Comparison of Left Ventricular Function and Contractile Reserve After Successful Recanalization by Thrombolysis Versus Rescue Percutaneous Transluminal Coronary Angioplasty for Acute Myocardial Infarction

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To determine how coronary reperfusion affects rest and exercise ventricular function after acute myocardial infarction (AMI), 63 patients with a patent infarct artery after intravenous thrombolytic therapy (lysis) were compared with 27 patients who failed thrombolysis but had successful acute recanalization by percutaneous transluminal coronary angioplasty (PTCA) as a "rescue" procedure. Contrast ventriculography was performed acutely and on day 7. Resting radionuclide ventriculography was performed at 24 hours and repeated with exercise on day 30. There were no differences in global ejection fraction (EF) between the 2 groups during acute contrast ventriculography. However, by 24 hours, the EF had deteriorated in the rescue group (40 ± 17 vs 49 ± 11% in the lysis group, p ≤0.05). No improvement occurred in either group on day 7. By day 30, an improvement in resting radionuclide EF 5.9 ± 1.9% occurred in rescue patients and the difference between rescue and lysis groups was no longer significant (46 ± 14 vs 50 ± 11%, p = 0.12). A normal (≥5%) increase in EF with exercise occurred in 64%, with either normal or exercise-enhanced regional wall motion present in 67% of patients. A significant increase in EF occurred within the rescue group, from 46 ± 14% at rest to 50 ± 15% at peak exercise (p ≤0.0005). The EF increased with exercise from 50 ± 11 to 58 ± 15% in the lysis group (p ≤0.0001). With equivalent workloads, the lysis group had a significantly greater EF response to exercise compared with rescue patients (7.5 ± 7.5 vs 3.8 ± 4.7%, p <0.02). Despite successful acute recanalization in all patients, differences in ventricular function were apparent including: (1) greater preservation of ventricular function at 24 hours in patients with successful thrombolysis; (2) late improvement in resting EF with rescue PTCA; and (3) greater contractile reserve in patients with successful thrombolytic reperfusion. These data suggest that full recovery of myocardium may not be accurately assessed with a predischarge resting ventriculogram. Aggressive revascularization with thrombolysis or PTCA (or both) resulted in a normal EF response to exercise after AMI. Although successful thrombolytic reperfusion appears to be the most beneficial regimen, rescue PTCA may also be a viable strategy resulting in late improvement in EF and maintenance of EF response to exercise.

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Timely reperfusion of an occluded coronary artery may limit infarction size and result in substantial recovery in ventricular function.[1,2] Conversely, patients who fail to achieve thrombolytic reperfusion may show minimal improvement in wall motion despite the fallback use of percutaneous transluminal coronary angioplasty (PTCA) in an attempt to salvage the myocardium.[3] This lack of functional recovery may in part be due to prolonged "stunning" of the myocardium.[4] Delayed measurement of left ventricular function and the ejection fraction response to exercise may better assess the beneficial effects of reperfusion. This study was undertaken to compare how 2 methods of reperfusion, either successful thrombolytic reperfusion or recanalization by PTCA after failed thrombolysis, affect ventricular function and ejection fraction response to exercise.

METHODS

Inclusion criteria: Between February 1986 and March 1987, 170 patients with acute myocardial infarction (AMI) were enrolled in reperfusion trials at the University of Michigan as part of the multicenter Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) studies.[5,6] Patients receiving thrombolytic therapy had chest pain unresponsive to nitroglycerin lasting >20 minutes but <6 hours before the start of therapy. Additional inclusion criteria for this substudy were achievement of successful acute reperfusion and exercise radionuclide ventriculography performed at day 30. Of the 170 patients considered, 7 died and 2 experi-

enced cerebrovascular accidents and were unable to exercise. Seven additional patients with unsuccessful acute reperfusion were excluded. Because coronary artery bypass grafting may affect wall motion, 28 patients undergoing bypass grafting before day 30 were excluded. Thirty-six patients did not undergo exercise radionuclide ventriculography due to normal coronary arteries in 3, physician preference for exercise thallium rather than gated blood pool scan in 22 and patient refusal in 11. Thus, 90 patients comprised the study group.

