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Cardiac Rupture Associated With Thrombolytic Therapy: Impact of Time to Treatment in the Late Assessment of Thrombolytic Efficacy (LATE) Study

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Objectives. **This prospective ancillary study was conducted to determine the association between the time from symptom onset to treatment and cardiac rupture in patients with acute myocardial infarction.**

Background. **There is strong evidence that the time window for thrombolytic therapy should be extended to at least 12 h; however, many clinicians are concerned that late treatment may cause an excessive occurrence of death from cardiac rupture. Because up to 30% of patients with acute myocardial infarction arrive in the hospital >6 h from symptom onset, resolving this issue is of paramount clinical importance.**

Methods. **A total of 5,711 patients with acute myocardial infarction were randomized to receive intravenous recombinant tissue-type plasminogen activator (rt-PA) (100 mg over 3 h) or matching placebo, within 6 and 24 h from symptom onset. Both groups received immediate oral aspirin, and a majority of patients received intravenous heparin during the initial 48 h.**

Results. **By 35 days, 177 patients had died, with the cause of death specified as cardiac rupture (53 patients), electromechanical dissociation (42 patients) or asystole (82 patients). An additional 370 patients had died of other causes. In patients treated within 12 h, the proportion of rupture deaths in the group given rt-PA was higher than that observed in those who received placebo, but the difference was not statistically significant. In patients treated after 12 h, there was no evidence of an increased incidence of rupture with rt-PA, and the proportion of deaths due to rupture in this group was lower than that in patients given placebo. However, there was evidence of a difference between rt-PA and placebo with respect to the time that rupture became clinically manifest (treatment by time to death interaction, $p = 0.03$).**

Conclusions. **This study provides unequivocal evidence that late treatment (6 to 24 h after symptom onset) with rt-PA is not associated with an increased risk of cardiac rupture. However, for reasons that are unclear, coronary thrombolysis appears to accelerate rupture events, typically to within 24 h of treatment.**

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Several large-scale clinical trials (1–5) have demonstrated that thrombolytic therapy improves survival among patients with acute myocardial infarction. Although the benefits derived from late thrombolysis are less certain, emerging evidence suggests strongly that the time window for treatment should be extended to at least 12 h (5–7). The Late Assessment of Thrombolytic Efficacy (LATE) study, a randomized, double-blind trial of 5,711 patients with symptoms and electrocardiographic (ECG) criteria consistent with acute myocardial infarction, demonstrated a 25% mortality reduction in favor of treatment with recombinant tissue-type plasminogen activator (rt-PA) and suggested that some patients may benefit even when treated >12 h after symptom onset (7). Current enthusiasm for late thrombolysis has been tempered somewhat by ongoing concern that it increases the risk of cardiac rupture. Although data from randomized clinical trials supporting this contention are not available, the findings of a meta-analysis performed by Honan and colleagues (8) are widely quoted. In their report, the odds ratio of cardiac rupture correlated directly with time to treatment. Further support may be found in the observations made by the Fibrinolytic Therapy Trialists' collaborative group (9), which cited an "early hazard" among patients treated with thrombolytic agents after 12 h from symptom onset. The purpose of our study was to examine, in a prospectively designed LATE ancillary study, the incidence of cardiac rupture as a cause of death in patients with myocardial infarction treated with rt-PA or matching placebo between 6 and 24 h after symptom onset.

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Methods

The methods employed, participating centers and investigators in the LATE study have been described previously (7). Briefly, the trial was performed in 230 centers (Australia 35, Canada 21, Europe 146, United States 28) beginning in April 1989 and ending in February 1992. Patients >18 years of age were considered for study entry if they fulfilled the following criteria: 1) They had chest pain of suspected cardiac origin lasting ≥30 min. 2) An ECG exhibited one or more of the following: ST elevation ≥0.1 mV in two or more limb leads or ≥0.2 mV in two or more chest leads, ST depression ≥0.2 mV in at least two leads and thought to represent a non-Q wave infarction. Patients with old or equivocal ECG changes or bundle branch block were considered for study entry in the presence of elevated serum cardiac enzyme levels. 3) Treatment could be initiated 6 to 24 h after symptom onset. Exclusion criteria were as follows: serious bleeding within the previous 6 months, a history of stroke, a transient ischemic attack or neurosurgery within the previous 6 months, major surgery or trauma within the previous month, shock with systolic blood pressure <80 mm Hg, hypertension (blood pressure >200 mm Hg systolic or 110 mm Hg diastolic not controlled within the 6- to 24-h time window) and inability to give informed consent or comply with the protocol.

