Lesson 19, Volume 14 Thrombolytic Therapy in Massive and Submassive Pulmonary Embolism

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Objectives

1. Define massive and submassive pulmonary embolism.
2. Understand the rationale for the use of thrombolytic therapy in pulmonary embolism.
3. Detail the pathophysiologic events leading to death from pulmonary embolism.
4. List the indications and contraindications of thrombolytic therapy.
5. Determine the recommended guidelines for administration of thrombolytic therapy.

Key words

echocardiography; pulmonary embolism, massive and submassive; right ventricular dysfunction; thrombolytic therapy

Abbreviations

MAPPET = Management Strategy and Prognosis of Pulmonary Embolism Registry; PE = pulmonary embolism; rt-PA = recombinant tissue plasminogen activator; RV = right ventricular; VTE = venous thromboembolism

Pulmonary embolism (PE) and deep vein thrombosis encompass the syndrome of venous thromboembolism (VTE). In the United States, VTE has a reported incidence of 1 in 1,000 persons yearly and account for approximately 250,000 hospitalizations each year.1 As many as 50 to 60% of patients with deep vein thrombosis develop symptomatic or asymptomatic PE.2 The case-fatality ratio for PE has been reported to be approximately 4 to 12%.1,3 The International Cooperative Pulmonary Embolism Registry has demonstrated a 3-month mortality rate of 17.5% for PE. This alarming observation has led many clinicians to re-evaluate the use of thrombolytic therapy in PE. This lesson will focus on the natural course of heparin-treated massive and submassive PE, the risk stratification of patients with PE, and the current recommendations for thrombolytic therapy for this disease.
Definitions and Incidence

Massive PE is best defined by hemodynamic instability rather than by a percentage of pulmonary vascular occlusion. It is a clinical syndrome associated with a high mortality rate. The pathophysiology of massive PE is highlighted by acute and significant pulmonary vascular occlusion leading to sudden elevation in pulmonary arterial pressure and right ventricular (RV) failure. These patients have unstable hemodynamics, significant hypoxemia, and signs of tissue hypoperfusion. The percentage of pulmonary occlusion required for hemodynamic instability and RV dysfunction can vary depending on preexisting cardiopulmonary disease. For example, a previously healthy patient may require more than 50% vascular occlusion before RV dysfunction is detected. In patients with preexisting cardiopulmonary disease, even as little as 20% pulmonary vascular occlusion can precipitate hemodynamic instability.4

PE can also present with significant pulmonary vascular occlusion ( > 30%) but stable hemodynamics. For the purposes of this lesson, this manifestation of VTE will be called a major or submassive PE.

In the absence of absolute contraindications, thrombolytic therapy for massive PE is clearly indicated.1,3,4 A more difficult clinical decision is the administration of thrombolytic therapy in hemodynamically stable, submassive PE. Emergent data suggest that a subset of these patients may have a high in-hospital and outpatient mortality rates. Can this subset of patients be identified utilizing bedside diagnostic examinations and techniques? Does thrombolytic therapy improve survival in submassive PE?

Natural Course of Heparin-Treated PE

To understand the benefits of thrombolytic therapy, the natural course of heparin-treated PE must be reviewed. Utilizing serial catheterization and angiograms, Dalen et al 5 demonstrated little hemodynamic improvement or angiographic resolution of clot during the first 7 days of treatment with heparin. Prediletto et al6 showed that a large part of the perfusion abnormalities detected by scintigraphy improved as late as 30 days from embolization. This delay in the therapeutic effects of heparin is due to the fact that heparin does not lyse the clot already lodged in the pulmonary circulation. The resolution of PE is dependent on the intrinsic fibrinolytic system. Thus, the role of heparin therapy is primarily a form of secondary prevention through inhibition of further thrombus formation.7 Nevertheless, heparin therapy followed by oral anticoagulation reduces the risk of recurrent VTE and death by 80 to 90%.8 The risk for recurrent PE and death with anticoagulation still ranges from 5 to 10%.9,10

Recent studies detect a disturbingly higher mortality rate for PE than that previously described. For example, the International Cooperative Pulmonary Embolism Registry found a 3-month mortality rate of 17.5%.11 In a second study of patients 65 years of age or older suffering from PE, a 30-day mortality rate of 13 to 14% was reported.12 This increased mortality rate may be due to the underlying chronic medical conditions rather than to recurrent VTE. Nevertheless, these data reinforce the urgent need to study the role of primary intervention (ie, thrombolytic therapy) for the treatment of acute PE.

