

TISSUE PLASMINOGEN ACTIVATOR IN CARDIAC ARREST WITH PULSELESS ELECTRICAL ACTIVITY

RIYAD B. ABU-LABAN, M.D., M.H.Sc., JAMES M. CHRISTENSON, M.D., GRANT D. INNES, M.D., CATHERINA A. VAN BEEK, R.N., B.S.N., KAREN P. WANGER, M.D., R. DOUGLAS MCKNIGHT, M.D., IAIN A. MACPHAIL, M.D., M.H.Sc., JOE PUSKARIC, E.M.A.-3, RICHARD P. SADOWSKI, E.M.A.-3, JOEL SINGER, Ph.D., MARTIN T. SCHECHTER, M.D., Ph.D., AND VICTOR M. WOOD, M.D.

ABSTRACT

Background Coronary thrombosis and pulmonary thromboembolism are common causes of cardiac arrest. We assessed whether the administration of tissue plasminogen activator (t-PA) during cardiopulmonary resuscitation would benefit patients with cardiac arrest and pulseless electrical activity of unknown or presumed cardiovascular cause.

Methods Patients who were older than 16 years of age and who had more than one minute of pulseless electrical activity that was unresponsive to initial therapy outside the hospital or in the emergency department were eligible. Patients were randomly assigned to receive 100 mg of t-PA or placebo intravenously over a 15-minute period in a double-blind fashion. Standard resuscitation was then continued for at least 15 minutes. The primary outcome was survival to hospital discharge.

Results During the study period, 1583 patients with cardiac arrest were treated and 233 patients were enrolled (117 in the t-PA group and 116 in the placebo group). The characteristics of the patients in the two groups were similar. One patient in the t-PA group survived to hospital discharge, as compared with none in the placebo group (absolute difference between groups, 0.9; 95 percent confidence interval, -2.6 to 4.8; $P=0.99$). The proportion of patients with return of spontaneous circulation was 21.4 percent in the t-PA group and 23.3 percent in the placebo group (absolute difference between groups, -1.9; 95 percent confidence interval, -12.6 to 8.8; $P=0.85$).

Conclusions We found no evidence of a beneficial effect of fibrinolysis in patients with cardiac arrest and pulseless electrical activity of unknown or presumed cardiovascular cause. Our study had limited statistical power, and it remains unknown whether there is a small treatment effect or whether selected subgroups may benefit. (N Engl J Med 2002;346:1522-8.)

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OUT-OF-HOSPITAL cardiac arrest results in some 250,000 deaths annually in the United States and Canada.^{1,2} Patients with pulseless electrical activity constitute 20 percent of victims of cardiac arrest, and only about 4 percent of such patients survive to be discharged from the hospital.³ Unlike other rhythms, pulseless electrical activity is frequently considered a state of

severe shock, since some forward blood flow can occur.⁴⁻⁶ This observation has prompted heightened vigilance for reversible causes during treatment of pulseless electrical activity.⁷ That low-grade cerebral and coronary perfusion may persist during pulseless electrical activity supports the concept that the outcome can be good, even after prolonged cardiopulmonary resuscitation (CPR), if the cause of cardiac arrest is identified and addressed.

Few studies have characterized the causes of cardiac arrest, but acute coronary thrombosis and pulmonary thromboembolism are clearly important.^{8,9} Given the benefit of fibrinolytic (thrombolytic) agents in myocardial infarction and pulmonary embolism, there is increasing interest in the potential role of these drugs in cardiac arrest. Both theoretical reasoning and studies in laboratory animals support the hypothesis that fibrinolytic agents could be effective during CPR.¹⁰⁻¹⁴

Many studies have suggested that the administration of fibrinolytic agents during CPR can have a dramatic effect,¹⁵⁻²⁵ but there have been no randomized trials of this approach. We undertook this study to evaluate the effect of the administration of tissue plasminogen activator (t-PA) during CPR in adults with undifferentiated pulseless electrical activity (i.e., with an unknown or presumed cardiovascular cause) that was not responsive to initial therapy.