Randomization and treatment. Patients were treated with intravenous rt-PA (Alteplase, Genentech, Inc.), given as a 10-mg bolus and a 50-mg infusion over 1 h followed by 20 mg in each of the next 2 h, or matching placebo. All patients received aspirin on study entry and 75 to 360 mg daily for the duration of follow-up. The use of heparin was at the discretion of the investigators, but intravenous heparin use during the initial 48 h was encouraged either as 1) an initial 5,000-U bolus before administration of the study drug, a second bolus of 5,000 U on completion of administration of the study drug followed by 1,000 U/h, or 2) an initial bolus of 5,000 U before administration of the study drug followed immediately by a continuous infusion of 1,000 U/h. All other medications and intravenous therapies were at the discretion of the participating physicians, with the exception of oral beta-adrenergic blocking agents, which were strongly recommended.

Adverse events. Details of all deaths were given and the primary cause was identified by the admitting physician. This information was scrutinized in blinded manner by the international study coordinator, and the cause of death was categorized as 1 of 24 possible causes on the basis of the information provided. Where specifically indicated, these included cardiac rupture, electromechanical dissociation or asystole. Because postmortem examinations were not mandatory for deaths within the LATE study, precise identification of all cardiac rupture events was not possible. Because it can be argued that cardiac rupture is implicated in many deaths attributed to electromechanical dissociation and asystole, this combined group of outcomes was considered in the first instance (10).

Statistical methods. Differences among the groups of patients who died of cardiac rupture, those who died of other causes and those who were alive at 35 days were assessed by using analysis of variance techniques for continuous variables, logistic regression for two-level factor variables and log-linear models for multilevel factor variables. In each analysis, the comparison for all three groups was made by fitting both the main effects model and the null model and assessing the change in deviance. The separate comparisons of patients who died of rupture with those who died of other causes and with those who were alive were made by considering the ratio of the estimate of the appropriate coefficient with its standard error in the main effects model. Comparison of deaths due to rupture versus other deaths, taking into consideration the treatment received and the time of onset of treatment, were made by using logistic regression.

Table 1. Patient Groups in the LATE Study: Baseline Characteristics

	Death From Cardiac Rupture, EMD, Asystole (n = 177)	Death From Other Causes (n = 370)	Alive at 35 Days (n = 5,164)	p Value*
Age (yr)	69.8 ± 8.4	70 ± 8.4	61.9 ± 10.8	< 0.0001
Male (%)	62.1	61.9	73.5	< 0.0001
MI (%)				
Q wave	76.8	70	59.2	< 0.001
Non-Q wave	14.1	20	23.4	
Anterior	48	48.9	39.4	< 0.0001
Inferior	23.7	24.1	34.2	
Previous	21.5	31.1	20.9	< 0.0001
Recurrent	7.9	18.4	3.1	< 0.0001
Active smoker (%)	27.1	25.7	42.4	< 0.0001
Weight (kg)	72.1 ± 12.4	73.2 ± 13.4	76.5 ± 13.8	< 0.0001
NYHA class (%)				
I	24.3	27.3	36	< 0.0001
II	37.3	30.3	41.6	
III	37.9	42.2	22.3	
Time to bolus of rt-PA or placebo	14.4 ± 5.2	14.4 ± 5.3	14.8 ± 5.3	0.2803
Heparin (%)	54.8	55.4	65.2	< 0.0001

* p value represents comparison of all three groups. Data are presented as percent of patients or mean value ± SD. EMD = electromechanical dissociation; LATE = Late Assessment of Thrombolytic Efficacy; MI = myocardial infarction; NYHA class = New York Heart Association functional class; rt-PA = recombinant tissue-type plasminogen activator.

