Significance of a Negative Exercise Thallium Test in the Presence of a Critical Residual Stenosis After Thrombolysis for Acute Myocardial Infarction

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Background. After thrombolytic therapy for acute myocardial infarction, increasing emphasis is placed on early submaximal exercise testing, with further intervention advocated only for demonstrable ischemia. Although significant residual coronary artery lesions after successful thrombolysis are common, many patients paradoxically have no corresponding provokable ischemia.

Methods and Results. The relation between significant postthrombolytic residual coronary artery disease and a negative early, submaximal exercise thallium-201 tomogram was studied among 101 consecutive patients with uncomplicated myocardial infarction and at least 70% residual stenosis of the infarct artery. A negative test occurred in 49 (48.5%) patients with a mean 88% residual infarct artery stenosis. Further characteristics of the group were as follows: mean time to treatment was 3.1 hours; mean age was 54±10 years; 80% were male; 47% had anterior infarction; 39% had multivessel disease; mean left ventricular ejection fraction was 53±14%; and mean peak creatine kinase level was 3,820±3,123 IU/ml. A similar group of 52 (51.5%) patients, treated within 3.3 hours from symptom onset, with a mean postthrombolysis stenosis of 90%, had a positive exercise test. Characteristics of this group were as follows: age was 58±10 years; 92% were male; 56% had anterior infarction; 40% had multivessel disease; and mean left ventricular ejection fraction was 54±15%. The peak creatine kinase level associated with the infarction, however, was lower: 2,605±1,805 IU/ml (p=0.04). There was no difference in performance at exercise testing with respect to peak systolic pressure, peak heart rate, or time tolerated on the treadmill between the two groups. By multivariate logistic regression, only peak creatine kinase level predicted a negative stress result in the presence of a significant residual stenosis (odds ratio, 4.2; 95% confidence interval, 1.1–16.3).

Conclusions. The explanation for the relatively frequent finding of a negative early stress 201TI tomogram after apparently successful reperfusion appears to be more extensive myocardial necrosis and not delay in therapy or inadequate exercise performance. (Circulation 1991;83:1278–1286)

The results of several large clinical trials have established an unequivocal role for early intravenous thrombolytic therapy for acute myocardial infarction for the reduction of mortality and the improvement of left ventricular function.1–5 Despite the overriding benefits of thrombolytic inter-

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vention, there remain several major shortcomings of this strategy, including the limited 50–75% early (60–90-minute) coronary thrombolytic efficacy of presently available agents and the 5–15% rate of early reocclusion.6,7 In addition, after successful thrombolysis, a significant residual stenosis of the recanalized infarct vessel persists in more than 70% of patients.8–10 The clinical significance of the post-thrombolysis residual stenosis is uncertain, and the optimal, noninvasive functional assessment of this lesion remains undefined.

The necessity, optimal timing, and clinical setting for additional mechanical intervention by either bypass surgery or percutaneous transluminal coronary angioplasty (PTCA) remain the focus of intense
clinical investigation. Previous studies demonstrated no further improvement in predischarge left ventricu-
lar ejection fraction after empiric dilatation of the 
residual stenosis during the immediate postthromb-
olysis period compared with a deferred PTCA strat-
egy 1–10 days later.11–13 Furthermore, no significant 
advantage in mortality or reinfarction rates has been 
demonstrated when an empiric, deferred PTCA strategy is used compared with an elective approach 
only for patients with recurrent angina or subse-
quent, abnormal stress tests.14

Increasing emphasis is now placed on the functional 
assessment of coronary artery flow beyond the resid-
ual stenosis after thrombolytic therapy, with addi-
tional mechanical intervention advocated only in the 
presence of spontaneous or provokable ischemia. Para-
doxically, many patients have no inducible ischemia 
during early exercise testing despite the established 
frequency of a significant, postthrombolysis residual 
stenosis.14 To study the clinical relevance of an angio-
graphically severe infarct-related coronary artery ste-
nosis after interventional therapy, we analyzed 16 
clinical and angiographic variables among 101 consecu-
tive patients treated for uncomplicated myocardial 
infarction, and we determined the influence of each 
variable on a subsequent negative stress test result. 
We analyzed the significant characteristics of the 
cohort of patients with significant residual infarct 
artery stenoses who may be routinely excluded from 
invasive postthrombolysis evaluation and further re-
vascularization in favor of conservative management 
because of an absence of provokable ischemia.

