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Tissue Plasminogen Activator and Acute Pulmonary Embolism

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We assessed the efficacy and safety of peripheral intravenous recombinant human tissue-type plasminogen activator (rt-PA) in 47 patients with angiographically documented pulmonary embolism (PE). We administered 50 mg/2 h and, if necessary, an additional 40 mg/4 h. By 6 hours, 94% of the patients had angiographic evidence of clot lysis that was slight in 5, moderate in 12, and marked in 27 patients. Among the 34 patients with pulmonary hypertension prior to treatment, average pulmonary artery pressure decreased from 43/17 ($\overline{27}$) to 31/13 ($\overline{19}$) mm Hg ($P < 0.0001$). The average lung scan perfusion defect decreased from 37% before therapy to 16% ($P < 0.01$) after therapy among the 19 patients who had pre- and post-treatment lung scans. Of 7 patients with pre- and post-treatment imaging and Doppler echocardiograms, hypokinetic right ventricular wall movement (mild in 1, moderate in 2, and severe in 4) normalized in 5 and improved to mild hypokinesis in 2. Right ventricular diameter decreased from 3.9 ± 1.0 to 2.0 ± 0.5 cm ($P < 0.005$). Fibrinogen decreased 33% from baseline at 2 h and 42% from baseline at 6 h. However, patients with the greatest degree of angiographic clot lysis at 2 h had a preponderance of fibrinogenolysis over fibrinolysis, demonstrated by a lower ratio of cross-linked fibrin degradation products to fibrin(ogen) degradation products (0.14 ± 0.09 vs. 0.54 ± 0.82) ($P < 0.04$). Among selected patients, peripheral intravenous rt-PA is associated with rapid lysis of PE, improved pulmonary perfusion, and improved right ventricular function.

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Pulmonary embolism (PE) is a common illness that can cause both immediate and late mortality, chronic pulmonary hypertension, and right ventricular failure. PE is responsible annually for approximately 300,000 hospitalizations and 50,000 deaths in the United States [1]. During the past decade, the case fatality rate from this illness has continued to be approximately 15% with no substantive improvement [2]. There is a great need to improve the clinical outcome of patients with PE.

The two available methods to treat PE are 1) thrombolysis (to dissolve the clot that has formed) followed by standard heparin anticoagulation (to prevent new clots from forming), or 2) heparin alone, without thrombolysis. This latter approach relies on endogenous fibrinolytic mechanisms to lyse the clot. For patients with major PE who are treated with anticoagulation therapy alone, complete resolution of pulmonary artery clot may fail to occur in 75% of patients after 1–4 weeks [3] and in 50% after 4 months [4] of follow-up.

Urokinase (UK), a thrombolytic agent, was compared with heparin, an anticoagulant, in phase I of the Urokinase Pulmonary Embolism Trial (UPET) and was shown to dissolve pulmonary arterial clot within 24 h of treatment and in certain instances to reverse clinical shock [5]. However, even though the Food and Drug Administration approved its use (and that of streptokinase [SK]) in 1977, thrombolytic agents have not been widely utilized. In UPET, there was a hint that thrombolytic therapy might reduce both mortality and recurrent PE compared with heparin treatment. However, the differences between these two treatment modalities did not attain statistical significance, possibly owing to a relatively small sample size. Physicians in a typical large teaching hospital in the United States will use UK or SK on average only once or twice per year to treat PE because thrombolytic therapy causes more bleeding complications than heparin and has not been shown definitively to reduce the recurrence or mortality rate.

Recombinant human tissue-type plasminogen activator (rt-PA), produced with recombinant DNA technology, is a relatively fibrin-specific serine protease composed of 527 amino acids with a molecular weight of 59,000 (unglycosylated). The amino terminal end has a high degree of sequence homology with the kringle regions of plasminogen and may, consequently, be responsible for the relatively fibrin specific activation of t-PA. The carboxy terminal end contains a domain responsible for the protease activity. The successful utilization of rt-PA in myocardial infarction treatment has reawakened interest in thrombolytic therapy for PE. In experimental studies of venous thromboembolism (Table I), t-PA appeared more potent than UK or SK and possibly safer [6–9]. Unlike SK, rt-PA has not been reported to be antigenic [10]; rt-PA has not been causally linked to allergic reactions.