Interventional regimen: The treatment algorithm is shown in Figure 1. All patients received intravenous thrombolytic therapy within 6 hours of symptom onset. The thrombolytic regimen consisted of intravenous tissue plasminogen activator in 79 patients (150 mg over 6 hours). The remaining 21 patients received combined therapy with tissue plasminogen activator (25 mg to 1.0 mg/kg) and urokinase (500,000 to 2,000,000 U) administered intravenously. Emergent coronary arteriography and left ventriculography were performed. Infarct vessel patency was determined 90 minutes after initiating thrombolytic therapy according to the Thrombolysis In Myocardial Infarction study classification.[7] Infarct vessels with grade 0 to 1 flow were considered to be occluded and underwent successful mechanical reperfusion with angioplasty. This subset was referred to as the "rescue" angioplasty group. Patients with grade 2 to 3 flow at the 90-minute angiogram were considered to have successful thrombolytic reperfusion and were referred to as the "lysis" group. Adjunctive PTCA was performed in 62% of the lysis patients, either during the acute catheterization (29 patients) or at the time of follow-up angiography (10 patients). All patients continued receiving intravenous heparin for 4 to 7 days as well as aspirin (325 mg/day) and diltiazem (120 to 240 mg/day). Follow-up cardiac catheterization was performed on day 7 in 87 of 90 patients (97%).

Catheterization analysis: The percent diameter stenosis of the infarct artery was determined at the completion of the acute intervention and at follow-up angiography on day 7. End-diastolic frames from the coronary arteriogram demonstrating the most severe stenosis were digitized and stored in an ADAC computer (DPS 4100C). Arteriograms were quantitated by a previously validated automated edge-detection computer algorithm enabling precise determination of percent diameter stenosis.[8] When it was not possible to perform computer quantitation because of inadequate film quality or vessel overlap, the infarct vessel stenosis was determined by calipers.

Contrast left ventriculography was performed in the 30° right anterior oblique projection. End-diastolic and end-systolic outlines were traced by a single technician, blinded to patient identity, therapy and time of study. Technically inadequate ventriculograms due to ventricular tachycardia or poor opacification were excluded. This resulted in exclusion of 13 acute and 14 follow-up ventriculograms. Paired acute and day 7 contrast ventriculograms were suitable for analysis in 70 patients. Ejection fraction was calculated by the area-length

method and regional wall motion by the centerline chord method.[9]

Rest and exercise radionuclide ventriculography: All patients underwent exercise testing with radionuclide ventriculography on day 30. Cardiac medications were not discontinued for the study. All patients were taking aspirin and diltiazem and 8% of patients were receiving β-blocker therapy. Exercise was performed using a supine bicycle ergometer. After a 2-minute "warm-up" period at a workload of 25 watts, staged exercise testing was performed with a 25-watt increase in workload every 4 minutes. Exercise was continued until limited by symptoms of fatigue, chest pain or ventricular arrhythmias. Exercise electrocardiograms were considered to be positive if a horizontal or downsloping ST-segment depression ≥1 mm occurred. The pressure rate product at peak exercise was determined by heart rate × systolic blood pressure/100.

Portable resting radionuclide ventriculograms were obtained in 48 patients within 24 hours of completion of the acute intervention. The remaining 42 patients did not have a study within 24 hours due to scheduling difficulties. On day 30, radionuclide ventriculographies were obtained both at rest and at peak exercise in all 90 patients. Three views (10° right anterior oblique, 45° left anterior oblique and left lateral) were acquired at rest. The 45° left anterior oblique view was repeated at symptom-limiting maximal exertion. At least 1 minute was allowed to elapse for stabilization of heart rate prior to acquisition of exercise gated images. The right anterior oblique and left lateral views were obtained immediately after peak exercise. Data were acquired on a General Electric standard field-of-view gamma camera and analysis performed on a Siemens MicroDelta minicomputer system. In a standard fashion, semiauto-

