

Thrombolytic Therapy of Pulmonary Embolism*

A Comprehensive Review of Current Evidence

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Pulmonary embolism (PE) is a common disorder that is accompanied by significant morbidity and mortality. Although anticoagulation is the standard treatment for PE, thrombolytic therapy, with its ability to produce rapid clot lysis, has long been considered an attractive alternative. Although many studies have been performed over the past three decades, however, the indications for the use of thrombolytic agents in patients with PE remain controversial. In this article, we review the medical literature and provide evidence-based guidelines for the use of thrombolytic therapy. We will also discuss the practical aspects of PE thrombolysis. (CHEST 1999; 115:1695-1707)

Key words: fibrinolysis; pulmonary embolism; recombinant tissue-type plasminogen activator; streptokinase; thrombolytic therapy; urokinase

Abbreviations: ICH = intracranial hemorrhage; PAIMS 2 = Plasminogen Activator Italian Multicenter Study 2; PE = pulmonary embolism; PTT = partial thromboplastin time; rt-PA = recombinant tissue-type plasminogen activator; PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis; SK = streptokinase; UK = urokinase; UPET = Urokinase Pulmonary Embolism Trial; USET = Urokinase-Streptokinase Embolism Trial; V/Q = ventilation-perfusion

Pulmonary embolism (PE) is a common disorder and an important cause of morbidity and mortality. It has been estimated that PE occurs in approximately 600,000 patients annually in the United States and causes or contributes to 50,000 to 200,000 deaths.¹⁻⁴ The importance of this disorder is further highlighted by data suggesting that PE may be responsible for, or at least accompanies, up to 15% of all in-hospital deaths.^{2,5,6} The true incidence of PE is unknown, however, because its many nonspecific clinical features produce one of the most difficult diagnostic challenges in all of medicine.^{7,8} It has been reported, for example, that only one third of patients dying with PE have a correct antemortem diagnosis.⁷

Anticoagulation is an effective treatment for PE. Studies have clearly demonstrated that heparin reduces both mortality and the incidence of recurrent PE.^{2,9-29} Anticoagulation, by preventing clot propa-

gation, allows endogenous fibrinolytic activity to dissolve existing thromboemboli. The rate at which this process occurs is variable. Although complete clot lysis has been reported after as little as 7 days, resolution typically occurs over several weeks or months; in many patients, however, resolution is incomplete after several months.^{12,23,30-32} In these patients, organization of thromboemboli may occur, leading to chronic narrowing or obliteration of the pulmonary vascular bed.

Thrombolytic therapy, by actually dissolving thromboemboli, has several potential advantages over anticoagulation in the treatment of patients with PE. First, it should produce more rapid clot lysis and result in faster improvement in pulmonary perfusion, hemodynamic alterations, and gas exchange. Second, thrombolysis should eliminate venous thrombi and thereby reduce the incidence of recurrent PE. Third, rapid and complete clot resolution should prevent the development of chronic vascular obstruction and reduce the incidence of pulmonary hypertension. Finally, through all of these mechanisms, thrombolytic therapy should reduce morbidity and mortality from PE.

This article provides a comprehensive and systematic review of studies evaluating thrombolytic therapy of patients with PE. Based primarily on information derived from randomized controlled trials, we will address the following questions:

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1. What are the proven advantages of thrombolytic therapy?
2. How do available thrombolytic agents compare with regard to efficacy and safety?
3. Should thrombolytic agents be administered systemically or locally?
4. What is the role of bolus thrombolytic therapy?
5. What is the optimum time window for PE thrombolysis?
6. What are the complications of thrombolytic therapy?
7. What are the indications for thrombolytic therapy of PE?

We will also discuss several practical aspects of treatment, including the diagnostic evaluation prior to PE thrombolysis, patient selection, and the method of administering thrombolytic and anticoagulant therapy.

METHODS OF LITERATURE SEARCH AND GRADING OF STUDIES

MEDLINE records from 1966 to 1998 were searched to identify all studies evaluating thrombolytic therapy for PE. The terms *thrombolytic therapy*, *thrombolysis*, *fibrinolysis*, *urokinase* (UK), *streptokinase* (SK), *recombinant tissue-type plasminogen activator* (rt-PA), and *pulmonary embolism* were utilized as Medical Subject Headings terms and text words. The reference lists of all articles were examined to identify additional studies. Investigators were not contacted in person, and no attempt was made to evaluate unpublished data.

All relevant studies were reviewed and graded according to the levels of evidence proposed by the Fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy.³³ These levels of evidence can be summarized as follows³³:

Level I: large randomized trials or meta-analyses with sufficient power to detect or reliably exclude a difference between treatment groups.

Level II: randomized trials or meta-analyses with insufficient power to reliably exclude a difference between treatment groups.

Level III: nonrandomized comparisons between contemporaneous patients who did and did not receive therapy.

Level IV: nonrandomized comparisons between current patients who received therapy and historical controls.

Level V: uncontrolled case series.