Results

A total of 5,711 patients were enrolled in the LATE study. By 35 days, 175 of these patients had died of a cause specified as cardiac rupture (n = 51), electromechanical dissociation (n = 42), or asystole (n = 82). Two other patients, who were classified as having had a recurrence of infarction in the hospital are considered with the group that died of rupture, bringing the total to 177. An additional 370 patients had also died by 35 days. Overall, 5,164 patients were alive at 35 days.

Differences among the groups with respect to baseline characteristics are presented in Table 1. The patients who died of cardiac rupture did not differ from those who died of other

causes in terms of age, gender, confirmed diagnosis, site of infarction, body weight, New York Heart Association functional class and smoking history. As expected, however, there were large differences in each instance between the group that died of rupture and those who were alive at 35 days. Patients who died of rupture were more likely to have experienced a prior infarction or to have had a recurrent infarction than were those who died of other causes.

Table 2 considers differences between rt-PA and placebo for patients treated ≤12 or >12 h from symptom onset, comparing deaths due to rupture with all deaths. Among patients treated within 12 h, the proportion of deaths attributable to rupture was higher in the rt-PA group than in the placebo group, whereas for those treated after 12 h, the proportion of deaths due to rupture was lower in the rt-PA group. There was no evidence of an interaction between treatment and time to treatment. There was modest evidence of a treatment by time to treatment interaction for the number of deaths due to rupture compared with all deaths in the group of patients with ST elevation ($p = 0.0809$). For the other groups considered, patients treated with or without adjunctive heparin therapy and those treated ≤3 or >3 h from admission, there was no evidence of interaction effect. There was no evidence that late therapy (>12 h) increased the likelihood of rupture in any subgroup.

Treatment with rt-PA was not associated with significant increases in the incidence of rupture either in those patients who received heparin or in those who did not. However, it is not possible with these data to determine whether treatment with heparin is itself associated with more rupture events. Heparin therapy was not randomized, and it is not clear and indeed unlikely that the group receiving heparin was directly comparable to the group that did not receive heparin.

Table 3 indicates the day of occurrence of each case of rupture, electromechanical dissociation or asystole, considering all patients and those treated with rt-PA within or after 12 h. A logistic regression analysis considering those who died of rupture and those who died of other causes was performed on the overall results to determine whether there was a significant treatment by time to death interaction effect, and a significant interaction was observed ($p = 0.0346$). Hence, the time of onset of rupture after rt-PA therapy was different from that after placebo therapy. The occurrence of rupture in the rt-PA group was in general earlier; hence, it can be said that rt-PA therapy accelerates the onset rather than increases the frequency of cardiac rupture.

Table 2. Mortality in Patients According to Time to Treatment (≤12 or >12 h), Other Treatment Variables and Cause of Death

	Deaths From Cardiac Rupture, EMD, Asystole	Total Deaths	p Value*
Overall†			
≤12 h			
rt-PA	34	93	0.2502
Placebo	40	123	
>12 h			
rt-PA	43	154	
Placebo	56	168	
ST elevation			
≤12 h			
rt-PA	28	68	0.0809
Placebo	24	87	
>12 h			
rt-PA	29	98	
Placebo	36	107	
Heparin			
≤12 h			
rt-PA	19	53	0.2093
Placebo	21	63	
>12 h			
rt-PA	22	88	
Placebo	35	97	
No heparin			
≤12 h			
rt-PA	15	39	0.7663
Placebo	19	59	
>12 h			
rt-PA	21	66	
Placebo	21	71	
Delay time‡ ≤3 h			
≤12 h			
rt-PA	30	68	0.1368
Placebo	34	98	
>12 h			
rt-PA	20	67	
Placebo	34	93	
Delay time‡ >3 h			
≤12 h			
rt-PA	4	25	0.6501
Placebo	6	25	
>12 h			
rt-PA	23	87	
Placebo	22	75	

*p value represents test for treatment by time to treatment interaction. † There were 25 patients (including 9 who died) who did not start treatment or who did not have data indicating whether they were treated at <12 h or >12 h after symptom onset. ‡ Delay time from hospital arrival to treatment. Abbreviations as in Table 1.

