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EDITORIAL COMMENT

PEITHO Long-Term Outcomes Study

Data Disrupt Dogma*

Samuel Z. Goldhaber, MD[a,b]

Pulmonary embolism (PE) is a fascinating and frustrating topic. Optimal management to minimize long-term complications has eluded clinician investigators. The most controversial and vexing immediate treatment decision revolves around patients with newly diagnosed acute high-risk submassive PE. In this subgroup, which accounts for up to 20% of all patients with PE, use of thrombolytic therapy has been both championed (**Table 1**) and decried (**Table 2**). Senior clinicians have championed opposing viewpoints to persuade and win over the undecided, and generations of health care providers have learned a curriculum that has its basis in dogma rather than data.

The rationale for immediate administration of thrombolysis is rapid reversal of right ventricular failure secondary to pressure overload and prevention of hemodynamic collapse caused by worsening right ventricular dysfunction (1). The long-term benefit of thrombolysis has been postulated to include reduction of recurrent PE by dissolving the presumed source of thrombus in the pelvic and deep leg veins. The hypotheses favoring thrombolysis must be weighed against the certain increased risk of catastrophic hemorrhage, especially intracranial hemorrhage, compared with the use of heparin alone.

With respect to long-term benefit, there was evidence in a substudy of 40 patients with PE from 2 randomized controlled thrombolysis versus heparin-alone trials sponsored by the National Institutes of Health that patients allocated to receive streptokinase or urokinase maintained improved pulmonary capillary blood volume and pulmonary diffusing capacity at 1 year after initial thrombolytic therapy (2). The pulmonary capillary blood volume was abnormally low in the heparin-alone group at 2 weeks and at 1 year. However, it was normal in the thrombolysis group at 2 weeks and at 1 year. The pulmonary diffusing capacity was 69% of predicted at 2 weeks and 72% at 1 year in the heparin-alone group, compared with 85% and 93%, respectively, in the thrombolysis group.

Of these 40 patients, 23 were restudied an average of 7 years after their initial randomization to thrombolysis versus heparin alone. These patients underwent right-sided heart catheterization both at rest and with supine leg exercise on a bicycle ergometer. At rest and with exercise, the pulmonary artery pressure and pulmonary vascular resistance were significantly higher in the heparin-alone group than in patients who had previously received thrombolysis plus heparin. These investigators concluded that thrombolytic therapy preserves the normal hemodynamic response to exercise in the long term and may prevent recurrent venous thromboembolism and the development of pulmonary hypertension (3).

A popular concept was that with administration of thrombolytic therapy, the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) would decrease because of improvement in gas exchange and reduction of in situ pulmonary arterial thrombus burden. However, the opposing argument contends that administering thrombolytic therapy should not have much influence on the development of CTEPH. Patients with CTEPH often have hypertensive pulmonary arteriopathy similar to that encountered in patients with pulmonary

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From the [a]Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts; and the [b]Harvard Medical School, Boston, Massachusetts. Dr. Goldhaber has provided consulting for Boehringer Ingelheim, Bayer, Portola, Daiichi-Sankyo, Janssen, BiO2 Medical, EKOS/BTG, BMS, and Zafgen.

TABLE 1 Historical Rationale for Administering Thrombolysis in Submassive PE

Reduction in death by rapid reversal of right ventricular dysfunction
Reduction in recurrent PE by lysis in situ of thrombus in the pelvic and deep leg veins
More rapid restoration of baseline functional status before PE
Reduction in long-term pulmonary hypertension
Reduction in chronic thromboembolic pulmonary hypertension

PE = pulmonary embolism.

hypertension of other causes. Among patients with CTEPH, there is a low correlation between the extent of central anatomic obstruction secondary to PE and the degree of pulmonary hypertension. There is also documented hemodynamic progression of CTEPH in the absence of clinically evident recurrent embolic events. In CTEPH, histopathological evidence of arteriopathic changes is usually evident in the resistance vessels of both PE-present and PE-absent portions of the pulmonary vascular bed (4).

Since the 1970s, the fundamental clinical question, whether to administer thrombolysis to patients with submassive PE, remains unanswered. Clarion calls have sounded for a robust clinical trial of sufficient sample size. Most "realists" believed that the design, funding, and execution of such a landmark trial were out of reach. Large-scale trials abound in the management of myocardial infarction, but PE poses different challenges. For example, PE is more difficult to diagnose than myocardial infarction, and patients with PE are usually dispersed throughout the hospital rather than grouped in a special PE care unit. Physicians who treat PE comprise a wide array of specialties, including internal medicine, vascular medicine, vascular surgery, pulmonary medicine, hematology, and cardiovascular medicine.

For decades, adequate communication and collaboration among diverse disciplines of PE doctors were lacking. The PE community and academic leaders seemed to comprise pessimists who were stuck and unable to move forward. Where were the optimists? For too many years, no core leadership group of energetic and idealistic clinical investigators emerged to ask the tough questions, including whether their own assumptions were evidence based. To move forward, a committed group would have to relinquish autonomy over the treatment course of their individual patients with PE and collaborate in running a large-scale trial that would transcend national boundaries, languages, and cultural differences.

TABLE 2 Rationale for Withholding Thrombolysis in Submassive PE

High rate of major bleeding complications, especially intracranial hemorrhage
Careful observation, which can detect patients with conditions likely to decompensate; the basis for the prudent "watch and wait" approach
Increased cost and prolongation of hospitalization
Lack of evidence that short-term benefits outweigh short-term risks
No evidence of long-term benefits of thrombolysis

PE = pulmonary embolism.