Level assignments of randomized controlled studies of PE thrombolysis were those determined by the Fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy.³³

MECHANISMS OF ACTION OF THROMBOLYTIC AGENTS

SK, UK, and rt-PA have been approved by the US Food and Drug Administration for the treatment of PE. All three drugs directly or indirectly convert the plasma protein plasminogen to plasmin.^{34–38} Plasmin, in turn, rapidly breaks down fibrin, which leads to clot lysis. Systemic plasminogen activation, which can occur with all of these agents, also interferes with blood coagulation by cleaving and inactivating fibrinogen and factors II, V, and VIII. Moreover, elevated levels of fibrin and fibrinogen degradation products contribute to the coagulopathy by both inhibiting the conversion of fibrinogen to fibrin and interfering with fibrin polymerization.^{34,35}

SK is a purified bacterial protein isolated from group C β -hemolytic streptococci.³⁸ It binds to plasminogen noncovalently to form an activator complex, which converts other plasminogen molecules to plasmin.^{34–38} SK is antigenic and cannot be readministered for at least 6 months, as circulating antibodies may both inactivate the drug and produce severe allergic reactions.³⁴

UK is isolated either from human urine or from cultured human embryonic renal cells and exists in both high- and low-molecular-weight forms.³⁸ Unlike SK, UK is not antigenic and produces a lytic state by directly converting plasminogen to plasmin.³⁴

Finally, rt-PA, the newest of the thrombolytic agents, is produced by recombinant DNA technology using various cell lines.^{39,40} Like UK, rt-PA is nonantigenic and directly converts plasminogen to plasmin, but it is more fibrin specific (*ie*, it produces less systemic plasminogen activation) than either SK or UK.^{35,39,40} Fibrin specificity is relative, however, and systemic fibrinogenolysis may occur after the administration of rt-PA.^{39,41–44}

WHAT ARE THE PROVEN ADVANTAGES OF THROMBOLYTIC THERAPY?

Early case reports and small series (level V) describing the use of SK and UK in patients with PE demonstrated rapid improvement in hemodynamic measurements and pulmonary perfusion.^{45–53} In 1970, the results of the National Institutes of Health-sponsored Urokinase Pulmonary Embolism Trial (UPET) were published.¹² In this large, prospective, level I trial, 160 patients with angiographically documented PE were randomized to receive either a 12-h infusion of UK followed by heparin or heparin alone. At 24 h, the degree of improvement in hemodynamic measurements and pulmonary blood flow, as assessed by angiography and perfusion scan,

was significantly greater in patients who had received UK. Serial perfusion scans revealed, however, that the difference in the amount of resolution between the two groups progressively decreased after 24 h, such that no difference was found at 5 or 14 days or at 3, 6, or 12 months. No difference in mortality or the rate of recurrent PE was detected between the two groups.

In a level II study of 40 patients who had participated in either the UPET or the subsequent Urokinase-Streptokinase Embolism Trial (USET; see below), Sharma et al⁵⁴ measured diffusing capacity and pulmonary capillary blood volume 2 weeks and 1 year after therapy with heparin or thrombolytic agents. Although no difference in the degree of perfusion scan resolution had been evident, both diffusing capacity and pulmonary capillary blood volume were initially low in the heparin-treated group and remained unchanged at 1 year. In contrast, in the group receiving thrombolytic therapy, both values were within the normal range at 2 weeks and improved further by 1 year. The authors concluded that thrombolytic therapy leads to more complete resolution of emboli in small, peripheral vessels that are beyond the resolution of perfusion scanning or angiography.

Since the UPET trial, eight smaller, randomized, level II studies have prospectively compared the effects of thrombolytic agents followed by heparin with heparin alone in patients with PE (Table 1). Tibbitt et al⁵⁵ assessed the relative efficacy and safety of intrapulmonary infusions of SK and heparin in 30 patients. At 72 h, patients who were randomized to receive SK had significantly greater improvement in pulmonary perfusion, as assessed by angiography, and in hemodynamic measurements. The mortality rate did not differ between groups. Ly et al⁵⁶ assigned patients to receive either IV SK or heparin. At 72 h, the degree of angiographic improvement was significantly greater in the group receiving SK. No follow-up assessments were performed, and there was no significant difference in mortality between the two groups. Marini et al⁵⁷ randomized 30 patients to receive either IV heparin or one of two UK regimens. When assessed between 24 h and 1 year, the rate at which gas exchange and pulmonary perfusion improved did not differ between the groups, and hemodynamic improvements were similar after 1 week. There were no deaths and no recurrent thromboembolic events in this study. As part of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study,⁵⁸ 13 patients were randomized to receive either IV rt-PA or heparin. A modest decrease in pulmonary vascular resistance was observed 1.5 h after the start of therapy in patients who received rt-PA, but no

significant difference in angiographic findings was noted between the groups at 2 h. Perfusion lung scans performed on days 1, 2, and 7 showed a trend toward greater improvement in the group receiving rt-PA, but this did not reach statistical significance. No difference in mortality was observed. Levine et al⁵⁹ conducted a randomized trial comparing a bolus regimen of rt-PA with heparin in 58 patients with PE. At 24 h, improvement in pulmonary blood flow, as assessed by perfusion scan, was significantly greater in patients who received rt-PA. By day 7, however, there was no difference in the degree of IV perfusion scan resolution between the two groups. The Plasminogen Activator Italian Multicenter Study 2 (PAIMS 2)¹⁸ was a randomized, multicenter trial that compared the relative efficacy and safety of rt-PA and heparin in 36 patients with angiographically diagnosed PE. As in prior studies, treatment with rt-PA resulted in significantly greater improvement in angiographic perfusion scores and hemodynamic variables soon after the start of therapy, but at days 7 and 30, there was no difference in the degree of resolution by perfusion lung scan. There was also no significant difference in mortality or the rate of recurrent PE between the two groups. In 1993, Goldhaber et al¹⁹ reported the results of a randomized trial of 101 patients treated with either IV rt-PA or heparin. In this study, echocardiography was used to assess baseline right ventricular function and was repeated 3 and 24 h after the start of therapy. Changes in pulmonary blood flow were evaluated by performing perfusion scans before and 24 h after initiation of treatment. Patients receiving rt-PA had a greater improvement in right ventricular function and pulmonary perfusion than those receiving heparin alone. Moreover, in the group receiving heparin, there were two fatal and three nonfatal clinically suspected PE recurrences during the first 14 days. None of the patients treated with rt-PA experienced a recurrence; this difference approached, but did not reach, statistical significance. In summary, randomized trials clearly demonstrate that thrombolytic therapy produces more rapid clot lysis than therapy with heparin alone. No difference in the mortality rate or the incidence of recurrent PE has been demonstrated, however. This may mean that there is, in fact, no difference or that the studies have not included a sufficient number of patients to detect one.

