Tissue Plasminogen Activator: Toronto (TPAT) Placebo-Controlled Randomized Trial in Acute Myocardial Infarction

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The efficacy and safety of recombinant tissue plasminogen activator (rt-PA) administered on a dosing per weight basis was evaluated in a randomized, placebo-controlled, double-blind trial in 115 patients with acute myocardial infarction. The principal outcomes were global and regional left ventricular function in the distribution of the qualifying myocardial infarction, determined 9 days after the onset of symptoms.

Global and regional ejection fraction values were significantly better for patients treated with rt-PA than for placebo-treated patients (the differences were 5.8 ± 2.7% units [p = 0.017] and 7.1 ± 3.1% units [p = 0.012], respectively). This benefit was also evident from visual assessment of left ventricular segmental wall motion. After adjustment for differences in important prognostic variables at baseline, the estimates of treatment effect were 4.0 ± 2.4% units (p = 0.048) for global and 4.3 ± 2.6% units (p = 0.047) for regional ejection fraction. Early patency of the infarct-related vessel was demonstrable in 7 (29%) of 24 placebo-treated patients and 18 (78%) of 23 rt-PA-treated patients, whereas 15 (56%) of 27 patients in the placebo group and 23 (72%) of 32 in the rt-PA group had a patent infarct-related vessel at hospital day 9.

There was no significant difference in irreversible or reversible defect size as assessed by thallium scintigraphy on day 7. There was no difference in maximal peak creatine kinase (CK) MB isoenzyme or area under the MB CK time-activity curve between the two groups; however, the time from symptom onset to peak MB CK was 12.9 ± 0.6 h in patients treated with rt-PA and 17.9 ± 0.6 h in those treated with placebo (p < 0.001). Twenty patients underwent coronary angioplasty or cardiac surgery in the hospital; 5 of these had received placebo and 15 had received rt-PA (p = 0.014); 12 of these procedures were performed at or after day 9. No instances of cerebral hemorrhage and no significant adverse effects were seen in this study. This study demonstrates the benefit of rt-PA on global and regional left ventricular function in the area of qualifying myocardial infarction.

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was related to total dosage of rt-PA, the dose of rt-PA administered in this study was adjusted to the body weight of recipients. Because it has been suggested that reperfusion therapy with rt-PA promotes further instability and increases the risk of recurrent myocardial ischemia, it has been reasoned that access to early mechanical revascularization is required. Given the substantial logistic and economic implications of this approach, in this study we restricted mechanical revascularization to individuals who developed pre-defined ischemic end points. This was done to assess the independent influence of pharmacologically induced coronary reperfusion on the principal outcomes of our study, regional and global left ventricular function on the 9th hospital day.

Methods

This was a randomized, placebo-controlled, double-blind trial. The principal outcomes were global and regional left ventricular function in the distribution of the qualifying myocardial infarction determined 9 days after the onset of symptoms. The protocol and consent form were approved by the Human Subjects Review Committee, University of Toronto and the institutional review boards of the participating hospitals.

Study patients. Patients aged 20 to 75 years with typical ischemic chest pain lasting \( \geq 30 \) min, ST segment elevation in the electrocardiogram (ECG) \( \geq 0.1 \) mV in two inferior leads or leads I and aVL or \( \geq 0.15 \) mV in at least two anterior precordial leads were considered for admission to the study. Patients were excluded if they presented \( > 3.75 \) h after the onset of chest pain or had cardiogenic shock, left bundle branch block, prior aortocoronary bypass surgery or recent (<1 month) percutaneous transluminal coronary angioplasty, obvious contraindications to thrombolytic therapy or inability to provide informed consent. Patients were recruited from 10 collaborating hospitals in Toronto and records were kept of those who met inclusion criteria but were not randomized. Randomization was balanced within each hospital according to blocks of four. Of these 10 hospitals, 3 were designated as core hospitals on the basis of their capacity to perform coronary angiography. Patients initially admitted to any of the seven non-core hospitals were transferred by random assignment to one of the three core hospitals on the 4th hospital day. All investigations after day 4, including ventricular function studies, were performed in one of these three core institutions.