METHODS

Location of the Study

This randomized, double-blind, placebo-controlled trial was conducted between February 12, 1998, and September 30, 1999, in the greater Vancouver region in Canada at seven advanced-life-support paramedic base stations and in the emergency departments of three tertiary teaching hospitals. This region has a population of over 2 million persons served by the British Columbia Ambulance Service. In this region, victims of out-of-hospital cardiac arrest are treated by paramedics using protocols based on American Heart Association guidelines,²⁶ and they are not transported to a hospital unless a perfusing rhythm develops, a shockable rhythm persists, or extenuating circumstances exist.

From the Division of Emergency Medicine, University of British Columbia, Vancouver (R.B.A.-L., J.M.C., G.D.I., C.A.B., K.P.W., R.D.M., I.A.M., V.M.W.); the British Columbia Ambulance Service, Victoria (J.M.C., K.P.W., I.A.M., J.P., R.P.S.); and the Centre for Health Evaluation Outcome Services, Vancouver, B.C. (J.M.C., G.D.I., J.S., M.T.S.) — all in Canada. Address reprint requests to Dr. Abu-Laban at the Department of Emergency Medicine, Vancouver General Hospital, 855 West 12th Ave., Vancouver, BC V5Z 1M9, Canada, or at abulaban@interchange.ubc.ca.

Patients

Victims of cardiac arrest who were older than 16 years of age were eligible if they had had pulseless electrical activity for more than one minute and had had no palpable pulse for more than three minutes during resuscitative efforts and at the time of the initiation of the study drug. Pulseless electrical activity was defined by the occurrence of more than 20 electrical complexes (excluding ventricular fibrillation and ventricular tachycardia) per minute in the absence of a palpable pulse. Before enrollment, all patients underwent endotracheal intubation, received ventilation with 100 percent oxygen, and were given at least 500 ml of normal saline and 1 mg of epinephrine intravenously.

The following were exclusion criteria: a do-not-resuscitate directive; trauma; overdose; pregnancy; a history of intracranial tumor or hemorrhage; a history of stroke or neurosurgery within the previous six weeks; hypothermia; evidence of tension pneumothorax or cardiac tamponade; evidence of hemorrhage, asphyxia, or airway compromise as a cause of the cardiac arrest; or renal dialysis. In addition, patients were excluded if a paramedic student was directing the resuscitation under practicum supervision.

Protocol

All patients received standard care during CPR. Eligible patients were randomly assigned to receive treatment with a drug kit containing two vials of lyophilized placebo or lyophilized t-PA (Activase, Hoffmann-LaRoche [supplied by Genentech]; 50 mg per vial). Batches of six kits were supplied to sites according to a block randomization scheme. The appearance of the t-PA and placebo before and after reconstitution was indistinguishable. The placebo and the t-PA were reconstituted by the addition of 100 ml of sterile water and administered as a peripheral intravenous infusion over a 15-minute period during CPR. Once commenced, the infusion was completed regardless of whether a pulse developed. Resuscitation efforts were continued for a minimum of 15 minutes after the infusion was completed, and further treatment was at the discretion of the CPR leader. The decision to administer heparin, aspirin, or both to survivors to hospital admission was at the discretion of the attending physician. Physicians could request that blinding be suspended if a patient's subsequent care required the identification of all agents given during CPR. With the exception of such cases, study personnel, caregivers, patients, and their families remained unaware of the treatment assignments. The sponsor was not involved in the design or operation of the trial; in the management, analysis, or interpretation of the data; or in the preparation of the manuscript.

Collection of Data

The CPR leader completed a questionnaire on each patient with cardiac arrest and pulseless electrical activity. Further information was obtained from the out-of-hospital or emergency department records. Those who survived to hospital admission were monitored by a research coordinator beginning no later than one day after admission, and postmortem findings were obtained for all patients who underwent autopsy.