ACUTE MI

IV THROMBOLYTIC RX

CORONARY ANGIOGRAPHY

TIMI 0-1   **TIMI 2-3**
                      (LYSIS)
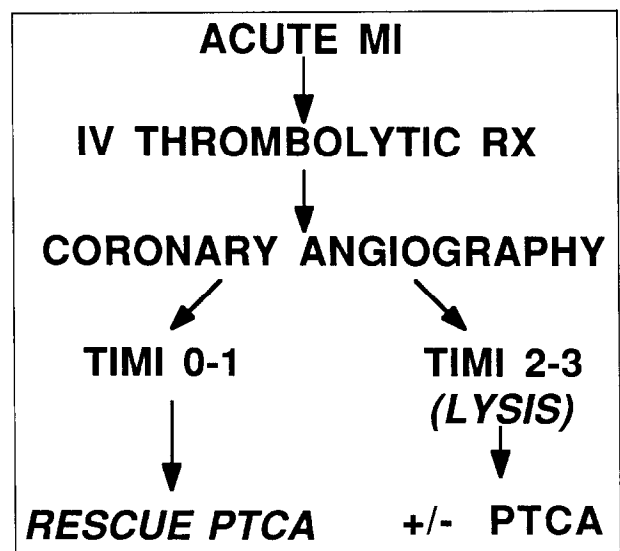
RESCUE PTCA   **+/- PTCA**

FIGURE 1. The treatment algorithm. Ninety patients were treated with thrombolytic agents within 6 hours from onset of AMI. Based upon flow in the infarct artery, patients were divided into 2 groups: lysis and rescue PTCA. All patients had successful acute recanalization.

TABLE I Baseline Characteristics

	Lysis (n = 63)	Rescue PTCA (n = 27)
Age (yrs)	54 ± 10	55 ± 10
Men (%)	84	85
Infarct coronary artery		
LAD (%)	42	44
LC (%)	14	8
Right (%)	44	48
No narrowed coronary arteries		
1 (%)	61	54
2 (%)	32	46
3 (%)	7	0
Thrombolytic regimen		
tPA (%)	76	74
tPA + urokinase (%)	24	26

No significant (p <0.05) differences were detected between the 2 groups.
LAD = left anterior descending; LC = left circumflex; tPA = tissue plasminogen activator.

TABLE II Angiographic Data

	Lysis	Rescue PTCA	p Value
Time to reperfusion (hrs)	4.1 ± 1.5	4.5 ± 1.2	0.12
Acute PTCA (%)	46	100	NA
Stenosis after acute intervention (%)	50 ± 23	40 ± 22	0.05
Reocclusion (%)	10	34	0.005
Delayed PTCA (%)	16	11	NS
Follow-up stenosis (%)*	39 ± 23	44 ± 30	NS

* Includes reocclusion patients as 100%, measured after delayed PTCA, if performed.
NS = not significant; Time to reperfusion = time from chest pain onset to angiographically documented infarct vessel patency.

mated, background-corrected time-activity curves were generated from the left anterior oblique views for determination of ejection fraction (normal resting ejection fraction ≥50%). Wall motion was evaluated by viewing the cardiac cycle in a continuous loop movie format with rest and peak exercise studies displayed side by side. From the 3 views, 5 anatomic sites were evaluated: anterior, septal, inferior, lateral and apical. Wall motion was qualitatively assessed by consensus agreement among 4 experienced observers blinded to the results of coronary interventions. Wall motion for each region was graded on a 5 point scale as follows: 3 = normal; 2 = mild hypokinesis; 1 = severe hypokinesis; 0 = akinesis and −1 = dyskinesis. Exercise-induced wall motion changes were considered to have occurred if the score between resting and exercise studies differed by at least 1 grade.

Statistical evaluation: Data are presented as mean ± 1 standard deviation unless otherwise stipulated. Student t and Fisher exact tests were used for statistical analysis where appropriate. Differences were considered significant at the p ≤0.05 level.

RESULTS

Baseline characteristics of the 2 subgroups are listed in Table I. Sixty-three patients with a patent infarct artery at 90 minutes comprise the lysis group. Twenty-seven patients with failed thrombolysis achieved successful recanalization with PTCA and comprise the res-

