Moderate Pulmonary Embolism Treated With Thrombolysis (from the "MOPETT" Trial)

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The role of low-dose thrombolysis in the reduction of pulmonary artery pressure in moderate pulmonary embolism (PE) has not been investigated. Because the lungs are very sensitive to thrombolysis, we postulated that effective and safe thrombolysis might be achieved by a lower dose of tissue plasminogen activator. The purpose of the present study was to evaluate the role of this "safe dose" thrombolysis in the reduction of pulmonary artery pressure in moderate PE. During a 22-month period, 121 patients with moderate PE were randomized to receive a "safe dose" of tissue plasminogen activator plus anticoagulation (thrombolysis group [TG], n = 61 patients) or anticoagulation alone (control group [CG], n = 60). The primary end points consisted of pulmonary hypertension and the composite end point of pulmonary hypertension and recurrent PE at 28 months. Pulmonary hypertension and the composite end point developed in 9 of 58 patients (16%) in the TG and 32 of 56 patients (57%) in the CG ($p < 0.001$) and 9 of 58 patients (16%) in the TG and 35 of 56 patients (63%) in the CG ($p < 0.001$), respectively. The secondary end points were total mortality, the duration of hospital stay, bleeding at the index hospitalization, recurrent PE, and the combination of mortality and recurrent PE. The duration of hospitalization was 2.2 ± 0.5 days in the TG and 4.9 ± 0.8 days in the CG ($p < 0.001$). The combination of death plus recurrent PE was 1 (1.6%) in TG and 6 (10%) in the CG ($p = 0.0489$). No bleeding occurred in any group, and despite a positive trend in favor of a "safe dose" thrombolysis, no significant difference was noted in the rate of individual outcomes of death and recurrent PE when assessed independently. In conclusion, the results from the present prospective randomized trial suggests that "safe dose" thrombolysis is safe and effective in the treatment of moderate PE, with a significant immediate reduction in the pulmonary artery pressure that was maintained at 28 months. **(Am J Cardiol 2013;111:273−277)**

Thrombolysis is an effective tool in the treatment of massive pulmonary embolism (PE).[1,2] It has also been recommended for "submassive PE," in which hemodynamic stability is present but with right ventricular (RV) enlargement or hypokinesia or the elevation of biomarkers of RV injury.[1−5] The dreaded complication of thrombolysis is intracerebral hemorrhage, which has been noted in 0.7% to 6.4% of patients receiving thrombolysis.[6,7] This frequency, albeit low, has caused a reluctance in the use of thrombolysis for symptomatic PE without hemodynamic instability. Our experience with percutaneous endovenous intervention for deep venous thrombosis has suggested an exquisitely favorable pulmonary response to low-dose thrombolysis.[8] The lungs are uniquely sensitive to thrombolysis, because they are the only organ receiving the entire cardiac output. Furthermore, they are the point of convergence for the entire molecules of the thrombolytic agent, no matter through which vein the drug is administered. It is therefore intriguing to postulate that a lower dose of the thrombolytic drug might be effective in PE, with the additional benefit of enhancing its safety profile. No data are available on peripheral intravenous administration of low-dose thrombolysis for "moderate" PE in the reduction of pulmonary artery pressures after 2 years. The present study was, therefore, undertaken to assess the effects of low-dose tissue plasminogen activator (tPA) on pulmonary artery systolic pressure in patients with "moderate" PE at 28 months.

Methods

The Moderate Pulmonary Embolism Treated with Thrombolysis trial was a prospective, controlled, randomized, single-center open study that enrolled 121 adult patients with symptomatic "moderate" PE. All patients provided written informed consent, and the institutional review board approved the study protocol.

Adult patients presenting with signs and symptoms suggestive of PE plus imaging documentation on computed tomographic angiography or ventilation/perfusion scanning were potentially eligible for the study. "Moderate" PE was defined as the presence of signs and symptoms of PE plus computed tomographic pulmonary angiographic involvement of >70% involvement of thrombus in ≥2 lobar or left or right main pulmonary arteries (Figure 1) or by a high probability ventilation/perfusion scan showing ventilation/perfusion mismatch in ≥2 lobes. Interpretation of the