Methods

Patient Population

Clinical data were gathered from 126 consecutive 
patients treated at the University of Michigan Med-
ical Center for uncomplicated myocardial infarction 
who underwent early, submaximal exercise single-
photon emission computed tomographic (SPECT) 
thallium-201 scintigraphy on the third or fourth 
hospital day.15–17 Only patients who were admitted 
within 6 hours of the onset of acute myocardial 
infarction, with symptoms persisting for more than 20 
minutes, and with electrocardiographic and enzym-
atic evidence of myocardial injury were studied. 
Creatine kinase (CK) elevation, with a myocardial 
band fraction more than 3% of the total measured 
enzyme, was a requirement for inclusion in the 
statistical analysis. ST segment elevation of 1.0 mm 
or more in at least two contiguous leads without prior 
Q wave infarction in the same myocardial territory 
was also necessary to establish satisfactorily the 
diagnosis of myocardial infarction. Patients whose clin-
cial course was complicated by persistent ventricular 
arrrhythmias, unstable angina (defined as spontane-
ous ischemia symptoms with associated electrocar-
diographic ST segment changes while at bed rest), 
reinfarction, and poorly controlled noncardiac con-
ditions were necessarily not eligible for early exercise 
treadmill testing.

Interventional Therapy

All patients received thrombolytic intervention with tissue-type plasminogen activator (t-PA) with 
varying dose regimens11,18 and underwent emergency 
cardiac catheterization as rapidly as possible. Intra-
venous heparin therapy was initiated in all patients, 
with an initial intravenous bolus of 5,000 units ad-
ministered after vascular access was achieved in the 
cardiac catheterization laboratory. Patients greater 
than 75 years of age and those with a recent history of 
cerebral vascular disease, uncontrolled hypertension, 
surgery, trauma (including resuscitative chest compres-
sions for more than 10 minutes), or bleeding 
were excluded from thrombolytic treatment.

Cardiac catheterization was performed as close as 
possible to 90 minutes after initiation of thrombolytic 
therapy, and only patients with more than 70% 
residual narrowing by caliper measurement of the 
infarct artery after thrombolytic therapy, including 
those patients with failed thrombolysis, were selected 
for analysis. Rescue PTCA was performed in 48 
patients at the discretion of the attending cardiolo-
gist in cases of thrombolytic failure at the time of 
acute catheterization, whereas patients with patent 
infarct arteries were managed conservatively if al-
lowed by their clinical status. There were 11 patients 
from this subset who underwent uncomplicated im-
mediate PTCA of a critical residual stenosis at the 
time of the initial angiographic assessment. No pa-

tient was returned to the catheterization laboratory 
before the predischarge exercise test. Thus, all pa-

tients studied had a patent infarct vessel demonstrated 
by angiography before leaving the catheterization 
labory, and no clinically apparent recurrent ischemia 
developed before the early stress test was performed.

Exercise Testing

All patients underwent submaximal treadmill exer-
cise testing on the third or fourth hospital day, with 
12-lead electrocardiographic monitoring and SPECT 
201TI scintigraphy. When the day of the stress test 
ocurred on a weekend or holiday, a designated on-call 
team was available to perform the study. A submaximal 
protocol was used, with termination of stress at a target 
peak heart rate of 140 beats/min in the absence of 
clinical or electrocardiographic evidence of ischemia. 
One minute before exercise termination, 3 mCi 201TI 
was administered intravenously, and SPECT imaging 
was performed immediately and again 3–4 hours later. 
The electrocardiographic diagnosis of stress-induced 
ischemia required 2.0 mm of downsloping ST segment 
depression in two or more contiguous leads.