PULMONARY ANGIOGRAPHY

Since 1985, we have used rt-PA to treat acute PE and have demonstrated that this second generation thrombolytic agent causes rapid clot lysis within 2–6 h. We designed and organized a multicenter trial (Brigham and Women's Hospital, Beth Israel Hospital, George Washington University Medical Center, The Veterans Administration Medical Center at Brockton/West Roxbury) and treated 47 acute PE patients

TABLE I. Experience With t-PA in Experimental Venous Thromboembolism*

Animal model	Drugs compared	Results
Canine superficial femoral venous thrombosis [4]	1 mg t-PA vs. 1 million IU UK	50% more lysis with t-PA
Rabbit jugular venous thrombosis [5]	1 mg t-PA vs. 500,000 IU UK	50% more lysis with t-PA
Rabbit jugular venous thrombosis [6]	0.15 mg/kg per h × 4 h t-PA vs. 16,000 units/kg per h × 4 h SK	49% more lysis with t-PA
Rabbit pulmonary embolism [7]	0.35 mg t-PA vs. 1,000,000 UK	33% more lysis with t-PA

*t-PA = tissue-type plasminogen activator; SK = streptokinase; UK = urokinase. (Reprinted from [13] with permission.)

with open label rt-PA using a dose of 50–90 mg delivered throuqh a peripheral vein, as described in detail elsewhere [11–13]. Ninety-four percent of the patients responded within 6 h after initiating rt-PA treatment by demonstrating angiographic evidence of clot lysis, that was graded qualitatively as moderate or marked in 83% (Fig. 1) and slight in 11%. Among patients with pulmonary artery hypertension, the pulmonary artery pressures improved during the acute treatment period from 43/17 ($\overline{27}$) to 31/13 ($\overline{19}$) mm Hg. The hemodynamic and angiographic improvement was also accompanied by improvement in pulmonary perfusion [14] (Fig. 2) and right ventricular function [15,16] (Figs. 3, 4) among subsets of patients who were evaluated before and after rt-PA. Two of the 47 rt-PA treated patients had bleeding problems that required surgical intervention, mediastinal tamponade after open heart surgery, and hemorrhage into the pelvis in a patient with a newly diagnosed pelvic tumor. Both patients subsequently did well and were discharged home uneventfully.

PERFUSION LUNG SCANNING

Serial pulmonary angiography provides information on the effectiveness of thrombolytic agents in lysing emboli. However, changes in pulmonary perfusion can only be assessed with perfusion lung scanning. In UPET, only anterior and posterior views were obtained on rectilinear scanners. However, modern lung scanning techniques utilize six views (rather than two) obtained with a gamma scintillation counter. Therefore, Parker and colleagues developed a new semiquantitative method that emphasizes pulmonary anatomy by integrating data from all of the images to derive a score for each lung segment [14]. Using this six-view segmental method, there was a 57% improvment in pulmonary perfusion after rt-PA treatment [14].

DOPPLER ECHOCARDIOGRAPHY

Another technique that provides information complementary to pulmonary angiography is Doppler imaging and echocardiography, which can determine the presence and magnitude of right ventricular dysfunction. To assess abnormalities of right heart function and their reversal with rt-PA in PE, serial echocardiographic studies were performed before and after treatment in a subset of 7 of the 47 patients. Coincident with clot lysis and restoration of pulmonary blood flow, as determined by serial pulmonary angiography and perfusion lung scanning, pulmonary artery systolic pressure decreased (from 42 $\pm$ 11 to 26 $\pm$ 7 mm Hg, $P < 0.005$), and right