Discussion

The importance of myocardial salvage and improved patient survival achieved by successful coronary thrombolysis represent major advances in the management of acute myocardial infarction. However, there is compelling evidence that late reperfusion also favorably affects clinical outcome (7,11–14). Because >30% of patients with myocardial infarction seek medical care between 6 and 24 h after symptom onset, it is of utmost importance to establish firmly the risks and benefits of late thrombolysis. Although widespread concern has been raised about cardiac rupture, our findings—obtained in the largest study to examine the benefit of thrombolysis for patients treated 6 to 24 h from symptom onset—suggest strongly that late administration of thrombolytic therapy is not associated with an increased risk of this predominantly fatal event.

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Table 3. Patient Deaths From Cardiac Rupture, Electromechanical Dissociation or Asystole According to Time to Treatment

	All Patients		Time to Treatment ≤12 Hours		Time to Treatment >12 Hours	
Cause of Death	rt-PA	Placebo	rt-PA	Placebo	rt-PA	Placebo
*Rupture, EMD or asystole (combined)						
Total	79	98	34	40	43	56
Day 0–1	43	29	19	14	23	13
Day 2–7	30	49	13	21	16	28
Day 8–35	6	20	2	5	4	15
Rupture only						
Total	29	24	15	10	13	12
Day 0–1	18	5	9	2	8	1
Day 2–7	10	17	5	7	5	10
Day 8–35	1	2	1	1	0	1
EMD only						
Total	16	26	8	12	8	14
Day 0–1	7	13	3	7	4	6
Day 2–7	9	10	5	5	4	5
Day 8–35	0	3	0	0	0	3
Asystole only						
Total	34	48	11	18	22	30
Day 0–1	18	11	7	5	11	6
Day 2–7	11	22	3	9	7	13
Day 8–35	5	15	1	4	4	11

*There were 25 patients (including 9 who died) for whom treatment was not started or it was not possible to determine if they were treated <12 h or >12 h after symptom onset. Abbreviations as in Table 1.

Mechanisms of cardiac rupture. Cardiac rupture is a catastrophic complication of acute myocardial infarction responsible for 5% to 20% of all in-hospital deaths (15–19). It can take several forms, including free wall rupture, ventricular pseudoaneurysm formation, ventricular septal rupture, papillary muscle rupture and, less frequently, atrial rupture. In the prethrombolytic era, rupture usually occurred in the 1st 2 weeks after infarction with a peak incidence at 5 days (20,21). In contrast, cardiac rupture now may be accelerated by thrombolysis and coronary reperfusion.

There is firm evidence that transmural infarction is a prerequisite for cardiac rupture (20,22). In nontransmural infarction, the wave of necrosis that commonly extends from the endocardial to the epicardial surface in transmural infarction is arrested, leaving a shell of viable subepicardium. This shell, containing normal structural components and mechanical properties, may offer resistance to rupture. Thus, early successful thrombolysis and myocardial salvage would be expected to decrease the overall risk of rupture (23).

Myocardial hemorrhage, dissecting into an area of infarction, may contribute to cardiac rupture. In the prethrombolytic era most infarctions were described as anemic under gross or microscopic examination (24,25). In contrast, reperfusion achieved by thrombolysis (26) typically causes hemorrhagic infarction that is most pronounced in areas of extensive myocardial necrosis (27–29). Systemic anticoagulation with heparin could, at least theoretically, increase the overall extent of myocardial hemorrhage. In our study, heparin administration failed to influence the incidence of cardiac rupture in patients treated with rt-PA. However, because treatment with heparin was not randomized in the LATE study, it is difficult to draw firm conclusions about the effect of this agent (or anticoagulation in general).

At autopsy, hearts with rupture have been shown to have a virtual absence of collagen at the involved site (30,31). Diminution of collagen begins almost immediately after infarction and may be mediated by collagenases (32). Plasmin, a nonspecific proteolytic enzyme generated by all thrombolytic agents, increases collagen breakdown both through direct mechanisms and by activating latent tissue collagenases (33). Late thrombolysis could increase collagen breakdown at the time when neutrophil-mediated collagenase activity has already begun to weaken the supporting fibroskeleton (34), thereby predisposing to rupture. However, in this randomized, placebo-controlled trial of >5,000 patients, we were unable to show increasing risk for rupture with late thrombolysis, even in those who received treatment up to 24 h after symptom onset.

