Tissue Plasminogen Activator in Acute Pulmonary Embolism*

Samuel Z. Goldhaber, M.D., F.C.C.P.

The use of thrombolytic therapy to treat AMI has reawakened interest in thrombolysis for acute pulmonary embolism (PE). We have investigated the use of recombinant human tissue-type plasminogen activator (rtPA) in patients with acute PE. In an open label study, rtPA achieved more than 90% efficacy and safety. In a trial comparing rtPA with an FDA-approved dose of urokinase (UK), rtPA appeared more rapid and safer. We are now conducting a comparative trial of rtPA with a novel dosing regimen of UK. In addition, a concurrent trial is comparing rtPA vs heparin for improvement in right ventricular function, assessed by echocardiography, among PE patients. However, the greatest challenge in PE research is to undertake a large-scale trial that compares thrombolysis and heparin for reduction of clinically relevant end points such as mortality and recurrent PE.

Should thrombolysis be used to treat only life-threatening pulmonary embolism (PE) or be employed more routinely in the management of PE? This issue must be addressed in carefully conducted clinical trials, because the death rate from PE has not declined in the past decade (Fig 1).1

Seven potential advantages of thrombolysis are: (1) reduction of the mortality rate, (2) accelerated reversal of right heart failure, (3) reduced rate of recurrent PE (by lysing in situ the source of the initial PE), (4) reduced risk of chronic pulmonary hypertension (by lysing residual thrombus in the pulmonary arteries), (5) accelerated pulmonary tissue reperfusion, (6) accelerated clot lysis, and (7) improved pulmonary capillary blood volume. The first 4 potential advantages are promising hypotheses that should be tested. The latter 3 advantages have been demonstrated but have not resulted in use of thrombolysis for routine PE treatment. In the Urokinase Pulmonary Embolism Trial (UPET),4 in which patients were randomized to urokinase (UK) or heparin, patients assigned to UK had accelerated pulmonary tissue reperfusion on lung scanning and clot lysis on angiography. Improved pulmonary capillary blood volume was sustained even 1 year after thrombolytic therapy.5 However, radiologic end points such as lung scanning and angiography do not guarantee clinical benefit, and the clinical significance of improved pulmonary capillary blood volume is uncertain.

While several of the potential advantages of thrombolysis remain to be proved, there are two immediately apparent disadvantages: increased hemorrhagic risk and increased cost. In addition, the more frequent use of thrombolytic agents requires an investment of time to educate nursing, laboratory, and pharmacy staff. Because of these immediately apparent disadvantages, thrombolysis has been used in only a small percentage of patients with PE, even though the FDA approved UK (and streptokinase [SK]) for PE treatment in 1977. The FDA has sanctioned moderate doses of UK or SK administered for 12–24 h (Table 1). In 1980, an NIH Consensus Development Panel urged more widespread use of thrombolysis in venous thromboembolism.6 However, these recommendations have had little discernible impact on clinical practice.

The use of thrombolytic therapy to treat AMI in the early 1980s spurred a renewed interest in thrombolysis for PE. A second-generation, relatively fibrin-specific agent, human tissue-type plasminogen activator (rtPA), was developed with recombinant DNA technology. In animal studies of venous thromboembolism, rtPA appeared more efficacious and potentially safer than UK or SK (Table 2).7-10 In lysis of acute coronary artery thrombosis causing MI, rtPA caused patency of the infract-related artery more often than SK.8,10 Therefore, we embarked on an open label study of rtPA to test its efficacy and safety in the treatment of acute PE.

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21594/)

**Table 1—FDA Approved Thrombolytic Regimens for PE**

| Urokinase: 2,000 U/lb bolus followed by 2,000 U/lb/h for 12–24 h | Streptokinase: 250,000 U bolus followed by 100,000 U/h for 24 h |

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Table 2—Experience with tPA in Experimental Venous Thromboembolism*

<table>
<thead>
<tr>
<th>Animal Model</th>
<th>Drugs Compared</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canine superficial femoral venous thrombosis (5)</td>
<td>1 mg tPA vs 1 million IU UK</td>
<td>50% more lysis with tPA</td>
</tr>
<tr>
<td>Rabbit jugular venous thrombosis (6)</td>
<td>1 mg tPA vs 500,000 IU UK</td>
<td>50% more lysis with tPA</td>
</tr>
<tr>
<td>Rabbit jugular venous thrombosis (7)</td>
<td>0.15 mg/kg h × 4 h, tPA vs 16,000 units/kg/h</td>
<td>49% more lysis with tPA</td>
</tr>
<tr>
<td>Rabbit pulmonary embolism (8)</td>
<td>0.35 mg tPA vs 1 million UK</td>
<td>33% more lysis with tPA</td>
</tr>
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</table>

*tPA = tissue-type plasminogen activator; SK = streptokinase; UK = urokinase. (Reprinted with permission from J Am Coll Cardiol 1987; 10:971-78.)