The SPECT studies were interpreted by one or 
more licensed nuclear medicine staff physicians who 
were unaware of the patient's clinical history. Studies 
revealing only fixed perfusion defects were consid-
ered negative as were those studies that resulted in fixed defects with small areas of peri-infarction redistribution in the absence of clinical or electrocardiographic evidence of myocardial ischemia during the stress phase of the test. A significant completely or partially redistributing $^{201}$TI defect in any myocardial region or a predominantly fixed defect with peri-infarction redistribution in association with an abnormal exercise electrocardiogram were each considered positive results that may result in invasive assessment of coronary anatomy in a typical, conservatively managed postthrombolysis patient.

Statistical Analysis

Data were entered from a standardized form to the University of Michigan Terminal System (model AN319), and univariate analysis and multivariate logistic regression were performed by a biostatistician, using BMDP statistical software (BMDP Statistical Software, Inc., Los Angeles). Data are expressed as mean±SD. Univariate evaluation was accomplished with the $\chi^2$ test or Fisher’s exact test for discrete elements and by $t$ test analysis for continuous variables.

Logistic Regression Variables

The independent correlates of a negative stress test result were determined among all variables by use of multivariate stepwise logistic regression analysis with an $\alpha$ value to remove variables of 0.15. Only probability values of 0.05 or less were considered significant. In addition to demographic data, including patient age and sex, 14 additional variables were analyzed for their influence on a negative stress test result. The time from symptom onset to initial thrombolytic therapy was included to evaluate the influence of late treatment at the extremes of the 4–6-hour inclusion limit. The location of the infarction, the infarct-related artery, and the presence of multivessel disease or history of prior myocardial infarction were analyzed. The percent residual stenosis of the reperfused infarct artery after thrombolytic therapy alone, the impact of PTCA, and the residual narrowing after dilatation in patients undergoing subsequent mechanical revascularization were included in the analysis. Variables correlating with the degree of myocardial necrosis, including peak CK level, left ventricular ejection fraction by contrast ventriculography, and the presence of congestive heart failure by chest roentgenogram and physical examination for pulmonary rales or a third heart sound, were recorded. Last, to evaluate the influence of stress test performance on a negative study result, we noted peak heart rate, systolic blood pressure during exercise, and the duration of the treadmill stress.

Results

Patient Population

Among the 126 patients with uncomplicated myocardial infarction enrolled in the study, 25 had no significant residual narrowing of the infarct vessel at early catheterization. These patients (with residual narrowings <70%) were excluded from analysis. Of 101 (80% of 126) patients found to have a residual infarct coronary artery lesion of 70% or more, 52 patients (51%) were found to have provokable ischemia by early, submaximal exercise SPECT $^{201}$TI testing. Of note, nearly half the patients (49 of 101 patients) lacked inducible ischemia despite the documented presence of a tight residual coronary artery lesion at early angiography and aggressive management (Table 1). Most patients who were tested displayed an abnormal resting electrocardiogram in the distribution of the infarct zone being analyzed at the time of early treadmill testing ($n$=88, 87%). Limited, exercise-induced ST segment changes among these patients were considered an unreliable indicator of ischemia, particularly in the absence of related angina. No patient from this subset was prevented from completing the submaximal stress protocol because of electrocardiographic changes alone. There were four patients with exercise-provoked anginal symptoms whose performance was limited because of associated ST segment changes. All four of these patients displayed subsequent ischemia with $^{201}$TI scintigraphy. Notably, only two of the 13 patients with normal resting electrocardiograms had stress-related ST depression interpreted as ischemia, and both patients proved to have significant redistributing defects in the infarct region. Thus, no patient displayed clinical ischemia during stress testing without subsequently associated $^{201}$TI redistribution. Q waves may develop early or several days after acute myocardial infarction; the distinction between Q wave and non-Q wave infarction after thrombolysis was not considered universally reliable and was not included in the analysis.