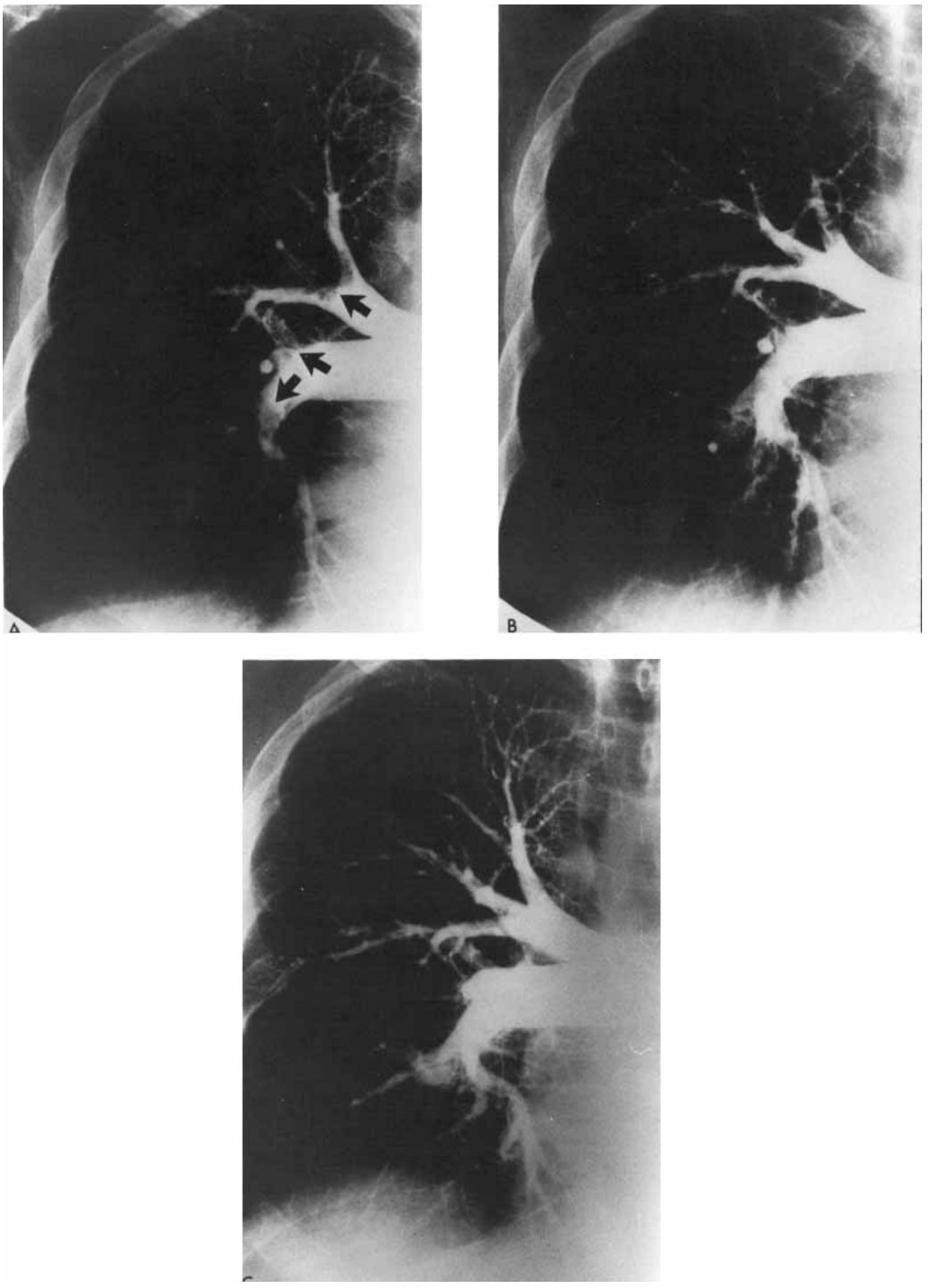

Figure 1.