Outcomes

All outcomes were defined a priori, and applicable data were collected according to the Utstein style.²⁷ The primary outcome was survival to hospital discharge. Secondary outcomes were return of spontaneous circulation (defined by a palpable pulse of any duration), length of hospital stay, hemorrhage, and neurologic outcome. Hemorrhage was categorized as major or minor according to standard definitions.^{28,29} Neurologic outcome was assessed with the use of four validated scales: the Glasgow Coma Scale,³⁰ the Glasgow-Pittsburgh Cerebral and Overall Performance Scales,^{31,32} the Modified Mini-Mental State Examination,³³ and the Functional Status Questionnaire.³⁴ Survivors were followed for one year after hospital discharge.

Approval, Monitoring, and Consent

The study was monitored as part of the investigational-drug program of Health Canada by an independent data and safety monitoring committee whose members were aware of the patients' treatment assignments. Approval was obtained from the institutional review board of the University of British Columbia, the research ethics committees of participating hospitals, and the British Columbia Ambulance Service. As in other studies of cardiac arrest, the study was conducted according to a policy of implied (presumed) consent. The operative assumption was that during a life-threatening event, a reasonable person would consent to potentially lifesaving experimental intervention if it were possible to do so.³⁵ Before the study began, a press release was issued to notify the community of the study. Survivors or their proxy decision makers were notified that the patients had been enrolled, and written informed consent was obtained for the collection of follow-up data.

Statistical Analysis

Since only 4 percent of patients with pulseless electrical activity survive, and most who do have a response to initial interventions,^{3,36} we estimated that 1 percent of eligible patients would survive to hospital discharge. We assumed that 32 percent of patients with pulseless electrical activity have coronary or pulmonary thrombosis,⁸ and that 30 percent of the patients in this subgroup who received t-PA would survive to discharge, as compared with 1 percent of those without these conditions given t-PA and 1 percent of those given placebo. The study was therefore designed with 80 percent power to detect an absolute increase in the rate of survival to hospital discharge of 9.3 percent (an overall change from 1 percent to 10.3 percent). A two-sided calculation of the sample size, based on an alpha level of 5 percent, showed that 230 patients would need to be enrolled. Two interim analyses were planned, and the O'Brien-Fleming procedure for a three-stage design was applied, wherein the significance level for the final analysis of the primary outcome was 0.045 or less. Outcomes were evaluated with use of the chi-square test for proportions, Fisher's exact test, or the Wilcoxon rank-sum test. A P value of 0.05 or less was considered to indicate statistical significance in the case of secondary outcomes. The analyses were conducted according to the intention-to-treat principle, and all t-tests were two-sided.

RESULTS

Study Population

During the study period, CPR was performed on 1583 persons in the study area, 756 (47.8 percent) of whom had a qualifying episode of pulseless electrical activity. Of 289 eligible patients, 233 (80.6 percent) were enrolled (117 in the t-PA group and 116 in the placebo group). Of 467 ineligible patients, 29 (6.2 percent) were excluded because a paramedic student was directing the resuscitation under practicum supervision. In the case of four patients (1.7 percent), the treatment assignment was unblinded. Paramedics enrolled 224 patients outside the hospital (96.1 percent), and emergency physicians enrolled 9 patients in the hospital (3.9 percent). Data were missing on four unenrolled victims of cardiac arrest during the study period (0.3 percent).

Base-Line Characteristics of the Patients

The characteristics of the patients were similar in the two groups (Table 1), and there were no significant differences between the groups with respect to

