Comparative Efficacy of a Two-Hour Regimen of Streptokinase Versus Alteplase in Acute Massive Pulmonary Embolism: Immediate Clinical and Hemodynamic Outcome and One-Year Follow-Up

NICOLAS MENEVEAU, MD, FRANÇOIS SCHIELE, MD, DAMIEN METZ, MD,* BENOÎT VALETTE, MD,† PIERRE ATTALI, MD,‡ ALAIN VUILLEMENOT, MD, GILLES GROLLIER, MD,† JACQUES ELAERTS, MD,§ JEAN-MARIE MOSSARD, MD,‡ JEAN-FRANÇOIS VIEL, MD,§ JEAN-PIERRE BASSAND, MD, FACC
Besançon, Reims, Caen and Strasbourg, France

Objectives. This study sought to compare the efficacy of 2-h regimens of alteplase and streptokinase in acute massive pulmonary embolism. The primary end point was immediate hemodynamic improvement, and secondary end points included early clinical efficacy and safety, as well as 1-year clinical outcome.

Background. Several thrombolytic regimens have been compared for the past 10 years in randomized studies, showing that 2-h infusion regimens of alteplase or urokinase lead to faster hemodynamic improvement than former 12- to 24-h administration protocols in acute massive pulmonary embolism. Many trials have focused on immediate hemodynamic and angiographic outcomes, but none has addressed long-term follow-up after thrombolysis.

Methods. Sixty-six patients with acute massive pulmonary embolism (Miller score >17 and mean pulmonary artery pressure >20 mm Hg) were randomly assigned to receive either a 100-mg 2-h infusion of alteplase (n = 23) or 1.5 million IU of streptokinase over 2 h (n = 43). In both groups, heparin infusion was started at the end of thrombolytic infusion and adapted thereafter. Total pulmonary resistance was monitored over a 12-h period. Pulmonary vascular obstruction was assessed 36 to 48 h after thrombolytic therapy. One-year follow-up information included death, cause of death, recurrent pulmonary embolism, chronic thromboembolic pulmonary hypertension, stroke, and bleeding.

Results. Both groups had similar baseline angiographic and hemodynamic characteristics of severity, with maintained cardiac output in 64 (97%) of 66 patients. The results (mean ± SD) demonstrated that despite a faster total pulmonary resistance improvement observed at 1 h in the alteplase group compared with the streptokinase group (33 ± 16% vs. 19 ± 16%, p = 0.006), a similar hemodynamic efficacy was obtained at 2 h when both thrombolytic regimens were completed (38 ± 18% vs. 31 ± 19%). There was no significant difference in either pulmonary vascular obstruction at 36 to 48 h or bleeding complication rates. One-year event-free survival was similar in both groups, as most events were related to concomitant diseases.

Conclusions. These results suggest that a 2-h regimen of streptokinase can be routinely used in patients with massive pulmonary embolism and maintained cardiac output without obviously compromising efficacy or safety.

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Thrombolysis is widely accepted as the treatment of choice for acute massive life-threatening pulmonary embolism, defined as severe pulmonary vascular obstruction resulting in hemodynamic instability. In this condition, thrombolytic therapy has been proved to clear pulmonary artery thrombus and improve hemodynamic status faster than does intravenous heparin (1–4). Moreover, it has been very recently reported from registry data that early thrombolytic treatment may reduce in-hospital overall mortality and recurrence of pulmonary embolism, at the cost of an increased rate of major bleeding episodes (5). Several thrombolytic regimens have been compared for the last 10 years in randomized studies, showing that 2-h infusion regimens of alteplase or urokinase lead to faster hemodynamic improvement compared with former 12- to 24-h administration protocols (6–8). Moreover, a bolus injection of alteplase was found to be neither more efficient nor safer than a 2-h infusion (9,10).

Newer generation thrombolytic agents such as alteplase are commonly used in clinical practice. However, a recent randomized trial comparing a 100-mg 2-h infusion of alteplase with 1.5 million IU of streptokinase over 12 h clearly demonstrated that hemodynamic improvement occurred more rapidly in the
alteplase group, but with no further significant difference at 6 and 12 h when both thrombolytic infusions were completed (11). In addition, in a recent small randomized trial, a significant reduction in mortality rate was observed with intravenous streptokinase as compared with heparin in life-threatening, massive pulmonary embolism (12). Furthermore, the third International Study of Infarct Survival (ISIS-3) and the Global Utilization of Streptokinase and TPA for Occluded arteries (GUSTO) trial have shown that streptokinase induced fewer bleeding complications than did alteplase and anistreplase (13,14). Hence, streptokinase remains worthwhile for thrombolysis in acute massive pulmonary embolism.