A similar number of patients from the negative and positive stress test groups underwent immediate or rescue PTCA at the time of initial invasive assessment, with successful reduction of the residual stenosis in 86% of patients. Of note, only patients with a residual stenosis of 70% or more were included in the analysis, whether or not angioplasty was performed. Excluding the effect of PTCA, the results proved similar among the 42 patients treated with thrombolytic therapy alone; there was no significant influence on stress test outcome by PTCA (Table 2). The demographic characteristics were comparable between the two stress test result groups; no significant differences occurred in sex (92% versus 80% male) or mean age (58 versus 54 years) for those patients with a positive compared with a negative stress test result, respectively.

Univariate Analysis

There was little difference between the negative and positive stress test groups with respect to the time delay before treatment initiation, the presence of multivessel disease, or a history of prior myocardial infarction, either non-Q wave or Q wave infarction in another vascular territory. Neither the infarct-related
TABLE 1. Clinical Data for All Patients With 70% or Greater Residual Stenosis

<table>
<thead>
<tr>
<th></th>
<th>Positive ETT</th>
<th>Negative ETT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>52</td>
<td>49</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58±10.4</td>
<td>54±10.0</td>
</tr>
<tr>
<td>Male sex (n)</td>
<td>48 (92)</td>
<td>39 (80)</td>
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<tr>
<td>Time to t-PA therapy (min)</td>
<td>199±89</td>
<td>186±132</td>
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<tr>
<td>Prior myocardial infarction (n)</td>
<td>8 (15)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Infarct location (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior/lateral</td>
<td>29 (56)</td>
<td>23 (47)</td>
</tr>
<tr>
<td>Inferior/posterior</td>
<td>23 (44)</td>
<td>26 (53)</td>
</tr>
<tr>
<td>Infarct artery (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>29 (56)</td>
<td>23 (47)</td>
</tr>
<tr>
<td>RCA</td>
<td>18 (35)</td>
<td>21 (43)</td>
</tr>
<tr>
<td>LCx</td>
<td>5 (10)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Bypass Graft</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Peak CK level (IU/ml)</td>
<td>2,605±1,805</td>
<td>3,820±3,123*</td>
</tr>
<tr>
<td>Multivessel disease (n)</td>
<td>21 (40)</td>
<td>19 (39)</td>
</tr>
<tr>
<td>LVEF by ventriculography (%)</td>
<td>54±15</td>
<td>53±14</td>
</tr>
<tr>
<td>Residual stenosis of infarct vessel (%)</td>
<td>90±9</td>
<td>88±9</td>
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<tr>
<td>Heart failure (Killip's class II or III) (n)</td>
<td>33 (63)</td>
<td>28 (57)</td>
</tr>
<tr>
<td>PTCA performed (n)</td>
<td>29 (56)</td>
<td>30 (62)</td>
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<tr>
<td>Post-PTCA residual stenosis (%)</td>
<td>61±33</td>
<td>55±29</td>
</tr>
<tr>
<td>Exercise thallium study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak heart rate (beats/min)</td>
<td>123±18</td>
<td>129±19</td>
</tr>
<tr>
<td>Peak systolic pressure (mm Hg)</td>
<td>154±33</td>
<td>150±34</td>
</tr>
<tr>
<td>Time stressed (min)</td>
<td>6±3</td>
<td>8±12</td>
</tr>
</tbody>
</table>

Values are mean±SD where appropriate; values in parentheses are percentage.

ETT, exercise thallium-201 test; t-PA, tissue-type plasminogen activator; LAD, left anterior descending coronary artery; RCA, right coronary artery; LCx, left circumflex coronary artery; CK, creatine kinase; LVEF, left ventricular ejection fraction; PTCA, percutaneous transluminal coronary angioplasty.

*p=0.04; with the retrospective analysis and Bonferroni correction, this difference should be considered marginally significant at the 0.05 level.

vessel nor the location of the infarction served to stratify the patients, except among those not undergoing PTCA. In this subset of patients, more residual ischemia was noted among those with an uncomplicated anterior or lateral myocardial infarction (70%) than among those admitted with an inferior or posterior infarction (37%, p=0.03) (Table 2).