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	TISSUE PLASMINOGEN	
	ACTIVATOR GROUP (N=117)	PLACEBO GROUP (N=116)
Age — yr		
Mean ±SD	70±13.1	69±15.6
Range	34–95	26–95
Sex — no. (%)		
Female	36 (30.8)	28 (24.1)
Male	81 (69.2)	88 (75.9)
Estimated weight — no. (%)		
<40 kg	0	1 (0.9)
40–60 kg	24 (20.5)	18 (15.5)
61–80 kg	60 (51.3)	57 (49.1)
>80 kg	28 (23.9)	35 (30.2)
Unrecorded	5 (4.3)	5 (4.3)
Location of incident — no. (%)		
Home	82 (70.1)	72 (62.1)
Other	30 (25.6)	41 (35.3)
Unrecorded	5 (4.3)	3 (2.6)
Medical history — no. (%)		
Stroke or transient ischemic attack	15 (12.8)	9 (7.8)
Cardiac arrest	2 (1.7)	1 (0.9)
Myocardial infarction	33 (28.2)	23 (19.8)
Angina	16 (13.7)	16 (13.8)
Congestive heart failure	13 (11.1)	11 (9.5)
Dysrhythmia	8 (6.8)	6 (5.2)
Hypertension	28 (23.9)	25 (21.6)
Diabetes	23 (19.7)	16 (13.8)
Other	59 (50.4)	51 (44.0)
Unknown	15 (12.8)	20 (17.2)
Medications — no. (%)		
Nitrates	23 (19.7)	42 (36.2)
Beta-blockers	13 (11.1)	22 (19.0)
Calcium-channel blockers	10 (8.5)	8 (6.9)
Antidysrhythmic agent	3 (2.6)	5 (4.3)
Other cardiac agents	42 (35.9)	31 (26.7)
Diabetes-related agents	16 (13.7)	10 (8.6)
Diuretic	31 (26.5)	26 (22.4)
Anticoagulant	6 (5.1)	6 (5.2)
Aspirin	8 (6.8)	5 (4.3)
Other, noncardiac agents	62 (53.0)	52 (44.8)
Unknown	18 (15.4)	21 (18.1)
Site of enrollment — no. (%)		
Out of hospital	112 (95.7)	112 (96.6)
Emergency department	5 (4.3)	4 (3.4)

variables predictive of survival (Table 2). Twenty-six minor protocol violations occurred, all of which involved the continuation of CPR for slightly less than 15 minutes after the infusion was completed. All patients were intubated and received the required intravenous saline and epinephrine before the administration of t-PA or placebo. No ineligible patients were given t-PA or placebo. Table 3 outlines the medications administered during CPR. Figure 1 provides an overview of critical steps in resuscitation and the timing of these steps, thus indicating the point at which patients received t-PA or placebo.

Outcomes

Primary and secondary outcomes are summarized in Table 4. Of the 77 patients who were transported

TABLE 2. PREDICTORS OF SURVIVAL.

VARIABLE	TISSUE PLASMINOGEN	
	ACTIVATOR GROUP (N=117)	PLACEBO GROUP (N=116)
	no. (%)	
Witnessed collapse	66 (56.4)	65 (56.0)
Compression provided by bystander*	41 (36.9)	32 (29.4)
Ventilation provided by bystander*	42 (37.8)	34 (31.2)
Shock provided by automated external defibrillator†	20 (17.1)	24 (20.7)
Initial rhythm		
Pulseless electrical activity	57 (48.7)	67 (57.8)
Ventricular fibrillation	31 (26.5)	24 (20.7)
Asystole	28 (23.9)	24 (20.7)
Ventricular tachycardia	1 (0.9)	1 (0.9)

*Data were unavailable for six patients in the tissue plasminogen activator group and seven in the placebo group.

†This category refers to cases in which first responders arrived before advanced-life-support paramedics.

TABLE 3. MEDICATIONS GIVEN DURING CARDIOPULMONARY RESUSCITATION.

MEDICATION	TISSUE PLASMINOGEN	
	ACTIVATOR GROUP (N=117)	PLACEBO GROUP (N=116)
	no. (%)	
Epinephrine	117 (100)	116 (100)
Atropine	70 (59.8)	77 (66.4)
Sodium bicarbonate	108 (92.3)	109 (94.0)
Lidocaine	51 (43.6)	41 (35.3)
Procainamide	11 (9.4)	4 (3.4)
Calcium	5 (4.3)	2 (1.7)

to a hospital, 29 arrived with a pulse and 13 survived to hospital admission. One patient in the t-PA group survived to hospital discharge (0.9 percent; 95 percent confidence interval, 0.0 to 4.7 percent), whereas none did so in the placebo group (0 percent; 95 percent confidence interval, 0.0 to 3.1 percent). The absolute difference in survival between the t-PA group and the placebo group was 0.9 percent (95 percent confidence interval, -2.6 to 4.8 percent; P=0.99). The rate of survival to discharge among the 467 ineligible patients was 4.7 percent.

