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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]

Contemporary Pulmonary Embolism Thrombolysis*

Samuel Z. Goldhaber, MD, FCCP

Lack of familiarity with pulmonary embolism (PE) thrombolysis is understandable because most hospitals treat just a few patients each year with recognized massive PE. Therefore, most physicians are inexperienced in administering PE thrombolysis, even though they utilize these agents routinely for acute myocardial infarction. Current estimates are that no more than 10% of patients with PE receive thrombolysis in the United States. This situation may be changing now, because PE thrombolysis appears to have expanded indications.

Recognized venous thromboembolism (which comprises both pulmonary embolism [PE] and deep venous thrombosis [DVT]) is responsible each year for more than 250,000 hospitalizations¹ and approximately 50,000 deaths in the United States. The immediate cause of death from PE is usually acute right heart failure. The major long-term morbidity of PE is chronic pulmonary hypertension.

Unfortunately, during the past three decades, the fatality rate from PE has not declined² (Fig 1). This is not too surprising because the standard treatment of PE with anticoagulation alone has remained essentially unchanged since the 1960s. The lack of progress in improving outcome from PE may be due, in part, to too much reliance on anticoagulation alone and insufficient use of thrombolysis. Not only does thrombolytic therapy accelerate clot lysis, it also hastens pulmonary tissue reperfusion, reversal of right heart failure, and improvement of pulmonary capillary blood volume.

Lack of familiarity with PE thrombolysis among individual physicians is understandable because most hospitals have just a few patients each year who present with recognized massive PE. Therefore, most physicians are inexperienced in administering PE thrombolysis, even though they may feel perfectly confident in administering thrombolytic therapy to treat acute myocardial infarction. Current estimates are that no more than 10% of PEs are treated with thrombolysis in the United States. In Europe, it appears that a higher proportion of patients received

Contemporary PE thrombolysis can now be given with simpler, less expensive protocols than were previously available. In the past, this treatment strategy had been rightly regarded as a heroic measure that consumed hospital resources and physicians' time. Today, PE thrombolysis can be applied with a 2 week "time window," no mandatory angiography in many cases, a brief infusion through a peripheral vein, and no special laboratory tests. (Chest 1995; 107:45S-51S)

thrombolytic therapy for venous thromboembolism, particularly for DVT.

Acute increases in right ventricular pressure can adversely affect left ventricular function because of the anatomic juxtaposition of the two ventricles and "ventricular interdependency." Moderate right ventricular hypertension can displace the interventricular septum toward the left ventricle, resulting in decreased left ventricular diastolic filling and end-diastolic volume (Fig 2). By relieving obstruction to pulmonary artery blood flow, thrombolysis can rapidly lower the abnormally elevated pulmonary artery pressure, thereby reversing cardiogenic shock and possibly reducing the mortality rate from PE. Because of interventricular dependency, improved right ventricular function augments left ventricular function which, in turn, helps reverse cardiogenic shock.

Among patients with major PE who are treated with anticoagulation therapy alone, pulmonary artery clots may fail to resolve completely. Dissolution of the thrombus should improve pulmonary tissue perfusion which, in turn, should prevent chronic pulmonary hypertension as a late effect of PE and improve the quality of life. Pulmonary embolism

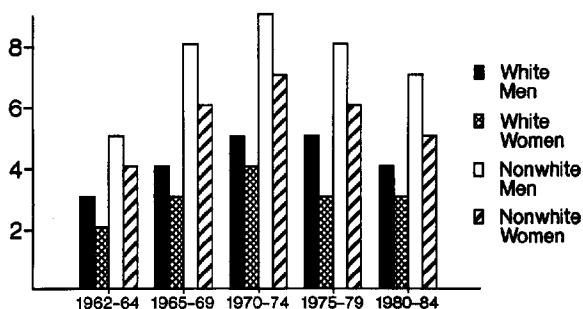


FIGURE 1. Death rate from PE per 100,000 in the United States from 1962 through 1984, based on data from the National Hospital Discharge Survey (from Lilienfeld et al²).

