Fibrinolysis of Pulmonary Emboli — Steer Closer to Scylla

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According to Homer, Odysseus was forced to choose whether to steer his ship closer to Scylla, a six-headed sea monster, or Charybdis, a shipswallowing whirlpool. Odysseus steered closer to Scylla, risking the loss of a few sailors, rather than risking an entire ship and crew.

Much like Odysseus, the physician treating a patient with acute pulmonary embolism occasionally must navigate treacherous waters. The risk of fatal thromboembolism stands on one side, and the risk of fatal bleeding lies just opposite. Unlike Odysseus, the physician has empirical evidence to guide decisions, but tragic outcomes occur sometimes, no matter how carefully the physician navigates.

Acute pulmonary embolism is a common disorder with a wide clinical spectrum. Current estimates suggest that physicians diagnose pulmonary embolism in more than 200,000 patients annually in the United States. Anticoagulant agents provide effective and safe treatment for the majority of patients with acute pulmonary embolism. However, in a subgroup of patients with pulmonary emboli, the risk of death is increased despite anticoagulant treatment. Therefore, current practice embraces risk stratification of patients with pulmonary embolism, so that higher-risk therapies are offered to patients with the greatest chance of benefit.

Not surprisingly, physicians have long recognized that hypotension or cardiac arrest predicts high early mortality (>15%) associated with acute pulmonary embolism. Authors of evidence-based guidelines suggest that such patients undergo systemic fibrinolysis when a high risk of bleeding is not present. The absence of hemodynamic decomposition identifies patients who are unlikely to die from pulmonary embolism if they receive anticoagulant therapy promptly. The size of the emboli does not predict risk. In this regard, the terms massive and submassive pulmonary embolism can mislead physicians.

Controversy remains over the role of fibrinolysis among normotensive patients with an intermediate risk of death after acute pulmonary embolism. Investigators have suggested that right ventricular dysfunction detected with echocardiography, myocardial injury defined by elevated biomarker levels, and the absence of hypotension characterize this intermediate-risk group. The increased risk of fatal bleeding conferred by fibrinolysis and uncertainty about the risk of death among patients with right ventricular dysfunction and myocardial injury have fueled debates about the treatment of such patients.

In this issue of the Journal, Meyer et al. report the main results of the Pulmonary Embolism Thrombolysis (PEITHO) trial. In the PEITHO trial, investigators at 76 centers randomly assigned 1006 patients who had acute pulmonary embolism and right ventricular dysfunction, as well as a positive cardiac troponin test, to initial treatment with anticoagulants and fibrinolysis or with anticoagulants and placebo. The primary end point of death or hemodynamic decompensation within 7 days after randomization oc-


DOI: 10.1056/NEJMe1402388
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curred in 13 of 506 patients (2.6%) in the fibrinolysis group and 28 of 499 patients (5.6%) in the placebo group (P=0.02). Hemodynamic decompensation occurred in 25 of 499 patients (5%) in the placebo group and was responsible for the difference in the primary end point between the two study groups. As expected, major bleeding occurred more often in patients assigned to fibrinolysis. Although patients who were at increased risk for major bleeding were excluded, the rate of hemorrhagic stroke in the fibrinolysis group (2.0%) was 10 times as high as that in the anticoagulation group (0.2%).

This trial clarifies the risk of death among patients with acute pulmonary embolism who were initially normotensive and had myocardial injury and right ventricular dysfunction. The rate of death from any cause during the first 7 days was low (1.2% in the fibrinolysis group and 1.8% in the placebo group, which included patients who received rescue fibrinolysis only if hemodynamic decompensation had occurred). The low mortality rate among patients who received anticoagulants is a key observation. The trial data suggest that careful monitoring and rescue fibrinolysis can minimize deaths from pulmonary emboli. In this trial, only 17 of 500 patients (3.4%) who were assigned to initial treatment with an anticoagulant and placebo received rescue thrombolysis. This approach averts the increased risk of major bleeding, especially hemorrhagic stroke, for the majority of patients. Another approach to reduce bleeding risk that has been studied in the management of myocardial infarction but not, as far as I know, in the management of pulmonary embolism is the use of half-dose fibrinolysis for patients 75 years of age or older.

Now, the critical question: What course should physicians chart when confronted with a normotensive patient with acute pulmonary embolism? Data from the PEITHO trial provide valuable insight but no definitive answer. The data strengthen the case for risk stratification and for careful monitoring of patients who have an intermediate risk of death. The data also show the relative safety of withholding fibrinolysis unless hemodynamic decompensation occurs. Therefore, it may be that overall risk can be minimized with a strategy of initial anticoagulation and rescue fibrinolysis for hemodynamic decompensation. In the end, physicians must guide their patients, since no strategy is perfect. The goal, as the lesson of Scylla and Charybdis teaches, is to steer toward the lower risk.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMe1401025
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