Treatment protocol. Study treatment consisted of double-chain recombinant tissue plasminogen activator (rt-PA) (Burroughs Wellcome Co.) or matching placebo. The first 39 patients received the study drug at 0.4 MU/kg per h intravenously for h 1, 0.14 MU/kg per h for h 2 and 0.03 MU/kg per h for the subsequent 8 h. The final 79 patients received 0.4 MU/kg per h for h 1, 0.08 MU/kg per h for h 2, and 0.03 MU/kg per h for h 1,0.14 MU/kg per h for h 2 and 0.03 MU/kg per h for the subsequent 4 h. Ten percent of the h 1 dose was given as a bolus injection initially. All patients received heparin, concomitant with the study drug, commencing with a bolus injection of 4,000 IU followed by an infusion of 1,000 IU/h. Heparin administration was continued for 96 h and monitored by periodic partial thromboplastin times with the objective of maintaining the partial thromboplastin time between 1.5 and 2 times the control value. In all patients, 325 mg/day of enteric-coated aspirin was given orally before cessation of heparin therapy. All patients received prophylactic lidocaine therapy for the first 24 h.

Assessment of left ventricular function. Left ventricular function was assessed with radionuclide ventriculography \( 3.8 \pm 0.8 \) h after initiation of treatment and again on day 9. Studies were acquired in the anterior, \( 45^\circ \) left anterior oblique and \( 70^\circ \) left anterior oblique views using multigated acquisition of 32 frames/cardiac cycle after in vitro labeling of red blood cells with \( 30 \) mCi of technetium-99m. On day 9, the \( 45^\circ \) left anterior oblique view study was repeated 2 min after the administration of 0.6 mg of sublingual nitroglycerin. All day 1 radionuclide studies were transferred from the 10 participating hospitals to the core nuclear laboratory as were all day 9 studies performed at the 3 core hospitals. One technologist who did not know the clinical data analyzed all day 1 and day 9 studies on a single computer system.

Global left ventricular ejection fraction was calculated with use of a semiautomated method for definition of end-diastolic and end-systolic regions with calculation of background from a left paraventricular region of interest. Regional ejection fractions in the \( 45^\circ \) left anterior oblique view were calculated for one inferoapical, two septal and two posterolateral segments, each segment encompassing \( 60^\circ \) of the circumference of the ventricle. Assignment of segments for regional calculations was keyed to the qualifying electrocardiogram (ECG). For anterior infarction, the inferoapical and the two septal segments were averaged, and for inferior infarction the inferoapical and the two posterolateral segments were averaged to give the regional ejection fraction in the area of infarction.

Segmental wall motion was assessed in five segments in the anterior view, in five in the \( 45^\circ \) left anterior oblique view and in two inferior segments in the \( 70^\circ \) left anterior oblique view and were scored 0 to 4 according to whether the segment was normal [0], mildly hypokinetic [1], severely hypokinetic [2], akinetic [3] or dyskinetic [4]. Wall motion was assessed by two experienced observers unaware of treatment assignment: differences were mediated by consensus. All readings were conducted at the core nuclear laboratory. A wall motion score was calculated as the sum of the segmental score divided by the total number of assessed segments for global and regional measurements, respectively.

Enzymatic assessment of myocardial infarction was obtained by utilizing serum levels of creatine kinase (CK) and
MB CK in international units per liter determined at 4 h intervals for the first 36 h. Thereafter, CK activity in international units per liter was determined at 12 h intervals throughout the hospital course. Reinfarction was defined as an increase of ≥50% in MB CK activity over a previously established basal level. Creatine kinase activity was determined with the use of Boehringer Mannheim automated analysis with N-acetylcysteine reagents, and MB CK activity with the use of Isoimmune-CK (Roche).

