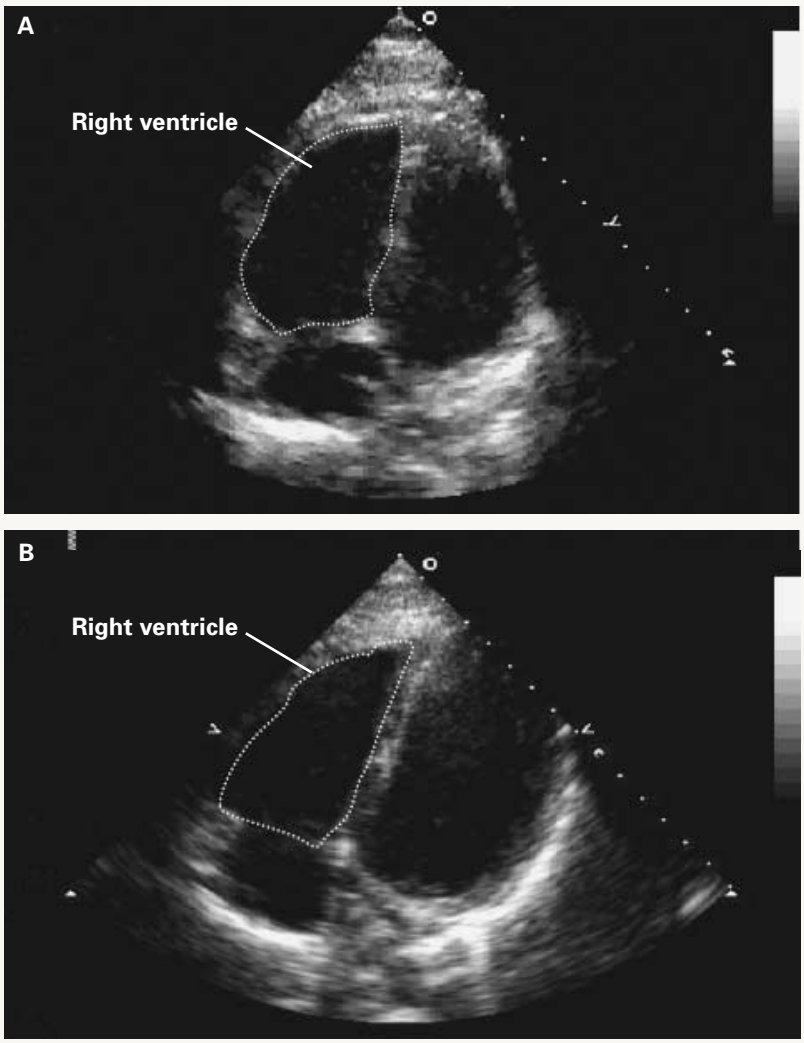
PERSPECTIVE

# Thrombolysis for Pulmonary Embolism

The primary therapy for acute pulmonary embolism is anticoagulation with heparin and warfarin to prevent additional thromboembolism. Traditional teaching relegates the use of thrombolysis to the rare situation in which massive pulmonary embolism causes cardiogenic shock. Thrombolytic agents such as alteplase (recombinant tissue plasminogen activator) act on plasminogen by cleaving the peptide bond between arginine at position 560 and valine at position 561, thereby converting plasminogen to plasmin, which dissolves the embolus. Should we expand the indications for thrombolysis to encompass pulmonary embolism in patients with right ventricular dysfunction, even in the presence of normal systemic arterial pressure (see Figure)? This simple question lacks a straightforward answer and continues to generate intense controversy after three decades of debate.




Echocardiograms before and after Thrombolysis.

A 29-year-old woman presented with progressive shortness of breath. A computed tomographic scan of the chest showed a central "saddle" pulmonary embolism. An echocardiogram (Panel A) showed an enlarged right ventricle and hypokinetic motion of the right ventricular free wall. After treatment with alteplase, the right ventricular size and wall motion returned to normal (Panel B). Echocardiograms courtesy of Scott D. Solomon, M.D., and Jose M. Rivero. (Videos of these images are available with the full text of this article at http://www.nejm.org.)

Right-sided heart failure is the usual cause of death from pulmonary embolism, and right ventricular dysfunction is a crucially important warning of a possible adverse outcome. Physical examination may reveal distention of the neck veins, an accentuated pulmonic heart sound, or a tricuspid regurgitation murmur. The electrocardiogram may show right ventricular strain with an $S_1Q_3T_3$ pattern (prominence of the S wave in lead I and a Q wave and T-wave inversion in lead III), right bundle-branch block, or T-wave inversion in leads $V_1$ through $V_4$. However, the most objective, uniform, and quantifiable measure is the echocardiogram, which can be used to estimate pulmonary-artery systolic pressure and can show right ventricular dilatation and hypokinesis.

