these findings in a large number of patients evaluated in three separate studies makes it unlikely that the lack of relation between time to treatment and improvement in left ventricular function is artifact.

None of the studies reported to date, including ours, have had a large number of patients treated within the first hour of symptom onset. A recent meta-analysis demonstrated a direct relation between time to treatment and survival,\textsuperscript{39} results that are not reflected in the ventricular function data in this study. Patients treated within the first hour had a mortality reduction that was substantially greater than that predicted by the logistic regression model relating time to treatment to mortality. These results suggest that treatment within the first hour may result in markedly enhanced survival, perhaps due in part to preservation of left ventricular function, as well as other potential mechanisms such as improved healing and better electrophysiological properties.\textsuperscript{40,41} Later treatment may result in quantitatively less survival enhancement because the ability to salvage sufficient myocardium to preserve systolic left ventricular function is lost.

Study Limitations

It must be emphasized that this study had no control or placebo group (i.e., all patients received intravenous thrombolytic therapy), and thus no conclusion can be drawn with respect to the effect of these coronary reperfusion strategies on left ventricular function compared with patients not treated with intravenous thrombolytics.

Although contrast left ventriculography is the gold standard for measuring left ventricular systolic function, some disadvantages are present. Left ventricular angiography, analyzed in the right anterior oblique view, can miss wall motion abnormalities in the posterolateral wall. This limitation is not major because in only 12% of the population was the circumflex the infarct-related artery.
In addition, whenever contrast ventriculography is used to measure left ventricular function, substantial dropout occurs, predominately in the sickest patients. The requirement for invasive 7-day restudy eliminated some of the highest-risk patients as reflected by the lower-risk characteristics and lower in-hospital mortality (Table 2) in patients with paired ventriculographic data.

The 7-day end point may not be adequate to define serial change in left ventricular function after coronary reperfusion. Res and colleagues, however, evaluating patients treated with intracoronary streptokinase, demonstrated improvement in ejection fraction 2 weeks after infarction but found no further change when ejection fraction was remeasured at 3 months. Our data reevaluating left ventricular function at 6 months and the TIMI data at 1 year did not show further change in left ventricular function compared with the 1-week, predischARGE end point.

Implications

We believe that this study has three major implications. Clinically, our findings reinforce the general principle that patients with the most myocardium in jeopardy benefit the most from reperfusion. No other criteria for selection of patients with more to gain from treatment could be identified. Successful reperfusion is associated with this improvement, so means of achieving reperfusion in a higher proportion of patients should be sought. Second, in comparative trials or analyses, the magnitude of differences in left ventricular function between treatments can be expected to be small. Finally, the large body of clinical data demonstrating the failure of reperfusion therapy to dramatically improve left ventricular function points to the need for a better understanding of the underlying pathophysiology following coronary reperfusion. Studies designed to compare infarct size and systolic function as well as basic investigation of the mechanism of irreversible injury could lead to new therapies to further enhance the benefit of coronary reperfusion.

Acknowledgment

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