Therefore, the aim of the trial was to compare the efficacy of 2-h regimens of alteplase and streptokinase in acute massive pulmonary embolism. The primary end point was immediate hemodynamic improvement, and secondary end points included early clinical efficacy and safety, as well as 1-year clinical outcome.

Methods

This study was a single-blind randomized trial conducted in four French centers.

Patient selection. Any patient >18 years old who was referred for recent symptoms (<5 days) suggestive of acute massive pulmonary embolism was considered for entry into the study. After routine clinical examination, patients were referred to the catheterization laboratory for pulmonary angiography. Thrombolytic therapy was administered after informed consent was obtained, if the Miller score was >17/34 and if the mean pulmonary artery pressure (MPAP) was >20 mm Hg regardless of clinical presentation.

Exclusion criteria included 1) significant preexisting cardio-pulmonary disease; 2) recent puncture of a noncompressible vessel or organ biopsy; 3) recent application of a vena cava filter or current treatment with Coumadin; 4) pregnancy, puerperium or lactation; 5) head trauma or cerebrovascular accident within the past 6 months; 6) history of cerebral hemorrhage, intracranial or intraspinal surgery; 7) bleeding disorder or platelet count <100,000/mm³ on admission; 8) proliferative or hemorrhagic diabetic retinopathy; 9) systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg, or both; 10) known dissecting or other aneurysms; 11) major operation or trauma within the past 10 days; 12) known pericarditis or endocarditis; 13) occurrence of allergic reactions, severe hypotension or cardiac arrest during initial pulmonary angiography; 14) gastrointestinal bleeding within the previous year; and 15) recent external cardiac resuscitation maneuvers.

Pulmonary angiography. Selective right and left pulmonary angiography was performed, preferably through the brachial venous access, before initiation of thrombolytic treatment. Standard large-format cut-film angiography or 35-mm cine films were used. Each pair of coded angiograms was reviewed by a panel of two experienced readers who were unaware of the chronologic order of the angiograms and study treatment. Severity of embolism was assessed using the method of Miller et al. (15). The individually allocated scores were reviewed by the panel and a consensus score was derived.

Hemodynamic measurements. MPAP was recorded before the first pulmonary angiogram. After enrollment in the study, serial measurements of heart rate, respiratory rate, systolic, diastolic and mean pulmonary artery pressures and cardiac output (CO) were done before initiation of thrombolysis and at 30 min and 1, 2, 6 and 12 h by means of a five-way Swan-Ganz thermodilution catheter with a rapid-response thermistor inserted into the pulmonary artery immediately after the initial pulmonary angiogram (Edwards 93A-431H-7.5 F). Total pulmonary resistance (TPR) was derived as TPR = (MPAP/CO) × 80 in dynes cm⁻² s, with CO in liters/min and MPAP in mm Hg.

Medication. After providing informed consent, patients were randomly assigned to receive either alteplase or streptokinase on a 1:2 basis. In the alteplase group, patients received a 100-mg infusion of alteplase over a 2-h period, 10 mg of which was injected as a bolus. For patients weighing <65 kg, the dose was reduced to 70 mg over 2 h, with an initial bolus injection of 7 mg (7). In the streptokinase group, patients received a 1.5-million IU infusion of streptokinase over 2 h. In both groups, intravenous heparin infusion was started at the end of thrombolytic infusion, maintained at a dose of 1,000 IU/h and adapted to achieve an activated partial thromboplastin time ratio of two to three times the control value. Any other medication needed by the patient was left to the discretion of the attending physician. The dosage of inotropic or vasoactive drugs, if any, was maintained constant during the period of hemodynamic measurements. Oral anticoagulant therapy was introduced on day 5 and pursued over 6 months. Patients were followed up to day 10 and then discharged from the hospital.

Perfusion lung scanning. Perfusion lung scans were taken within 36 to 48 h after the onset of treatment. Six-view ventilation and perfusion lung scans were obtained in a single session with a high resolution, low energy, large field camera (Sophy Camera DS7) with an inhaled spray solution of diethylenetriaminepentaacetic acid labeled with technetium-99m for the ventilation scan and with human serum albumin microaggregates labeled with technetium-99m for the perfusion scan.