In 2004, the marvelous tale of PEITHO (Pulmonary Embolism Thrombolysis trial) began when European investigators convened their first meeting in Vienna. I had the privilege of being invited to and participating in that meeting. Those who gathered had willpower but no financial resources. Thus began a slow and arduous 5-year process of constructing a clinical trial protocol, obtaining rudimentary "shoestring" funding, acquiring insurance policies that provided indemnification, obtaining donation of the thrombolytic agent tenecteplase and its placebo, and constructing a committee structure that was equitable and that encouraged expression of multiple viewpoints from its diverse specialists. Enrolling patients proved challenging, but over the ensuing 5 years after the protocol was finalized, PEITHO investigators recruited 1,006 patients with high-risk submassive PE from 76 sites in 13 countries to participate in a double-blind, double-dummy randomized trial of full-dose systemically administered tenecteplase plus heparin versus heparin alone (5). Thus, PEITHO was a 10-year project from inception to publication.

Peitho is the Greek goddess of persuasion. These clinical researchers intended to settle the question whether thrombolysis should be administered to or withheld from patients with high-risk submassive PE. Their bottom-line results were mixed. Thrombolysis halved the number of patients who died or who had hemodynamic collapse (5.6% with heparin vs. 2.6% with tenecteplase). However, this benefit extracted a high price, a 10-fold increase in hemorrhagic stroke (0.2% with heparin vs. 2.0% with tenecteplase). These mixed results raised as many questions as were answered. For example, was the dose of tenecteplase too high? Moreover, because a disproportionately high number of bleeding complications occurred in older patients, should older patients generally be excluded from receiving full-dose systemically administered thrombolysis? Would pharmacomechanical catheter-directed therapy with

a lower dose of lytic agent preserve the efficacy of thrombolysis but reduce the hemorrhagic risk?

At the conclusion of the primary trial, the PEITHO investigators did not want to disband. They had a unique opportunity to make further contributions to the field by amending the protocol to include long-term follow-up. What was the long-term (median 38-month follow-up) mortality rate in each of the treatment groups? What proportion of patients who were administered thrombolysis plus heparin versus heparin alone would have residual symptoms related to the initial PE after years of follow-up? Would patients who initially received thrombolysis less often develop persistently elevated estimated pulmonary artery pressures on echocardiography? As described by Konstantinides et al. (6) in this issue of the *Journal,* 28 PEITHO sites that had randomized a total of 709 patients agreed to extend PEITHO to assess long-term survival and to provide long-term clinical and echocardiographic follow-up.

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There were no differences in baseline characteristics in the 709 patients who underwent long-term follow-up compared with the 296 patients who were not followed in the long term, except for higher weight and more frequent previous venous thromboembolism among patients who were not followed up. With respect to overall mortality, from the time of randomization through long-term follow-up, there were 73 deaths in the tenecteplase group compared with 63 deaths in the heparin-alone group ($p = 0.43$). Only 17 deaths overall were ascribed to cancer. "Unknown cause" was the classification for 67 of the overall 136 deaths. A subgroup of 290 patients underwent long-term echocardiographic follow-up. There was no difference between the tenecteplase and heparin-alone treatment groups with respect to estimated residual pulmonary hypertension or right ventricular dysfunction. CTEPH developed in 4 patients who were administered tenecteplase and in 6 patients who received heparin only.

I found the presence of persistent clinical symptoms to be fascinating. In this study, 36% of the tenecteplase-treated patients and 30% of the heparin-alone group patients reported persistent symptoms, mostly mild exertional dyspnea; 12% of the tenecteplase-treated patients and 11% of the heparin-only group patients were in New York Heart Association functional class III or IV.

PE is a chronic illness with long-term adverse outcomes. PEITHO, even with its limitations, provides us with good long-term data on the effect of thrombolysis (Table 3). There appears to be no reduction in mortality rates, no reduction in functional limitation or persistent shortness of breath, and no reduction in CTEPH among those patients allocated to thrombolysis plus anticoagulation. These findings are disappointing.

TABLE 3 Long-Term Outcomes in PEITHO

Thrombolysis in submassive PE **did not:**
Reduce mortality at 2 yrs
Reduce functional limitation, as assessed by symptoms of chronic dyspnea, which persisted in one-third of patients
Reduce frequency of pulmonary hypertension as assessed by estimated pulmonary artery systolic pressure on echocardiography
Reduce frequency of right ventricular dysfunction as assessed by echocardiography
Reduce confirmed cases of CTEPH

CTEPH = chronic thromboembolic pulmonary hypertension; PE = pulmonary embolism.

On a positive note, PEITHO paves the path for future clinical research in thrombolytic therapy of PE. For example, have we focused too much on the large vessels without sufficient attention to the pulmonary microvasculature? Was there undetectable microhemorrhage in the pulmonary microvasculature with full-dose systemically administered thrombolysis? Would one-half-dose systemically administered thrombolysis (7) have improved the benefit-to-risk ratio? Would one-quarter-dose thrombolysis administered with pharmacomechanical catheter-directed techniques have decreased hemorrhagic risk even further? Would the postulated acoustic streaming and thrombus conditioning generated by ultrasound-facilitated thrombolysis (8) have demonstrated early improvements in the pulmonary microvasculature that would lead to long-term decreases in pulmonary artery pressure and symptoms of dyspnea?

Optimal management of submassive PE continues to elude us. The most precious lesson of PEITHO is that contemporary clinical investigation can tackle challenging questions and achieve monumental success if genuine collaboration is fostered and flourishes. Another PEITHO-like trial is not in the pipeline, so the results of the PEITHO long-term outcome substudy constitute a landmark that will not be readily replicated and that will withstand the test of time in the field of PE clinical investigation.

ADDRESS FOR CORRESPONDENCE: Dr. Samuel Z. Goldhaber, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: sgoldhaber@partners.org.

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