Effects of Thrombolytic Therapy Administered 6 to 24 Hours After Myocardial Infarction on the Signal-Averaged ECG

Results of a Multicenter Randomized Trial

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Background

Thrombolytic therapy reduces mortality after acute myocardial infarction (MI) by approximately 25%, 1-3 Greater mortality reduction is observed when earlier thrombolysis is achieved and is clearly demonstrable within 6 hours of symptom onset after MI. Recently, one large randomized trial (the Late Assessment of Thrombolytic Efficacy [LATE] trial) 4 concluded that the benefit of thrombolytic therapy extends to patients presenting 6 to 12 hours (and possibly up to 24 hours) after MI, especially when the initial ECG demonstrates ST elevation.

Both in-hospital and post–hospital discharge mortality are reduced by thrombolytic therapy. Early mortality is related predominantly to pump failure, whereas most deaths after hospital discharge for acute MI are sudden and presumably arrhythmic. Sustained ventricular tachyarrhythmias are the primary cause of sudden death, most often sustained ventricular tachycardia that degenerates to ventricular fibrillation.5 Several clinical factors predict the probability of sudden death, including left ventricular ejection fraction, spontaneous ventricular arrhythmia on Holter ECG, measures of autonomic tone, and the results of the signal-averaged ECG (SAECG). The SAECG is a noninvasive computerized surface ECG recording that can detect low-amplitude cardiac signals in the terminal portion of the QRS complex or within the ST segment; these “late potentials” are believed to represent slow, fragmented myocardial conduction that represents the substrate required for ventricular tachyarrhythmias.6 Several prospective studies after MI 7-9 demonstrated that the duration of ventricular activation (QRS duration) on the SAECG is the most sensitive and powerful variable predictive of sustained ventricular tachyarhythmias. Although the SAECG appears to retain its prognostic value in patients treated with thrombolytic agents,10 it is not clear to what extent the SAECG is affected by thrombolysis.

Although the mortality benefit of thrombolytic therapy is apparent, the underlying mechanism is incompletely understood. Surprisingly, the mortality benefit of thrombolytic therapy is not entirely explained by improvement in myocardial systolic function11 even with early thrombolysis. The gap in understanding has led to speculation regarding alternative mechanistic explana-
tions. One such mechanism is enhancement of electrical stability.\textsuperscript{12-17} Nonrandomized, uncontrolled, or retrospective studies\textsuperscript{12-17} have suggested this to be the case, as assessed by the SAECG, although the results have been conflicting\textsuperscript{18} and compromised by design limitations.

The era of placebo-controlled trials of thrombolytic therapy, either early or late, has come to a close. The present study afforded a unique and probably final opportunity to definitively investigate the possible mechanisms of benefit of thrombolysis during acute MI. Specifically, we tested the hypothesis that thrombolytic therapy with recombinant tissue-type plasminogen activator (rTPA) improves electrical stability, as assessed by the SAECG, in patients treated 6 to 24 hours after MI. This question was addressed with a prospective, randomized, placebo-controlled, double-blind multicenter ancillary study of LATE involving 310 patients.

Methods

The LATE Trial

LATE was an international multicenter double-blind placebo-controlled study in which patients with suspected acute MI 6 to 24 hours after onset of symptoms were randomized to rTPA or placebo. The major objective of the trial was to determine whether late treatment with rTPA reduces total mortality. All patients were given oral aspirin at hospital admission and for the duration of study participation.

Patients were eligible if they were >18 years of age and presented with suspected acute MI between 6 and 24 hours after the onset of symptoms. Acute MI was defined as chest pain consistent with coronary ischemia of >30 minutes’ duration and an abnormal ECG defined as ST elevation ≥1 mm in two or more standard leads or ≥2 mm in two or more chest leads, ST depression ≥2 mm in two or more leads, new Q waves, T-wave inversion in two or more leads, or elevated cardiac enzymes with nondiagnostic ECGs.

Major exclusion criteria included any previous stroke, transient ischemic attack within 6 months, active peptic ulcer disease within 6 months, gastrointestinal or genitourinary bleeding within 6 months, trauma or surgery within 1 month, head or spinal surgery within 6 months, use of an oral anticoagulant, known bleeding diathesis, known diabetic proliferative retinopathy, systolic blood pressure >200 or diastolic blood pressure >110, or vigorous CPR.

rTPA was given as an initial bolus of 10 mg, followed by an infusion of 50 mg in the next hour and 20 mg in each of the next 2 hours. Oral aspirin, 150 to 325 mg/d, was begun on hospital admission. Intravenous heparin was not mandated by the protocol but was strongly encouraged. All further treatment and investigations (including cardiac catheterization) were at the discretion of individual treating physicians.