In 1995, Jerjes-Sanchez et al⁶⁰ reported the results of a very small study in which eight patients with shock related to massive PE randomly received bolus SK or heparin therapy. All patients receiving heparin alone died, whereas no deaths occurred in the SK group. To our knowledge, this was the first randomized trial to show a survival advantage with throm-

Table 1—Randomized Trials Comparing Thrombolytic and Heparin Therapy

Study (Year)	No. of Patients	Treatment Regimens*	Mortality, No. of Cases (%)	Recurrent PE, No. of Cases (%)†	Major Hemorrhage, No. of Cases (%)‡
UPET ¹² (1970)	78	Heparin	7 (8.9)	15 (19)	21 (27)
	82	UK, 2,000 U/lb bolus, 2,000 U/lb/h for 12 h	6 (7.3)	12 (15)	37 (45)
Tibbitt et al ⁵⁵ (1974)	17	Intrapulmonary heparin	1 (5.8)	1 (5.8)	1 (6)
	13	Intrapulmonary SK, 600,000-U bolus, 100,000 U/h for 72 h	0	0	1 (8)
Ly et al ⁵⁶ (1978)	11	Heparin	2 (18.2)	NA§	2 (18)
	14	SK, 250,000-U bolus, 100,000 U/h for 72 h	1 (7.1)		4 (29)
Marini et al ⁵⁷ (1988)	10	Heparin	0	0	0
	10	UK, 800,000 U/d infused over 12 h for 3 d	0	0	0
	10	UK, 3,300,000 U infused over 12 h	0	0	0
PIOPEDES ⁵⁸ (1990)	4	Heparin	0	NA§	0
	9	rt-PA, 40 to 80 mg over 40 to 90 min and concomitant heparin	1 (11.1)		1 (11.1)
Levine et al ⁵⁹ (1990)	25	Heparin	0	0	0
	33	rt-PA, 0.6 mg/kg over 2 min	1 (3)	0	0
PAIMS 2: Dalla-Volta et al ¹⁸ (1992)	16	Heparin	1 (6.3)	3 (18.8)	2 (12.5)
	20	rt-PA, 100 mg over 2 h	2 (10)	1 (5)	3 (15)
Goldhaber et al ¹⁹ (1993)	55	Heparin	2 (3.6)	5 (9.1)	1 (1.8)
	46	rt-PA, 100 mg over 2 h	0	0	2 (4.3)
Jejjes-Sanchez et al ⁶⁰ (1995)	4	Heparin	4 (100)	NA§	0
	4	SK, 1,500,000 U over 1 h	0		0

*Unless specified, treatment was administered. In all studies, heparin was adjusted to maintain a therapeutic PTT. In the majority of the studies, thrombolytic therapy was followed by heparin infusion.

†Recurrent PE rate includes clinically suspected but unconfirmed cases as well as those episodes confirmed by objective tests.

‡The definition of major hemorrhage varied between trials but usually included intracranial hemorrhage, bleeding that required surgery, transfusion or resulted in death, or a decrease in hematocrit of

> 10 or 15 percentage points.

§NA = data not available.

||p < 0.05. All other comparisons did not reach statistical significance.

bolytic therapy. The results are difficult to interpret, however, since the patients receiving heparin had a much longer delay between the onset of symptoms and the initiation of therapy than those receiving SK.

During 1993 and 1994, a total of 1,001 patients with major PE were entered into the Management Strategy and Prognosis of Pulmonary Embolism Registry by 204 centers throughout Germany.²¹ Recently, the clinical course of patients presenting with right ventricular dysfunction and/or pulmonary hypertension, based on echocardiography or right heart catheterization, was reviewed.²¹ Patients with shock were excluded from this analysis. In this nonrandomized, level III study of 719 patients, 169 patients initially received thrombolytic therapy and 550 were treated with heparin alone. In the group undergoing thrombolysis, mortality at 30 days was significantly lower than in the heparin-treated group (4.7 vs 11.1%). In addition, recurrent PE was significantly less frequent in the patients receiving thrombolytic therapy (7.7% vs 18.7%). To our knowledge, this study is the first to demonstrate a survival advantage with thrombolytic therapy in patients without shock and supports the trend noted previously by Goldhaber and colleagues¹⁹ for thrombolysis to reduce the risk of recurrent PE. Because of its nonrandomized design, however, this study has several important limitations. Since treatment was left to the discretion of the attending physician, selection bias was unavoidable. In fact, patients receiving heparin were significantly older and much more likely to have underlying pulmonary or cardiac disease than those treated with thrombolysis. These factors, in turn, may have influenced the risk of mortality and recurrent PE.