cue group. There were no significant differences in age, sex, location of the infarct artery, presence of multivessel disease or thrombolytic regimen used between the 2 groups. Angiographic data for the 2 groups are listed in Table II. As expected, it required a somewhat longer time (4.5 hours) to achieve reperfusion in patients who failed thrombolysis and required rescue PTCA to restore flow. By definition, arterial patency occurred before the 90-minute angiogram in the lysis group. The 4.1 hours listed, however, is the time from chest pain onset to the 90-minute coronary arteriogram. By definition, acute PTCA was required for restoration of flow in all patients in the rescue group. Despite having a patent infarct artery, 29 of 63 patients (46%) in the lysis group also received acute PTCA. The residual stenosis at the completion of the acute intervention was less in the rescue group (40 ± 22 vs 50 ± 23%, p <0.05), reflecting the effect of mechanical revascularization. By day 7 catheterization, 9 of 27 patients (34%) requiring rescue PTCA had reoccluded, compared with only 6 patients (10%) in the lysis group (p <0.005). Delayed PTCA was performed in 16% of lysis and 11% of rescue patients. Due to the high incidence of reocclusion in the rescue group and the addition of delayed PTCA, the mean infarct vessel percent stenosis at the completion of follow-up angiography was no longer different between the 2 groups. Although a greater number of patients were discharged with a critical (≥70%) stenosis in the rescue group (5 of 27, 19%) than in the lysis group (6 of 63, 10%), this was not statistically significant (p = 0.5).

Resting ventricular function: There were no significant differences in global ventricular function between rescue and lysis groups during acute contrast ventriculography (51 ± 9 vs 54 ± 12%, respectively, p = 0.2). Within the group of 48 patients who had paired acute and 24-hour ventricular function studies, a greater reduction in ejection fraction at 24 hours was present in the rescue than in the lysis group (−9.7 ± 13.7 vs −3.7 ± 10.1%, respectively, p = 0.11). Thus, at the time of 24-hour radionuclide ventriculography, the ejection fraction was now worse in the rescue than in the lysis group (40 ± 17 vs 49 ± 11%, respectively, p ≤0.05). These changes at 24 hours could not be accounted for
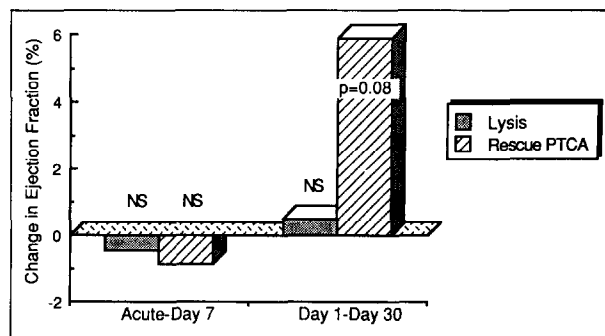
FIGURE 2. Serial changes in ejection fraction from paired contrast ventriculograms obtained acutely and on day 7, and paired radionuclide ventriculograms between day 1 and day 30. A trend for late improvement in ejection fraction occurred in the rescue PTCA group.

by differences in demographic, angiographic or acute ventricular function in patients who did not have a 24-hour study. At day 7 follow-up, the contrast ejection fraction still tended to be worse in the rescue group (49 ± 11 vs 54 ± 12%, p = 0.09). However, by day 30, these differences were no longer significant (46 ± 14 vs 50 ± 11%, respectively, p = 0.2). As shown in Figure 2, there was no significant improvement in paired acute and day 7 contrast ejection fraction in either group. Furthermore, the lysis population failed to demonstrate a significant improvement between paired day 1 and day 30 radionuclide ventriculography. Conversely, the rescue group showed an increase in ejection fraction of 5.9 ± 1.9% between day 1 and day 30 studies (p = 0.08). Regional wall motion of the infarct zone improved from acute to day 7 studies in both lysis +0.55 standard deviation (p <0.005) and rescue groups +0.53 standard deviation (p <0.005). However, an improvement of ≥1 standard deviation in regional wall motion occurred in only 27% of patients (31% of lysis and 19% of rescue PTCA patients).

Exercise ventricular function: Individual paired data for rest and exercise ejection fraction at day 30 are plotted in Figure 3. Both groups demonstrated an intact contractile reserve to exercise. Within the lysis group, the mean resting ejection fraction increased from 50 ± 11 to 58 ± 15% at peak exercise (p <0.0001). The rescue PTCA group also demonstrated an increase from 46 ± 14 at rest to 50 ± 11% with exercise (p <0.0005). The pressure rate product measured at peak exercise was identical in both lysis (202 ± 60) and rescue groups (202 ± 42). Despite identical workloads, lysis patients had a significantly greater increase in ejection fraction in response to exercise (7.5 ± 7.5%) compared with 3.8 ± 4.7% in the rescue group (p <0.05) (Figure 4). Conventionally, contractile reserve is described as normal (≥5% increase), flat or affected by an abnormal reduction (>5% decrease) in ejection fraction with exercise. Overall, 64% of patients had a normal ejection fraction response to exercise. An increase in ejection fraction of at least 5% was seen in 70% of the lysis group compared with 48% of rescue patients (p <0.05) (Figure 5). A flat ejection fraction response to exercise occurred in 23% of

lysis and 52% of rescue patients. With the aggressive revascularization strategy adopted, nobody in the rescue group and only 4 patients (7%) in the lysis group experienced a significant reduction in ejection fraction. Ischemic electrocardiographic changes were present in only 2 patients.

