EDITORIAL

Defining a Role for Thrombolytic Therapy in the Management of Pulmonary Embolism

Treatment options for pulmonary embolism (PE) include agents that prevent propagation of thrombus and recurrent thromboembolic events or agents that can dissolve the embolus. The standard treatment involves anti-coagulation with heparin and warfarin. Data from the NIH-sponsored PIOPED study has shown that mortality from PE may be as low as 2.5% with standard anti-coagulant therapy (*1*).

Heparin is a glycosylated polypeptide which potentiates the effects of endogenous antithrombin. Antithrombin in turn inhibits thrombin and other activated coagulation factors of the intrinsic and common pathways. Warfarin is a vitamin K antagonist, inhibits the formation of several coagulation factors (II, VII, IX, X). Both heparin and warfarin have little, if any, effect on formed thrombus and exert their effect primarily by preventing propagation of clot. Lysis of formed thrombus is accomplished by the endogenous fibrinolytic system and by thrombolytic agents. Although thrombolytic agents are not routinely used to treat PE they include streptokinase, recombinant tissue plasminogen activator (alteplase, rt-PA) and urokinase. Streptokinase is a protein produced by beta hemolytic streptococci and forms a stable complex with plasminogen. This complex produces a conformational change in plasminogen resulting in the release of plasmin: a protease enzyme responsible for the degradation of fibrin and several coagulation factors. The action of streptokinase is not dependent on fibrin and therefore, administration of this agent induces a systemic fibrinolysis. Recombinant tissue plasminogen activator is a human protein produced by recombinant DNA technology which, in the presence of fibrin, activates plasminogen to form plasmin. Under physiological conditions the action of rt-PA is dependent on the presence of fibrin, which limits the development of systemic fibrinolysis. Urokinase is isolated from cultured human cells and currently has very limited usage since it offers no advantages over streptokinase or rt-PA.

Thrombolytic therapy can accelerate clot lysis within the pulmonary artery or iliofemoral veins, thereby reestablishing pulmonary perfusion and decreasing the probability of recurrent PE. In addition, thrombolytic agents may prevent the release of neurohormonal factors (5-hydroxytryptophan, platelet derived growth factor, thromboxane A_2) which may have a direct pulmonary vasoconstrictor effect and therefore affect right ventricular function.

The role of fibrinolytic agents in the management of patients with PE remains unclear in routine clinical practice. It has been established that fibrinolytic agents dissolve newly formed clots and accelerate the restoration of normal pulmonary physiology in patients with PE. Unfortunately, these agents cannot distinguish a pathological clot (vascular thrombus or embolus) from a "good" clot (hemostatic plugs). This results in an increased incidence of bleeding complications with thrombolytic therapy as compared to standard anti-coagulation. Because of this, thrombolytic therapy is generally reserved for patients who are hemodynamically compromised by PE or who have relatively large clot burdens within the pulmonary vasculature.

Thrombolytic therapy should be reserved for patients with large and clinically significant pulmonary emboli (*2*). Clinicians generally accept that occlusion of greater than 50% of the pulmonary vascular bed warrants thrombolysis; however, in some circumstances clinicians may consider thrombolytic therapy for obstructions of as small as 25% to 33% of the pulmonary vascular bed. For example, in patients with pre-existing cardiac or pulmonary disease, the consequences of relatively small clot burden may be substantial, warranting the use of thrombolytic therapy. Regardless of the anatomic location of the obstructed pulmonary vasculature, thrombolytic therapy should be considered whenever clinicians detect hemodynamic instability or respiratory compromise (*3*). In addition, in stable patients with large pulmonary emboli as demonstrated by echocardiography, any evidence of right ventricular dysfunction or dilatation may be used as additional rationale for treatment with thrombolytic therapy (*4*). A prospective, randomized trial in hemodynamically stable patients with acute PE assessed the effects of rt-PA plus heparin versus heparin alone. Patients receiving rt-PA plus heparin demonstrated both a more rapid quantitative and qualitative improvement in the right ventricular function and pulmonary perfusion than those treated with heparin alone. Clinically suspected recurrent PE occurred in 9% (5 of 55) of patients randomized to treatment with heparin alone. In two of these patients, the recurrent PE proved fatal. None of the patients treated with rt-PA plus heparin died or developed clinically recurrent PE within 2 wk of entry (*5*). Despite these results, the issue of whether thrombolytic therapy results in better long-term outcome or is more cost effective than standard heparin therapy remains unanswered.