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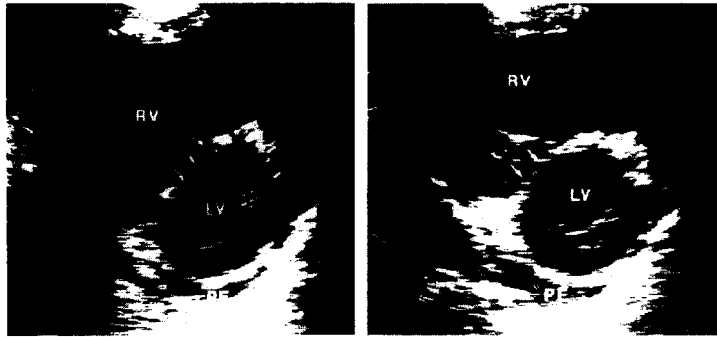


FIGURE 2. Parasternal short axis views of the right ventricle (RV) and left ventricle (LV) in diastole (left) and systole (right). There is diastolic and systolic bowing of the interventricular septum (arrows) into the left ventricle compatible with right ventricular volume and pressure overloads, respectively. The right ventricle is appreciably dilated and markedly hypokinetic, with little change in apparent right ventricular area from diastole to systole. PE=small pericardial effusion (from Come²⁵).

thrombolysis might also reduce the rate of recurrent PE by lysing the source of the PE *in situ*, usually thrombus in the pelvic or deep leg veins.

After pulmonary embolization, the release of neurohumoral factors, such as serotonin and thromboxane A₂, can cause vasoconstriction and bronchospasm. Serotonin, a potent neural and smooth muscle agonist, is stored primarily in the dense bodies of platelets and mediates bronchospasm in the small airways. Activated platelets also secrete thromboxane A₂, a potent vasoconstrictor and bronchoconstrictor. By dissolving thrombus quickly, thrombolytic agents may also minimize the potentially adverse impact of the neurohumoral response to PE.

PROGNOSIS WITH HEPARIN ALONE

Among patients treated with heparin alone, the rate of death or recurrent PE within 2 weeks of diagnosis is at least 10%. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) group reported on the clinical course of PE among 399 patients.³ Only 2.5% died, and most deaths were caused by recurrent PE. Overall, the rate of PE recurrence was 8.3%. This report on 399 patients with PE was based on a highly selected patient population. Of 5,587 patients who underwent lung scans, 1,523 refused to participate in PIOPED, and an additional 1,032 were excluded because pulmonary angiography was contraindicated. Another 1,539 patients were ineligible for PIOPED for other reasons. Undoubtedly, the recruitment process for PIOPED excluded many patients with large PEs who were considered too ill to participate. This selection process may have skewed the report toward the inclusion of patients with less life-threatening PE than those who were omitted.

Overall, only 6% of the 399 patients with PE received thrombolytic therapy. When 1-year mortality rates from all causes were assessed in the

PIOPED cohort, patients who had received anticoagulation alone had a 19% mortality rate. In contrast, the lowest all-cause mortality rate—9%—was in the group treated with thrombolytic therapy. Thus, even in this nonrandomized observational report of selected patients with PE, a hint exists that thrombolysis administered short term may improve long-term prognosis.

INITIAL CLINICAL TRIALS

In phase 1 of the Urokinase Pulmonary Embolism Trial (UPET), a 24-h urokinase (UK) infusion followed by heparin was compared with heparin alone.⁴ Urokinase dissolved PE more rapidly than heparin alone and, in certain instances, reversed clinical shock. In UPET, there was a trend with UK toward reduction of mortality and recurrent PE that did not achieve statistical significance, possibly due to a relatively small sample size of 160 patients.

In the Urokinase-Streptokinase PE Trial, acute thrombolysis of PE followed by heparin improved pulmonary capillary blood volume at 2 weeks and at 1 year more than heparin alone.⁵ When a subgroup of these patients was followed up for an average of 7 years, those assigned initially to thrombolysis appeared to have a more complete resolution of PE as assessed by preservation of the normal pulmonary vascular response to exercise.⁶ In addition, patients who had received PE thrombolysis followed up for an average of 7 years had less functional disability than those who had initially received heparin alone. This suggests that thrombolysis given at the time of acute PE may improve the long-term quality of life.