All patients were followed for at least 6 months.

SAECG Recording

An SAECG was recorded in all participating patients by a previously described method.\textsuperscript{7} Briefly, the SAECG was recorded from three orthogonal leads to a preprocessing noise value in the TP segment of <0.3 μV with a Corazoinx Predictor.

SAECG Analyses

The three leads were combined into a vector sum that had been processed with a bidirectional Butterworth filter at a bandpass setting of 40 to 250 Hz. The QRS onset and offset set by computer algorithm were manually overread by an observer unaware of the patient’s treatment status. Three measure-

ments were obtained from the amplified and filtered vector composite: (1) total QRS duration (tQRS); (2) root mean square voltage in the terminal 40 milliseconds of the QRS (V₉₀); and (3) low-amplitude terminal signal duration <40 μV (LAS). On the basis of several analyses of large data sets,\textsuperscript{19,20} the SAECG was abnormal when the tQRS was >120 milliseconds. Definitions of abnormal SAECG variables also included V₉₀ <20 μV and an LAS >38 milliseconds. Because of the difficulty encountered in interpreting the SAECG in the presence of bundle-branch block, these patients were excluded from analysis.

Ancillary Study Organization

At 23 LATE participating sites (see “Appendix”) in Canada, the United Kingdom, and the United States, all LATE-enrolled patients were screened for enrollment in the LATE ancillary studies. SAECG acquisition was performed at individual sites before hospital discharge according to the standardized protocol designed to promote comparability of recordings by ensuring a uniform and low noise end point.\textsuperscript{21} SAECG recordings were shipped by computer disk to the SAECG Core Laboratory located at St Luke's-Roosevelt Hospital Center. Reading of the SAECG was performed by automated algorithm (see above) and reviewed by an experienced investigator at the Core Laboratory who was blinded to all patient characteristics, including treatment assignment.

All LATE patients were potentially eligible to participate regardless of ECG finding (ie, Q wave or non-Q wave, inferior or anterior MI site) on admission. Only patients with bundle-branch block or intraventricular conduction defect (QRS duration >120 milliseconds) and patients whose SAECGs were unreadable were excluded. Given an assumption of a frequency of abnormal SAECG of 30% in the placebo group and an α error of .05 and β error of .20, a sample size of approximately 300 was established as the goal to detect a 50% reduction in the rate of SAECG abnormality. Prespecified subgroup analyses were planned to examine the effects of time to treatment (6 to 12 versus 12 to 24 hours)\textsuperscript{22} and ST elevation or new Q waves on admission ECG (ST elevation versus no ST elevation).

Statistics

Data are presented as mean±SD. Primary comparisons were made between all placebo-treated patients and all rTPA-treated patients. Comparisons included SAECG variables (tQRS, V₉₀, LAS) and rates of abnormal SAECG, according to the definition stated above. Continuous variables were compared with Student's t test. Categorical variables were compared with the χ² test and with Fisher's exact test. ANOVA was used to test time to treatment and treatment assignment interactions. The null hypotheses were rejected and/or intergroup differences deemed statistically significant at a value of P<.05.

Results

Patient Population

Between August 13, 1990, and April 30, 1992, 310 patients were enrolled, representing 81% of all LATE patients at the 23 participating sites during the period of the ancillary study. Of the total group, 160 were randomized to receive placebo and 150 were randomized to receive rTPA. The placebo and treatment groups were well balanced for baseline characteristics (see Table 1). Notably, these patient groups did not differ in age, time to thrombolytic therapy after MI onset, site of MI, peak creatine phosphokinase, left ventricular function, medical therapy, or hospital course. The day of SAECG recording was similar between the two groups. The
baseline characteristics were comparable to the population of the main LATE trial.4

SAECG Results in the Total Group

Table 2 shows the SAECG results according to the treatment assignment. The fQRS was shorter in the rTPA group (P=.05), but the V_a and the LAS, although improved by rTPA, were not statistically different between the treatment groups. The magnitude of the absolute difference in fQRS was relatively small, approximately 3%. The proportion of patients with fQRS >120 milliseconds was 19% in the placebo-treated patients compared with 12% in the rTPA-treated patients, a reduction of 37% (95% CI, −64%, +6%; P=.087). There were no differences in the proportion of patients with abnormal V_a or LAS according to treatment assignment.