Cardiac catheterization protocol. Cardiac catheterization was performed according to a predetermined protocol. For the 47 patients who were initially admitted to the three core institutions with facilities for cardiac catheterization, patency of the infarct-related coronary artery was determined 18 ± 6 h after administration of the study drug. All coronary angiograms were independently reviewed without knowledge of clinical or other data at a core angiographic site and infarct-related vessel patency was classified according to the criteria of the Thrombolysis in Myocardial Infarction (TIMI) investigators (7). Patency of the infarct-related vessel was defined as TIMI perfusion grade 2 or 3, and patients with a patent vessel were restudied on day 9 to document the reocclusion rates in this subset. The 59 patients initially admitted to a hospital without facilities for catheterization were transferred by random assignment to one of the three core hospitals on day 4 and underwent coronary angiography on day 9 to provide an unbiased estimate of late coronary patency. Nine additional randomized patients (five assigned to placebo and four assigned to rt-PA) did not undergo coronary angiography because of patient refusal (three cases), death (two cases), urgent revascularization (three cases) and an administrative problem (one case).

Exercise thallium scintigraphy. All patients underwent symptom-limited exercise thallium scintigraphy on day 8 according to the Bruce protocol. After intravenous injection of 3.0 mCi of thallium-201 during peak exercise, the patient exercised for 1 additional min and was then placed in the supine position. Five minutes after exercise, an anterior planar image was obtained followed by continuous acquisition of images beginning in the 45° right anterior oblique projection and moving clockwise around the heart to +135° left anterior oblique; these images were stored on a minicomputer in a 64 x 64 matrix at 3° intervals. Thallium images were obtained in the three core hospitals that performed cardiac catheterization and data were transferred to the core nuclear laboratory. Thallium tomograms were reconstructed and a polar coordinate map of activity was obtained and displayed in a "bull's-eye" format; 4 h delayed images were similarly acquired and processed. The stress and 4 h bull's-eye displays were compared with limits defined from 17 normal subjects; activity 2.5 SD below these limits was considered abnormal. Stress defects were quantitatively determined and localized to either anterior or inferior vascular territories and their size was expressed as the percent of the total bull's-eye display. The area of the initial defect that was reversible or nonreversible was calculated by comparison of the stress and 4 h studies.

Post-treatment protocol. Patients were systematically monitored for clinical and ECG evidence of recurrent ischemia. Particular attention was given to the avoidance of associated interventions that could affect study outcome. Therefore, coronary angioplasty and aortocoronary bypass surgery within the first 10 days were confined to those patients experiencing any of the following: 1) two or more episodes of recurrent ischemic chest pain during a 48 h period despite maximal medical therapy; 2) ischemic chest pain with >2 mm ST segment shift; or 3) development of hemodynamic instability. Revascularization at and after day 10 was performed at the discretion of the attending cardiologist, who had access to exercise scintigraphic and angiographic data. There was no difference between the anti-ischemic and other medical therapy of placebo- and rt-PA-treated groups at day 5 or at hospital discharge.

Clinical assessment of cardiac functional status was performed on admission and daily throughout the hospital course. Clinical follow-up study was undertaken after hospital discharge to assess mortality as well as morbidity, defined as recurrent ischemic events and need for revascularization, up to 90 days after randomization.

Statistical analysis. The demographic and clinical baseline characteristics of the two treatment groups are summarized in terms of means and standard errors (±SE) for continuous data and relative frequencies (ie. percentages) for categorical features. Similar summaries were used for efficacy outcomes with the addition of formal significance tests. Student's t test was used for comparing treatment means and Fisher exact test for proportions. In general, one-tailed tests were performed where clear, predetermined directional hypotheses existed. Provision was made before unblinding for comparison of treatments with the use of unadjusted and adjusted analyses. The adjusted analyses used a regression approach, i.e., analysis of covariance, which both corrects the observed treatment difference for any imbalances and baseline factors that influence outcome and also improves the sensitivity of the comparison by eliminating variation due to the baseline characteristic. We adjusted for a predetermined set of baseline covariants given in Table 1.

