Evolving Concepts in Thrombolytic Therapy for Pulmonary Embolism*

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

Twenty years ago, thrombolysis for pulmonary embolism (PE) was introduced to the medical community as a complex, heroic, and somewhat desperate undertaking. This therapy required immense dedication of hospital resources and personnel and was, therefore, cumbersome, costly, and reserved for patients who were on the brink of death. Although the Food and Drug Administration (FDA) approved streptokinase in 1977 and urokinase in 1978 for acute PE treatment, this therapy was viewed as so impractical that it fell into virtual disuse until the mid-1980s. At that time, renewed interest in thrombolysis for acute myocardial infarction led to reexamination of the potential benefits of thrombolysis for acute PE. A series of clinical trials was subsequently undertaken, which resulted in a contemporary approach to PE thrombolysis that is safer, more rapid, and far less costly than that recommended 2 decades ago. These advances (Fig 1) may result in more widespread utilization of thrombolytic agents for PE treatment.

Time Window

It used to be taught that PE thrombolysis had to be initiated within 5 days of symptoms or signs of the disease. The rationale was that after 5 days, fibrinolysis was completely ineffective. Indeed, I can recall patients with massive PE from the early 1970s who were not treated with thrombolytic agents solely because they presented 6 or 7 days after the onset of symptoms. Therefore, in our research group's first PE trial (Table 1), we instituted an exclusion criterion that made patients ineligible for the trial if they had no new symptoms or signs of PE within 5 days. When we reviewed the results in the 47 patients in this trial, all of whom received rt-PA, we found to our surprise that patients enrolled 3 to 5 days after symptoms had as much clot lysis as patients enrolled 0 to 2 days after clinical manifestations. Therefore, in our subsequent PE trials, we extended our time window to 14 days. We have analyzed the results in the second and third trials and have found that patients enrolled 6 to 14 days after PE symptoms or signs had as much benefit from PE thrombolysis as patients enrolled 0 to 5 days after the onset of clinical features of the illness.

Diagnosis of PE

Pulmonary angiography prior to thrombolysis used to be considered virtually mandatory prior to publication of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) trial results. The PIOPED protocol required pulmonary angiography for patients with suspected PE and abnormal lung scans. The results showed that among patients with a high clinical suspicion for PE and a high-probability ventilation-perfusion lung scan, the likelihood of PE at angiography was 96%. Therefore, among this subset of patients, the diagnostic accuracy for PE equals or exceeds that for acute myocardial infarction. As is the case with myocardial infarction thrombolysis, angiography is not required in patients in whom the diagnostic certainty is this high. Consequently, in our fourth and fifth PE trials, we have not required pulmonary angiography at some of the participating centers in cases with both high clinical suspicion of PE and high-probability ventilation-perfusion scans.

In certain circumstances, patients in whom PE is suspected will present to the emergency department with hypotension due to cardiogenic shock. These patients will be on the verge of dying of right heart failure due to PE. They represent a subset of patients too unstable for either lung scanning or pulmonary angiography. In such a setting, which might arise once or twice a year in a large hospital, it is appropriate to diagnose PE on the basis of an emergently obtained

PE Thrombolysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Old</th>
<th>New</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Window</td>
<td>&lt; 5 days</td>
<td>&lt; 14 days</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Angio</td>
<td>Scan/ECHO</td>
</tr>
<tr>
<td>Infusion</td>
<td>Prolonged</td>
<td>Short</td>
</tr>
<tr>
<td>Route</td>
<td>PA catheter</td>
<td>Peripheral vein</td>
</tr>
<tr>
<td>Labs</td>
<td>Many</td>
<td>None</td>
</tr>
<tr>
<td>Location</td>
<td>ICU</td>
<td>Ward</td>
</tr>
</tbody>
</table>

Figure 1. New concepts in PE thrombolysis. PA = pulmonary artery.

*From the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston. Reprint requests: Dr Goldhaber, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA 02115.
portable 2-dimensional echocardiographic examination with Doppler flow imaging across the tricuspid valve. If the typical features of right heart failure due to PE are present—right ventricular dilatation, bowing of the interventricular septum into an abnormally compressed left ventricle, right ventricular hypokinesis, and tricuspid regurgitation—then such a patient can be treated appropriately with thrombolysis in the absence of major contraindications to its use.