Proponents of expanded criteria for thrombolysis claim a potential survival benefit, fewer recurrences of pulmonary embolism (through dissolution of the clot at its source, in the pelvic veins and deep veins of the leg), long-term prevention of pulmonary hypertension, and improved quality of life. Opponents contend that the bronchial collateral circulation provides continued pulmonary perfusion and usually makes thrombolysis unnecessary in patients with pulmonary embolism. They cite complications of throm-

bolysis, especially intracranial hemorrhage, and increased use of hospital resources such as beds in the intensive care unit and more extensive use of laboratory tests. They note that most patients who are treated with anticoagulation alone will catch up with thrombolysis-treated patients within several days. Most important, they remind us that trials of thrombolysis for pulmonary embolism have not shown decreased mortality rates or decreased rates of recurrence.

Thirty years ago, advocates of thrombolysis for pulmonary embolism administered 24-hour infusions — "prolonged baths" — of streptokinase or urokinase to dissolve large emboli. We subsequently learned that extended exposure to thrombolytic agents provokes major hemorrhage and is less effective than infusing these agents at a high concentration over a short period.

In 1990 the Food and Drug Administration (FDA) approved a contemporary thrombolysis dosing regimen: 100 mg of alteplase as a continuous peripheral intravenous infusion over a two-hour period. No subsequent regimen of thrombolysis for pulmonary embolism has received FDA approval, primarily because pharmaceutical companies are not currently focusing on the use of thrombolytic agents for this indication. The FDA label recommends thrombolysis for the treatment of "massive pulmonary embolism" but does not define "massive." From the practitioner's viewpoint, there is tremendous ambiguity in this recommendation. Does "massive" mean cardiogenic shock, profound hypoxemia, impending respiratory failure, or perhaps simply an anatomically large pulmonary embolism on pulmonary angiography or computed tomography of the chest? Imaging criteria are the most clear-cut but do not account for underlying cardiopulmonary disease, older age, or coexisting conditions that modify the physiological response to pulmonary embolism.

In this issue of the *Journal,* Konstantinides and colleagues (pages 1143–1150) report findings from the largest trial of thrombolysis for pulmonary embolism ever conducted. They recruited the most controversial group of patients, those with "submassive" pulmonary embolism, defined as right ventricular dysfunction but preserved systemic arterial pressure. They show that a combination of alteplase (100 mg given over a two-hour period) and heparin prevented the need for escalation of treatment (with open-label alteplase, catecholamine infusion, or mechanical ventilation) due to clinical deterioration more often than a combination of placebo and heparin. Clinical deterioration usually meant worsening symptoms, especially worsening respiratory failure.

Does this trial expand the indications for considering the use of thrombolysis among properly selected patients with pulmonary embolism who present with normal blood pressure and right ventricular dysfunction? Definitely. Is the controversy now resolved? Hardly. Critics will point out that in the study by Konstantinides et al. there was no significant difference in mortality between the two treatment groups. They will denounce the end point of an escalation of treatment because of clinical deterioration as "soft" and inadequately objective. Nevertheless, no one is currently planning to launch a trial of similar or larger scope. Organizing trials of thrombolysis for pulmonary embolism is challenging for several reasons: the illness is difficult to detect, collaboration among the physicians from multiple disciplines who care for patients with pulmonary embolism is unwieldy, and public awareness of this major cardiopulmonary illness is unacceptably low.

Every reader of the current report will note the remarkable near-absence of hemorrhagic complications, including intracranial hemorrhage, among the patients assigned to receive alteplase and heparin. In contrast, in the International Cooperative Pulmonary Embolism Registry, the largest prospective registry of management of pulmonary embolism to date, 304 of 2454 patients received thrombolysis, with an intracranial-hemorrhage rate of 3.0 percent.

My advice is to use echocardiography for risk stratification by identifying patients who have either evidence on scanning of proximal pulmonary-artery thromboembolism or underlying cardiopulmonary disease, regardless of the size of the pulmonary embolism. The risk of major hemorrhage should be assessed. For patients with contraindications to thrombolysis who nevertheless require more intensive therapy than anticoagulation alone, alternative strategies, such as catheter-based or surgical embolectomy, should be considered. On the basis of the current report, we should seriously consider expanding the indications for thrombolysis and administering 100 mg of alteplase over a two-hour period in carefully selected, normotensive patients with pulmonary embolism who have moderate or severe right ventricular dysfunction.

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