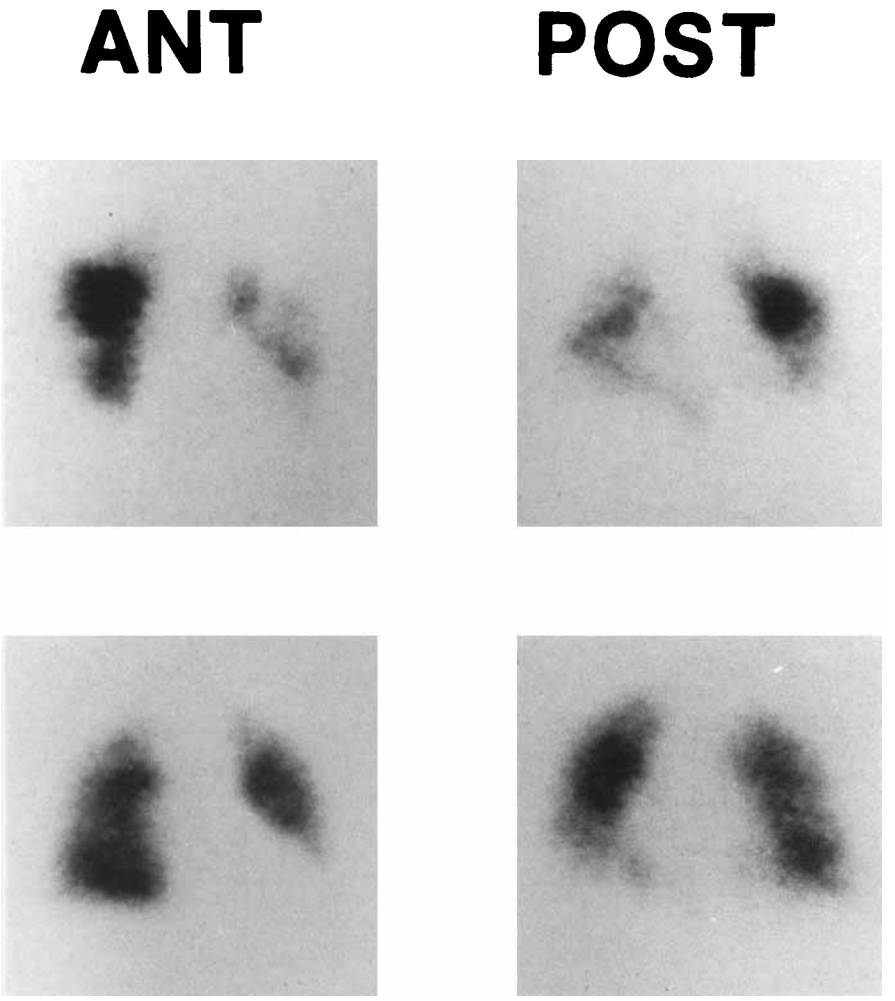

Fig. 2. Anterior and posterior views of perfusion lung scans in a 66-year-old man who presented with syncope. **Top:** Before recombinant tissue-type plasminogen activator (rt-PA) therapy the scans show massive pulmonary embolism. Except for a region in the midportion of the right lung, there is marked reduction and irregularity of perfusion in both lung fields. **Bottom:** A lung scan performed a day after therapy with 90 mg of rt-PA shcws nearly complete resolution of the defects. The only remaining perfusion defect is at the left base on the posterior view. ANT = anterior; POST = posterior. (Figure kindly provided by J. Anthony Parker, M.D., Ph.D., and reprinted from [16] with permission of the publisher.)

Fig. 1. Anteroposterior right pulmonary angiograms in a 66-year-old man with pulmonary embolism. **A:** Emboli in the right upper pulmonary lobe, right middle lobe, and right lower lobe (arrows). **B:** After 2 hours of rt-PA therapy, there is a partial resolution in the anterior and posterior segments of the right upper lobe but complete occlusion of the branch supplying the apical segment. There is partial resolution of the emboli in the right lower lobe. **C:** After 6 h of rt-PA, there has been almost complete resolution of emboli in all segments of the right lung. (Reprinted from [13] with permission.)