Only one study (to our knowledge), which was published solely in abstract form, has attempted to evaluate the long-term effects of thrombolytic therapy. Sharma et al⁶¹ performed right heart catheterization in 23 patients a mean of 7 years after they had been randomized to receive either heparin or thrombolytic therapy with SK or UK. The group that had received heparin alone had elevated resting pulmonary artery pressure and pulmonary vascular resistance, both of which increased significantly with exercise. The group treated with thrombolytic agents, on the other hand, demonstrated normal resting values as well as a normal response to exercise.

Conclusions

1. Thrombolytic therapy results in more rapid clot resolution than treatment with heparin alone. Within 5 to 7 days, however, both treatments produce

similar improvements in pulmonary perfusion, as assessed by perfusion scan (level I and II evidence).

2. Based on data from a small randomized study, thrombolytic therapy appears to reduce mortality in patients with shock due to massive PE, probably by rapidly restoring pulmonary blood flow and improving right ventricular function (level II evidence).

3. In hemodynamically stable patients, thrombolysis has not been proven to reduce mortality or the risk of recurrent PE (level I and II evidence).

4. In the subset of patients with normal systemic arterial pressure and right ventricular dysfunction, thrombolytic therapy may decrease both mortality and recurrent thromboembolism (level II and III evidence).

5. Based on one level II study, thrombolytic therapy may enhance the resolution of small, peripheral emboli and improve the hemodynamic response to exercise. Whether thrombolysis reduces the risk of symptomatic thromboembolic pulmonary hypertension is not known.

HOW DO AVAILABLE THROMBOLYTIC AGENTS COMPARE WITH REGARD TO EFFICACY AND SAFETY?

Randomized, controlled trials comparing SK, UK, and rt-PA are summarized in Table 2. The earliest and largest of these was USET.¹³ In this level II study, 167 patients with angiographically demonstrated PE were randomized to receive 12 h of UK, 24 h of UK, or 24 h of SK. At 24 h, similar improvements in angiographic severity scores and hemodynamic variables were found in each of the groups. Similar improvements in perfusion scans were also noted at 24 h, although patients with massive embolism had significantly greater resolution after 24 h of UK than with SK therapy. No difference in the resolution of lung scan defects was noted between groups at 3 or 6 months. Finally, there were no significant intergroup differences in mortality, recurrent PE, or major hemorrhage.

Subsequent trials (all level II) have compared 2-h infusions of rt-PA with 24-, 12-, and 2-h regimens of UK, and with 12- and 2-h infusions of SK.^{44,62-65} In 1988, Goldhaber et al⁴⁴ reported the results of a study in which 45 patients were randomized to receive either a 24-h infusion of UK or a 2-h infusion of rt-PA. Two hours after the start of treatment, angiographic resolution and hemodynamic improvement were significantly greater in patients receiving rt-PA. By 24 h, however, the degree of improvement in pulmonary blood flow, as assessed by perfusion lung scan, was no different between the two groups. Although mortality did not differ, major hemorrhage

Table 2—Randomized Trials Comparing the Efficacy and Safety of Thrombolytic Agents

Study (Year)	No. of Patients	Treatment Regimens*	Mortality, No. of Cases (%)	Recurrent PE, No. of Cases (%)†	Major Hemorrhage, No. of Cases (%)‡
USET Phase 2 ¹³ (1974)	59	UK, 2,000 U/lb bolus, 2,000 U/lb/h for 12 h	4 (7)	1 (1)	8 (14)
	54	UK, 2,000 U/lb bolus, 2,000 U/lb/h for 24 h	5 (9)	4 (7)	10 (19)
	54	SK, 250,000 U bolus, 100,000 U/h for 24 h	5 (9)	2 (4)	6 (11)
Goldhaber et al ⁴⁴ (1988)	23	UK, 2,000 U/lb bolus, 2,000 U/lb/h for 24 h	2 (8.7)	1 (4)	11 (48)
	22	rt-PA, 100 mg over 2 h	2 (8.7)	0	4 (18)
Meyer et al ⁶² (1992)	29	UK, 4,400 U/kg bolus, 4,400 U/kg/h for 12 h	1 (3.4)	2 (6.9)	8 (28)
	34	rt-PA, 80 to 100 mg over 2 h	3 (8.8)	2 (5.9)	7 (21)
Goldhaber et al ⁶³ (1992)	46	UK, 1,000,000 U over 10 min, 2,000,000 U over 110 min	1 (2)	3 (6.5)	6 (13)
	44	rt-PA, 100 mg over 2 h	2 (4.5)	0	9 (20)
Meneveau et al ⁶⁴ (1997)	25	SK, 250,000 U bolus, 100,000 U/h for 12 h	1 (4)	2 (8)	3 (12)
	25	rt-PA, 100 mg over 2 h	1 (4)	0	4 (16)
Meneveau et al ⁶⁵ (1998)	43	SK, 1,500,000 U over 2 h	0	1 (2.3)	3 (7.0)
	23	rt-PA, 100 mg over 2 h	0	2 (8.7)	5 (21.7)

*In all studies, heparin was adjusted to maintain a therapeutic PTT. In the majority of the studies, thrombolytic therapy was followed by heparin infusion.