There proved to be no significant relation between the qualitative assessment of the degree of residual narrowing by routine angiography, with or without PTCA, and the incidence of a negative stress test result. An average 90% residual infarct artery stenosis was present among those patients with a positive result compared with an 88% stenosis among those with a negative result. Although patients were selected for analysis on the basis of a postthrombolysis residual stenosis of 70% or more, it is important to note that most patients (73%) actually had a residual infarct artery lesion of 90% or more. This is reflected in Table 1 by the narrow range of standard deviation associated with the reported mean residual stenosis of the infarct vessel.

Although there were no essential differences in the incidence of clinically recognized heart failure or resting left ventricular ejection fraction between the two patient subsets, a greater extent of myocardial necrosis was evident within the negative stress test result group. There was a substantial difference in peak CK levels, with a mean 3,820 IU/ml peak for patients in the negative outcome group and a mean 2,605 IU/ml for patients in the positive outcome group (p=0.04). Importantly, this proved to be the only single variable that significantly differed between the two groups categorized by stress test results.

The stress test results did not differ by variable physical performance. Patients from both groups attained a similar peak heart rate and systolic blood pressure, and performance was comparable with respect to time tolerated on the treadmill. Among patients with single-vessel disease, a significantly lower peak heart rate was attained by those patients with provokable ischemia (Table 3).

Characterization of the 21 patients with a positive stress test in the presence of multivessel disease included only two patients (9.5%) considered to have a positive study because of 301T1 redistribution distant from the infarct zone. Two patients had fixed defects in the infarct zone and had redistributing defects in another region. Among the 17 (81%) remaining
patients with multivessel disease, there was evidence of infarct zone ischemia, with 10 patients displaying at least one additional area of ischemia and seven patients displaying infarct zone ischemia only. In contrast, six patients with single-vessel disease had ischemia distant from the infarct zone only, and 14 patients with single-vessel disease with redistribution in the infarct zone had another area of ischemia distant from the infarct territory.

### Logistic Regression Model Analysis

The results of the multivariate logistic regression analysis are illustrated in Figure 1. The odds ratios and confidence intervals are depicted in graph form;

<table>
<thead>
<tr>
<th>Infarct Zonal Ischemia</th>
<th>Single-Vessel Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior/lateral</td>
<td>10</td>
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<tr>
<td>Inferior/posterior</td>
<td>7</td>
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<tr>
<td>Multivessel disease</td>
<td>6</td>
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</table>

### Table 2. Stress Test Outcome for Patients Treated With Thrombolysis Alone

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Positive ETT (n=23)</th>
<th>Negative ETT (n=19)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>57±10</td>
<td>51±10</td>
<td>0.06</td>
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<tr>
<td>Infarct location (n)</td>
<td></td>
<td></td>
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<tr>
<td>Anterior/lateral</td>
<td>16 (70)</td>
<td>7 (37)</td>
<td>0.03</td>
</tr>
<tr>
<td>Inferior/posterior</td>
<td>7 (30)</td>
<td>12 (63)</td>
<td>0.03</td>
</tr>
<tr>
<td>Multivessel disease (n)</td>
<td>6 (26)</td>
<td>5 (26)</td>
<td>0.98</td>
</tr>
<tr>
<td>Time to t-PA therapy (min)</td>
<td>175±85</td>
<td>202±173</td>
<td>0.50</td>
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<td>Peak CK level (IU/ml)</td>
<td>2,399±1,443</td>
<td>3,290±2,504</td>
<td>0.04*</td>
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<td>LVEF by ventriculography (%)</td>
<td>56±14</td>
<td>55±13</td>
<td>0.64</td>
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<td>Heart failure (Killip’s class II or III) (n)</td>
<td>12 (52)</td>
<td>9 (47)</td>
<td>0.76</td>
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<tr>
<td>Postthrombolytic stenosis (%)</td>
<td>85±15</td>
<td>82±17</td>
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### Table 3. Stress Test Outcome for Patients With Single-Vessel Disease Only