Previous studies. The GISSI-I trial (2), which entered patients with symptoms of myocardial infarction up to 12 h after symptom onset, reported a significantly higher rate of cardiac rupture among late entry patients treated with streptokinase (35). In a meta-analysis (8) including 58 patients with cardiac rupture among 1,638 patients from four trials, cardiac rupture directly correlated with time to treatment. The odds ratio for rupture was 0.4 at 7 h, 0.93 at 11 h and 3.21 at 17 h. An analysis of 4,692 deaths among 44,346 patients from 42 clinical trials demonstrated that the odds ratio of death was also directly correlated with time to treatment: 0.72 at 3 h, 0.88 at 14 h and 1.00 at 21 h. The conclusions drawn were that late treatment increased the risk of cardiac rupture but that thrombolytic therapy still offered overall benefit even when given as late as almost 24 h after symptom onset. Our findings in the LATE study support the hypothesis that the time window for thrombolysis with rt-PA should be extended to at least 12 h and possibly longer in selected patients. However, we were unable to show that cardiac rupture increases with treatment initiated after 12 h. There are several potential reasons for this negative finding. First, our study included 5,711 patients randomized to receive either rt-PA or placebo between 6 and 24 h after symptom onset. Unlike meta-analyses that use average time to treatment for groups of patients, we evaluated individual patients with suspected cardiac rupture. It is therefore likely that we were able to assess the effect of time to treatment on risk with greater precision. Second, rt-PA was the thrombolytic agent used in the LATE study. In contrast, streptokinase was the thrombolytic agent used in GISSI-I and in each of the four clinical trials included in the meta-analysis of Honan et al. (8). Although this concept has not previously been explored, it is possible that if the systemic lytic state contributes to cardiac rupture, nonselective thrombolytic agents may ultimately pose a greater risk than that of selective agents. We are currently investigating this possibility.

Limitations of the study. To increase the likelihood of including all potential cases of cardiac rupture, we included patients with electromechanical dissociation and asystole in the final analysis. It is therefore possible that we overestimated the actual occurrence of rupture. This possibility is balanced by the likelihood that we missed cardiac rupture in some patients without arrhythmia stigmata or autopsy; such patients are, in fact, highly likely to confound the data because of miscategorization. We analyzed the data by individual diagnosis (rupture, electromechanical dissociation or asystole) as well as by their composite. The findings were essentially unchanged. Although cardiac rupture was not an autopsy-confirmed diagnosis in each case, the similar autopsy rates and consistent classification criteria in the groups given rt-PA and placebo make it highly unlikely that a reporting bias influenced our results.

The LATE study, similar to other large scale clinical trials (2,10,35), grouped cardiac deaths into those resulting from nonmechanical failure (rupture, electromechanical dissociation, asystole) and those related directly to mechanical failure (shock, left ventricular failure, respiratory arrest). The decision to group cardiac rupture, electromechanical dissociation and asystole together represents a precedent set by the ISIS-I investigators (10). Clearly, it is not possible to obtain detailed pathologic confirmation in each suspected case of rupture in clinical trials including thousands of patients. A broader definition is preferred and allows greater applicability of the findings.

Conclusions and clinical implications. There is unequivocal evidence that early coronary thrombolysis improves survival in patients with myocardial infarction. The evidence is also strong that late treatment, up to and in some instances after 12 h from symptom onset, may offer significant benefit as well. Despite previous concerns, the findings of our prospectively designed study show conclusively that late treatment does not increase the incidence of cardiac rupture. However, they do suggest that the time course of rupture may be accelerated by thrombolysis. Although the present study was not designed to explore mechanisms, it seems plausible that successful reperfusion may accelerate rupture of type I (abrupt slitlike tear) or type II (erosion of the infarct zone) ruptures, while decreasing type III events (characterized by early aneurysm formation) (18). Clearly, this area warrants further investigation.

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