Rationale for Thrombolytic Therapy in PE

The benefits of thrombolytic therapy were first studied by initial clinical trials, such as the Urokinase Pulmonary Embolism Trial and Urokinase-Streptokinase PE trials. These studies demonstrated that patients receiving thrombolytic therapy had a more rapid resolution of angiographic obstruction and
hemodynamic disturbances than those receiving heparin alone.\textsuperscript{13,14} In fact, a trend towards improved survival was observed in one of the studies.\textsuperscript{13} When compared to heparin therapy, the long-term benefits of thrombolytic therapy, such as increased preservation of pulmonary capillary blood volume and diffusion capacity, were observed even after 1 year.\textsuperscript{15} These benefits suggest that thrombolytic therapy may resolve distal and diffuse PE, maintaining pulmonary vascular reserve.

After these early trials, other small, randomized studies were published. These studies have been summarized by Arcasoy et al\textsuperscript{3} (Table 1). Because of the small numbers of patients studied, these studies were not designed to demonstrate a reduction in mortality or recurrent VTE. Approximately 1,000 subjects would be needed to demonstrate a statistically significant reduction in these two major endpoints. These studies do support the following important conclusions: (1) early in the course of PE, thrombolytic therapy results in superior improvements in hemodynamics and reperfusion compared to heparin therapy alone, but the amount of reperfusion may be equivalent 7 days after the PE\textsuperscript{3}; (2) in major PE with stable hemodynamics, thrombolytic therapy has not been demonstrated to improve survival or reduce the risk of recurrent PE.\textsuperscript{3}

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Patients</th>
<th>Treatment Regimens</th>
<th>Mortality</th>
<th>Recurrent VTE</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No. of cases</td>
<td>%</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Urokinase Pulmonary Embolism Trial (UPET, 1970)</td>
<td>78</td>
<td>Heparin</td>
<td>7</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>82</td>
<td>UK 12 h</td>
<td>6</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Tibbutt (1974)</td>
<td>17</td>
<td>Intrapulmonary heparin</td>
<td>1</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>Intrapulmonary SK for 72 h</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ly (1978)</td>
<td>11</td>
<td>Heparin</td>
<td>2</td>
<td>18</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>SK for 72 h</td>
<td>1</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Marini (1988)</td>
<td>10</td>
<td>Heparin</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>UK over 12 h for 3 days</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>UK 12 h</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Prospective Investigation of Pulmonary Embolism Diagnosis</td>
<td>4</td>
<td>Heparin</td>
<td>0</td>
<td>NA</td>
<td>0</td>
</tr>
</tbody>
</table>
The available clinical data should be separated by the type of pulmonary embolus. In patients with massive PE, various studies support the role for thrombolytic therapy. In a 1995 study performed by Jerjes-Sanchez et al., patients with massive PE (with hemodynamic instability) were randomized to an IV bolus of streptokinase or to heparin therapy alone. The goal of the study was to enroll 40 subjects. This study was stopped prematurely after enrolling only eight patients. All patients randomized to heparin died, and all four patients treated with thrombolytic therapy survived. Although a small study, it strongly supports the current indication for thrombolytic therapy in massive PE.