Open Label rtPA Trial

In 1985–86, 47 patients were enrolled in our initial rtPA trial.11-12 All patients received baseline pulmonary angiograms. We infused 50 mg of rtPA (Activase) through a peripheral vein over 2 h (25 mg/h) and repeated the angiogram immediately thereafter. If this showed clot lysis, the study was terminated. If no clot lysis occurred, an additional 40 mg of rtPA was administered over the ensuing 4 h (10 mg/h), and a third angiogram was performed. Unlike most of the rtPA trials in MI, no patient received concomitant heparin and rtPA. Of the 47 patients, 44 had angiographic evidence of clot lysis after 2–6 h of treatment with rtPA. When improvement occurred, it was slight in 11%, moderate in 27%, and marked in 62%. Two patients had a major hemorrhagic complication. One bled from a pelvic tumor and the other developed mediastinal tamponade 8 days after coronary artery bypass surgery. Both patients required surgery to control the bleeding; they subsequently did well.

Figure 2. M-mode echocardiograms using subcostal approach before (left) and after (right) thrombolytic therapy show marked decrease in the diameter of the right ventricle (RV), from 6.0 to 2.35 cm, and an increase in diameter of the left ventricle (LV), from 3.1 to 4.2 cm. RV wall movement, very hypokinetic during acute pulmonary embolism, improved appreciably after lytic therapy. EKG = electrocardiogram; PW = posterior wall; SEP = septum; TV = tricuspid valve. (Reprinted with permission from J Am Coll Cardiol 1987; 10:971-78.)

Figure 3. Subcostal two-dimensional images at end-diastole corresponding to the M-mode tracings shown in Figure 2. Before recombinant tissue-type plasminogen activator (rtPA) therapy (left), the right ventricle (RV) is markedly enlarged and left ventricular (LV) diameter reduced. After infusion of rtPA (right panel), a remarkable decrease in RV size and a corresponding increase in the size of the left ventricle. RA = right atrium; other abbreviations as in Figure 2. (Reprinted with permission from J Am Coll Cardiol 1987; 10:971-78.)
and were discharged home uneventfully. This study demonstrated that rtPA was efficacious and safe among more than 90% of PE patients enrolled in this trial.

Several important ancillary studies were carried out on subsets of these 47 patients who received rtPA to treat acute PE. In UPET, rectilinear scanners were used and only anterior and posterior views were obtained. However, modern lung scanning employs 6 views (rather than 2) and utilizes a gamma scintillation counter. Therefore, Parker and colleagues developed a new semiquantitative method that emphasizes pulmonary anatomy by integrating data from all of the perfusion scan images to derive a score for each lung segment. With this six-view segmental method, there was a 57% improvement in pulmonary perfusion after rtPA treatment.

To assess abnormalities of right heart function and their reversal with rtPA in PE, serial echocardiographic studies were performed before and after treatment in 7 of the 47 patients. Right ventricular wall movement, initially mildly, moderately, or severely hypokinetic in 1, 2, and 4 patients, respectively, normalized in 5, and improved to mild hypokinesis in 2. Tricuspid regurgitation was present before lytic therapy in 6 patients but was detected only after lytic therapy in 2. Thus, rtPA treatment is associated with significant and early reversal of right ventricular dilatation, hypokinesis, and tricuspid regurgitation (Fig 2 and 3). The early reversal of the detected abnormalities suggests that the right ventricle is not "stunned" but rather is capable of recovering quickly in response to a decrease in right ventricular afterload.

To help assess the extent to which fibrin specificity was associated with angiographically demonstrated clot lysis after rtPA administration, we compared 10 patients who responded to rtPA with 14 patients who had only slight or no improvement at 2 h after initiation of therapy. Among these 24, we measured fibrinogen, fibrinogen degradation products (FDP), and XDP (D-dimer) and calculated the XDP/FDP ratio at baseline and at 2 h. An increase in the XDP/FDP ratio indicates relatively specific fibrinolysis, whereas a decrease in the ratio corresponds to a preponderance of nonspecific fibrinolysis. Before therapy, there were no significant differences in fibrinogen, FDP, XDP, or XDP/FDP ratio when responders and nonresponders were compared (Table 3). However, the posttreatment XDP/FDP ratio in the 2 groups fell an average of 56% in the responders compared with a decrease of only 3% in nonresponders (p<0.04) (Table 4). Thus, administration of rtPA produced both significant fibrinolysis and a disproportionate increase in FDPs over XDPs, particularly in the responders. The significantly lower XDP/FDP ratio in responders suggests that some degree of fibrinogenolysis may support or enhance thrombolysis in the setting of acute PE.