The study plan was to randomize 150 patients per group on the basis of anticipated beneficial effect of rt-PA on global and regional ejection fraction. The study was terminated sooner than planned when rt-PA became generally available and the steering committee believed it was no longer ethical to randomize patients to receive placebo.

Study organization. The data coordination center for this trial was the Department of Clinical Epidemiology and Biostatistics at McMaster University (Hamilton, Ontario, Canada). The records of all patients who were randomized
were assessed by a central adjudications committee with respect to admission and exclusion criteria, departures from protocol, and serious adverse effects. An external safety monitoring committee, consisting of individuals independent of the trial, was provided efficacy and safety data at 3 month intervals to monitor the progress of this study and terminate study entry if the results warranted such action. The chairman of the safety monitoring committee was the only individual with knowledge of individual treatment allocations.

### Results

**Patient assignment to treatment groups.** Between June 1 and December 23, 1987, 600 patients met the inclusion criteria; 412 of these were excluded because of late presentation (>3.75 h after the onset of chest pain) (51.4%), age >75 years (24.5%), shock (3.4%), contraindications to thrombolytic therapy (4.3%) and other reasons (16.5%). Of the 188 patients eligible for the study, 70 were not randomized for administrative reasons or because consent was not obtained from the patient or the attending physician. Of the 118 patients who were randomized, 3 were subsequently ruled ineligible because they did not have myocardial infarction (1 patient with pericarditis, 1 with a chronic ventricular aneurysm and 1 with fixed repolarization abnormalities and left ventricular hypertrophy). There were no differences in the baseline characteristics between the 70 patients who were eligible and not randomized and the study group. Of the remaining 115 patients, 56 were assigned to receive placebo and 59 to receive rt-PA.

**Baseline characteristics** (Table 1). Whereas randomization produced reasonably well balanced treatment groups, a history of prior infarction and infarct location were less well matched. Adjustment for potentially important influences of baseline variables on the assessment of treatment effect was accomplished by analysis of covariance with use of the predefined baseline characteristics outlined in Table 1.

**Radionuclide ventriculography** (Table 2). Global and regional ejection fraction were significantly better at day 9 for patients treated with rt-PA than for those treated with placebo (the differences from baseline were 5.8 ± 2.7% units (p = 0.017) and 7.0 ± 3.1% units (p = 0.012), respectively). This benefit was also evident from the visual assessments of left ventricular global and regional wall motion. After adjustment for baseline differences, the treatment effects were 4.0 ± 2.4% units (p = 0.048) and 4.3 ± 2.6% units (p = 0.047) for global and regional ejection fraction, respectively. Similarly, the adjusted treatment effect was -0.27 ± 0.12 (p = 0.017) and -0.32 ± 0.16 (p = 0.02) for global and regional visual score, respectively.

**After sublingual nitroglycerin,** the global ejection fraction improved by 2.1 ± 0.6% units for placebo and 2.4 ± 0.6% units for rt-PA, whereas regional ejection fraction improved by 2.8 ± 0.6% units for placebo and 3.7 ± 0.8% units for rt-PA. The effects of rt-PA on global and regional left ventricular function at day 9 and the incremental change achieved by nitroglycerin are shown in Figure 1. When the five patients (three assigned to placebo and two to rt-PA) who underwent coronary angioplasty or cardiac surgery before day 9 were excluded, the significant differences in favor of rt-PA persisted. It is important to emphasize that there was also no difference in the treatment effect when analysis was conducted according to the two different rt-PA maintenance regimens.