CONTEMPORARY CLINICAL TRIALS

In the 1980s, recombinant tissue-type plasminogen (rt-PA) was developed for PE treatment because initial animal studies suggested that it was more potent than UK or streptokinase and possibly safer. In

1992, the PAIMS-2 investigators in Italy⁷ reported the results of their randomized clinical trial in which 36 patients with angiographically proved PE were randomized to receive 100 mg of rt-PA over 2 h or heparin alone. Clot lysis at posttreatment angiography, assessed by the Miller index, occurred in the rt-PA group (with the Miller index improving from 28.3 ± 2.9 to 24.8 ± 5.2) but not in the patients who received heparin alone. Mean pulmonary artery pressure decreased from 30.2 ± 7.8 mm Hg to 21.4 ± 6.7 mm Hg in the rt-PA group, but increased in patients who received heparin alone. Two patients who had received rt-PA died (one from renal failure following cardiac tamponade and one from intracranial bleeding), and one patient who received heparin alone died from recurrent PE.

European Cooperative Study Group Investigators compared 100 mg of rt-PA over 2 h with a 12-h weight-adjusted infusion of UK (4,400 U/kg bolus, followed by 4,400 U/kg/h for 12 h).⁸ The principal end point was reduction in total pulmonary resistance, defined as pulmonary artery mean pressure divided by cardiac index. At 2 h, total pulmonary resistance decreased by 36% in the rt-PA group, compared with a decrease of 18% in the UK-treated patients ($p=0.0009$). However, by 6 h, UK appeared to "catch up" to rt-PA, and hemodynamic differences between the two groups did not persist.

In Boston, we have coordinated five trials of PE thrombolysis. The fifth trial was international, included investigators from Italy, Canada, and the United States, and tested the hypothesis that a smaller bolus of rt-PA administered over 15 min is safer than a larger dose administered over 2 h.⁹

PE Trial 1

This was an open label study of 47 patients with angiographically documented PE that showed that 50 to 90 mg of rt-PA administered over 2 to 6 h caused clot lysis in 94% of patients.¹⁰⁻¹² Among patients with pulmonary artery hypertension, the pulmonary artery pressures decreased during the short-term treatment period from 43/17 (27) to 31/13 (19) mm Hg, without any change in systemic arterial pressure. Hemodynamic and angiographic improvement was accompanied by recovery in pulmonary perfusion.¹³ One day after rt-PA, there was a 57% increase in perfusion among the 19 patients who had follow-up lung scans. Right ventricular function also improved, as judged by Doppler echocardiography on seven patients with PE before and after they received rt-PA.¹⁴ The early reversal of the hallmarks of right heart failure—right ventricular dysfunction, right ventricular dilatation, and tricuspid regurgitation—suggests that thrombolytic agents might reduce the mortality from acute PE.

All patients received 50 mg of rt-PA over 2 h, followed immediately by a research angiogram. If clot lysis had not occurred, as judged by the investigator at the time of the angiogram, an additional 40 mg of rt-PA was administered over the subsequent 4 h and was followed immediately by a third angiogram. Two-thirds of the patients received more than 2 h of rt-PA. During the third and subsequent hours of rt-PA therapy, however, an increased frequency of bleeding, particularly at the femoral vein puncture site used for pulmonary angiography, caused us to shorten the duration and raise the rt-PA dose in our subsequent trials.

PE Trial 2

This was a randomized trial comparing 100 mg of rt-PA over 2 h vs 4,400 U/kg of UK as a bolus followed by 4,400 U/kg/h for up to 24 h.¹⁵ The Food and Drug Administration (FDA) considered this trial to be a pivotal study when it approved rt-PA for PE treatment. The principal end points were improvement on the 2-h angiogram and 24-h lung scan compared with the baseline studies. All 45 patients received the full dose of rt-PA, but UK infusions were terminated prematurely in 9 of 23 patients because of allergy in 1 and uncontrollable bleeding in 8. By 2 h, 82% of rt-PA-treated patients showed clot lysis compared with 48% of UK-treated patients ($p=0.0008$). Thus, in the dosing regimens employed, rt-PA was more rapid and safer than UK. However, at 24 h, there was no difference in scintigraphic improvement between patients who had received rt-PA and UK. Furthermore, at 2 and 24 h after initiation of thrombolysis, the fibrinogen levels were similar in both treatment groups.