†Recurrent PE rate includes clinically suspected but unconfirmed cases as well as those episodes confirmed by objective tests.

‡The definition of major hemorrhage varied between trials but usually included intracranial hemorrhage, bleeding that required surgery, transfusion or resulted in death, or a decrease in hematocrit of > 10 or 15 percentage points.

was much more common with UK than with rt-PA (11 vs 4 patients; $p = 0.06$). This difference, however, was most likely influenced by the study design, since patients in the UK group received a prolonged drug infusion. In 63 patients with massive PE, Meyer et al⁶² compared therapy with rt-PA and a 12-h infusion of UK. At 2 h, treatment with rt-PA was accompanied by a significantly greater improvement in pulmonary artery pressures, pulmonary vascular resistance, and cardiac index. By 12 h, however, no significant hemodynamic differences were noted between the two groups. Repeat angiography was performed between 12 and 18 h after the start of treatment and showed no significant difference in the rate of clot resolution. There was no difference in the rates of mortality, recurrent PE, or major hemorrhage. Goldhaber and colleagues⁶³ then compared the efficacy and safety of 2-h infusions of rt-PA and UK in 90 patients with PE. The rate of clot lysis, assessed by angiography at 2 h and perfusion lung scan at 24 h, and the incidence of major hemorrhage were not different between the two groups. Meneveau et al⁶⁴ evaluated the efficacy and safety of a 2-h rt-PA infusion and a 12-h SK regimen in 50 patients with massive PE. Treatment with rt-PA was accompanied by a significantly more rapid improvement in pulmonary artery pressure and pulmonary vascular resistance. By 12 h, however, there was no difference between groups in the degree of hemodynamic improvement, and angiograms repeated at 24 to 48 h and perfusion scans at day 10 showed no difference in the extent of clot resolution. Both

regimens were associated with a similar risk of mortality and major hemorrhage. Finally, a recently published study by Meneveau and colleagues⁶⁵ compared the efficacy and safety of 2-h infusions of rt-PA and SK. Both regimens were accompanied by a rapid improvement in cardiac output, mean pulmonary artery pressure, and pulmonary vascular resistance. Although pulmonary vascular resistance decreased more rapidly in patients receiving rt-PA, no hemodynamic differences were found between the groups after 2 h. Perfusion scans performed 36 to 48 h after the start of therapy showed no difference in the extent of clot resolution. There was no significant difference in the rate of recurrent PE or major hemorrhage.

Conclusions

1. The three thrombolytic agents appear to be equally effective and safe when equivalent doses are delivered at the same rate over a short period of time (level II evidence).

2. A 2-h infusion of rt-PA results in more rapid clot lysis when compared with the 12- or 24-h regimens of UK and SK (level II evidence).

SHOULD THROMBOLYTIC AGENTS BE ADMINISTERED SYSTEMICALLY OR LOCALLY?

Local thrombolytic therapy has several potential advantages over systemic administration. First, by delivering the drug directly into the pulmonary

artery, local therapy might be accompanied by more rapid and/or more complete clot lysis. Second, because of high local drug concentrations, low doses might achieve the same degree of thrombolysis as higher systemic doses. Finally, local therapy might be accompanied by a lower risk of bleeding, especially if lower doses are used. The drawback of local therapy, of course, is the need to perform pulmonary artery catheterization, which increases the risk of bleeding from vascular access sites. Uncontrolled trials (level V) using local thrombolytic therapy have demonstrated that successful clot lysis can, in fact, be achieved.^{52,66-73} To our knowledge, only one controlled study (level II) has compared intrapulmonary and systemic thrombolysis. Verstraete et al⁷⁴ randomized patients with angiographically proven massive PE to receive either intrapulmonary or IV rt-PA in a dose of 50 mg over 2 h. Angiography was then repeated, and a second dose of 50 mg was infused over a 5-h period if sufficient improvement had not occurred. Although rapid and significant improvement in pulmonary artery pressure and pulmonary perfusion occurred with both IV and intrapulmonary rt-PA, no significant differences were found between the two groups. In addition, the risk of major hemorrhage was not influenced by the route of drug administration. Recently, local pharmacomechanical thrombolysis using low doses of UK or rt-PA and either high-pressure intraembolic infusion or mechanical clot disruption has been investigated.^{66,75} In one report, six patients with contraindications to systemic thrombolysis received low-dose intraembolic thrombolytic therapy using specialized catheters.⁶⁶ In this nonrandomized, level V study, systemic fibrinogenolysis and bleeding did not occur, and all patients were found to have at least a 20% angiographic improvement by 1 h and 50 to 90% improvement by 24 h.⁶⁶

Conclusion

The limited available data do not support the use of intrapulmonary thrombolytic therapy (level II and V evidence). Further research is needed to determine the role of local pharmacomechanical thrombolysis employing low doses of thrombolytic agents, especially in the treatment of patients with PE who are at high risk for bleeding complications.

WHAT IS THE ROLE OF BOLUS THROMBOLYTIC THERAPY?