**Coronary artery patency.** Early patency of the infarct-related coronary artery, defined as TIMI perfusion grade 2 or
At rest, both global and regional ejection fractions (open bars) were significantly greater for patients treated with recombinant tissue-type plasminogen activator (rt-PA) than for patients treated with placebo (p = 0.017 and p = 0.012, respectively). The improvement in global and regional ejection fractions after administration of sublingual nitroglycerin (solid bars) did not differ between patients treated with rt PA and those treated with placebo with p = 0.36 for the improvement in global and p = 0.17 for the improvement in regional ejection fraction, respectively.

Cardiac enzymes (Table 3). The time from symptom onset to peak MB CK activity was 12.9 ± 0.6 h in the rt-PA-treated patients and 17.9 ± 0.6 h in the placebo-treated patients (p < 0.001). There was no difference between the two groups in the maximal MB CK or in the area under the MB CK time-activity curves.

Figure 1. Results of radionuclide angiography performed on day 9. At rest, both global and regional ejection fractions (open bars) were significantly greater for patients treated with recombinant tissue-type plasminogen activator (rt-PA) than for patients treated with placebo (p = 0.017 and p = 0.012, respectively). The improvement in global and regional ejection fractions after administration of sublingual nitroglycerin (solid bars) did not differ between patients treated with rt PA and those treated with placebo with p = 0.36 for the improvement in global and p = 0.17 for the improvement in regional ejection fraction, respectively.

Thallium scintigraphy (Fig. 2). Although there was a trend toward smaller irreversible and larger reversible defects in both global and regional estimates for rt-PA-treated patients, these differences did not achieve statistical significance. Similarly, the ratio of reversible to irreversible defect size did not differ significantly between rt-PA- and placebo-treated patients.

Clinical outcome. Twenty patients underwent either coronary angioplasty or bypass surgery in the hospital. 5 who had received placebo and 15 who had received rt-PA (p = 0.014). Two of the 20 required emergency repair of a ventricular septal defect (1 with concomitant coronary bypass surgery); both subsequently died in the hospital and both had received rt-PA therapy. Six patients required urgent coronary angioplasty before day 9 because of recurrent ischemia as defined by protocol; three had received placebo and three had received rt-PA. Twelve patients underwent revascularization in the hospital on or after day 9 (coronary angioplasty in nine and bypass surgery in three). Four additional patients underwent revascularization between hospital discharge and day 90: two of these had received placebo and two had received rt-PA. Reinfarction occurred in three placebo-treated and three rt-PA-treated patients.

Eight patients, including five from the placebo group, died in the hospital. Two additional deaths occurred in the placebo group after hospital discharge and before day 90. Thus, the 90-day mortality rate was 12.5% for placebo-treated patients and 5.1% for rt-PA-treated patients (p = 0.15).

Side effects. Few serious adverse effects were observed in this study. Although superficial bleeding and oozing from puncture sites was common, only four patients, including

![Graph](image.png)

**Figure 2.** Results of quantitative tomographic thallium scintigraphy. Trends toward smaller global and regional irreversible thallium defects (hatched bars) among patients treated with tissue-type plasminogen activator (rt-PA) do not achieve statistical significance. Reversible thallium defects (open bars), both global and regional, did not differ between placebo and rt-PA groups. Measurements are expressed as mean values ± SE.

### Table 3. Creatine Kinase (CK) Data

<table>
<thead>
<tr>
<th>CK Measure</th>
<th>Placebo Group</th>
<th>rt-PA Group</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Time to peak MB CK (h)</td>
<td>17.9 ± 0.6</td>
<td>12.9 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(n = 55)</td>
<td>(n = 57)</td>
<td></td>
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<tr>
<td>Maximal MB CK (IU/liter)</td>
<td>43.0 ± 4.0</td>
<td>45.4 ± 3.4</td>
<td>0.66</td>
</tr>
<tr>
<td>(n = 56)</td>
<td>(n = 59)</td>
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<td></td>
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<tr>
<td>Area under the MB CK curve (IU/liter)</td>
<td>911.9 ± 85.1</td>
<td>861.1 ± 62.3</td>
<td>0.65</td>
</tr>
<tr>
<td>(n = 55)</td>
<td>(n = 57)</td>
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rt-PA = recombinant tissue-type plasminogen activator.
three from the placebo group, required transfusions because of a decrease in hemoglobin level to <10 g/100 ml. There were no instances of cerebral hemorrhage and no other unexpected adverse effects in this study.