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Positive ETT (n=31)</th>
<th>Negative ETT (n=30)</th>
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<tr>
<td>Male sex</td>
<td>57±10</td>
<td>54±11</td>
<td>0.31</td>
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<tr>
<td>Prior MI</td>
<td>27 (87)</td>
<td>23 (77)</td>
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<td>Infarct artery (n)</td>
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<td>LAD</td>
<td>20 (65)</td>
<td>16 (53)</td>
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<td>RCA</td>
<td>10 (32)</td>
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<td>LCx</td>
<td>1 (3)</td>
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<tr>
<td>Time to t-PA therapy (min)</td>
<td>183±94</td>
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<td>Peak CK level (IU/ml)</td>
<td>2,396±1,891</td>
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<td>LVEF by ventriculography (%)</td>
<td>57±14</td>
<td>52±13</td>
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<td>Heart failure (Killip’s class II or III) (n)</td>
<td>15 (48)</td>
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<td>Postthrombolytic stenosis (%)</td>
<td>87±15</td>
<td>88±11</td>
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<td>PTCA performed (n)</td>
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<tr>
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<tr>
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<td>Peak heart rate (beats/min)</td>
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<td>Time stressed (min)</td>
<td>6±3</td>
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<td>0.48</td>
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Values are mean±SD where appropriate; values in parentheses are percentage. ETT, exercise thallium-201 test; MI, myocardial infarction; LAD, left anterior descending coronary artery; RCA, right coronary artery; LCx, left circumflex coronary artery; t-PA, tissue-type plasminogen activator; CK, creatine kinase; LVEF, left ventricular ejection fraction; PTCA, percutaneous transluminal coronary angioplasty.
Logistic Regression Analysis Model—Prediction of a negative stress test

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<th>1.5</th>
<th>2.0</th>
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<td>Post t-PA stenosis</td>
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<td>0.97</td>
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<td>Post PTCA stenosis</td>
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<td>0.99</td>
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<td></td>
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<td>1.02</td>
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<tr>
<td><strong>Infarct Extent</strong></td>
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<td>CK peak</td>
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<td>LVEF</td>
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<tr>
<td><strong>Stress Performance</strong></td>
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<tr>
<td>Exercise time</td>
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<tr>
<td>Peak systolic pressure</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>1.02</td>
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<tr>
<td>Peak heart rate</td>
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<tr>
<td>Stress induced angina</td>
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<td>0.94</td>
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Figure 1. Tabulation of results of the stepwise, logistic regression analysis, with odds ratios and confidence intervals. Statistical values are depicted in graph form; odds ratios (■) greater than 1.0 predict a negative stress test result, whereas values less than 1.0 correlate with a higher probability for a positive stress test result. Only variables for which the confidence interval, represented by the horizontal line, are exclusive of the value, 1.0, are significant. C.I., confidence interval; MI, myocardial infarction; t-PA, tissue-type plasminogen activator; PTCA, percutaneous transluminal coronary angioplasty; CK, creatine phosphokinase; LVEF, left ventricular ejection fraction.

Odds ratios greater than 1.0 project a greater probability for a negative stress test result, whereas those less than 1.0 are more predictive of a positive stress test response (Figure 1). Confidence intervals intersecting the value of 1.0 denote an insignificant statistical finding, whereas those exclusive of 1.0 verify the significance of the odds ratio. Only peak CK level proved to be a significant predictor of a negative stress test result. This result was consistent with the univariate analysis findings. All other variables were excluded from the stepwise logistic regression model as insignificant. By categorizing the continuous CK variable into nine discrete ranges (Figure 2), we found that patients proved to be 4.2 times as likely to have a negative SPECT 201Tl stress test if the peak CK level associated with the infarction fell into the next highest categorical range (95% confidence interval, 1.1–16.3).