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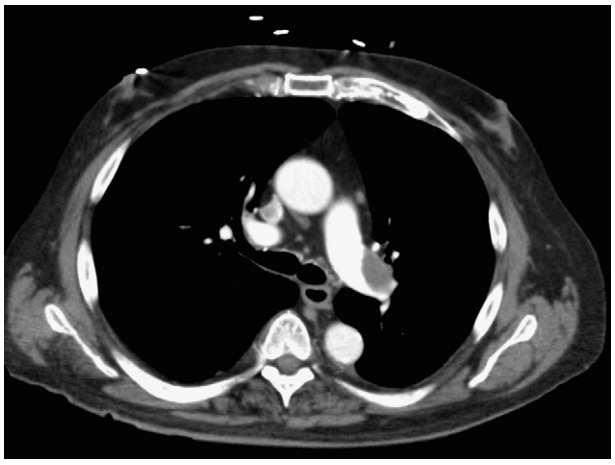

Figure 1. Representative example of computed tomographic angiogram demonstrating >90% stenosis of distal left main pulmonary artery by acute PE.

radiologic findings were performed by radiologists not participating in the study. To be eligible for enrollment, the patients were required to have a minimum of ≥2 new signs and symptoms consisting of chest pain, tachypnea (respiratory rate at rest ≥22 breaths/min), tachycardia (heart rate at rest ≥90 beats/min), dyspnea, cough, oxygen desaturation (oxygen partial pressure <95%) or elevated jugular venous pressure ≥12 cm H_2O. RV enlargement or hypokinesia and elevation of biomarkers of RV injury (troponin I and brain natriuretic peptide), although measured, were not a requirement for enrollment. The exclusion criteria included an onset of symptoms >10 days; >8 hours since the start of parenteral anticoagulation; systemic arterial systolic blood pressure <95 or ≥200/100 mm Hg; eligibility for full-dose thrombolysis; a contraindication to unfractionated or low-molecular-weight heparin; severe thrombocytopenia (platelet count <50,000/mm^3); major bleeding within <2 months requiring transfusion; surgery or major trauma within <2 weeks; brain mass; neurologic surgery, intracerebral hemorrhage, or subdural hematoma within <1 year; end-stage illness with no plan for PE treatment; and an inability to perform echocardiography because of chest deformities, bandages, or catheters.

The primary end points of the study were the development of pulmonary hypertension as assessed by echocardiography and the composite end point of pulmonary hypertension and recurrent PE at intermediate-term follow-up. The results were adjudicated after a mean follow-up of 28 ± 5 months. The secondary end points were total mortality, duration of hospital stay and bleeding at index hospitalization, recurrent PE, and the composite end points of mortality and recurrent PE.

Echocardiography was performed within 2 hours after randomization and before administration of tPA and was repeated 24 to 48 hours after and at 6-month intervals. Pulmonary artery systolic pressure was estimated from the tricuspid valve regurgitant jet velocity using the modified Bernoulli equation $4v^2$ + right atrial pressure. The right atrial pressure was estimated at 10, 15, and 18 mm Hg for mild, moderate, and severe right atrial enlargement, respectively.[9] In the standard 4-chamber view if the maximum dimension of the right atrium/left atrium was 1 to 1.2, right atrial enlargement was arbitrarily considered as mild, 1.3 to 1.5 as moderate, and >1.5 as severe. In the latter case, the diameter of the inferior vena cava had to be ≥2.5 cm as an additional requirement to assign a value of 18 mm Hg for the right atrial pressure, otherwise it was still considered moderate, right atrial enlargement. If the right atrial size was less than that of the left atrium, the right atrial pressure was assumed to be 5 mm Hg. Interpretation of the echocardiographic findings was performed by a cardiologist who was unaware of the patients' treatment assignments and using digitized videos. A dichotomous value of pulmonary artery systolic pressure of ≥40 mm Hg was used to define pulmonary hypertension. Right ventricular enlargement was defined as an RV/left ventricular ratio of >0.9. The videos were also evaluated for RV hypokinesia, defined as a reduction in the anticipated normal wall motion of the RV myocardium.

All patients received either unfractionated heparin or subcutaneous enoxaparin, with initial preference given to the latter drug. Enoxaparin was given to 48 of 61 (79%) of the patients in the thrombolysis group (TG) and 49 of 60 (81%) in the control group (CG). Administration of unfractionated heparin was determined by the presence of renal insufficiency or patient preference. In the TG, enoxaparin was given as 1 mg/kg subcutaneously twice daily, with the initial dose not to exceed 80 mg. For unfractionated heparin in the same group, it was given at 70 U/kg as a bolus but not to exceed 6,000 U, with subsequent dose adjustment to keep the activated partial thromboplastin time at 1.5 to 2 times the baseline value. Although tPA was infused, the maintenance dose of unfractionated heparin was kept at 10 U/kg/hour and not to exceed 1,000 U/hour. At 3 hours after termination of thrombolysis, the dose of unfractionated heparin was increased to 18 U/kg/hour. In the CG, enoxaparin was given at 1 mg/kg subcutaneously twice daily and unfractionated heparin at 80 U/kg as a bolus followed by 18 U/kg/hour, with the same partial thromboplastin time target.