**Discussion**

This study demonstrates that recombinant tissue plasminogen activator (rt-PA) administered early after presentation with acute myocardial infarction results in improvement in both global and regional left ventricular function 9 days after hospital admission. We used double-chain tissue plasminogen activator (Burroughs Wellcome Co.) in this study, which is a purified rt-PA produced from large scale cultures of a well characterized mammalian cell line that contains the gene for human tissue plasminogen activator isolated from Bowes melanoma cells. Results from biologic activity assays show no discernible difference in biologic activity between Burroughs Wellcome rt-PA and Bowes melanoma t-PA. The strategy of dosing on a per weight basis in this study was derived from preliminary studies (5) in which this approach was found to achieve effective reperfusion and minimize bleeding complications. The maintenance infusion of rt-PA was changed part way through the trial because of a policy decision related to data that were acquired independent of the trial; these data (6) indicated a lack of benefit of longer infusions of rt-PA on the incidence of reocclusion and an increased incidence of bleeding complications associated with total dose and duration of infusion of rt-PA.

These are the first human data attesting to the functional efficacy of this rt-PA preparation. In contrast to previous studies of the effects of rt-PA on left ventricular function, in which measurements of regional function were either unavailable or failed to show a treatment effect, our study provides evidence that the improvement in global function is mediated through enhanced contraction in the infarct zone. The validity of the quantitative computer-based regional ejection fraction measurements in this study is substantiated by the independent visual wall motion analysis.

**Comparison with previous studies.** It is of interest to compare this study with two previous randomized trials of rt-PA in myocardial infarction (8,9) that reported left ventricular function measurements both within the first 24 h after admission and later during the hospital convalescence. Although Guerci et al. (8) demonstrated a beneficial effect of rt-PA on left ventricular function on day 10, the magnitude of this effect may have been exaggerated by a corresponding decline in left ventricular function in their placebo group. In contrast, our study showed a trend to improved left ventricular function between early and late hospital assessments in placebo-treated patients that was consistent with previous natural history studies of left ventricular function after myocardial infarction (10,11). The placebo-treated patients in the study of Guerci et al. (8) received concomitant medical therapy, including intravenous nitroglycerin for 48 h and calcium channel blockers throughout the hospital course. Moreover, initiation of heparin therapy was delayed 1 to 6 h after completion of study drug administration until cardiac catheterization was performed in all patients and a subset was submitted to early angioplasty. In view of the unfavorable outcome of the placebo-treated patients in their trial and the ancillary treatments employed, it is difficult to assess the independent treatment effect of rt-PA.

The Australian National Heart Foundation study (9) demonstrated a benefit of rt-PA on global left ventricular function assessed by single plane contrast ventriculography 5 to 7 days after infarction. Despite this improvement in global function, a parallel improvement in regional function was not demonstrated and the benefit of rt-PA therapy could not be confirmed by radionuclide ventriculography at any time during the 90 day follow-up period. These findings notwithstanding, there was a suggestion of a treatment effect in patients with anterior infarction as early as day 2. Examination of our own early functional data shows a similar trend to improved early function in the rt-PA group, as suggested by Topol et al. (12). However, our study was not designed to address this question and we cannot exclude that this finding is influenced by differences in baseline variables.