According to methods derived from the method used in the Prospective Investigation of Pulmonary Embolism Diagnosis
Normality was evaluated with the Shapiro-Wilk statistic. Changes in hemodynamic measurements over time were analyzed using repeated measures analysis of variance. Differences between both groups were performed using the unpaired Student t test. Comparison of continuous data between both groups was performed using the unpaired Student t test. Changes in hemodynamic measurements over time were analyzed using repeated measures analysis of variance. Normality was evaluated with the Shapiro-Wilk statistic (threshold value: \( p = 0.15 \)). A p value <0.05 was considered significant. All reported p values were two-sided.

### Hematologic and hemostatic measurements
Blood samples for determination of blood cell counts, hemoglobin and plasma fibrinogen were taken before thrombolytic treatment and 12, 24 and 48 h and 10 days thereafter. In addition, plasma fibrinogen and coagulation variables were assessed at baseline and 2, 6, 12 and 24 h after initiating thrombolysis.

### Adverse events
Adverse events were noted throughout the hospital stay. Major bleeding was prospectively defined as bleeding that required blood transfusion, surgical control or discontinuation of the study treatment; hemorrhagic stroke confirmed by computed tomography or autopsy; bleeding causing a fall of 15% in hematocrit within 72 h after the onset of therapy; or any bleeding complications causing death. Other important bleeding, defined as a fall of 10% in hematocrit, such as retroperitoneal, gastrointestinal or genital bleeding, hematomas or prolonged external bleeding at puncture sites, hemoptysis, epistaxis and hematuria, was also recorded (9–11).

### Follow-up
Patients were contacted by study coordinators at 1 year to ascertain recurrent hospital admissions and other study information, including death, cause of death, recurrent pulmonary embolism, chronic thromboembolic pulmonary hypertension, cancer, stroke and bleeding. In case of recurrent hospital admission, appropriate data were abstracted from hospital records to document the nature of end-point events.

### Statistical analysis
In view of the consistent clinical data obtained with a 2-h alteplase regimen, patients were randomized to receive either a 2-h alteplase infusion or a 2-h streptokinase infusion in a 1:2 allocation ratio. Calculation of sample size demonstrated that ~65 patients were required to show a difference of 15 points between treatment groups in percent reduction of TPR 2 h after the onset of thrombolysis, with 80% power and a two-sided level of significance of 0.05, assuming a standard deviation of ~20 points. Data were analyzed according to the intention-to-treat principle.

All results are expressed as the mean value ± SD. Categoric data analyses were performed using the chi-square test and the Fisher exact test (2 × 2 table). Comparison of continuous data between both groups was performed using the unpaired Student t test. Changes in hemodynamic measurements over time were analyzed using repeated measures analysis of variance. Normality was evaluated with the Shapiro-Wilk statistic (threshold value: \( p = 0.15 \)). A p value <0.05 was considered significant. All reported p values were two-sided.

### Results
Sixty-six patients were enrolled in the study: 43 received streptokinase and 23 alteplase. There were no significant differences between the two treatment groups in terms of demographic and clinical characteristics (Table 1). Both groups had similar baseline angiographic and hemodynamic characteristics of severity, with maintained CO in 64 (97%) of 66 patients. Complete hemodynamic monitoring was obtained in every patient. The total dose of the allocated drug was effectively administered to 64 of 66 patients. In two patients, injection of streptokinase was discontinued because of a systolic blood pressure drop of ≤80 mm Hg during injection; one patient received only 250,000 IU of streptokinase and the other 1 million IU of streptokinase. Only two patients received an inotropic agent (dobutamine in each patient at a dose of 10 μg/kg body weight per min). A perfusion lung scan was obtained in all but one patient who required emergency embolectomy because of a recurrent embolism.

### Clinical course and adverse events (Table 2)
The clinical course was uneventful in 18 alteplase-treated patients (78%) and in 32 streptokinase-treated patients (74%) \((p = \text{NS})\). A significant decrease in respiratory rate was observed in both study groups over the first 12 h (considered early symptomatic relief), with no intergroup difference \((-23% \text{ in alteplase group vs. } -21% \text{ in streptokinase group; } p = \text{NS})\). No deaths occurred in either group. Recurrent nonfatal pulmonary embolism occurred in one streptokinase-treated patient who needed emergency embolectomy and in two alteplase-treated patients. A blood pressure drop of ≤80 mm Hg was more frequent in the streptokinase group than in the alteplase group, but the difference was not statistically significant. Heparin-induced thrombocytopenia—immediately regressive and without complication after introduction of oral anticoagulant agents

### Ethical considerations
The study protocol was submitted to the Ethics Committee of Hôpital Universitaire Saint-Jacques, which gave formal approval for conduction of the study.
and discontinuation of heparin infusion—occurred in two streptokinase-treated patients and in one alteplase-treated patient.