PE Trial 3

This compressed the 24-h dose of UK to make it more comparable to the high concentration/short infusion period that was used for rt-PA.¹⁶ The novel UK dose was 3,000,000 U/2 h, with the first 1,000,000 U given as a bolus over 10 min. This trial enrolled 90 patients. Repeated pulmonary angiograms at 2 h were performed in 87 patients and then graded by a blinded panel. The results indicated that a 2-h regimen of rt-PA and a new concentrated dosing regimen of UK exhibit similar efficacy and safety for treatment of acute PE. The one substantive difference between the two agents was that 8 of 46 patients who had received UK, compared with 0 of 44 patients who had received rt-PA suffered rigors ($p=0.004$), even though all patients who had received UK were pretreated with hydrocortisone, diphenhydramine, and acetaminophen. The rt-PA-treated patients received no premedication.

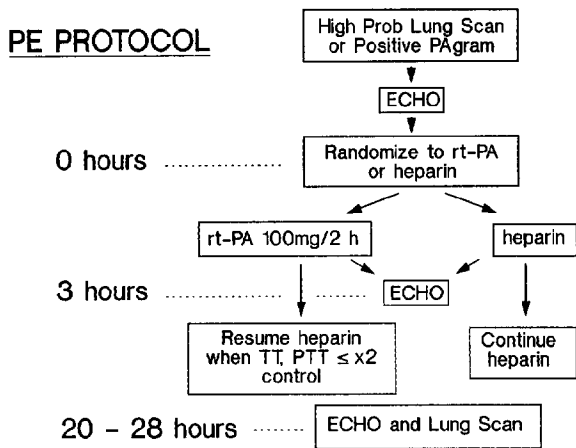


FIGURE 3. Protocol for PE Trial 4. Please refer to text.

PE Trial 4

This tested the hypothesis that rt-PA followed by anticoagulation accelerates the improvement of right ventricular function and pulmonary perfusion after PE more rapidly than anticoagulation alone (Fig 3).¹⁷ In this multicenter randomized controlled trial, 101 patients were randomized: 46 to rt-PA, 100 mg/2 h followed by heparin, and 55 to heparin alone.¹⁷ Thus, PE trial 4 is the largest thrombolysis vs heparin trial that has been undertaken since phase 1 of Urokinase Pulmonary Embolism Trial.⁴ All patients who entered this trial were hemodynamically stable. No patient presented with an initial systolic arterial pressure less than 90 mm Hg. At baseline, about half of the patients with PE had entirely normal right ventricular function. Only 20% of the patients underwent diagnostic pulmonary angiograms. The others were enrolled on the basis of high-probability lung scans.

Right ventricular wall motion was assessed qualitatively, and right ventricular end-diastolic area from the apical four-chamber view was planimetered on serial echocardiograms at baseline, 3 h, and 24 h. (An abnormally large right ventricular end-diastolic area indicates right ventricular dilatation.) Pulmonary perfusion scans were obtained at baseline and 24 h. The results indicated that rt-PA (100 mg/2 h) followed by heparin provided striking improvement in right ventricular function and pulmonary perfusion compared with heparin anticoagulation alone.

Qualitative assessment of right ventricular wall motion at baseline vs 24 h demonstrated (Fig 4) that 39% of the rt-PA-treated patients improved and 2.4% worsened, compared with 17% improvement and 17% worsening among those who received heparin alone ($p=0.005$). Quantitative assessment showed that patients who had received rt-PA had a significant decrease in right ventricular end-diastolic area

BASELINE vs. 24H ECHO (N=89)