**Timing of assessment of left ventricular function.** The optimal time for assessment of the impact of thrombolytic therapy on left ventricular function is unclear. A review of reperfusion studies with functional outcomes highlights substantial differences in the agents employed, as well as in the measurement techniques for functional assessment and their time of application. The improvement in global ejection fraction 9 days after treatment that was seen in our study was similar in magnitude to that observed by O'Rourke et al. (13). They used radionuclide ventriculography to study patients with a first myocardial infarction who presented within 2.5 h of initial chest pain; they assessed the effects of rt-PA 21 days after infarction to minimize the possible influence of myocardial stunning. The failure of nitroglycerin in our study to significantly enhance the beneficial effects of rt-PA on global and regional left ventricular function provides further evidence that significant myocardial stunning may not be as important as previously believed, even at this relatively early phase in the convalescence of acute myocardial infarction. Alternatively, early rt-PA administration with commensurate rapid and effective reperfusion may minimize myocardial stunning.

The high early patency rate in the rt-PA–treated patients in our study attests to the thrombolytic efficacy of this form of rt-PA and is consistent with previous findings. The low rate of reinfarction in this study, as well as the low rate of documented reocclusion in the subset of patients with early catheterization in whom it was specifically sought, is in contrast to earlier data and may reflect our rt-PA dosing strategy or the combined effects of rt-PA, heparin and
address this issue. Our study was low and there was a tendency for it to be lower. The mortality rate in thrombolytic therapy in myocardial infarction, which show either no benefit or deleterious effects on both clinical outcome and left ventricular function. The finding is consistent with recent studies (17,18) of the acute effects of angioplasty as an adjunct to reperfusion therapy on left ventricular function or on patient risk of recurrent ischemia, reocclusion and reinfarction in rt-PA-treated patients. Although urgent revascularization for recurrent ischemia was infrequently required when taken in conjunction with the demonstrated high early rate of patency of the infarct-related coronary artery in a subset of these patients, it suggests successful early reperfusion. The similarity of area under the MB CK time-activity curve in the placebo and rt-PA groups, coupled with the improvement in left ventricular function afforded by rt-PA, suggests that the enzyme data of the rt-PA group were influenced by washout (15). The actual infarct size was likely reduced compared with that in the placebo group. The reasons for failure to demonstrate limitation of infarct size by thallium scintigraphy are unclear in light of the evidence of a favorable treatment effect afforded by both the functional and the enzymatic results. This result may reflect the insensitivity of this technique for detecting myocardial salvage, particularly with a relatively modest sample size. Alternatively, alteration of thallium kinetics in the acute phase of myocardial infarction may have confounded the ability to detect differences between infarcted and ischemic myocardium. Ritchie et al. (16) reported irreversible tomographic thallium defect sizes comparable with those noted herein and they were also unable to demonstrate a favorable impact of reperfusion therapy with intracoronary streptokinase. Revascularization after thrombolysis. At the time our study began, there was genuine concern about the increased risk of recurrent ischemia, reocclusion and reinfarction in rt-PA-treated patients. The incidence of reocclusion and reinfarction during hospitalization was low in both the placebo and the rt-PA groups. Although urgent revascularization for recurrent ischemia was infrequently required before day 9, revascularization during hospitalization was undertaken more frequently in patients treated with rtPA than in those receiving placebo even though their attending physicians remained unaware of treatment assignment throughout the study. The policy of restricting revascularization to clinical need did not reduce the beneficial effect of reperfusion therapy on left ventricular function or on patient outcome. This finding is consistent with recent studies (17,18) of the acute effects of angioplasty as an adjunct to thrombolytic therapy in myocardial infarction, which show either no benefit or deleterious effects on both clinical outcome and left ventricular function. The mortality rate in our study was low and there was a tendency for it to be lower in the rt-PA group; however, our trial was not designed to address this issue.

Unlike other studies, our study employed a dosing by weight strategy that was associated with a low risk of bleeding. The clearly demonstrable beneficial effect of rt-PA on coronary patency and global and regional left ventricular function in conjunction with a conservative approach to mechanical revascularization suggests that this therapeutic approach has wide applicability and promise for patients with acute transmural myocardial infarction.

Appendix*

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