At the end of the hemodynamic monitoring period, three patients from the streptokinase group were given an additional dose of alteplase: in the two patients previously mentioned because of hypotension resulting in incomplete thrombolytic infusion and in one patient because of insufficient hemodynamic improvement as determined by the physician in charge of the patient.

The frequency of bleeding complications was not significantly different between the two groups, but the alteplase group had a tendency toward more frequent major bleedings and, conversely, less frequent important bleedings compared with the streptokinase group. Changes in hemodynamic variables were significant over time in both groups. A significant intergroup difference was observed at 1 h (interaction treatment × time, p = 0.006), showing a faster TPR improvement in the alteplase group compared with the streptokinase group (−34 ± 13% vs. −21 ± 16%). At 2 h, when infusions were completed, no significant difference persisted between the two groups (−38 ± 18% vs. −31 ± 19% in alteplase and streptokinase groups, respectively) (Fig. 1). TPR did not decrease in two patients in the streptokinase group. One patient (mentioned earlier) received an additional dose of 90 mg of alteplase over 2 h, when the fibrinogen level increased up to 1 g/liter, with a significant decrease in TPR over 12 h (−35%). The other patient did not receive further thrombolysis and was not referred for pulmonary embolectomy.

Residual pulmonary vascular obstruction on the 36- to

### Table 2. In-Hospital Clinical Course and Adverse Events*

<table>
<thead>
<tr>
<th></th>
<th>Alteplase (n = 23)</th>
<th>Streptokinase (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital uneventful clinical course</td>
<td>18 (78%)</td>
<td>32 (74%)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blood pressure drop</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Recurrent nonfatal pulmonary embolism</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding complications (total)</td>
<td>5 (20%)</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5 (20%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Hematoma (vascular access)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other important bleeding</td>
<td>0</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Hematoma (vascular access)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Surgical embolectomy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Septicemia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Heparin-induced thrombocytopenia</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*p = NS for all comparisons. Data presented are number (%) of patients.

### Table 3. Hemodynamic Results

<table>
<thead>
<tr>
<th></th>
<th>rt-PA</th>
<th>SK</th>
<th>rt-PA</th>
<th>SK</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>93 ± 18</td>
<td>93 ± 15</td>
<td>88 ± 18</td>
<td>92 ± 15</td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>4.2 ± 1.4</td>
<td>4.1 ± 1.5</td>
<td>4.4 ± 1.4</td>
<td>4.2 ± 1.6</td>
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<tr>
<td>MPAP (mm Hg)</td>
<td>33 ± 8</td>
<td>35 ± 10</td>
<td>28 ± 9</td>
<td>31 ± 10</td>
</tr>
<tr>
<td>TPR (dynes·cm⁻²·s)</td>
<td>721 ± 361</td>
<td>790 ± 415</td>
<td>579 ± 317</td>
<td>674 ± 368</td>
</tr>
<tr>
<td>SVO₂ (%)</td>
<td>62 ± 10</td>
<td>62 ± 9</td>
<td>65 ± 9</td>
<td>65 ± 8</td>
</tr>
</tbody>
</table>

Data presented are mean value ± SD. CO = cardiac output; HR = heart rate; MPAP = mean pulmonary artery pressure; rt-PA = recombinant tissue-type plasminogen activator; SK = streptokinase; SVO₂ = hemoglobin saturation of mixed venous blood; TPR = total pulmonary resistance.

*Figure 1. Evolution of TPR in 66 patients. The difference between the two groups was significant at 1 h, but not thereafter. Data are presented as mean value ± SD. Solid curve = streptokinase (n = 43); dashed curve = alteplase (n = 23).
48-h lung scans was similar in the alteplase and streptokinase groups (29 ± 13% and 30 ± 11%, respectively; p = NS).

Hematologic and coagulation data. There were no differences between the two groups in hematocrit or platelet count at baseline or at 24 or 48 h. Streptokinase infusion resulted in prolonged fibrinolytic activation, as shown by a fall of 87 ± 17% in the fibrinogen level after 2 h, 84 ± 12% after 6 h and 77 ± 14% after 24 h. In the alteplase group, the fall in the fibrinogen level after 2 h (72 ± 25%) was significantly lower than that observed in the streptokinase group (p = 0.01). Similarly, at 6 and 24 h, the magnitude of the fall in the fibrinogen level was significantly lower in the alteplase group than that in the streptokinase group (69 ± 17% and 48 ± 22%, p = 0.007 and p < 10^{-5}, respectively).