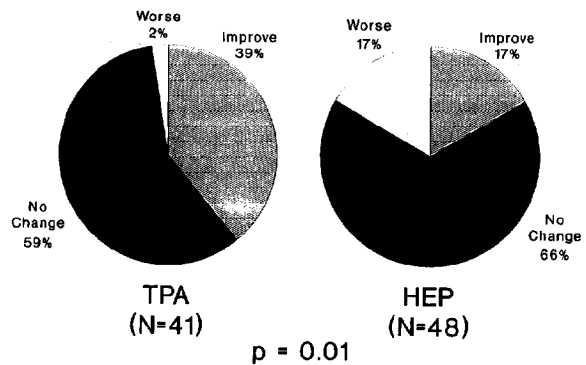


FIGURE 4. Qualitative assessment of right ventricular wall motion. Please refer to text.

during the 24 h after randomization compared with none among those allocated to heparin alone ($p=0.01$) (Fig 5). The rt-PA-treated patients also had an absolute improvement in pulmonary perfusion of 14.6% at 24 h, compared with 1.5% improvement among patients treated with heparin alone ($p<0.0001$).

Most importantly, no clinical episodes of recurrent PE occurred among rt-PA-treated patients, but there were five (two fatal and three nonfatal) clinically suspected recurrent PEs within 14 days in patients randomized to heparin alone ($p=0.06$). All five presented initially with right ventricular hypokinesis on echocardiogram. This latter observation suggests that echocardiography may help identify a subgroup of patients with PE at high risk of adverse clinical outcomes if treated with heparin alone. Such patients, in particular, would appear to be excellent candidates for thrombolytic therapy in the absence of contraindications. Thus, rapid improvement of right ventricular function (Fig 6) and pulmonary perfusion, accomplished with thrombolytic therapy followed by heparin, may lead to a lower rate of death and recurrent PE. Among hemodynamically stable patients who present with right ventricular hypokinesis, thrombolysis may prevent the downhill spiral of right heart failure.

PRACTICAL POINTS

The US FDA approved the use of streptokinase in 1977 and UK in 1978 for treatment of PE; rt-PA was approved for this use in 1990. All three regimens (Table 1) use fixed or weight-adjusted doses of thrombolytic agents. Therefore, there is no need to obtain laboratory tests during the thrombolytic infusion because no dosage adjustments are made.

Peripheral intravenous and local pulmonary arterial infusion of rt-PA were compared among patients

RVED Area (cm²) vs. TIME

General Linear Models Procedure

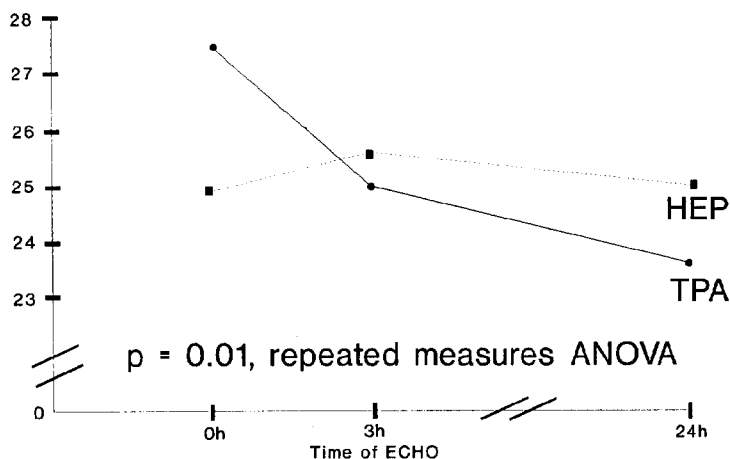


FIGURE 5. Right ventricular end-diastolic area (RVED) (cm²) over time among patients randomized to rt-PA followed by heparin vs heparin alone. The RVED area is based on measurements planimetered by the echocardiogram reading panel, and time points are at baseline, 3 h, and 24 h. Using a general linear models procedure, the change over time in patients receiving rt-PA vs heparin differed significantly (p=0.01 using repeated measures analysis of variance [ANOVA]). The patients who received heparin alone showed no change, whereas the RVED area of rt-PA-treated patients decreased at 3 h and at 24 h (from Goldhaber et al¹⁷).

with angiographically documented PE.¹⁸ In a randomized controlled trial, both routes of administration caused similar rates of lysis, bleeding, and induction of a systemic lytic state. Therefore, locally delivered rt-PA appears to confer no advantage over peripheral administration of the drug.