In the present study, tPA was the only thrombolytic drug used. The dose of tPA was ≤50% of the standard dose (100 mg) commonly used for the treatment of PE, which we termed "safe dose" thrombolysis. For patients weighing ≥50 kg, the total dose was 50 mg, which was given as a 10-mg bolus by an intravenous push within 1 minute followed by infusion of the remaining 40 mg within 2 hours. For those weighing <50 kg, the total dose was calculated as 0.5 mg/kg, which was given as a 10-mg initial bolus followed by the remainder within 2 hours. Warfarin was started at admission in all patients.

A significant paucity of data is available on the changes of pulmonary artery systolic pressure from before treatment to intermediate follow-up in patients with moderate PE, who have received thrombolysis versus anticoagulation alone. In 1 study, there was a 55% reduction in the RV systolic pressure at 6 months in patients receiving 100 mg of tPA versus only a 15% reduction in those treated with anticoagulation alone, leading to a difference in reduction of 40%.[10] In another study of 12 patients, who had received urokinase or streptokinase, the mean pulmonary artery pressure decreased from 28 to 17 mm Hg in 7.5 years (39%

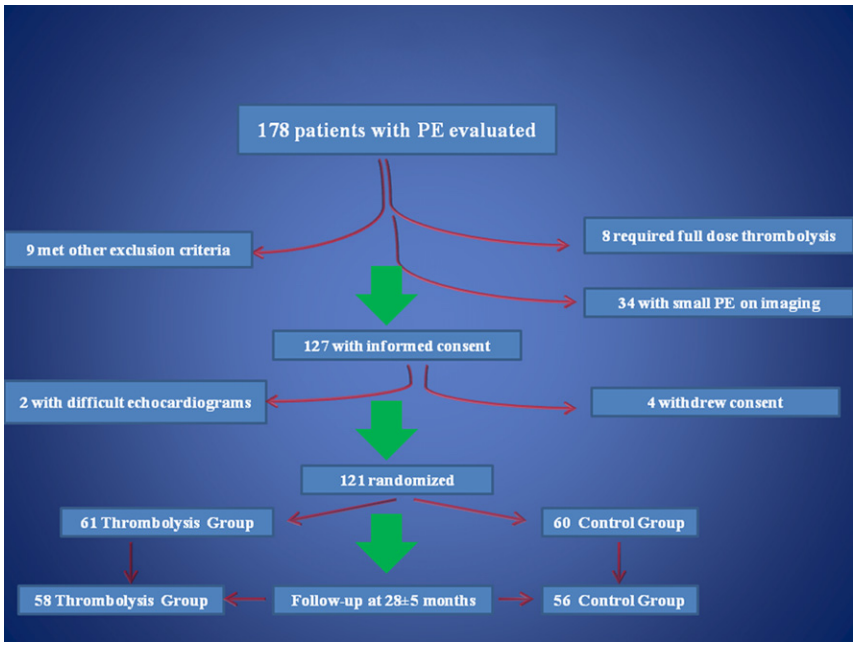

Figure 2. Flow diagram demonstrating patient enrollment in the study.

Table 1
Clinical characteristics of treatment groups

Variable	TG (n = 61; 100%)	CG (n = 60; 100%)	p Value
Men	28 (46%)	27 (45%)	0.92
Age (yrs)	58 ± 9	59 ± 10	0.56
Weight (kg)	84 ± 14	83 ± 13	0.68
Previous or concomitant disease			
Hypertension	32 (52%)	31 (52%)	0.93
Diabetes mellitus	23 (38%)	25 (40%)	0.66
Cardiovascular	35 (57%)	37 (62%)	0.80
Hypercholesterolemia*	27 (33%)	25 (30%)	0.77
Pulmonary	22 (36%)	25 (42%)	0.53
Renal	8 (13%)	9 (15%)	0.77
Current smoker	12 (20%)	15 (25%)	0.48
Unprovoked pulmonary embolism	28 (46%)	27 (45%)	0.92
Estrogen therapy	6 (10%)	7 (12%)	0.75
Cancer			
Active	8 (13%)	9 (15%)	0.77
History	3 (5%)	3 (5%)	0.98
Known prothrombotic state	6 (10%)	5 (8%)	0.77
Previous venous thromboembolism	13 (21%)	12 (20%)	0.86
Concomitant deep venous thrombosis	35 (57%)	33 (55%)	0.79

Data are presented as mean ± SD or n (%).
Differences among the 2 groups were not significant.
* Total cholesterol >200 mg/dl.