By achieving a higher drug concentration over a shorter period of time, bolus thrombolysis offers the potential for both improved clot lysis and decreased risk of bleeding. Initial uncontrolled, level V studies

showed significant hemodynamic and angiographic improvement after systemic or local bolus thrombolytic therapy, although bleeding still occurred in some patients.^{52,68,76,77} Two prospective, randomized, level II trials have compared bolus dose rt-PA with the traditional 2-h regimen.⁷⁸⁻⁸⁰ These studies found no significant differences in the rate of angiographic, lung scan, and hemodynamic improvement, although pulmonary vascular resistance improved more rapidly with the 2-h rt-PA regimen. Despite a lower level of fibrinogenolysis with bolus therapy, the bleeding rate was similar in both groups.^{42,78}

Conclusion

Bolus dose rt-PA therapy is not safer or more effective than the approved 2-h regimen (level II evidence).

WHAT IS THE OPTIMUM TIME WINDOW FOR PE THROMBOLYSIS?

Early studies of PE thrombolysis clearly established the enhanced benefit of early therapy but excluded patients who presented > 5 days after the onset of symptoms.^{12,13} In UPET, for example, UK was more effective in patients with symptoms of < 2 days' duration than in those whose symptoms had been present for 2 to 5 days.¹² Subsequent trials, which have extended the time limit for thrombolysis to as long as 14 days, have demonstrated the benefit of thrombolytic therapy even in patients presenting long after the development of PE.^{19,44,63,78,79,81} Recently, Daniels and colleagues⁸² examined the relationship between duration of symptoms and the efficacy of thrombolytic therapy by combining data from 308 patients who participated in five multicenter trials (four level II and one level IV) published between 1986 and 1994. Based on the degree of improvement in perfusion scans, this study documented a progressive decrease in the efficacy of thrombolytic therapy with increasing symptom duration. Pulmonary perfusion increased in 86% of patients presenting within 24 h by an average of 16%, whereas an average improvement of only 8% was noted in 69% of patients treated > 6 days after the onset of PE.

Conclusion

Thrombolytic therapy is most effective when administered soon after PE, but benefit may extend up to 14 days after symptom onset. In general, PE thrombolysis should be performed as early as possible after the diagnosis is established (level I and II evidence).

WHAT ARE THE COMPLICATIONS OF THROMBOLYTIC THERAPY?

The most important complication of thrombolytic therapy is hemorrhage.⁸³ Bleeding most commonly occurs at vascular puncture sites, although spontaneous hemorrhage, especially GI, retroperitoneal, and intracranial, may also occur. As shown in Tables 1 and 2, the reported incidence of major hemorrhage with thrombolytic and heparin therapy has varied between 0% and 48%, and 0% and 27%, respectively.^{12,13,18,19,44,55–60,62–65} This marked variability is largely due to two factors. First, a high incidence of bleeding was encountered in early studies, in which venous cutdowns were routinely performed for angiography and right heart catheterization. Second, the definition of “major hemorrhage” has varied considerably among these trials. If major hemorrhage is arbitrarily defined as fatal hemorrhage, intracranial hemorrhage (ICH), or bleeding that requires either surgery or transfusion, contemporary studies can be analyzed to provide a more accurate estimate of the bleeding risk. A review of studies comparing thrombolytic and heparin therapy yields an average incidence of 6.3% and 1.8%, respectively.^{18,19,57–59} If data from recent studies comparing different thrombolytic agents are also considered, the overall incidence of major hemorrhage with PE thrombolysis increases to 11.9%.^{44,62–65} Pooling the data from all of these studies also illustrates that the rate of major hemorrhage is similar among the three thrombolytic agents (13.7%, 10.2%, and 8.8% for rt-PA, UK, and SK, respectively).^{18,19,44,57–59,62–65}

The most feared bleeding complication is, of course, ICH. As shown in Table 3, when data are pooled from 18 randomized level I and II studies in which 896 patients received IV thrombolytic therapy, the overall incidence of ICH is 1.2%, with death occurring in about half of these patients.^{12,13,18,19,44,55–60,62–65,74,78,80} ICH has not been reported in the relatively small number of patients treated with SK, whereas the incidence of ICH in patients treated with UK and rt-PA in these randomized studies is 1.3% and 1.6%, respectively. Spontaneous ICH did not occur in any of the patients treated with heparin alone. In large clinical trials of coronary thrombolysis, ICH has been shown to occur more often with rt-PA than with SK.⁸³ The low overall incidence of ICH following PE thrombolysis, however, does not allow a conclusion to be made about the relative safety of the three thrombolytic agents. Intracranial aneurysm or neoplasm, recent cerebral hemorrhage or infarction, and recent CNS trauma or surgery clearly increase the risk of ICH. In addition, an overview of five previously published studies (four level II and one level IV) identified elevated diastolic BP at the time of presentation as an additional risk factor for ICH.⁸⁴

Other complications of thrombolytic therapy include the following: fever; allergic reactions such as flushing, urticaria, and hypotension; and minor adverse effects, including nausea, vomiting, myalgia, and headaches. These reactions are most commonly associated with SK and can be treated with acet-

Table 3—The Incidence of Intracranial Hemorrhage in Randomized Studies of PE Thrombolysis