### Table 3—Comparison of Hematologic Values and
Quantitative Score for Responders and Nonresponders
Before Treatment

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Responders (n = 10)</th>
<th>Nonresponders (n = 14)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen, mg %</td>
<td>370±125</td>
<td>340±110</td>
<td>NS</td>
</tr>
<tr>
<td>FDP µg/ml</td>
<td>6.0±3.0</td>
<td>7.2±5.2</td>
<td>NS</td>
</tr>
<tr>
<td>XDP µg/ml</td>
<td>2.1±2.1</td>
<td>1.9±1.7</td>
<td>NS</td>
</tr>
<tr>
<td>XDP/FDP ratio</td>
<td>0.33±0.33</td>
<td>0.56±0.79</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values are mean ± SD. (Adapted with permission from Circulation 1987; 75:1202.*

### Table 4—Comparison of Hematologic Values and
Quantitative Score for Responders and Nonresponders
after Treatment

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Responders (n = 10)</th>
<th>Nonresponders (n = 14)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen, mg %</td>
<td>235±71</td>
<td>227±91</td>
<td>NS</td>
</tr>
<tr>
<td>FDP µg/ml</td>
<td>190±151</td>
<td>140±150</td>
<td>NS</td>
</tr>
<tr>
<td>XDP µg/ml</td>
<td>17±12</td>
<td>29±16</td>
<td>.02</td>
</tr>
<tr>
<td>XDP/FDP ratio</td>
<td>0.14±0.09</td>
<td>0.54±0.82</td>
<td>.04</td>
</tr>
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</table>

*Values are mean ± SD for both groups of patients after the administration of 50 mg rtPA over a 2-h period. (Adapted with permission from Circulation 1987; 75:1202.)

**rtPA vs UK Trial**

The next step was to compare rtPA with a standard, FDA-approved thrombolytic regimen. We wanted to test rtPA against the most effective and safest thrombolytic regimen to determine whether rtPA offered any advantages over first-generation thrombolysis. Although the FDA had approved both UK and SK for PE treatment, we chose to compare rtPA with UK (Abbokinase, supplied by Abbott Labs) rather than SK, because there is more published experience with UK than SK, and because UK causes fewer allergic reactions and less fibrinogen depletion than SK. We chose a 24-h rather than 12-h UK regimen because we wished to compare rtPA with the most potent FDA-approved regimen available.

In regard to rtPA dosing, we chose to administer a fixed 100-mg dose over 2 h rather than the dose of 50–90 mg over 2–6 h that we had used in our initial study. This strategy permitted us to forego a third pulmonary angiogram and to take advantage of an observation we had made in our prior trial, in which we were unable to give the fully intended 6-h dose of rtPA to 7 patients in whom enlarging groin hematomas developed. Gold and colleagues had a similar experience in 25% of their patients with unstable angina when they attempted to infuse rtPA for 12 h.

Based on the results of the open label trial, we made 3

**FIGURE 4. Study protocol for the completed rtPA vs UK trial in PE.**
additional changes in the protocol. First, we extended the treatment window from 5 days (in the first study) to 14 days following symptoms or signs of PE, because none of our 3 treatment failures in the first study had been entered toward the end of the 5-day treatment window. Second, we included in the randomized trial patients with a past history of PE. Finally, we extended the postoperative exclusion period from 7 to 10 days to enhance safety.

We carried out our rtPA vs UK randomized trial of 45 patients in 1987. The principal end points were improvement on the 2-h angiogram and 24-h lung scan. All patients underwent baseline lung scanning and pulmonary angiography (Fig 4). The rtPA patients received a fixed dose of 100 mg through a peripheral vein over 2 h (50 mg/h). The UK patients received 2,000 U/lb as an IV bolus followed by 2,000 U/lb/h for 24 h. If the investigator thought the 2-h angiogram indicated significant clot lysis, the UK infusion was discontinued. (The decision about discontinuing UK was made on the spot, before formal analysis of the angiograms.) After rtPA or UK, heparin was given without a bolus when the thrombin time or partial thromboplastin time was less than twice control. A follow-up lung scan was obtained 24 h after the initiation of thrombolytic therapy.