Table 2
Primary end points at 28 ± 5 mo of follow-up

Variable	TG (n = 58; 100%)	CG (n = 56; 100%)	p Value
Pulmonary hypertension*	9 (16%)	32 (57%)	<0.001
Pulmonary hypertension plus recurrent pulmonary embolism	9 (16%)	35 (63%)	<0.001

* Pulmonary artery systolic pressure ≥40 mm Hg.

Table 3
Secondary end points

Variable	TG (n = 61; 100%)	CG (n = 60; 100%)	p Value
Recurrent pulmonary embolism	0	3 (5%)	0.08
Total mortality	1 (1.6%)	3 (5%)	0.30
Total mortality plus recurrent pulmonary embolism	1 (1.6%)	6 (10%)	0.049
Hospital stay (days)	2.2 ± 0.5	4.9 ± 0.8	<0.001
Bleeding	0	0	—

Data are presented as mean ± SD or n (%).

reduction). In the 11 patients, who received heparin only, the decrease in pressure was from 26 to 22 mm Hg in 7.3 years (15% reduction), leading to a difference in the reduction of 24%.[11] We assumed a lower change and to be conservative, anticipated a difference in the percentage of reduction of 10. To show the significance of this difference with a power of 90% and a 2-sided α of 0.05, and an estimated SD of 9, 55 patients were required in each group. We increased this number to 60 for an estimated 10% attrition rate. A comparison between the 2 groups was made using unpaired *t* test for continuous variables and Fisher's exact test for categorical variables (2-tailed). The data are expressed as mean ± SD. Statistical analyses were performed with Statistica software, version 10 (StatSoft, Tulsa, Oklahoma).

Table 4
Differences in pulmonary artery systolic pressure between the 2 groups

Timing	Pulmonary Artery Systolic Pressure (mm Hg)		p Value
	TG	CG	
On admission	50 ± 6	51 ± 7	0.4
Within 48 h	34 ± 7	41 ± 4	<0.001
6 mo	31 ± 6	49 ± 8	<0.001
28 ± 5 mo	28 ± 7	43 ± 6	<0.001

Data are presented as mean ± SD.

Results

During a 22-month period from May 2008, 178 patients with PE were considered for enrollment in the present study. The patient flow is shown in Figure 2. Ultimately, 121 patients were randomized. The randomization process occurred after the inclusion and exclusion criteria were satisfied, and the patients had provided written informed consent. After evaluation of the patient, the study investigator placed a telephone call to the study center, and, by opening of sealed envelopes, randomization to the TG or CG was made. A total of 61 patients were randomized to the TG and 60 to the CG. The baseline clinical characteristics were similar between the 2 groups (Table 1). Follow-up was obtained for 58 patients in the TG and 56 in the CG. The mean follow-up period was 28 ± 5 months. The primary and secondary end points are listed in Tables 2 and 3, respectively.

The changes in pulmonary artery systolic pressure are listed in Table 4. RV enlargement on the initial echocardiogram was noted in 12 of 61 (20%) of the TG and 14 of 60 (23%) of the CG. RV hypokinesia was found in 3 of 61 (4.9%) of the TG and 4 of 60 (6.6%) of the CG. An elevation in brain natriuretic peptide or troponin I was seen in 40 of 61 (66%) of the TG and 42 of 60 (70%) of the CG. All differences were nonsignificant.

Discussion

The results have demonstrated that "safe dose" tPA is safe and effective in the treatment of moderate PE, leading to a significant early reduction in the pulmonary artery systolic pressure that was maintained through the intermediate term. This finding is consistent with the few published reports in this area. Only 4 reports have addressed the effects of pulmonary artery pressure changes after thrombolysis from a total of 257 patients[10–13] with PE. The largest of these was a prospective, nonrandomized study that consisted of 200 normotensive patients with PE, with 21 of them receiving 100 mg of alteplase.[10] In this group, the RV systolic pressure was 45 mm Hg, which decreased to 20 mm Hg at 6 months (55% decrease). Patients who did not receive thrombolysis had only a 15% decrease in RV systolic pressure. One half of the patients treated with anticoagulation alone manifested an increased or persistently elevated RV systolic pressure, 46% of whom had either dyspnea at rest or exercise intolerance. This was in contrast to the absence of worsening of the RV systolic pressure in any patient of the thrombolysis group.[10] In a small series of 7 patients who underwent catheter-directed thrombolysis with urokinase and heparin for massive PE, the pulmonary artery systolic pressure decreased from a pretreatment value of 61 mm Hg to 25 and 24 mm Hg at 6 days and 15 months, respectively.[12]