Relation of SAECG Results to Time of Treatment

Patients were subdivided into groups based on time after MI onset when study treatment was initiated. By ANOVA, there was no effect of time on treatment on the SAECG results. In the placebo group, 38 patients received treatment within 6 to 12 hours and 122 patients within 12 to 24 hours. The fQRS was 108±13 and 109±15 milliseconds in these two groups, respectively. In the rTPA group, 48 patients were treated within 6 to 12 hours and 102 patients within 12 to 24 hours. The fQRS was 105±13 and 106±14 milliseconds, respectively. The benefit of rTPA was still apparent in each of the treatment time windows. The V_a and LAS showed no differences in relation to timing of study treatment.

Relation of SAECG and Delay of Treatment

The LATE protocol permitted patient enrollment after admission as long as patients remained within the 24-hour time window. Thus, patients were randomized after a period of deferral in some cases; this period of deferral was a strong predictor of lack of rTPA benefit in the parent trial.4 In the ancillary study, 82 patients (26%) received study therapy within 3 hours of presentation, and 228 patients (74%) received therapy 3 to 24 hours after admission. The benefit of rTPA on fQRS was much more apparent in the ≤3 hour delay group, an interaction that was statistically significant (P=.01). When rTPA treatment was initiated within 3 hours of admission, the fQRS was 7% less prolonged than in the placebo treatment patients. The rTPA benefit was much more modest, 2%, when treatment was initiated after >3 hours delay. The frequency of abnormal SAECG was greatly reduced by rTPA in the ≤3 hour delay group (11% versus 31%, P=.03) but not in the >3 hour delay group (13% versus 16%, P=NS).

SAECG Results in the Subgroup With ST Elevation on Qualifying ECG

A prior assumption was that patients who presented with ST elevation were most likely to benefit from rTPA therapy. Those patients whose ECG at the time of LATE qualification showed ST elevation were thus subgrouped and analyzed separately. Table 3 shows the results within this subgroup. The placebo-treated patients had a significantly longer fQRS than rTPA-treated patients (P=.01). The difference in these absolute values was approximately 4.5%. As in the total group, V_a did not differ. There was a trend toward a longer LAS in the placebo-treated group (P=.09). The
propion of patients with a prolonged fQRS >120 milliseconds was greatly reduced by rTPA therapy. In the placebo group, 23% had a prolonged fQRS versus 11% in the rTPA group (P=.011). Hence, rTPA resulted in a 52% reduction (95% CI, 4%, 77%) in the proportion of this subset of patients with an abnormal SAECG. There was no difference in the frequency of abnormal Vm or LAS according to treatment assignment. It is also evident that rTPA treatment has produced a striking improvement in the proportional distribution of patients relative to fQRS throughout the fQRS range. As shown in Fig 1, patients treated with rTPA were shifted to the left of the placebo-treated patients. There was a consistent increase in the proportion of patients with shorter fQRS at all values. In addition, the leftward shift becomes accentuated at the longer fQRS values, where the change in distribution was dramatic.

In contrast to patients with ST elevation, those without ST elevation on admission showed no difference in the SAECG after rTPA therapy compared with placebo (Fig 2). The proportion of patients with a prolonged fQRS duration was 14% regardless of treatment assignment in these 125 patients. The absolute values were similar as well: 105.7±16.9 milliseconds for the 66 rTPA patients and 105.6±14.4 milliseconds for the 59 placebo patients (P=NS).

In-Hospital Ventricular Fibrillation and Mortality After MI

Ventricular fibrillation was experienced by one patient treated with placebo and two patients treated with rTPA in the acute phase of MI. Before hospital discharge, there were three deaths in the placebo group and one death in the rTPA group. Two additional patients in the placebo group and one additional patient in the rTPA group died at 1-month follow-up.

Discussion

The SAECG has been used extensively in the past few years to predict the risk of sustained ventricular tachyarrhythmias. When used in prospective post-MI studies, the presence of an abnormal SAECG conferred a marked increase (from 3- to 11-fold) in risk of a life-threatening arrhythmic event7-9 and was independent of both left ventricular ejection fraction and Holter monitor results.7 The SAECG accurately and noninvasively measures characteristics of ventricular conduction and thus can portray the status of a critical determinant of ventricular arrhythmia substrate.