Follow-up data (Table 4). One-year follow-up data were obtained in all but one patient. The average follow-up period was 13 ± 2 months. One-year event-free survival was similar in both groups (78% in alteplase group vs. 77% in streptokinase group, p = NS) (Table 3). Two deaths occurred in the alteplase group at 6- and 8-month follow-up; they were related to cancer in both patients, one case preexisting when the patient was included in the trial. No events related to thromboembolic disease occurred in the alteplase group. In contrast, late recurrent pulmonary embolism occurred in two streptokinase-treated patients (at 7- and 8-month follow-up) after discontinuation of oral anticoagulation in both patients. One streptokinase-treated patient experienced chronic thromboembolic pulmonary hypertension responsible for right heart failure. It should be noted that despite no change in right heart hemodynamic data at the end of the thrombolytic infusion, this patient did not receive further thrombolysis and was not referred for pulmonary embolectomy. Most events leading to recurrent hospital admission were related to concomitant diseases. Bleeding complication (hematuria) occurred in only one patient who received oral anticoagulation.

**Table 4. One-Year Follow-Up Data**

<table>
<thead>
<tr>
<th></th>
<th>Alteplase (n = 23)</th>
<th>Streptokinase (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-yr event-free survival</td>
<td>18 (78%)</td>
<td>33 (77%)</td>
</tr>
<tr>
<td>Death (cancer)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent hospital admission</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Recurrent pulmonary embolism</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Chronic thromboembolic pulmonary hypertension</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Polycystic kidney</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Prostatic adenoma</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Data presented are number (%) of patients.

Although no randomized trial has demonstrated that thrombolytic therapy is capable of reducing the in-hospital mortality rate when administered to patients with acute massive pulmonary embolism, this therapeutic option has been widely accepted for this particular indication because it has been shown to lead to faster right heart hemodynamic improvement compared with heparin. However, a recent study based on a multicenter registry reported a significant reduction in in-hospital overall mortality and recurrence of pulmonary embolism in patients who underwent primary thrombolysis compared with those initially treated with heparin alone. In that report, thrombolytic therapy was shown, by multivariate analysis, to be an independent predictor of survival, thus providing the first link between hemodynamic benefits and clinically relevant end points (5).

Similar angiographic improvement has been demonstrated after a 2-h infusion of recombinant tissue-type plasminogen activator or urokinase, thus suggesting that the efficacy of thrombolysis in massive pulmonary embolism depends on the thrombolytic regimen rather than on the type of thrombolytic agent used (8). However, given the exponential relation that exists between pulmonary vascular obstruction and TPR (17), many studies assessing the efficacy of thrombolysis in acute pulmonary embolism have addressed right heart hemodynamic data as the most reliable surrogate end point.

Therefore, we have performed trials to assess the efficacy of different regimens of streptokinase, because no study except the Urokinase Streptokinase Pulmonary Embolism Trial (USPET) (2) has compared streptokinase with any other thrombolytic agent in the setting of massive pulmonary embolism (12,18–21).

**Efficacy of thrombolytic regimens.** In a previous trial, we compared a 2-h regimen of alteplase with a 12-h regimen of streptokinase. That trial showed that the decrease in pulmonary vascular resistance was achieved faster in the alteplase group, with consistently significant intergroup differences from 30 min up to 6 h after the onset of thrombolysis (11).

In the present study comparing 2-h regimens of streptokinase and alteplase, the decrease in TPR occurred again more rapidly with alteplase than with streptokinase. Although the difference was present up to 6 h after the onset of thrombolytic infusion, it was only statistically significant at 1 h and not thereafter. After 6 h, the two curves of pulmonary vascular resistance were confounded. This faster initial improvement did not result in better relief of pulmonary vascular obstruction, which was found to be identical 36 to 48 h after the onset of treatment, indicating that lysis of intrapulmonary thrombus was of the same magnitude in both treatment groups.

It is not possible to strictly compare the evolution of two groups of patients treated in two separate trials, even with similar inclusion criteria, demographic characteristics and initial pulmonary vascular obstruction. However, we can reasonably assume that infusion of streptokinase over 2 h produced faster hemodynamic improvement than that seen over 12 h,
because the decrease in TPR at 2 h was $-13 \pm 12\%$ in the 12-h regimen compared with $-31 \pm 19\%$ in the 2-h regimen.