A total of 21.4 percent of patients in the t-PA group and 23.3 percent of patients in the placebo group had a return of spontaneous circulation (absolute difference between groups, -1.9 percent; 95 percent confidence interval, -12.6 to 8.8 percent;

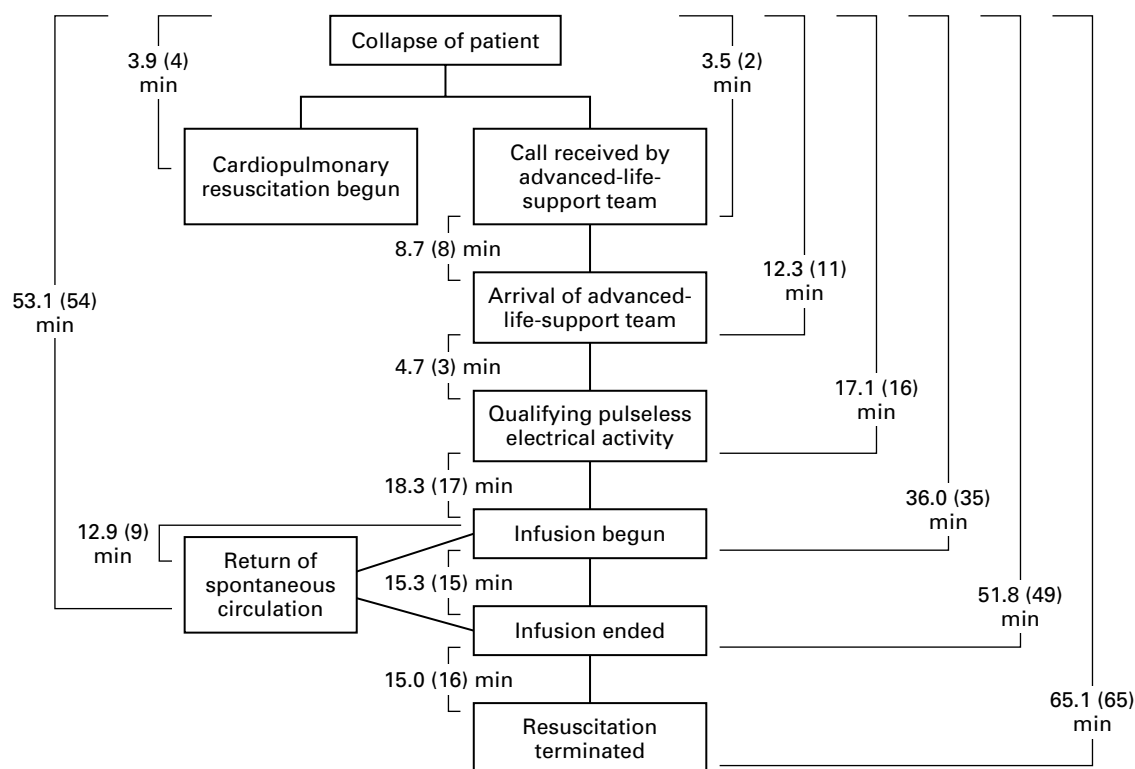


Figure 1. Time Course of Events in Patients with Cardiac Arrest Who Received Tissue Plasminogen Activator or Placebo. Values are mean (median) intervals between the specified events.

$P=0.85$). Four patients, all of whom were in the t-PA group, survived longer than 24 hours after hospitalization. The sole patient who survived to discharge was a 56-year-old man whose collapse had been witnessed, who did not receive CPR from a bystander, and who was pulseless for 36 minutes after an initial period of ventricular fibrillation followed by 20 minutes of pulseless electrical activity. After having a pulmonary hemorrhage and undergoing a percutaneous coronary intervention, he recovered completely, with a one-year score of 91 on the Modified Mini-Mental State Examination (maximum, 100) and a score of 80 on the Functional Status Questionnaire (maximum, 108).