By day 30, 67% of all patients demonstrated either normal or exercise-enhanced wall motion of the infarct zone (≥1 grade). This postexercise potentiation of infarcted myocardium occurred in 73% of lysis patients and 54% of rescue patients (difference not significant). Only 3 patients in each group experienced deterioration in infarct zone wall motion with exercise.

DISCUSSION

Resting ventricular function: Unsuccessful thrombolysis may be a poor prognostic marker[10,11] and, despite rescue PTCA, reocclusion rates remain high.[12] Our data confirm the high (34%) rate of reocclusion in those vessels that fail tissue plasminogen activator-mediated thrombolysis but are successfully opened with PTCA. Of the 9 vessels that reoccluded after rescue PTCA, 7 were right coronary arteries. Interestingly, because reocclusion occurred primarily in the right coronary artery, excluding these patients made no difference in the reported left ventricular functional parameters.

Although there were no differences in acute ejection fraction between the 2 groups, arterial patency at the 90-minute angiogram was associated with greater preservation of ventricular function at 24 hours. Because acute ventriculograms were obtained with radiographic contrast and 24-hour studies were acquired using radio-
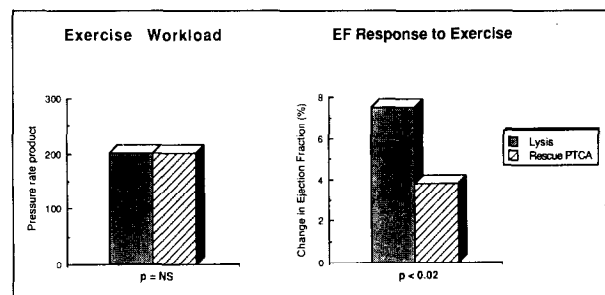
FIGURE 4. Despite identical workloads, the ejection fraction increased more with exercise in the lysis group (7.5 ± 7.5%) than in the rescue group (3.8 ± 4.7%).
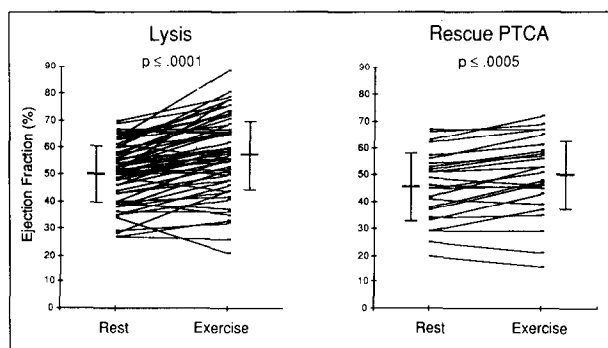
FIGURE 3. Both groups demonstrated a significant increase in ejection fraction with exercise, from 50 ± 11 to 58 ± 15% in lysis patients and from 46 ± 14 to 50 ± 15% in the rescue PTCA group.
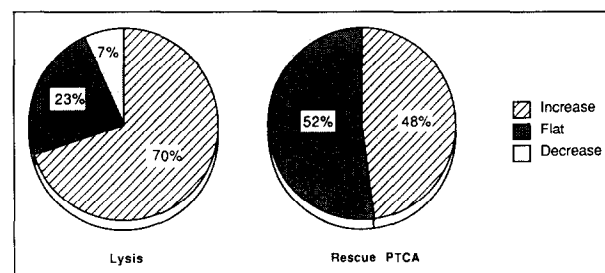
FIGURE 5. A greater proportion of patients in the lysis group had an increase in ejection fraction (≥5%) with exercise. Only 4 patients experienced a ≥5% decrease in exercise ejection fraction.