Although no statistical difference in TPR was observed in this study when both thrombolytic infusions were completed, it would be premature to conclude equivalence between the two thrombolytic agents for all patients with a pulmonary embolism. Based on the faster hemodynamic response demonstrated with alteplase, this thrombolytic agent might be more appropriate in patients with life-threatening pulmonary embolism with cardiogenic shock, in whom the earlier the hemodynamic improvement the better. However, the sample size and the initial clinical presentation of the study group fail to address the specific concern of mortality in this subset of patients.

The administered dosage of streptokinase was less than the dosage commonly used in acute myocardial infarction. Higher dosages or a shorter infusion period of streptokinase may be of interest given the promising results obtained with a streptokinase dosing regimen of 1.5 IU over 1 h in patients with massive pulmonary embolism and hemodynamic instability (12). The heparin regimen was similar between the two therapeutic groups and was started immediately at the end of the thrombolytic infusion, as currently recommended in European thrombolytic protocols in massive pulmonary embolism. However, data from the GUSTO trial suggest that heparin could be given earlier as a bolus injection at the onset of and as a perfusion during thrombolytic therapy (14).

Safety. The bleeding complication rate was similar in both groups and comparable to that reported in previous studies using equivalent definitions of bleeding complications (9–11,22). Most bleeding occurred at vascular access sites required for pulmonary angiography, known to be the major predisposing factor for bleeding (23). However, in most cases, the diagnosis of acute massive pulmonary embolism can be ascertained with noninvasive studies, with a lower bleeding rate in routine clinical practice.

The incidence of hypotension was more frequent with streptokinase than with alteplase, as observed in previous studies (13). Hypotension is likely to be more common if streptokinase is administered rapidly (24), but is usually reversible with temporary cessation of the infusion and intravenous administration of fluids.

Long-term follow-up. Few randomized trials have assessed the potential long-term benefits of thrombolytic therapy in acute massive pulmonary embolism (25–27). Long-term mortality was attributed to underlying comorbid diseases rather than to unresolved pulmonary embolism (28). Cancer, congestive heart failure, age >60 years and chronic lung disease were shown to be predictors of subsequent death (29). In patients without preexisting cardiac or pulmonary disease, the reported 1-year mortality rate ranged from 3% to 9%, similar to that observed in this trial (3%). The rate of recurrent pulmonary embolism was 7.5% in this study ($n = 5$), comparable to the 8.3% rate of recurrence at 1 year follow-up reported by Carson et al. (29), who showed that most recurrences of embolism occurred during the first week of follow-up and resulted in a high mortality rate.

The incidence of chronic thromboembolic pulmonary hypertension is low among patients with a history of acute pulmonary embolism who receive appropriate anticoagulant therapy (25,30–32). In our trial, right ventricular failure occurred in one patient in whom the MPAP was 34 mm Hg 12 h after initiation of streptokinase, with a residual lung scan defect of 37%. According to Moser et al. (33), incomplete thrombus dissolution leads to an aberrant path of recanalization, leaving endothelialized residua that obstruct or significantly narrow major pulmonary arteries, and is responsible for severe pulmonary hypertension and progressive right ventricular failure (33).

Study limitations. The primary end point of this study was to compare hemodynamic improvement resulting from 2-h regimens of streptokinase and alteplase. The sample size was calculated to achieve the statistical power required for such a comparison. However, given the size of the trial, the statistical power of the study was clearly insufficient to address secondary end points, such as safety, frequency of adverse events and long-term results.

It should be noted that despite evidence of angiographic and hemodynamic characteristics of severity, only two patients were in cardiogenic shock at presentation. Except for those patients, CO was maintained in the remaining 64 patients. Therefore, our finding may apply more accurately to patients with massive pulmonary embolism and maintained CO.

Clinical implications. The results of our study suggest that thrombolysis occurred more rapidly over the first hour of a 2-h infusion of alteplase than during a 2-h infusion of streptokinase in patients with massive pulmonary embolism and maintained CO. There was no significant difference in TPR after 2 h between the two groups, with a similar residual vascular obstruction at 36 to 48 h. Therefore, given the low cost of streptokinase compared with urokinase and alteplase, we can reasonably recommend that a 2-h regimen of streptokinase be routinely used in this setting, without obviously compromising safety and with a similar efficacy.

We are indebted to Sophie Boucher and Susan Sherman for their help in writing this report.

References