The rtPA and UK patients were well matched for baseline characteristics. All 22 rtPA-treated patients received the entire 100-mg dose of drug. Only 2 of 23 UK patients were judged by the local investigator to have angiographically proved clot lysis at 2 h. One of these 2 patients experienced an allergic reaction (with fever, rigors, back pain, and rash) at 1.75 h and, therefore, had the UK infusion terminated before completion of the full 2 h of treatment. Of the remaining 21, each of whom the investigators intended to treat with an additional 22 h of therapy, 9 had UK terminated prematurely, in 8 because of intolerable bleeding and 1 in error (Fig 5).

The angiograms were coded and scored by a panel of investigators who knew neither the timing of a particular angiogram nor which drug was administered. Panels graded changes within sets of angiograms as marked, moderate, slight, or absent. Of those who received rtPA, 82% had angiographic evidence of lysis compared with 49% of UK patients (p = 0.008). Moderate or marked lysis occurred in 59% of rtPA patients compared with 13% who received UK (p = 0.002) (Fig 6). After 2 h of therapy, average pulmonary artery pressures decreased among rtPA patients but remained unchanged among those receiving UK (Fig 7). In contrast to the angiographic results at 2 h, improvement in perfusion lung scans at 24 h was identical in both groups (Fig 8). An example of the angiogram, pulmonary artery pressure tracing, and lung scan is shown in a 58-year-old man with a 5-day history of dyspnea (Figs 9–11). Interestingly, there was no significant difference in plasma fibrinogen levels between the rtPA and UK groups (Fig 12).

We conclude from this randomized trial that rtPA (100 mg/2 h) lyases PE clot more rapidly and can be administered with greater safety than the 24-h, FDA-approved dosing regimen for UK. Of note is that by 24 h after initiating

**Figure 5.** Time in 2 “clocks,” each representing 12 h of UK infusion. The clock on the left represents 0–12 of UK; clock on the right represents 12–24 h of UK. Reasons for discontinuing UK were distributed evenly throughout the 24-h infusion period. If the protocol had required a 12-h rather than 24-h infusion of UK, 5 patients would have had the drug discontinued before completion of the intended infusion.

**Figure 6.** Lysis after 2 h of therapy: rtPA vs UK.
PROPORTION OF NONPERFUSED LUNG

![Graph]

**Figure 28.** Proportion of nonperfused lung segmental therapy, nonperfused segmental therapy.

We fibrinogen among UK. are 8. or there Further, now scoring lung levels decreased patients 24 treatment initiation upper and lower lobe arteries (arrows) before treatment. B (right), Evidence of clot lysis (arrows) 2 h after initiation of rtPA. (Reprinted with permission from Lancet 1988; 2:205).

We are now engaged in a trial comparing the same dosing regimen of rtPA with a novel dosing regimen of UK: 1 million U over 10 min followed by 2 million U over 110 min, for a total dose of 3 million U over 2 hs. To date, 24 patients have been enrolled. This novel dosing regimen of UK is similar to the dose administered in the German Activator Urokinase Study (GAUS), which compared the efficacy of rtPA and UK in achieving coronary artery patency among patients with AMI. In GAUS, rtPA and UK had similar efficacy and safety, although the dose of rtPA was 70 mg over 90 min, compared with 3 million U of UK over 90 min with the initial 1.5 million U given as a bolus.

Other investigators have studied rtPA in acute PE. Verstraete et al. compared intrapulmonary vs peripheral IV rtPA in 34 patients with massive PE. They found that intrapulmonary administration offered neither improved efficacy nor safety compared with the intravenous route. These European investigators are now comparing rtPA (100 mg/2 h) with a 12-h infusion of UK. The principal end points are angiographic and hemodynamic improvement. A group of American investigators led by Paul Stein, M.D., of Henry Ford Hospital, compared rtPA and heparin in 13 patients who underwent pretreatment and posttreatment pulmonary angiography. They found that rtPA accelerated clot lysis but was associated with more bleeding complications than heparin. A group of Italian institutions is embarking on a randomized trial of rtPA vs heparin and will use the same dosing regimen that we employed (100 mg/2 h). The Italian study plans to enroll 60 patients who will undergo pretreatment and posttreatment angiography.