What is the role of thrombolytic therapy in submassive PE without hypotension or shock? Recent studies have focused on this specific issue. The largest randomized, controlled clinical trial examining hemodynamically stable PE was published in 1993 by Goldhaber et al. A group of 101 patients were randomized to receive recombinant tissue plasminogen activator (rt-PA) followed by heparin or heparin alone. The goal was to study RV function with echocardiography at baseline and 24 h posttreatment. Thrombolytic therapy demonstrated a greater improvement in RV function and pulmonary perfusion compared to heparin treatment. In fact, a statistically significant reduction in recurrent PE was seen in the rt-PA-treated patients. During the first 2 weeks of follow-up, five of the heparin-treated patients died. Based on echocardiographic findings, these patients had already demonstrated significant RV hypokinesis despite having normal blood pressures. This study has sparked an interest in the evaluation of RV dysfunction as a marker for a patient population at high risk for recurrent PE and/or death.

In 1997, a second study supported the use of thrombolytic therapy in submassive PE with stable hemodynamics. This multicenter registry (Management Strategy and Prognosis of Pulmonary Embolism Registry, or MAPPET) was a prospective, nonrandomized evaluation of 719 patients with...
submassive or major PE. In the study design, the attending physicians were allowed to decide between heparin or thrombolytic therapy. The patients' baseline characteristics demonstrated that those treated with thrombolytic therapy were younger and less likely to have preexisting cardiopulmonary disease. The thrombolytic therapy group had a reduced 30-day mortality rate (4.7% vs 11.1%, p = 0.016) and reduced risk for recurrent VTE (7.7% vs 18.7%, p ≤ 0.001) compared to the heparin group. Major bleeding complications were significantly higher in the thrombolytic-treated patients (21.9% vs 7.8%). These studies champion the need for controlled and randomized clinical trials to address the role of thrombolytic therapy in submassive PE.

**Risk Stratification: The Right Ventricle in PE**

Death due to PE is caused by acute pulmonary vascular occlusion with sudden elevation of pulmonary arterial pressure. The right ventricle dilates with resultant RV failure. Autopsies of patients who died of acute PE have demonstrated RV dilatation and infarction. This is the most widely accepted pathophysiological explanation for death due to massive PE. Animal and human studies utilizing hemodynamic and echocardiographic data have demonstrated the development of pulmonary arterial hypertension with deviation of the interventricular septum into the left ventricle. This septal deviation leads to decrease in left ventricular preload, stroke volume, cardiac output, and finally, coronary perfusion. The phenomenon has been termed *ventricular interdependency*.

In submassive and hemodynamically stable PE, echocardiographic monitoring of RV function may serve as a tool for identifying patients at risk for death or recurrent VTE. Those with submassive PE have already survived the initial embolic event. Death is usually related to recurrent VTE, as seen in 5 to 7% of patients despite heparin treatment. Four recent PE registries have provided echocardiographic data demonstrating that the detection of RV hypokinesis is associated with a two- to three-fold increase in mortality. The mechanism by which RV dysfunction leads to increased risk for VTE or death is still uncertain. It is postulated that RV dysfunction leads to stasis and vascular congestion, an environment auspicious for further clot formation and migration. Another possible explanation is that patients with RV dyskinesis suffered a larger pulmonary vascular occlusion and may have increased residual clot in the lower extremities available for recurrent embolization.

Based on these observations, echocardiographic assessment of RV function should be considered in patients with submassive PE with > 30% pulmonary vascular occlusion. The degree of RV dysfunction may help to stratify patients into categories of increased risk for either recurrent VTE or death.

**Indications for Thrombolytic Therapy in PE**

Present therapy for PE consists of secondary prevention with systemic anticoagulation. In 1977, the FDA approved the use of thrombolytic therapy for PE associated with hypotension and significant hypoxemia despite oxygen supplementation. In the absence of absolute contraindications, many authors strongly recommend primary therapy with thrombolytics in massive PE.