Men made up 86% of patients in the study and were associated with a 2.4-fold, though insignificant, increase in the probability of a positive stress test result; this trend is likely related only to the preponderance of men admitted with myocardial infarction. Prior infarction and the presence of congestive heart failure tended to be associated more often with a positive stress test, whereas an inferior or posterior infarction and the performance of early PTCA were linked, though insignificantly, with a negative stress tests. Of note, angina

![Stress Results by CK Range](http://circ.ahajournals.org/)

Figure 2. Plot of direct relation between creatine kinase (CK) range and a negative submaximal exercise thallium-201 tomogram. Patients were assigned to one of nine categorical ranges for statistical analysis, and only peak CK level (IU/ml) proved to be a significant predictor of a negative exercise test result by logistic regression analysis. Percentages of myocardial infarction patients from each peak CK range who had a negative submaximal stress test result are plotted, demonstrating a direct relation.
reported by the patient during stress testing was significantly (3.7 times as likely) associated with a positive SPECT $^{201}$TI stress test result.

**Discussion**

Early, noninvasive assessment of infarct extent and residual coronary artery disease after thrombolytic therapy is important in deciding subsequent clinical management. This study was undertaken to define important clinical factors that predispose patients with critical postthrombolysis coronary artery stenoses to demonstrate no further ischemia on functional testing. These patients would ordinarily not be referred for further invasive study but would be managed conservatively and have an expected favorable clinical outcome.14

The observed paradox of a negative stress test in the presence of a critical postthrombolysis stenosis of the infarct artery was a frequent occurrence, noted in nearly half (49%) of the patients with 70% or more residual narrowing of the infarct artery after thrombolytic therapy. We have termed this observation a paradox because the patients had successful early reperfusion therapy with respect to infarct vessel patency and some preservation of regional wall function. Notably, despite a reduction of the mean residual infarct artery stenosis from 83±18% to 41±26% associated with successful early PTCA, the incidence of a positive stress test remained high (55%) among these patients. This observation may result from persistent abnormalities in coronary artery flow reserve,19,20 early restenosis, or a methodological problem of incorrectly diagnosing reversible ischemia.

The statistical analysis revealed only two significant predictors of subsequent stress test results. The only important variable in the prediction of a negative stress test result proved to be the peak CK level—an index of the extent of myocardial necrosis. Patients were more than four times as likely to have a negative predischarge stress test if the peak CK level associated with the infarction was included in the next higher categorical range (Figure 2). A significant predictor of a positive stress test result was the occurrence of angina symptoms during the stress phase of the test. There was nearly a threefold increase in the detection of significant residual ischemia by subsequent $^{201}$TI scintigraphy in this subset of patients.

**Comparison With Previous Studies**

A similar lack of provokable, residual ischemia after thrombolytic therapy, despite the established frequent presence of critical infarct vessel stenosis, has been evident in other trials. After those patients with overt ischemia among the 1,626 patients assigned to the conservative management group of the Thrombolysis In Myocardial Infarction (TIMI) phase 2B study were triaged to invasive evaluation, the incidence of provokable ischemia among the remaining patients without complications was only 17.7% before hospital discharge.14 By the time of the 6-week follow-up, only 19.4% of patients had demonstrable ischemia by exercise radionuclide ventriculography screening. Notably, the posttreatment coronary anatomy for this subset of patients was undefined before stress testing. Despite the observed 70–80% incidence of significant postthrombolytic infarct artery stenosis at early angiography,8–11 a substantial number of patients have a subsequent negative stress test. Unlike the present study, in which the total number of patients and follow-up is relatively limited, the results of exercise testing in the large TIMI 2 trial did not predict reinfarction.21

More extensive infarction has similarly been associated with late negative stress test results by Weiss et al,22 who studied 37 patients admitted with acute myocardial infarction. An immediate pretreatment planar $^{201}$TI image was obtained to define the total myocardial area at risk of infarction if thrombolytic therapy failed. After intravenous streptokinase treatment, a repeated image was obtained 10 days later to define the actual area of resulting myocardial necrosis. By logistic regression analysis, the most predictive variable for a positive stress planar $^{201}$TI or stress radionuclide ventriculogram was the amount of salvaged myocardium, defined as the difference between the size of the initial area “at risk” and the zone of eventual limited necrosis. Negative stress test results correlated with less salvaged myocardium; there was no correlation between the severity of residual stenosis and a positive or negative stress test result. Similarly, when imaging by multigated blood pool analysis was used by Marzoll and associates,23 a change in ejection fraction with exercise did not correlate with the severity of the infarct vessel residual stenosis after reperfusion.