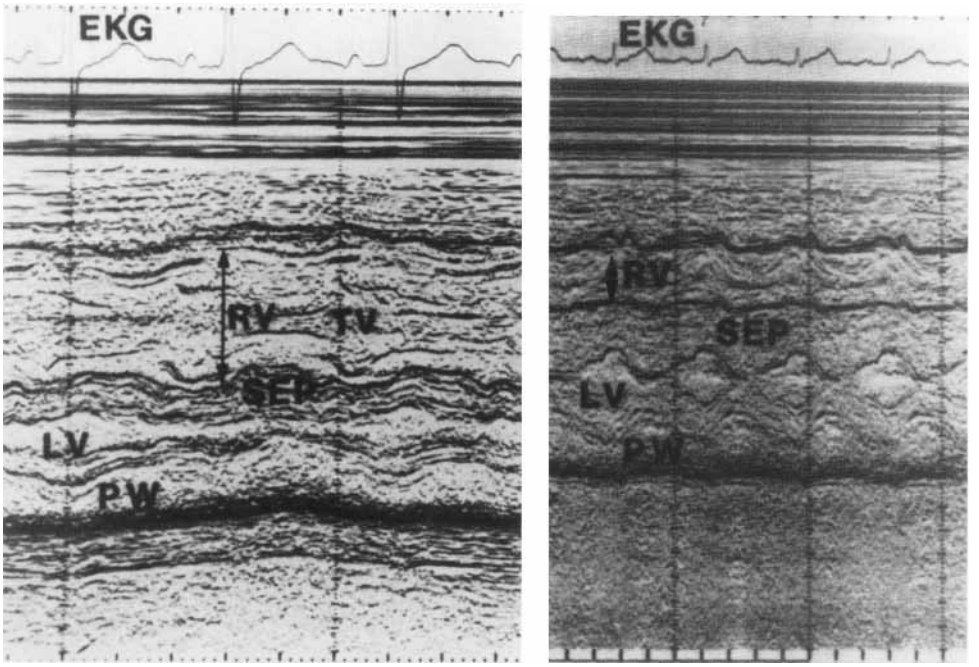

Fig. 3. M-mode echocardiograms obtained using a subcostal approach before **(left)** and after **(right)** thrombolytic therapy demonstrate a marked decrease in the diameter of the right ventricle (RV) from 6.0 to 2.35 cm, and an increase in the diameter of the left ventricle (LV) from 3.1 to 4.2 cm. Right ventricular wall movement, which was markedly hypokinetic during acute pulmonary embolism, improved appreciably after lytic therapy. EKG = electrocardiogram: PW = posterior wall: SEP = septum; TV = tricuspid valve. (Reprinted from [15] with permission.)

ventricular diameter decreased (from 3.9 ± 1.0 to 2.0 ± 0.5 cm, $P < 0.005$). Right ventricular wall movement, initially mildly, moderately, or severely hypokinetic in one, two, and four patients, respectively, normalized in five and improved to mild hypokinesis in two. Tricuspid regurgitation was present before lytic therapy in six patients but was detected early after lytic therapy in only two patients. Thus, rt-PA treatment is associated with significant and early reversal of right ventricular dilation, hypokinesis, and tricuspid regurgitation. These changes occur with decreases in pulmonary artery pressure and with evidence of both clot lysis on angiographic study and reperfusion on serial lung scanning. The early reversal of the detected abnormalities suggests that the right ventricle is not "stunned," but rather is capable of recovering quickly in response to a decrease in right ventricular afterload [15].

FIBRIN SPECIFICITY

An important yet unresolved issue is the extent to which rt-PA's efficacy is due to its relative fibrin specificity. Administration of sufficient rt-PA to yield optimal clinical results will predictably produce decreases in plasma fibrinogen (on the order of 40% from baseline) and increases in fibrin(ogen) (FDP) [13]. FDPs, as commonly measured [17], identify proteolytic derivatives of both fibrinogen and cross-linked fibrin and thus do not differentiate between fibrin specific vs. nonspecific lysis.