Autopsy Findings

Autopsies were carried out on 42 patients (18.0 percent), and death was attributed to a cardiovascular cause in 25 patients (59.5 percent), 9 of whom had an acute myocardial infarction (21.4 percent); hemorrhage (either aortic dissection or myocardial rupture) in 4 patients (9.5 percent); and pulmonary

embolism in 1 patient (2.4 percent). The remaining patients had miscellaneous causes of death.

DISCUSSION

A recent article highlighted the methodologic weaknesses of studies of fibrinolytic therapy in persons with cardiac arrest and called for clinical trials.³⁷ In our randomized, double-blind, placebo-controlled trial of t-PA in patients with undifferentiated pulseless electrical activity, we found no evidence that the administration of t-PA during CPR improved the likelihood of either survival to hospital discharge or a return of spontaneous circulation. Of 117 patients who received t-PA, only 1 survived to hospital discharge, as compared with none of 116 controls. Our 95 percent confidence intervals reliably exclude a t-PA-related absolute increase in the rate of survival to hospital discharge of more than 4.8 percent. Although treatment with t-PA could have a clinically relevant smaller effect, a much larger study would be required to detect this effect.

The results of several recent studies contrast sharply

TABLE 4. OUTCOMES.

VARIABLE	TISSUE PLASMINOGEN ACTIVATOR GROUP (N=117)	PLACEBO GROUP (N=116)	ABSOLUTE DIFFERENCE (95% CI)*	P VALUE
			%	
Return of spontaneous circulation — no. (%)	25 (21.4)	27 (23.3)	-1.9 (-12.6 to +8.8)	0.85
Median maximal duration — min†	28	11	+17 (-4 to +26)	0.45
Mean maximal duration — min†	395	182		
Died at scene — no. (%)	73 (62.4)	74 (63.8)	-1.4 (-13.8 to +11.0)	0.93
Transported to hospital — no. (%)	39 (33.3)	38 (32.8)	+0.5 (-11.6 to +12.6)	0.96
Arrived with pulse	19 (16.2)	10 (8.6)	+7.6 (-1.0 to +16.5)	0.12
Arrived without pulse	20 (17.1)	28 (24.1)	-7.0 (-17.4 to +3.4)	0.24
Enrolled at hospital and died in emergency department — no. (%)	5 (4.3)	4 (3.4)	+0.9 (-5.2 to +6.9)	0.99
Survived to hospital admission — no. (%)	7 (6.0)	6 (5.2)	+0.8 (-5.9 to +7.8)	0.99
Major hemorrhage — no. (%)	2 (1.7)	0	+1.7 (-1.7 to +6.4)	0.50
Minor hemorrhage — no. (%)	1 (0.9)	1 (0.9)	0.0 (-4.1 to +4.1)	0.99
Length of hospital stay — days				
Median	0.4	0.5	-0.1 (-0.4 to +2.5)	0.62
Mean	6.3	0.5		
Survival to hospital discharge — no. (%)	1 (0.9)‡	0§	+0.9 (-2.6 to +4.8)	0.99

*CI denotes confidence interval.

†The analysis excludes the sole patient who survived to discharge.

‡The 95 percent confidence interval for this value is 0.0 to 4.7 percent.

§The 95 percent confidence interval for this value is 0.0 to 3.1 percent.

with our findings. A review article summarized nine reports of a total of 67 patients who were treated with fibrinolytic agents during cardiac arrest.¹⁴ The majority of the patients had a known or suspected pulmonary embolism, and the overall survival rate was 75 percent. Only three survivors had documented neurologic sequelae, despite an overall mean duration of cardiac arrest of 51 minutes. A nonrandomized prospective study that included historic controls found that treatment with t-PA significantly increased the rate of return of spontaneous circulation and the rate of admission to the cardiac intensive care unit.²³ A nonrandomized, retrospective case-control study found that t-PA therapy was associated with significant increases in the rates of return of spontaneous circulation, 24-hour survival, and survival to discharge.²⁵ The discrepancies in results may be analogous to the situation regarding other interventions used in cardiac arrest, for which initial anecdotal reports and reports of nonrandomized studies suggested a benefit that was not supported by subsequent clinical trials. Alternatively, a different drug regimen or the same regimen in a different subgroup of patients might have a significant treatment effect.