Several uncontrolled studies have suggested a significant decrease in the frequency and severity of SAECG abnormalities after thrombolysis14-17 and even greater improvement in patients in whom the infarct artery was shown to be patent at angiography14-17,23-25 that is independent of changes in ejection fraction.16,17 However, there had been no prospective, randomized, or placebo-controlled studies of the effect of thrombolysis on the SAECG and arrhythmic risk.

In this investigation, the only prospective, randomized, and placebo-controlled study of its kind, the SAECG was significantly improved in patients who received rTPA 6 to 24 hours after MI compared with patients treated with placebo. Specifically, the filtered QRS duration, the most potent and sensitive SAECG risk variable,7,9 was shortened, and the proportion of patients with fQRS >120 milliseconds,19 a group at highest risk of sudden death, was reduced from 19% to 12% with rTPA. The improvement in filtered QRS duration was limited to patients presenting with ST elevation, in whom the frequency of abnormal SAECG was reduced by half and a favorable shift in fQRS distribution throughout its range was observed. This observation suggests that benefit is achieved in those patients with total coronary occlusion who are threatened with transmural MI but not in those in whom the infarct artery is patent and the extent of MI is less.
Although the degree of filtered QRS benefit was relatively small, there was a clear-cut shift in the distribution of SAECG abnormality toward less prolongation, especially in the patients with marked fQRS prolongation (Fig 1). The filtered QRS as a continuous variable is associated with increasing risk throughout its range; for every 3-millisecond prolongation of fQRS, the risk of sustained ventricular tachyarrhythmias increases 8%. This relation would suggest that the degree of filtered QRS reduction observed in the present study could translate into a ventricular tachyarrhythmia risk reduction of approximately 8% in all rTPA-treated patients and of 14% in rTPA-treated patients with ST elevation on the qualifying ECG. Thus, the findings in the present study could explain a major portion of the 30-day mortality reduction seen in LATE: 14% for all enrolled LATE patients and 20% for patients with ST elevation.

There was no gradient in treatment benefit related to the timing after symptom onset; ie, patients treated to 12 hours after symptom onset demonstrated similar fQRS improvement compared with patients treated in the 12 to 24 hour time window. The explanation for this finding is unclear but may relate to the issue of deferral; patients treated promptly (≤3 hours) after presentation had substantial improvement of the SAECG results, and those in whom rTPA treatment was deferred did not benefit. Deferred therapy was more likely to be initiated >12 hours after symptom onset. It is also possible that in many patients it is difficult to define with accuracy the precise onset of MI.

Possible Mechanisms of Benefit of Late Reperfusion

There are several mechanisms by which thrombolysis, even when it occurs relatively late after onset of MI, may benefit patients. Such mechanisms include improved left ventricular systolic function as well as prevention of infarct expansion, ventricular remodeling, and aneurysm formation. Additionally, the restoration of blood flow through the infarct-related artery can be an important source of coronary blood flow through collateral channels to a remote vascular bed that becomes ischemic. It is unknown whether late reperfusion is clinically important because it initiates and maintains patency of a previously occluded vessel or because it interrupts the dynamics of endogenous thrombosis/thrombolysis toward more sustained vessel patency and perfusion.

Another important mechanism by which reperfusion may be salutary is enhancement of cardiac electrical stability. Multicenter trials have suggested that primary ventricular fibrillation is reduced after early thrombolysis. Provocation of ventricular tachycardia by electrophysiological study has been correlated with the absence of early reperfusion. In a small but provocative study, Sager et al observed not only a high rate of ventricular tachycardia induction but also a high spontaneous rate of ventricular tachycardia and ventricular fibrillation in follow-up of patients without reperfusion compared with matched patients with severe left ventricular dysfunction and aneurysm but successful reperfusion. Last, the Coronary Artery Surgical Study demonstrated that bypass surgery (ie, restoration of perfusion) in patients with left ventricular dysfunction appeared to reduce the subsequent risk of sudden death.

Arrhythmia formation may be a highly complex and dynamic process. For example, the occurrence of ventricular tachycardia depends on the appropriate balance of myocardial conduction delay and recovery of excitation. These electrical properties may in turn be modulated by the pathology of the infarct, degree of ischemia, left ventricular volume or stretch, and sympathetic innervation, all of which may be related to the presence and degree of reperfusion.

