Thrombolysis in Pulmonary Embolism
A Large-Scale Clinical Trial Is Overdue

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Thrombolysis for acute pulmonary embolism (PE) remains a debatable indication because inadequate data exist to provide definitive management guidelines. As cardiologists, we have relied on large-scale randomized clinical trials to determine that thrombolysis benefits patients with ST-segment elevation acute myocardial infarction (MI). Yet, no clinical investigations similar in scope have been undertaken for pulmonary thromboembolism, even though this illness afflicts ≈100,000 patients annually in the United States and has a high case fatality rate.

Intuitively, thrombolysis makes sense, especially for massive PE with cardiogenic shock. Nevertheless, only one small randomized controlled trial of 8 patients has tested this strategy among these desperately ill PE patients. The thrombolytic regimen was streptokinase, given in the MI dose of 1,500,000 U administered over a period of 1 hour. All 4 patients receiving thrombolysis plus heparin survived, whereas none were treated successfully with anticoagulation alone. Although the investigators originally intended to enroll 40 patients, they halted their trial for ethical reasons after the first 8 patients yielded such disparate results between the 2 groups. Despite these dramatic differences between the 2 groups, we should not craft treatment policy on the basis of an 8-patient trial.

Shockingly, there are only 9 randomized trials of PE thrombolysis versus heparin, with a total of <300 patients. Only 2 of these trials have enrolled >100 patients. The first trial, the Urokinase Pulmonary Embolism Trial, enrolled 160 patients who were randomized to thrombolysis plus heparin or heparin alone. This has been the largest trial to date. The thrombolytic agent was urokinase, a drug that is currently not available. The investigators tested a 24-hour continuous-infusion dosing regimen of urokinase that we now know predisposes to major hemorrhage. Urokinase dissolved pulmonary arterial clot more rapidly than heparin alone and, in some patients, reversed clinical shock. Urokinase did not, however, lower the rate of death or recurrent PE. In a small ancillary study, patients receiving thrombolysis had improved pulmonary capillary blood volume at 2 weeks and at 1 year after treatment. After an average of 7 years of follow-up, those initially receiving thrombolysis maintained an improved pulmonary vascular response to exercise and better quality of life compared with patients treated with heparin alone.

The second trial tested a contemporary and now FDA-approved regimen of tissue plasminogen activator (tPA) 100 mg as a continuous infusion over a period of 2 hours. This latter trial of 101 PE patients who were all initially hemodynamically stable demonstrated that those receiving continuous intravenous heparin alone were more likely to suffer recurrent PE despite therapeutic levels of anticoagulation than were patients who were randomized to receive tPA followed by heparin. The difference in efficacy (zero recurrent PEs in the tPA group versus 5 in the heparin-alone group) approached but did not achieve statistical significance, with a probability value of 0.06. Although no tPA patients suffered intracranial hemorrhage in this trial, one of the patients assigned to heparin alone received tPA off protocol and did have intracranial bleeding.

In the tPA trial of 101 patients, all 5 who suffered recurrent PE despite intensive anticoagulation alone had presented with normal systemic arterial pressure and concomitant right ventricular dysfunction that worsened over the ensuing 24 hours on serial echocardiography. This observation raised the possibility that echocardiography of the right ventricle might help determine which PE patients should receive thrombolysis for PE.

There are problems, however, with translating these findings into clinical practice. First, the original observation requires confirmation in additional studies and in settings in which echocardiography might not be immediately available. Second, this triage strategy ignores the potential “catch-up” phenomenon and improvement in right ventricular function that might occur among patients who survive an initial 5 to 7 days. Third, the approach of thrombolysis based on right ventricular dysfunction does not take into account the shift in management of venous thromboembolism anticoagulation from continuous intravenous heparin to subcutaneous low-molecular-weight heparin, which may be more effective than unfractionated heparin. Finally, such a proposed strategy does not adequately address the potential risk of massive bleeding, including intracranial hemorrhage.

Nevertheless, at an increasing number of hospitals, including Brigham and Women’s, baseline echocardiography has become routine for PE patients, who, in the absence of contraindications, subsequently receive thrombolytic therapy with tPA if they have moderate or severe right ventricular dysfunction, even with normal systemic arterial pressure. For the most part, properly selected patients appear to improve rapidly and often dramatically. This treatment algorithm, however, has not undergone sufficient rigorous testing. Those who champion this strategy run the risk of becoming com-
placent and accepting this approach wholeheartedly, in the absence of a well-designed large-scale randomized clinical trial. As PE thrombolysis becomes more entrenched, the opportunity to perform a large-scale adequately powered trial will diminish. Therefore, a meticulously designed randomized, controlled clinical trial of PE thrombolysis versus anticoagulation alone is overdue, and time is running out.

At the Trousseau University Hospital in Tours, France, 153 patients with massive PE and right ventricular dysfunction on echocardiography were enrolled in a registry.\(^\text{15}\) Although the thrombolysis group had more improvement on follow-up lung scans 1 week later than patients treated with anticoagulation alone, their clinical outcome was worse. The mortality rate was 6\% in the thrombolysis-treated patients, whereas there were no deaths among those who received anticoagulation alone. Furthermore, the intracranial hemorrhage rate was 4.7\% after thrombolysis, compared with no intracranial bleeding in the anticoagulation-alone group.