Focusing on quantitative changes in cross-linked *fibrin* degradation products (XDPs), by use of a monoclonal antibody to the D-dimer [18], and comparing these fibrin specific derivatives to changes in FDPs, produces an index of fibrinolytic specificity, the XDP/FDP ratio. An *increase* in this ratio concomitant with the administration of a thrombolytic agent indicates *relatively specific fibrinolysis*, whereas a fall in the ratio corresponds to a preponderance of nonspecific fibrinogenolysis.

To help assess the extent to which fibrin specificity was associated with angiographically demonstrated clot lysis after rt-PA administration, we compared 10 patients who responded to rt-PA with 14 patients who had only slight or no improvement at 2 h after initiation of therapy [19]. Among these 24, we measured fibrinogen, FDP, and XDP and calculated the XDP/FDP ratio at baseline and at 2 h. Before therapy, there were no significant differences in fibrinogen, FDP, XDP, or XDP/FDP ratio when responders and nonresponders were compared (Table II). After 50 mg of rt-PA, fibrinogen fell by 36% in responders and by 24% in nonresponders, and FDPs increased 32-fold in responders and only 19-fold in nonresponders, but these values failed to reach statistical significance. XDPs increased in both groups, but were significantly higher in nonresponders. There was also a statistically significant difference in the posttreatment XDP/FDP ratio in the two groups (Table III). This ratio of fibrinolytic specificity fell an average of 56% in the responders compared with a decrease of only 3% in nonresponders ($P < .04$).

Thus, administration of rt-PA produced both significant fibrinogenolysis and a disproportionate increase in FDPs over XDPs, particularly in the responders. The significantly lower XDP/FDP ratio in responders than in nonresponders suggests that some degree of fibrinogenolysis may support or enhance thrombolysis in the setting

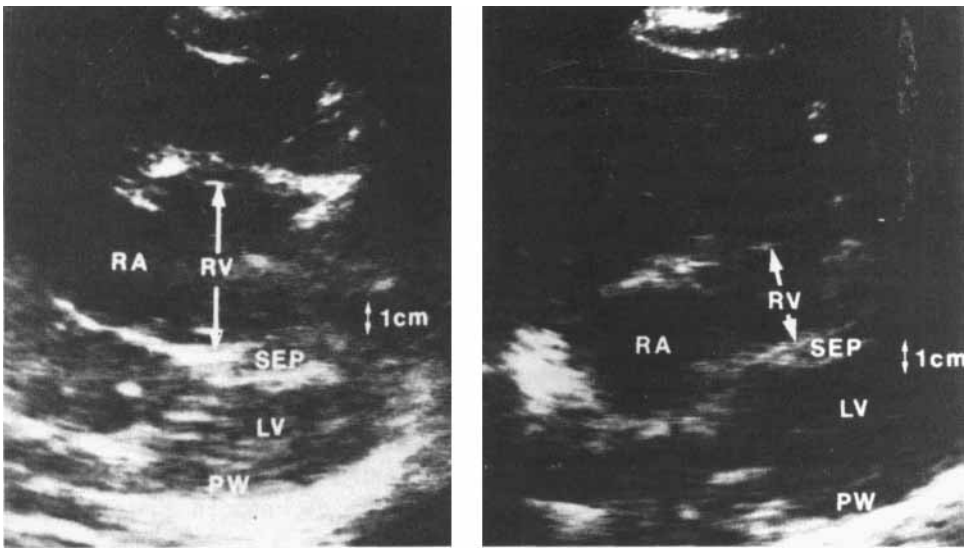

Fig. 4. Subcostal two-dimensional images at end-diastole corresponding to the M-mode tracings shown in Figure 3. Before recombinant tissue-type plasminogen activator (rt-PA) therapy **(left)**, the right ventricle (RV) is markedly enlarged, and left ventricular (LV) diameter is reduced. The study performed after infusion of rt-PA **(right)** shows a remarkable decrease in right ventricular size and a corresponding increase in the size of the left ventricle. RA = right atrium; other abbreviations as in Figure 3. (Reprinted from [15] with permission.)