Study (Year)	No. of Patients	No. of Patients With ICH	No. of Patients With Fatal ICH
UPET ¹² (1970)	82	1	0
USET ¹³ (1974)	167	1	1
Tibbitt et al ⁵⁵ (1974)	13	0	0
Ly et al ⁵⁶ (1978)	14	0	0
Marini et al ⁵⁷ (1988)	20	0	0
Goldhaber et al ⁴⁴ (1988)	45	0	0
Verstraete et al ⁷⁴ (1988)	34	0	0
PIOPED ⁵⁸ (1990)	9	0	0
Levine et al ⁵⁹ (1990)	33	0	0
Meyer et al ⁶² (1992)	63	1	1
Goldhaber et al ⁶³ (1992)	90	3	1
PAIMS 2: Dalla-Volta et al ¹⁸ (1992)	20	1	1
Goldhaber et al ¹⁹ (1993)	46	1	0
Goldhaber et al ⁷⁸ (1994)	87	3	1
Sors et al ⁸⁰ (1994)	53	0	0
Jerjes-Sanchez et al ⁶⁰ (1995)	4	0	0
Meneveau et al ⁶⁴ (1997)	50	0	0
Meneveau et al ⁶⁵ (1998)	66	0	0
Total	896	11(1.2%)	5(0.6%)

aminophen, antihistamines, and hydrocortisone. Anaphylactic reactions to thrombolytic agents are rare.

Conclusion

Thrombolytic therapy is accompanied by a significantly greater risk of major hemorrhage than is treatment with heparin alone. There is also a small, but clinically important, risk of ICH (level I and II evidence).

WHAT ARE THE INDICATIONS FOR THROMBOLYTIC THERAPY IN PATIENTS WITH PE?

In discussing the appropriate therapy for PE, patients have typically been placed into one of two categories: those who present with shock and evidence of systemic hypoperfusion (*eg*, hypotension, lactic acidosis, and/or reduced cardiac output) and “hemodynamically stable” patients who have no signs of impaired systemic blood flow. Based on its repeatedly demonstrated ability to rapidly reduce clot burden and improve hemodynamic parameters, as well as the survival advantage demonstrated by Jerjes-Sanchez et al,⁶⁰ patients with PE and circulatory shock should be treated with thrombolytic therapy unless an overwhelming contraindication exists. To our knowledge, thrombolysis has never been proven to reduce mortality or the risk of recurrent PE in hemodynamically stable patients. Given the increased risk of major hemorrhage that accompanies thrombolytic therapy, patients in this category should generally be treated with heparin alone.

Recently published studies have suggested, however, that it may be important from a therapeutic standpoint to divide patients in the hemodynamically stable group into those with and without evidence of right ventricular dysfunction. In the study by Goldhaber et al,¹⁹ in which patients randomized to receive heparin had a higher rate of recurrence than those treated with thrombolytic agents, PE recurred only in patients with baseline right ventricular hypokinesis. The authors suggested that the presence of right ventricular dysfunction might identify a subset of patients at risk for increased morbidity and mortality when treated with heparin alone. This was supported by data from the Management Strategy and Prognosis of Pulmonary Embolism Registry, which demonstrated a significantly higher risk of both recurrent PE and death in patients with baseline right ventricular dysfunction who did not receive thrombolytic therapy.²¹ Because right ventricular dysfunction usually occurs in patients with a large clot burden, it has been suggested that thrombolysis

might improve patient outcome by rapidly increasing pulmonary blood flow, reducing right ventricular afterload, and eliminating the source of recurrent emboli.^{85,86} At the present time, however, PE thrombolysis based solely on the presence of right ventricular dysfunction is controversial because insufficient data are available. In the study by Goldhaber et al,¹⁹ the overall rate of PE recurrence was low, and the difference between treatment groups did not reach statistical significance. The limitations of the nonrandomized registry data have previously been discussed. Clearly, a large, prospective, randomized trial is needed to settle this issue. Although some experts disagree,^{86,87} we and others⁸⁸ believe that until more data are available, right ventricular dysfunction, by itself, is not an indication for thrombolytic therapy.

Conclusions

1. Patients with hypotension or other signs of systemic hypoperfusion caused by PE should be treated with thrombolytic therapy (level II evidence).

2. Additional information is needed to determine whether right ventricular dysfunction and/or a large clot burden are, by themselves, indications for PE thrombolysis.

PRACTICAL ASPECTS OF PE THROMBOLYSIS

Diagnosis of PE Prior to Thrombolytic Therapy

Since thrombolysis is accompanied by a significant risk of major hemorrhage, it is essential to confirm the presence of PE prior to the initiation of treatment. On the other hand, pulmonary angiography, although certainly the most accurate diagnostic study, increases the risk of significant bleeding at the venous puncture site. Therefore, in patients considered for thrombolysis, the diagnosis of PE should, if possible, be based on noninvasive imaging techniques. In the presence of highly suggestive clinical features, a high-probability ventilation-perfusion (\dot{V}/\dot{Q}) scan is usually sufficient for the diagnosis of PE. Spiral CT of the chest with rapid dye injection through a peripheral vein may also be used to detect emboli in central (segmental or larger) pulmonary arteries.⁸⁹⁻⁹⁴ Studies comparing spiral CT with angiography have demonstrated positive and negative predictive values exceeding 90%.⁸⁹⁻⁹⁴ Since patients considered for thrombolysis would invariably have central emboli, spiral CT may be useful either as an initial study or in patients with a nondiagnostic result of a \dot{V}/\dot{Q} scan. Unfortunately, since spiral CT requires a 20- to 30-s breath-hold, it may not be

technically feasible in many patients with significant PE. Despite an increased risk of bleeding, pulmonary angiography remains the diagnostic gold standard and must be performed when PE cannot be reliably diagnosed or excluded using noninvasive testing.