**Limitations**

**Angiographic assessment.** Two issues regarding angiographic criteria in this study deserve mention. First, the stenosis was defined in the acute phase, and it is possible that infarct vessel remodeling or dissolution of thrombus occurred in the first few days after thrombolysis. In prior studies with serial angiography, this occurred in approximately 15% of patients at 7–10 days.11 Second, in this particular study, we used qualitative and caliper angiographic criteria to simulate current clinical decision making. It is acknowledged that computer-assisted assessment of the infarct vessel may have influenced the patient grouping and would be a more valid measurement of coronary artery stenosis.24

**Stress test sensitivity.** It is possible that the stress test used in the present study is not sensitive enough to detect ischemia that is actually present. With a submaximal exercise protocol and SPECT $^{201}$TI imaging to screen patients with uncomplicated infarction for residual ischemia, limited physical performance on the treadmill did not correlate with a negative stress test result. Among the subset of patients with single-vessel disease, demonstrable ischemia was associated with a significantly lower attainable peak
heart rate than those with a negative result, suggesting that the submaximal protocol was adequate.

Although sensitivity could be improved with delayed (24-hour) reimaging or less physical restriction during the test, we observed a limited 10–15% rate of conversion to a positive test on full symptom-limited SPECT 201Tl stress testing at the 6-week follow-up in this cohort of patients. Other investigators have observed little additional benefit from full, symptom-limited stress electrocardiogram testing at 6–8 weeks when the predischarge, submaximal study is negative, with a similar 8–9% rate of conversion from a negative to a positive study.25 Reinjection of 201Tl, as well as other methods,26–31 has enhanced the detection of viable myocardium within “irreversible” defects defined by routine SPECT 201Tl stress testing. For example, Dilsizian et al32 found that 42 of 85 regions (49%) with fixed 201Tl defects showed improved 201Tl uptake, suggestive of viable myocardium, with 201Tl reinjection at the time of delayed (24-hour) rest scanning.32

After reperfusion therapy, in particular, early 201Tl scintigraphy may incorrectly estimate the degree of myocardial salvage. 201Tl uptake may improve in the reperfused zone with repeated studies from 4 days to as long as 6 weeks after intervention for myocardial infarction,26 with late reimaging after a single stress,27,28 or with repeated 201Tl injection.32–34 Other alternative tests such as technetium-99m isonitrile or positron-emission tomographic paired metabolic and flow imaging may prove to be more sensitive techniques than what we used in the present study.29–31

Conclusion

The ideal postreperfusion functional test would, with a high degree of confidence, accurately detect and quantify the results of interventional therapy and provide meaningful long-term prognostic data. A present dilemma is whether a negative stress test result, in the presence of an unequivocally critical residual stenosis, signifies suboptimal or delayed myocardial reperfusion or inadequate sensitivity of the stress test method. Our results, albeit in a highly selected patient group, are somewhat discouraging in that they convey more extensive myocardial necrosis as the chief explanation for lack of provokable ischemia in the face of apparent successful myocardial reperfusion. The findings suggest the need for more efficient means of myocardial preservation and serve to accentuate further the lack of concordance between anatomic and functional studies after thrombolytic intervention. Indeed, Simoons and colleagues35 found no predictive value of the functional test during a 5-year follow-up after streptokinase therapy. Beyond the apparent paradox observed in the present study, it is hoped that better noninvasive tests, and a more precise definition of the specific benefits of additional intervention, will become available for risk stratification and subsequent management of postthrombolysis patients.

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KEY WORDS • myocardial infarction • thrombolysis • stress test • thallium • angioplasty • coronary intervention
Significance of a negative exercise thallium test in the presence of a critical residual stenosis after thrombolysis for acute myocardial infarction.

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