It is more difficult to make specific recommendations regarding thrombolytic therapy in submassive PE. Authors have argued for and against this intervention in this setting. Data suggest that patients with hemodynamically stable PE but moderate to severe RV dysfunction may benefit from thrombolytic therapy. In a randomized study by Goldhaber et al, patients with stable hemodynamics
received either heparin or tissue plasminogen activator. In 39% of patients, thrombolytic therapy improved RV wall motion abnormalities compared to 17% in the heparin group. In the patients with RV hypokinesis at the time of inclusion in the study, the effects of thrombolytic therapy on RV function were much more noticeable: 88% improvement and 6% worsening, in contrast with 44% improvement and 28% worsening in the heparin-treated group. In fact, the five episodes of recurrent thromboembolism (two fatal) were seen in patients with baseline RV dyskinesis treated with heparin alone. This difference in the number of recurrent thromboemboli approached but did not reach statistical significance (p = 0.06). Further evidence in support of thrombolytic therapy was provided by the MAPPET registry. This registry demonstrated an increased mortality rate in those patients with documented RV dysfunction who did not receive thrombolytic therapy. As described earlier, this study was not randomized and was biased by including a statistically higher number of older patients with LV dysfunction in the heparin-treated group.

Based on these data, thrombolytic therapy in submassive PE with RV dysfunction should be considered on an individual basis. The patient’s age, symptoms, physical examination, level of hypoxemia, and presence of RV dysfunction must be carefully studied. In the absence of contraindications, a patient with > 30% pulmonary vascular occlusion accompanied by dyspnea, hypoxemia, and evidence of moderate to severe RV hypokinesis could be considered for thrombolytic therapy. A future prospective, randomized clinical study may help settle this debate.

**Risks and Contraindications**

The major risk of thrombolytic therapy is bleeding, which commonly occurs at puncture and central line sites. Gastrointestinal, retroperitoneal, and intracranial bleeding are serious complications of thrombolytic therapy. Early studies utilizing prolonged 24-h infusions or intrapulmonary instillation of thrombolytics had a higher incidence of major bleeding (11 to 45%). Thanks to careful patient selection, minimization of patient instrumentation, and use of short-duration regimens via peripheral IV routes, the risk of bleeding has been reduced to between 6 and 12%. Nevertheless, studies such as the MAPPET registry reported an increased incidence of major bleeding (22%) in patients receiving thrombolytics compared to heparin control subjects (8%). In fact, 11% of the thrombolytic-treated patients required either discontinuation of lytic therapy or surgical intervention.

The most dreaded complication of thrombolytic therapy is intracranial hemorrhage, which occurs in approximately 1% of patients. This risk increases significantly with age, uncontrolled hypertension, and history of recent stroke or craniotomy. In a registry of approximately 300 patients receiving thrombolytics for PE, none of the patients < 55 years of age suffered from this complication.

The increased risk for serious bleeding with thrombolytic therapy must weigh heavily in the decision whether to use thrombolytic therapy for massive and submassive PE. The relative contraindications to thrombolytic therapy include the following: (1) major internal bleeding in the previous 6 months; (2) recent (within 2 months) stroke or intracranial or intraspinal trauma or surgery; (3) active intracranial disease; (4) uncontrolled hypertension (systolic BP > 200 mm Hg or diastolic BP > 110 mm Hg); (5) major surgery, puncture of a noncompressible vessel, organ biopsy, or obstetric delivery within the last 10 days (2 weeks for open-heart surgery); (6) bleeding diathesis (including that associated with renal or liver disease); (7) recent major or minor trauma, including cardiopulmonary resuscitation; (8) infective endocarditis; (9) pregnancy; (10) hemorrhagic retinopathy; (11) pericarditis; and (12) aneurysm.
Administration of Thrombolytic Therapy: Controversies

Careful evaluation of the clinical studies of thrombolytic therapy for PE raises the following questions: (1) Which thrombolytic agent is safest and most effective? (2) Should the agent be administered systemically or locally? (3) What is the time window for administration of thrombolytic therapy?

Which thrombolytic agent is safest and most effective? Many studies have demonstrated that streptokinase, urokinase, and rt-PA have equal safety profiles and efficacy in angiographic resolution of clot and in improvement of hemodynamic disturbances. A study performed by Meneveau et al compared two Food and Drug Administration (FDA)-approved thrombolytic regimens in massive PE: 12-h streptokinase infusion vs 2-h infusion of rt-PA. The shorter infusion of rt-PA led to a quicker improvement in hemodynamic disturbances. This advantage is most likely related to the rapid loading of thrombolytic activity rather than the specific thrombolytic agent used. The only short infusion currently approved by the FDA is the 2-h rt-PA infusion.