Frequently, of course, patients considered for thrombolytic therapy are in too unstable condition to leave the ICU for V/Q scan, spiral CT, or pulmonary angiography. In such cases, diagnosis must be based on clinical evaluation supplemented by indirect evidence of PE. Bedside transthoracic or transesophageal echocardiography may demonstrate signs of right ventricular pressure overload, including right ventricular hypokinesis and/or dilatation, while ruling out other causes of shock, such as left ventricular failure, pericardial tamponade, and aortic dissection.^{85,95-99} On occasion, large central emboli can be visualized using transesophageal echocardiography. Right heart catheterization, while increasing the risk of subsequent bleeding, may also strengthen the suspicion of massive PE by demonstrating elevated pulmonary artery and right ventricular pressures, a normal or low pulmonary artery occlusion pressure, and a low cardiac index. Right heart catheterization is also helpful in excluding other causes of shock.

Guidelines for the Administration of Thrombolytic Agents

The drug regimens approved by the Food and Drug Administration for PE thrombolysis are shown in Table 4. Based on studies that have demonstrated more rapid clot lysis, we believe that, among these regimens, rt-PA is the thrombolytic agent of choice.^{44,62,64} It is important to note, however, that 2-h infusions of SK and UK are as effective and safe as rt-PA.^{63,65} Before therapy is initiated, patients must undergo a thorough evaluation to elicit factors that increase the risk of major hemorrhage (Table 5).¹⁰⁰ This includes a detailed history as well as a physical examination to detect signs of intracranial abnormalities and GI bleeding. Initial laboratory tests should include measurement of hemoglobin, hematocrit, and platelet count; a blood sample

Table 4—Thrombolytic Agents Approved for Treatment of PE

Drug	Regimen*	Approval Date
SK	250,000 U over 30 min followed by 100,000 U/h for 24 h	1977
UK	4,400 U/kg over 10 min followed by 4,400 U/kg/h for 12 to 24 h	1978
rt-PA	100 mg over 2 h	1990

*All agents are administered as a continuous peripheral IV infusion.

Table 5—Relative Contraindications to Thrombolytic Therapy for PE

Recent (within 2 mo) cerebrovascular accident, or intracranial or intraspinal trauma or surgery
Active intracranial disease (aneurysm, vascular malformation, or neoplasm)
Major internal bleeding within the past 6 mo
Uncontrolled hypertension (systolic BP \geq 200 or diastolic BP \geq 110 mm Hg)
Bleeding diathesis, including that associated with severe renal or hepatic disease
Recent (< 10 d) major surgery, puncture of a noncompressible vessel, organ biopsy, or obstetric delivery
Recent major and minor trauma, including cardiopulmonary resuscitation
Infective endocarditis
Pregnancy
Hemorrhagic retinopathy
Pericarditis
Aneurysm

should be obtained for blood typing in case transfusion is required. The decision to use thrombolytic therapy must be based on a careful evaluation of its potential benefits, as well as its potential risks. No contraindication is absolute in the setting of massive PE and shock, and the decision to use thrombolytic therapy must be individualized.

Unlike the treatment of patients with myocardial infarction, heparin is not infused during PE thrombolysis. Since all regimens use fixed or weight-based dosages, there is no need to monitor the partial thromboplastin time (PTT), fibrinogen level, or any other coagulation parameter during the infusion. Following the completion of thrombolytic therapy, the PTT should be measured. If it is < 2.5 times the control value, a heparin infusion should be started and adjusted to maintain the PTT in the range of 1.5 to 2.5 times the control. If the initial PTT exceeds this upper limit, it should be remeasured every 2 to 4 h until it returns to the therapeutic range, at which time heparin therapy may safely be started.^{7,101,102} In situations in which PTT measurements cannot be performed rapidly, we recommend that a heparin infusion be started immediately after the completion of thrombolytic therapy and adjusted based on PTT results.

During thrombolytic therapy, the risk of hemorrhage can be minimized by avoiding phlebotomy, arterial puncture, and other invasive procedures. If bleeding occurs, its management depends on the location, severity, and cause. Bleeding from vascular sites can usually be controlled with manual pressure or compression dressings. Clinically important hemorrhage requires discontinuation of treatment with the thrombolytic agent, and cryoprecipitate and/or

fresh frozen plasma may be administered to reverse any associated coagulopathy. ICH is an emergency, and an emergent neurosurgical consultation must be obtained at the first sign of altered mental status or focal neurologic findings. The diagnosis of ICH can be confirmed and its severity assessed by performing a noncontrast CT of the brain.

SUMMARY

Unquestionably, thrombolytic therapy leads to much more rapid improvement in pulmonary vascular obstruction and hemodynamic abnormalities than treatment with anticoagulation alone. Despite many randomized, controlled trials performed during the past three decades, however, it has not been proven that this benefit translates into a reduction in morbidity or mortality. In patients with shock due to massive PE, the potential benefits of thrombolysis almost certainly outweigh the risk of significant hemorrhage. In those with small emboli that produce no hemodynamic disturbances, the risk of thrombolytic therapy is clearly not warranted. Additional information is required to assess the most appropriate therapy for patients who fall between these two extremes. In particular, future research must determine whether thrombolytic therapy reduces morbidity or mortality in patients with a large clot burden and/or right ventricular dysfunction who have no clinical signs of systemic hypoperfusion. Until then, clinicians must base a decision regarding thrombolytic therapy on careful consideration of the potential risks and benefits in the context of currently available data.

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