For patients with a high clinical suspicion for PE

and high-probability ventilation-perfusion lung scans, the likelihood of PE is approximately 96% in the PIOPED study.¹⁹ Therefore, these patients can receive thrombolytic therapy without angiographic confirmation of the diagnosis. However, angiography should be performed among patients with non-high-probability scans prior to administering thrombolytic

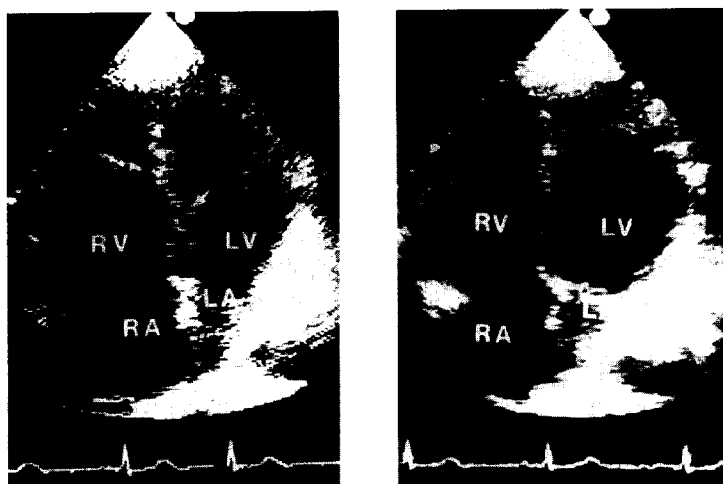


FIGURE 6. Echocardiograms (four-chamber view) in a 53-year-old previously healthy man with a high-probability lung scan for pulmonary embolism. *Left*, Right ventricular enlargement before treatment. The right ventricular end-diastolic area was 42.9 cm², and the interventricular septum (arrow) was displaced toward the left ventricle. *Right*, 3 hours after initiating rt-PA therapy, the right ventricle normalized in size (with a planimetered area of 25.7 cm²), and the interventricular septum resumed its normal configuration.

Table 1—FDA-Approved Thrombolytic Regimens for PE

Thrombolytic Regimen
<i>Streptokinase</i> : 250,000 IU as a loading dose over 30 min followed by 100,000 U/h for 24 h—approved in 1977
<i>Urokinase</i> : 4,400 IU/kg as a loading dose over 10 min, followed by 4,400 IU/kg/h for 12 to 24 h—approved in 1978
<i>rt-PA</i> : 100 mg as a continuous peripheral intravenous infusion administered over 2 h—approved in 1990

therapy. For hemodynamically stable patients admitted to the hospital in the evening or at night, we defer angiography until the next morning and empirically initiate heparin therapy. Heparin is held for several hours prior to angiography. Angiography is performed using a Cordis sheath with a side arm (for blood sampling) that is usually placed in the right femoral vein.²⁰

When considering PE thrombolysis, we do not have an arbitrary upper age limit (Table 2). Additionally, we do not consider the presence of cancer an exclusion criterion. We have found that patients with PE have a wide “time window” for effective use of thrombolysis. Specifically, patients who receive thrombolysis 6 to 14 days after new symptoms or signs have as effective a response as those patients who receive thrombolytic therapy within 5 days af-

Table 2—Practical Aspects of PE Thrombolysis

1. Take a careful neurologic history. For example, ask the patient if he has had episodes of right hand weakness and difficulty speaking rather than asking whether he has had transient ischemic attacks. Inquire about previous headaches. Determine the location, duration, and clinical course of prior headaches, along with associated visual changes or neurologic abnormalities that might have occurred. A history of migraine headaches in no way precludes administration of thrombolysis. However, it is best to elicit such a history *prior* to the therapy.
2. Prior to initiating thrombolysis, send a “clot” to the blood bank (in a red top tube) for “type and hold” (*ie*, “type and screen”).
3. Initiation of thrombolytic therapy (and pulmonary angiography) are most safely accomplished during “daylight hours” unless the patient cannot tolerate or fails heparin therapy. Remember that there is a 14-day “window” for administration of PE thrombolysis.
4. Choose an FDA-approved thrombolytic regimen (see Table 1). No coagulation tests are necessary during thrombolysis because the doses of thrombolytic agent are either fixed (streptokinase and rt-PA) or determined by weight (UK).
5. Minimize physical handling of the patient, and try not to draw blood during the infusion period.
6. Do *not* administer concomitant heparin. After thrombolysis, resume heparin therapy without a bolus dose when the partial thromboplastin time is less than 80 s.
7. Initiate warfarin therapy after heparin has been restarted and after the partial thromboplastin time is documented to be in the therapeutic range. Overlap heparin and warfarin therapy for a minimum of 5 days.