TABLE II. Comparison of Hematologic Values and Quantitative Score for Responders and Nonresponders Before Treatment*

	Responders (n=10)	Nonresponders (n=14)	*P* value
Fibrinogen (mg%)	370 ± 125	340 ± 110	NS
FDP (μg/ml)	6.0 ± 3.0	7.2 ± 5.2	NS
XDP (μg/ml)	2.1 ± 2.1	1.9 ± 1.7	NS
XDP/FDP ratio	0.33 ± 0.33	0.56 ± 0.79	NS

*Values are mean ± SD. (Adapted from [19] with permission.)

TABLE III. Comparison of Hematologic Values and Quantitative Score for Responders and Nonresponders After Treatment*

	Responders (n=10)	Nonresponders (n=14)	*P* value
Fibrinogen (mg %)	235 ± 71	257 ± 91	NS
FDP (μg/ml)	190 ± 151	140 ± 150	NS
XDP (μg/ml)	17 ± 12	29 ± 16	.02
XDP/FDP ratio	0.14 ± 0.09	0.54 ± 0.82	.04

*Values are mean ± SD for both groups of patients after the administration of 50 mg rt-PA over a 2-h period. (Adapted from [19] with permission.)

of acute PE. Furthermore, the findings suggest that XDPs cannot be utilized as an index of lysis of the embolus (Table III).

To summarize, rt-PA administration in PE patients produces both fibrinolysis and fibrinogenolysis. As gauged by the XDP/FDP ratio, an index of fibrin specificity, successful thrombolysis is associated with a preponderance of fibrinogenolysis over fibrinolysis.

ONGOING RESEARCH

Based on the encouraging results of our open label rt-PA trial, we embarked on a randomized comparison of rt-PA with UK. After baseline lung scanning, pulmonary angiography, and blood sampling, patients are assigned either to a fixed dose of 100 mg of rt-PA over 2 h or to the standard UK dose (2,000 U/lb as a bolus followed by 2,000 U/lb/h for 24 h). All patients then receive a follow-up angiogram at 2 h; therapy with UK is discontinued at this point if significant clot lysis is observed. At 24 h after initiation of treatment, all patients undergo follow-up lung scanning. This trial will permit us to compare the efficacy, safety, and fibrin specificity of standard thrombolytic therapy for PE (with UK) vs. short-course, high-dose rt-PA [20].

Two other groups of investigators are studying rt-PA treatment in PE. An international multicenter study in Europe has compared peripheral intravenous versus local intrapulmonary administration of rt-PA and has observed no difference in efficacy or safety [21]. Another approach, "burst therapy," is being investigated in Hamilton, Ontario, Canada. Eligible patients are receiving 0.6 mg/kg of rt-PA over 2 min [22].

FUTURE PERSPECTIVES

Synergistic combinations of thrombolytic agents may provide enhanced efficacy and safety [23,24,25]. For example, in a series of four patients with acute myocardial

infarction, the use of only 10 mg of rt-PA and 300,000 IU of UK appeared promising in coronary arterial thrombolysis [26].

The development of an optimal thrombolytic regimen in PE still leaves unanswered the fundamental question of when thrombolytic therapy should be employed, as opposed to standard heparin anticoagulation alone, without thrombolysis. The favorable angiographic, perfusion lung scan, and echocardiographic changes observed after administration of rt-PA in our patients suggest that such therapy might be effective in decreasing mortality from PE. Furthermore, one might reasonably hypothesize that while lysing pulmonary arterial clot, the source of the thrombus (often in the deep leg or pelvic veins) might be dissolved simultaneously, thereby decreasing the rate of recurrent PE. A definitive answer to this question of thrombolysis followed by anticoagulation vs. anticoagulation alone will persist unless a large-scale randomized trial is undertaken to compare these two treatment strategies.

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