The dreaded complication of thrombolysis is intracerebral hemorrhage, which has dissuaded physicians from embracing this form of therapy, even when there is clear indication for its use. The results from a multicenter registry reported a major bleeding rate of 21.9% in patients receiving thrombolysis compared to 7.8% receiving standard therapy.[4] All these patients had major PE.[4] However, in a randomized trial by the same lead investigator, major bleeding in the thrombolysis group was only 0.8%, with no intracerebral hemorrhage or fatal bleeding.[5] Levine[14] cited an 8.4% incidence of major bleeding and a fatal hemorrhage rate of 2.2% in patients receiving thrombolysis for PE. The International Cooperative of Pulmonary Embolism Registry reported a 3% incidence of intracerebral hemorrhage.[15] In another report, the frequency of intracerebral hemorrhage was 2.1%.[16]

The very high incidence of major bleeding reported in older studies is not consistent with the contemporary data or our experience and we believe is of historic interest. We did not witness any major or minor bleeding in any patients. This is in part owing to modification of the dose of parenteral anticoagulation administered concomitantly with tPA and the validity of the concept of "safe-dose" thrombolysis. It is important to modify the existing "standard parenteral anticoagulation protocols" in many hospitals if thrombolytic therapy is to be administered.[8] By doing so, the intense fluctuations in the partial thromboplastin time, which is usually noted during the first 1 to 2 days, is eliminated. Targeting a lower partial thromboplastin time of 1.5 to 2 times baseline was another contributing factor in reducing the bleeding risk.

In the present study, recurrent PE was found in no patients in the TG and 3 patients (5%) in the CG (p = NS). Konstantinides et al[5] reported no significant difference in the 4% (4 of 118) rate of recurrent PE in their thrombolysis group compared to the 2.9% (4 of 138) rate noted in the anticoagulation-only group. In an analysis of 13 placebo-controlled randomized trials, Jaff et al[3] concluded that no significant difference was seen in the rate of recurrent PE in patients receiving thrombolysis versus placebo.

To date, the emphasis of the published data has been the identification of patients with PE who would benefit from full-dose thrombolysis. We propose administration of "safe-dose" thrombolysis by expanding its use for moderate PE in which the risk of bleeding is reduced and its benefits are retained. Even lower doses of tPA than we have used might prove effective. Very low doses of 0.5 to 4 mg of tPA given as bolus have been successfully used in the treatment of intracardiac thrombus and PE during liver transplantation.[17]

There are some common sense concepts that deserve attention. One has to consider the uniqueness of the lungs and their exquisite sensitivity to thrombolysis. In contrast to any other organ, which receives a fraction of the cardiac output, the lungs receive its entirety (in the absence of shunting). From the existing guidelines, the "standard practice" uses the same or similar tPA dose for PE that is

used for thrombolysis in the systemic arterial circulation. For example, in acute myocardial infarction, 100 mg of tPA is given within 1.5 hours for a thrombus in the coronary circulation, which receives only 5% of the cardiac output. Similarly, 0.9 mg/kg of tPA is used in acute ischemic stroke in which the cerebral circulation receives 15% of the cardiac output. These doses have the potency to withstand "route attrition": tPA is given into the venous circulation, it traverses the lung capillaries, enters the arterial circulation, reaches a steady state, and is still capable of dissolving arterial clots. The 100 mg of tPA is poised to effectively meet these "challenges." However, the key question is whether it is necessary to use the same dose that has been designed for thrombolysis in the systemic circulation for the lungs? It is clear that all tPA molecules, no matter through which venous access site they are given, converge in the lungs. It stands to reason that a "first-pass" effect might exist, especially with a bolus dose, that would have a favorable effect in the lungs, thereby achieving thrombolysis with a much lower dose. The corollary of this perspective might be applied to catheter-directed thrombolysis. In contrast to almost every other vascular bed with thrombosis, which would benefit from catheter-directed thrombolysis, in the lungs it would probably not be necessary, because the lungs are the center of convergence of all venous flow, and, ultimately, all administered molecules of tPA would reach the lungs. We do not dispute the established efficacy of catheter-directed thrombolysis in the treatment of PE[18,19] but only suggest that a similar result might be obtained by thrombolysis through the peripheral venous circulation using similar low doses. This recommendation is in keeping with the current American College of Chest Physician's guidelines, which suggest peripheral administration instead of catheter-directed thrombolysis (grade 2C).[1]

Disclosures

The authors have disclosed no conflicts of interest.

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