ter the onset of PE. Therefore, we will consider patients suspected of having PE as potentially eligible for thrombolysis if they have had any new symptoms or signs within the 2 weeks prior to presentation.

None of the FDA-approved regimens for PE thrombolysis employs concomitant heparin therapy, an important difference when compared with the usual approach to thrombolysis in myocardial infarction. At the conclusion of the thrombolytic infusion, a partial thromboplastin time (PTT) should be obtained. As long as the test result is less than 80 s, heparin therapy can be initiated (or resumed) as a continuous intravenous infusion, without a loading dose. Occasionally, after termination of the thrombolytic infusion, the PTT will exceed 80 s. In these circumstances, the test should be repeated every 4 h until it declines into the range in which heparin therapy is safe. We leave the Cordis sheath in place until the next morning and discontinue the heparin infusion for several hours before removing the sheath. Heparin administration is resumed without a bolus after adequate hemostasis is achieved at the catheterization site.

BLEEDING COMPLICATIONS

Of greatest concern is the risk of intracranial bleeding that occurs in approximately 1% of patients with PE treated with thrombolytic therapy. If intracranial bleeding is suspected, thrombolytic therapy or heparin therapy should be discontinued immediately, and both neurologic and neurosurgical consultation should be obtained. Retroperitoneal hemorrhage can also be life threatening because the bleeding is often sustained, brisk, and difficult to diagnose. This complication can occur during the femoral vein catheterization for pulmonary angiography if an artery is inadvertently punctured above the inguinal ligament.

During the past decade, appropriate patient selection and minimizing the “handling” of patients during the thrombolytic infusion has lessened the bleeding rate. By 1987, the rate of severe bleeding in a multicentered European study of UK for PE had decreased to 4%.²¹

CONTEMPORARY PE THROMBOLYSIS

Pulmonary embolism thrombolysis used to require automatic admission to an ICU for careful clinical and laboratory monitoring. This was appropriate because bleeding complications often occurred with prolonged thrombolytic infusions. However, with short infusions of thrombolytic agents, many patients can be treated safely in an intermediate care (“step-down”) unit. The McMaster Group treated all 57 patients in their trial of 2-min rt-PA (or placebo) in-

fusion either in the Emergency Department or on the general medical ward.²² Contemporary PE thrombolysis should not require an ICU bed unless the patient is unstable and needs the ICU for reasons other than thrombolysis, such as Swan-Ganz monitoring or ventilatory assistance.

CONCLUSIONS

Many clinicians who practiced in the early and mid-1970s remember PE thrombolysis as a heroic measure that consumed hospital resources and physician time. Indeed, more than one in every four patients suffered a major hemorrhagic complication when a 24-h thrombolysis dosing regimen was used.⁴ This unfavorable experience soured some physicians who have been reluctant to reconsider PE thrombolysis in the 1990s. Fortunately, recently completed clinical trials have taught us how to make thrombolytic therapy safer, more streamlined, and more economic. Contemporary PE thrombolysis is characterized by a 2-week "time window," a brief infusion administered through a peripheral vein, and no special laboratory tests.

Future studies will require international collaboration and must focus on relevant clinical end points such as reduction of mortality, recurrent PE, and chronic pulmonary hypertension.²³ It is now time for a large trial not only in patients with massive embolism but also among those with smaller emboli that so often herald catastrophic events.²⁴ Fortunately, investigators at the international network of centers participating in PE trials 1 through 5 have demonstrated through their dedication and enthusiasm that future large-scale trials are feasible.

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