Since the pharmacokinetics of t-PA in patients

with cardiac arrest are poorly understood, the optimal dose is unknown. The Neuhaus regimen is the standard approach for the treatment of myocardial infarction: a 15-mg bolus of t-PA is followed by two infusions over a period of 90 minutes. This approach was used in the study by Lederer et al.²⁵ The study by Bottiger et al. used a 50-mg infusion given over a period of 2 minutes, and the dose was repeated after 30 minutes if no response occurred.²³ We chose to deliver the maximal amount of drug used in the treatment of myocardial infarction (100 mg) in the shortest period supported by the literature — 15 minutes.^{10,11,38} We also stipulated that patients receive a further 15 minutes of CPR after the infusion. We elected to leave the decision to administer heparin, aspirin, or both to the discretion of the attending physician and found that 5 of the 13 patients who were admitted were given heparin, 4 of whom also received aspirin. The study by Bottiger et al. also included heparin,²³ and a substantial number of patients in the study by Lederer et al.²⁵ received both heparin and aspirin, as did a patient in a recent case report.²⁴ Although the failure to require concomitant administration of t-PA, heparin, and aspirin may have undermined our ability to detect a sur-

vival benefit related to t-PA, given the mechanism and pharmacokinetics of these agents, we would still have expected to find an increased rate of return of spontaneous circulation if there had been an effect of t-PA treatment.

Since most cardiac arrests occur outside the hospital and we studied an undifferentiated population,³⁹ we did not use transthoracic or transesophageal echocardiography. These and other techniques could be used to identify patients who may be more likely to have a response to therapy.^{4,5} It is important to emphasize that our results cannot necessarily be generalized to highly selected patients with cardiac arrest, particularly those with a known or suspected pulmonary embolism¹⁵⁻²¹ or myocardial infarction meeting the criteria for the administration of fibrinolytic agents.²²

Our study has certain limitations. Although pulseless electrical activity is associated with pulmonary embolism,⁴⁰ only 1 percent of 42 patients were found to have this condition at autopsy. Autopsy series are notorious for selection bias, but if this value does indeed reflect the prevalence of pulmonary embolism in the study population, our ability to detect a treatment effect with respect to this condition would be low. Since our protocol stipulated only that pulseless electrical activity had to be present at some point during the resuscitation, 52 patients were enrolled (22.3 percent) who had an initial rhythm of asystole. It could be argued that the inclusion of such patients, given their low likelihood of survival, reduced our ability to detect a treatment effect. However, 55 patients (23.6 percent) had an initial rhythm of ventricular fibrillation, the rhythm most frequently associated with survival.

The stipulation that the trial include standard therapies, in particular at least 500 ml of intravenous saline, delayed the administration of t-PA. We believed that it would have been unethical to administer an unproved and potentially harmful therapy before standard interventions were carried out. The median time from the collapse of the patient to the commencement of the infusion was 35 minutes. Numerous intervening steps take place during this interval and are difficult to shorten. We believe that 35 minutes is a realistic estimate of the rapidity with which a complex protocol involving a reconstituted agent can be carried out outside the hospital, even by highly motivated and experienced paramedics. It is, however, conceivable that earlier administration of a fibrinolytic agent could have led to different results. Finally, when the trial was designed, bolus doses of fibrinolytic agents were unavailable and our results cannot necessarily be generalized to the use of such agents.

Although this study does not eliminate the possibility of a role for fibrinolytic agents in cardiac arrest,

our results suggest that a t-PA infusion offers no significant benefit to patients with cardiac arrest and undifferentiated pulseless electrical activity. Future researchers may choose to evaluate earlier administration of bolus fibrinolytic agents in highly selected patients, in whom cardiac arrest is suspected or known to have been precipitated by acute thrombus.

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