The most recent trend with thrombolytic therapy is to administer a high dose over a short period. For example,
Shiffman et al. in Winnipeg found that the rate of PE lysis in dogs was more rapid among those dogs receiving a 15-min infusion of rtPA compared with those receiving a 90-min infusion. Clinically, investigators in Hamilton, Ontario, have been studying the use of rapid rtPA administration in acute PE patients randomized to either rtPA 0.6 mg/kg as a bolus over 2 min or heparin alone. The principal end point of this trial will be scintigraphic improvement on perfusion lung scans.

To date, studies of thrombolytic therapy in PE have focused on hemodynamic or radiologic improvement. However, it is uncertain whether these parameters should be extrapolated to dictate the ideal management strategy in routine clinical practice. It is well-known that most patients with PE will eventually improve with heparin therapy. We are concerned, of course, that with heparin alone, as many as 75% of patients will fail to have complete angiographic resolution by 1 month and one-third of PE patients may not have complete scintigraphic recovery by 4 months after the PE. It is possible that residual thrombus in the pulmonary arteries can lead to the rare but dreaded complication of chronic pulmonary hypertension. It is also possible that some individuals with PE may have long-term residual right heart dysfunction that is of clinical significance. Furthermore, residual thrombus in the pelvic or deep leg veins may make patients who receive heparin alone more susceptible to recurrent PE. Most important, however, is the possibility that rapid, safe treatment with rtPA or other thrombolytic agents may lead to a reduction in mortality owing to prompt reversal of right heart failure (Fig 2 and 3).

During the past few years, several important trends have emerged in the area of thrombolysis for acute PE. First, as demonstrated by Terrin and Thrombolysis in Pulmonary Embolism (TIPE) coinvestigators, thrombolysis can be administered safely to half of the patients who present with acute PE. Until this extensive survey of 2,500 PE patients was undertaken, some had thought that thrombolysis might be contraindicated in almost all patients with acute PE. Second, as demonstrated by TIPE coinvestigators, there is more interest than ever among American investigators to consider using thrombolysis in PE. A total of 44 institutions (plus an additional 60 satellite centers) participated in the TIPE survey. Third, results from the unpublished Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) indicate that among patients with high-probability ventilation-perfusion lung scans, the positive predictive value of the scan for a positive pulmonary angiogram is 95% in the presence of high clinical suspicion. Almost half of patients with PE will present with high-probability lung scans. These individuals can, therefore, potentially receive thrombolysis without undergoing angiography and will thus be spared the delay, discomfort, cost, and bleeding risks associated with thrombolysis after pulmonary angiography. (Of course, based on PIOPED, we estimate that about half of the patients with PE will still require angiography for definitive diagnosis of PE.) Fourth, new approaches to thrombolysis have resulted in at least 1 potentially safer and more effective drug regimen (100 mg/2 h of rtPA) compared with the currently FDA-approved regimens (Table 1).
await with great interest the results of the Verstraete group's ongoing rtPA (100 mg/2 h) vs 12-h UK trial, which might confirm our previous findings. Our own ongoing rtPA vs UK trial might determine that UK 3 million U/2 h is also a useful (although non-FDA-approved) thrombolytic regimen for PE. Fifth, the advent of Doppler echocardiography, ultrasound imaging of the deep leg veins, and novel noninvasive approaches for assessment of pulmonary function permit investigation of additional clinical parameters of improvement.

Despite these encouraging trends, the most important question in PE thrombolysis remains unanswered: Can routine use of thrombolytic therapy reduce the morbidity (from recurrent PE and postphlebitic syndrome) and mortality of venous thromboembolism? Until a definitive answer is obtained, the future role of thrombolysis in PE will not be fully defined. We hope to organize a collaborative multicenter study in which patients (in the absence of contraindications to thrombolysis) with acute symptomatic PE will be randomized to rtPA or heparin. The principal end points will include mortality and other clinically meaningful morbid events. As currently envisioned, this trial will permit patient entry without mandatory angiography in the presence of a high-probability lung scan and high clinical suspicion.

Those of us who manage PE can learn much from the evolution of thrombolysis trials for acute MI. Initially, these trials were small to moderate sized and featured mandatory coronary angiography. It was not until multicentered collaborative efforts involving thousands of patients were undertaken that we learned conclusively that thrombolytic therapy can reduce the mortality rate of AMI. These larger studies of mortality were streamlined and straightforward and no longer required coronary angiography. At present, the greatest challenge in PE clinical research is to evolve from trials of 25–50 patients to trials that recruit hundreds or perhaps even thousands of patients. We should undertake a large-scale mortality trial of PE that includes other clinically relevant end points to answer the fundamental question of the proper role of thrombolysis in PE treatment.

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