Over a decade ago, Sharma et al. demonstrated better preservation of the carbon monoxide diffusing capacity (DLco) in patients treated with

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For correspondence or reprints contact: Abass Alavi, MD, Division of Nuclear Medicine, University of Pennsylvania Medical Center, 110 Donner Building, 3400 Spruce St., Philadelphia, PA 19104.

thrombolytic therapy than in those treated with heparin alone (*6*). The explanation proposed was that thrombolytic therapy better restores pulmonary capillary blood volume (pulmonary micro circulation) than standard heparin anti-coagulation. A follow-up evaluation of these patients revealed that those treated with thrombolytic agents had lower mean pulmonary arterial pressures and pulmonary vascular resistance at rest and during exercise than compared to heparin-treated subjects (*7*). However, the significance of the modest improvements in the pulmonary hemodynamics is unclear. The question remaining is whether the routine use of thrombolytic therapy for less than substantial PE is appropriate therapy for preserving the pulmonary micro-circulation.

In this issue of the *Journal*, Parker et al. suggest the use of a baseline perfusion lung scan as a method to predict which patients are more likely to respond to thrombolytic agents (*8*). The criteria for response include improvement in pulmonary perfusion pattern assessed by semi-quantitative methods. The baseline perfusion defect severity and shorter duration of symptoms correlated well with improvement in pulmonary arterial perfusion following therapy. Previous publications by the same author failed to demonstrate an inverse correlation between improvement in perfusion defects following therapy and duration of symptoms (*9*). In patients with acute PE, detection of new perfusion defects following institution of therapy may not necessarily be related to recurrent PE or fragmentation of proximal emboli. Development of parenchymal opacities (atelectasis, hemorrhagic edema or infarction) or occurrence of pleural effusions may also cause additional perfusion abnormalities. Improvement in pulmonary arterial perfusion following thrombolytic therapy may be related to improvements in reversible airway disease rather than a result of thrombolysis. The semiquantitation of perfusion defect severity using the segmental method described by Parker et al. involves grading each lung segment for both the amount and extent of perfusion reduction (*9,10*). While this anatomical technique takes into account the segmental distribution of PE, the size of segments are likely to be underestimated (*11,12*). In particular, perfusion defects within the medial basal segment of the lower lobe may be undetectable using planar imaging. The segmental method of quantifying perfusion defect severity is also more time consuming and may not be easily reproducible. This method should be extended to the use of SPECT with suitable attenuation and scatter correction algorithms. Quantitation with SPECT may allow accurate estimation of the extent and severity of perfusion abnormalities.

In the PIOPED trial, only 6% (23 of 399) of patients with acute PE were treated with thrombolytic agents and heparin (*1*). There was no significant reduction in the angiographically determined clot burden in patients treated with rt-PA and heparin compared with patients treated with heparin and placebo (*13*). The majority of deaths in patients who were correctly diagnosed and properly treated for acute PE were due to recurrent PE (*1*).

Despite the large body of data in the literature, several practical considerations have tempered enthusiasm for thrombolytic therapy in venous thromboembolic disease:

1. There is only limited long-term outcome data comparing thrombolytic therapy to standard anticoagulation,
2. Thrombolytic therapy carries a somewhat greater risk of bleeding than the standard anticoagulation,
3. The optimal dosage and regimen for thrombolytic therapy in pulmonary embolism have not yet been well established.

After a thrombolytic therapy course, standard anti-coagulation with intravenous heparin followed by either oral warfarin or maintenance subcutaneous heparin is still necessary to prevent recurrent thromboemboli. It is not clear whether rapid improvement in right ventricular function and resolution of perfusion translates into long term patient benefit. Therefore, additional data that include long-term functional outcome as the end point needs to be assessed.

Harold I. Palevsky
Abass Alavi
Bruce W. Zukerberg
University of Pennsylvania
Medical Center
Philadelphia, Pennsylvania

Daniel F. Worsley
Vancouver Hospital and Health
Sciences Center
Vancouver, Canada

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