The advantages of utilizing thrombolysis without pulmonary angiography among selected PE patients are readily apparent. First, without angiography, the morbidity from this procedure is averted. In most instances, such morbidity consists of a groin hematoma if the femoral vein is not successfully punctured percutaneously on the first attempt. More serious is the prospect of right ventricular perforation, which can lead to pericardial hemorrhage and tamponade when thrombolysis is employed. When angiography is obviated, the patient benefits because treatment is administered more quickly and at far less cost than would otherwise be entailed.

**Infusion Duration**

It used to be taught that a prolonged thrombolytic infusion was required for PE treatment because of the large size of the thrombus. Therefore, initial PE thrombolysis regimens were designed with 12- to 24-h infusions (Table 2). In 1990, rt-PA was approved in a fixed dose of 100 mg over 2 h, because this regimen was shown to be more effective and safer than a 24-h thrombolytic infusion. It has become apparent that the longer a thrombolytic agent is infused, the higher the bleeding complication rate will be. Other promising regimens of short duration for PE include a 2-h urokinase infusion (3,000,000 units total, with the first 1,000,000 units administered over 10 min) and even a 2-min weight-adjusted recombinant tissue plasminogen activator (rt-PA) infusion (0.6 mg/kg).

**Route of Administration**

Conceptually, it would seem that if thrombolysis were administered locally at the site of the thrombus, it could be utilized in a lower dose and more safely than if infused through a peripheral vein. However, a randomized trial by Verstraete et al. in 34 patients with massive PE demonstrated that locally administered rt-PA is no more effective and is not safer than rt-PA given peripherally. This means that thrombolysis need not be delayed until after insertion of a pulmonary arterial line and that PE thrombolysis need not be restricted to facilities that can readily insert this catheter. Analogous to avoiding pulmonary angiography, this simplified approach of using merely a peripheral intravenous line results in more rapid treatment and reduced cost.
COAGULATION TESTS

It used to be considered important to obtain multiple and serial coagulation tests to assess the systemic effects of thrombolytic therapy. Often, a disseminated intravascular coagulation screen would be obtained every 4 h during the prolonged thrombolytic infusion. This panel of tests usually includes fibrinogen, fibrin/fibrinogen degradation products, thrombin time, partial thromboplastin time, prothrombin time, and a platelet count. In the era before health-care providers paid much attention to costs, this type of serial testing was considered important in defining precisely the extent and time course of the systemic lytic state. However, such testing could result in drawing as much as 200 ml of blood within 24 h. None of the FDA-approved regimens utilizes concomitant heparin; therefore, coagulation testing during thrombolysis to adjust heparin dosing cannot be justified, because no heparin is administered. Furthermore, the results of this intensive coagulation testing should have no bearing on the doses of thrombolytics that are administered. All three FDA-approved thrombolytic regimens are administered according to a fixed schedule that is not dependent on coagulation testing. Streptokinase and rt-PA are given in fixed doses, and urokinase is administered according to the patient's weight. In addition to cost savings, elimination of coagulation testing during thrombolysis prevents venipuncture-associated hematomas and ecchymoses that would otherwise inevitably occur.

UTILIZATION OF INTENSIVE CARE UNIT

Pulmonary embolism thrombolysis used to mean automatic admission to an intensive care unit (ICU) for careful clinical and laboratory monitoring. This seemed appropriate because bleeding complications occurred often 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) administration on the general medical ward. Contem}

porary PE thrombolysis should not require ICU admission unless the patient's condition is unstable and the ICU is needed for reasons other than thrombolysis. For example, a patient who has a PE and is respirator-dependent warrants an ICU bed, as does a patient who requires Swan-Ganz monitoring. However, even with a Swan-Ganz line in place, thrombolitics should be administered through a peripheral vein.

SUMMARY

Many clinicians who practiced in the early and mid-1970s remember PE thrombolysis as an extraordinary enterprise that consumed hospital resources and physicians' time around the clock for at least several days. Indeed, more than 1 in every 4 patients suffered a major hemorrhagic complication when a 24-h dosing regimen was utilized. 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 many ways to make thrombolytic therapy safer, more streamlined, and more economical (Fig 1).

REFERENCES

6 PIOPED investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). JAMA 1990; 263:2753-59
8 Meyerowitz M. How to maximize the safety of coronary and pulmonary angiography in patients receiving thrombolytic therapy. Chest 1990; 97:1325-35S