nuclides, obvious technical differences may have contributed to these changes. A change of 3.7% in ejection fraction between acute and 24-hour studies in the lysis group may be due to differences in techniques alone. Deterioration of 9.7% in the rescue PTCA group is probably greater than what can be expected from the variability in techniques. Several mechanisms may contribute to these differences in ejection fraction. Because pretreatment angiography was not performed, the lysis group included those with spontaneous reperfusion, known to have greater preservation of ventricular function.[13–16] Time to reperfusion also affects myocardial salvage.[1,17] Angiographically documented time to reperfusion tended to be shorter in the lysis group (4.1 ± 1.5 vs 4.5 ± 1.2 hours, p = 0.12). Moreover, by definition, infarct arteries in the lysis group opened before the 90-minute angiogram. If accurate times to reperfusion were available, a difference favoring the lysis group would likely have been apparent.

During acute catheterization, contrast ventriculography was usually performed immediately after obtaining arterial access. During the additional time required to restore flow by rescue PTCA, further deterioration in ventricular function may have occurred resulting in a lower ejection fraction at 24 hours. Other investigators have noted an early regression of compensatory hyperkinesis of the noninfarct zone and a resultant decrease in ejection fraction.[18] Because only a left anterior oblique projection was acquired during 24-hour radionuclide ventriculography, the noninfarct zone function could not be accurately assessed. Contrast ventriculography on day 7 revealed regression of hyperkinesis (−0.58 ± 0.84 standard deviation) in patients whose ejection fraction deteriorated. Despite the trend for a lower ejection fraction in the rescue group at 24 hours and on day 7, by day 30 the differences were no longer significant. Thus, patients who are resistant to thrombolysis and undergo rescue PTCA may have late recovery of ventricular function due to "stunned" myocardium. Late recovery of ventricular function and preservation of ejection fraction response to exercise supports the clinical benefit of rescue angioplasty during acute MI.

Exercise ventricular function: The ejection fraction frequently fails to increase with exercise after myocardial infarction[19–22] even in the absence of multivessel disease.[23] It is possible that the presence of substantial regional scarring after AMI may result in loss of functional reserve. Although AMI patients not receiving thrombolytic therapy have been well studied, little data exist regarding the effect of successful coronary reperfusion on contractile reserve. Satler et al[24] demonstrated a greater increase in isoproterenol stress ejection fraction in patients with patent infarct vessels. Guerci et al[25] recently reported an increase in exercise ejection fraction in patients treated with combined thrombolytic therapy and angioplasty but no increase in the thrombolysis-only group. In our study, successful acute recanalization was achieved in all patients, yet those with a patent infarct artery after thrombolytic therapy (lysis) demonstrated a greater contractile reserve. The mechanism

may again relate to greater reduction in infarct size due to both earlier reperfusion and incomplete occlusion in the lysis group.

Previous studies have demonstrated an increase in both spontaneous and exercise-induced ischemia after thrombolytic therapy.[26–30] With the aggressive revascularization strategy that we adopted, 64% of patients maintained a normal (≥5%) increase in ejection fraction with exercise. Moreover, only 5 of 90 patients (4%) experienced a significant decrease in ejection fraction with exercise. In contrast to preinterventional trials, the exercise response in these patients who underwent successful recanalization was favorable. The ability to maintain a normal contractile reserve may indicate prognostic and functional benefits.

Improvement in regional wall motion after exercise, nitroglycerin or postextrasystolic potentiation is considered to indicate myocardial viability.[31] Our data demonstrated not only a normal ejection fraction response to exercise in most patients, but also normal or exercise-enhanced wall motion in 67%. Conversely, only 27% of patients demonstrated improved regional wall motion on day 7 resting studies. Our data, as well as that of others, indicate that early measures of resting ventricular function may underestimate the beneficial effects of reperfusion.[18–32]

Limitations: The results of this study must be interpreted with caution. The patients we studied comprise a low-risk group, i.e., only those with successful immediate recanalization, survival to day 30, ability to exercise and no coronary artery bypass grafting before follow-up studies. Furthermore, only 48 of 90 patients underwent repeat ejection fraction analysis within 24 hours. Interpretation of changes in ejection fraction at 24 hours may not be accurate for the entire population. Because rest and exercise radionuclide ventriculography were not obtained until day 30, an intervening coronary event such as restenosis or reocclusion may have occurred. Performing coronary arteriography on day 30 may provide better correlation of infarct vessel status and left ventricular functional parameters.

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