On the basis of our series of 312 patients receiving thrombolysis for PE in 5 clinical trials (only 1 of which\(^6\) tested thrombolysis against anticoagulation alone), there was a 1.9\% risk of intracranial bleeding.\(^16\) In the large prospective International Cooperative Pulmonary Embolism Registry of 2454 PE patients, a high rate of 3.0\% of patients who received thrombolysis suffered intracranial hemorrhage, which is cause for profound concern.\(^17\) Clearly, a registry is more likely to reflect the “real-world” hazards of thrombolysis than a clinical trial, which is designed with multiple exclusion criteria, checks, and balances. This principle is reinforced not only by the ICOPER and Tours registries but also by a separate registry from the Laennec Hospital in Paris. These investigators reported on 132 consecutive PE patients treated with tPA.\(^18\) Two suffered intracranial bleeding, and 2 others developed hemorrhagic pericardial tamponade.

It is evident that the risk of catastrophic bleeding is far higher with tPA administered for PE thrombolysis than with tPA given to treat acute MI. In the National Registry of Myocardial Infarction, 71 073 patients were enrolled from 1484 hospitals and received tPA for acute ST-segment elevation MI.\(^19\) Overall, the intracranial hemorrhage rate was 0.95\%. Risk factors for cerebral bleeding included increasing age and systemic arterial hypertension. As with PE thrombolysis, those patients who suffered hemorrhagic strokes had dismal outcomes. Half died, and one quarter had important residual neurological defects.

Thus, the potential benefit and safety of thrombolysis among high-risk PE patients remains an open question that requires testing in a large-scale randomized, controlled clinical trial. Depending on estimates of adverse clinical outcomes, the sample size will vary between 1000 and 2000 patients. The heparin-alone group in this future trial will receive low-molecular-weight heparin rather than continuous intravenous unfractionated heparin. This decision is based on the demonstrated efficacy and safety of tinzaparin in the treatment of acute PE\(^20\) as well as the superior efficacy of low-molecular-weight heparin compared with unfractionated heparin in the treatment of acute deep venous thrombosis.\(^21\)

PE will in almost all cases be documented noninvasively by contrast chest CT scan, high-probability lung scan, or moderate-probability lung scan in the presence of ultrasound-confirmed deep venous thrombosis. Only rarely will pulmonary angiography be necessary. High-risk patients will be identified primarily by hemodynamic instability or moderate or severe right ventricular dysfunction on echocardiogram. If echocardiography is unavailable, patients will be evaluated for high risk on the basis of a clinical scoring system such as the Geneva Prognostic Index.\(^22\)

Patients with conventional exclusion criteria for thrombolysis will not participate in this trial, which will place patient safety at a premium. The thrombolytic agent selected for testing will have the lowest possible rate of intracranial bleeding. On the basis of large-scale trials in acute MI, streptokinase might be the preferred lytic drug, with a dosing regimen of 1 500 000 U administered over a period of 1 hour. In ISIS-3, tPA, streptokinase, and anisoylated plasminogen streptokinase activator complex (APSAC; anistreplase) were tested in a randomized trial of 41 299 patients with acute MI.\(^23\) When streptokinase was compared with tPA, there was a significant excess of strokes with tPA, 1.39\% versus 1.04\%. Almost 3 times as many strokes were attributed to cerebral hemorrhage with tPA, 0.66\% versus 0.24\%. In the GISSI-2 and International Study Group trial of 20 768 acute MI patients,\(^24\) patients treated with tPA had a small but significant excess of stroke compared with those who received streptokinase.

Organization of this large-scale PE thrombolysis trial will be challenging administratively. The size of the trial will make this study 10 times larger than the largest PE thrombolysis versus heparin trial so far undertaken. To achieve the desired patient enrollment, the trial will be multicenter and international in scope. The European Society of Cardiology is proposing to undertake this type of large-scale investigation. In North America, separate preparations for a large-scale PE thrombolysis trial are under way.

Identification of appropriate clinical investigators and eligible patients will not be easy. After all, PE patients do not receive treatment from one particular group of physicians. General practitioners, internists, pulmonologists, hematologists, vascular surgeons, vascular medicine physicians, or cardiologists might manage them. Furthermore, the patients will be scattered widely through different areas of the hospital, including medical and surgical intensive care units. In contrast, most acute MI patients can be readily identified because they are initially hospitalized in the Coronary Care Unit.

Despite the challenges of undertaking a large-scale PE thrombolysis trial, this effort is warranted and timely. The rationale for this PE thrombolysis trial is compelling. Widespread and concerted endorsement of this concept will mobilize the medical community as well as granting agencies to support the funding and execution of this important clinical investigation.

References


Key Words: Editorials | embolism | pulmonary heart disease | thrombolysis | thrombus | veins
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Circulation. 2001;104:2876-2878
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/104/24/2876

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