Infarct Artery Patency and Late Reperfusion

Evidence is accumulating that a major benefit of thrombolysis is mediated to a large extent by restoration of patency to a previously occluded infarct artery independent of when patency occurs. There are several lines of evidence, independent of extensive myocardial salvage, that lend credence to this supposition. Infarct artery patency predicts improved survival and also improves two important determinants of survival: infarct expansion and SAECG abnormalities. Even when rTPA is administered late after acute MI, the majority (approximately 65%) of patients will still achieve patency with TIMI grade III reperfusion. The results of the present study probably reflect the benefit on the electrophysiological substrate resulting from late restoration of infarct artery patency. The fact that benefit was observed largely in the group with ST elevation lends further credence to the patent infarct artery hypothesis. These patients, as evidenced by ST elevation, probably had an occluded artery on presentation and therefore would have the most to gain from successful reperfusion. Since coronary angiography was not a required part of the LATE protocol or the ancillary studies, this remains a matter of reasoned speculation.

Conclusions

At a time in which little myocardial salvage can be expected, late thrombolysis (6 to 24 hours after onset of symptoms associated with acute MI) results in less SAECG abnormality, principally in patients who present with ST elevation on the ECG. These observations probably reflect a more stable electrical substrate achieved through infarct artery reperfusion and probably represent an important mechanism of mortality benefit of late thrombolysis.

Acknowledgments

This study was supported by a grant from Genentech, Inc, San Francisco, Calif. The authors are extremely grateful for the expert technical assistance of Edith Menchavez-Tan, RN, of the SAECG Core Laboratory; Christine Beck, RN, and Wanda Sutherland, RN, of the University of Toronto; Carroll Gomez and Eileen Lee of the Sunnybrook Epidemiology Unit; and Rosalie Sinkler for preparation of the manuscript. The authors also thank Drs Robert Wilcox and Alan Skene for their superb assistance at the LATE Data Coordinating Center in Nottingham, UK.

Appendix

The following are the sites and the research personnel of the LATE Ancillary Study (listed in order of patient enrollment):
Royal Columbian Hospital, BC (Dr J David Hilton); Hum- ber Memorial Hospital, Weston (Dr Ming-Tat Cheung); Mon- treal Heart Institute, Montreal (Dr Pierre Theroux, Dr Mario Talajic); Toronto East General, Toronto (Dr Charles A. Lefkowitz); St Luke’s-Roosevelt Hospital Center, New York (Dr Judith Hochman, Dr Henry Greenberg); University Hospital, Nottingham, UK (Dr Robert Wilcox); Sunnybrook Health Science Center, Toronto (Dr Christopher Morgan); Montefiore Medical Center, Bronx, NY (Dr Hiltrud Mueller); University of Sherbrooke, Quebec (Dr Vincent Dangoisse); Manchester General Hospital, UK (Dr Simon Handley); Tor-onto Western Hospital, Toronto (Dr Paul Daly); Scarborough Grace Hospital, Toronto (Dr John L. Charles); York Finch General Hospital, Downsview (Dr Ivan Hronsly); North Ties General Hospital, Cleveland UK (Dr R.H. Smith); Toronto General Hospital, Toronto (Dr Paul Daly); Veterans Administra- tion Medical Center, Danville, Ill (Dr Nasser Gayed); York District Hospital, York, UK (Dr R.M. Boyle); St Jo- seph’s Health Center, Toronto (Dr Narasimhan Ranga- nathan); Victoria General Hospital, NS (Dr Karen A. Sam- ple); Mother Francis Hospital, Tyler, Texas (Dr Robert Carney); York Central Hospital, Richmond Hill (Dr John Blakely, Dr Martin Richmond); Columbia Presbyterian Medical Center, New York (Dr Hal S. Wasserman, Edith L. Escala, RN); St. Michael’s Hospital, Toronto (Dr Paul Armstrong); LSU School of Medicine, New Orleans (Dr Pramilla Subra- manian).

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Dr Paul W. Armstrong (Chair), Dr Judith S. Hochman, Dr Christopher D. Morgan, Dr Jonathan S. Steinberg, Dr Pierre Theroux, and Dr Eric J. Topol.

Signal-Averaged ECG Core Laboratory
Dr Jonathan S. Steinberg (Director) and Edith Menchavez-Tan.

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_Circulation_. 1994;90:746-752
doi: 10.1161/01.CIR.90.2.746

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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