Should the agent be administered systemically or locally? Thrombolytic therapy should be administered systemically through a peripheral IV. A single study has compared systemic and local thrombolytic therapies. Vestraete et al randomized patients to receive 50 mg of rt-PA over 2 h, either through a pulmonary artery catheter or peripheral IV. Equivalent angiographic improvement was seen with both infusions. Pulmonary arterial administration with a catheter is associated with increased risk of bleeding at puncture sites and retroperitoneum. There are reports of locally administered thrombolytic therapy using smaller doses than those used systemically, with improvement in angiographic scores and perfusion. This technique may allow for lower doses of thrombolytic agents and, thus, safer administration of thrombolytic agents patients at increased risk of bleeding.

What is the time window for administration of thrombolytic therapy? In the setting of massive PE, thrombolytic therapy should be administered without delay. In less urgent cases, the time window for therapy is reported as 14 days from the onset of clinical manifestations of pulmonary embolus. This broad therapeutic window provides the clinician with time for a careful decision regarding the use of thrombolytic therapy in submassive PE. Therefore, most authors recommend that thrombolytic therapy be administered during the daytime hours to allow for availability of hospital facilities, physicians, and ancillary services. Four clinical trials reported equal benefit when thrombolysis was administered within the first 5 days compared to 6 to 14 days from the onset of symptoms. In a retrospective review by Daniels et al, 308 patients from five clinical trials were studied to revisit this issue. For each day's delay in starting thrombolytic therapy, a 0.8% decline in lung tissue reperfusion was detected. Nevertheless, the study concluded that thrombolytic therapy was still useful 6 to 14 days from the onset of symptoms.

Administration of Thrombolytic Therapy

Once the decision to use thrombolytic therapy is made, some guidelines should be considered to increase the safety and efficacy of these agents. It is recommended that an FDA-approved regimen be utilized. Only rt-PA is approved for the shorter 2-h infusion. In two clinical studies, this regimen improved resolution of angiographic obstruction in the first 12 h after PE better than the longer 12-h, FDA-approved streptokinase infusion. The recommended protocol for thrombolytic therapy for PE is...
delineated in Table 3.3,10

### Table 2 Thrombolytic Agents Approved for Treatment of PE*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regimen</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>250,000 U over 30 min, followed by 100,000 U/h for 24 h</td>
<td>1977</td>
</tr>
<tr>
<td>Urokinase</td>
<td>4,400 U/kg over 10 min, followed by 4,400 U/kg/h for 12-24 h</td>
<td>1978</td>
</tr>
<tr>
<td>rt-PA</td>
<td>100 mg over 2 h</td>
<td>1990</td>
</tr>
</tbody>
</table>

*Reproduced from Arcasoy and Kreit.3 All agents administered as a continuous peripheral infusion.

### Table 3 Practical Aspects of PE Thrombolysis*

1. Obtain a careful history (especially neurologic history) and perform a physical examination, focusing on detecting contraindications to thrombolytic therapy.
2. Order initial laboratory tests, including hemoglobin and hematocrit levels, platelet count, and blood typing.
3. Remember that no contraindication is absolute in massive PE and shock. In submassive PE, the decision to use thrombolytic therapy must be individualized to each patient's presentation and clinical manifestations.
4. Initiate thrombolytic therapy in the daytime hours, unless clinical deterioration or shock develops. Remember, there is a 14-day therapeutic window.
5. Stop heparin infusion and initiate a FDA-approved thrombolytic regimen (see Table 2).
6. Minimize the use of phlebotomy, arterial punctures, or other invasive procedures during infusion. Minimize handling of the patient.
7. Discontinue infusion in the setting of noncompressible bleeding or important hemorrhage. Treat thrombolytic-induced bleeding with cryoprecipitate and fresh frozen plasma.
8. Obtain emergency neurosurgical consultation and noncontrasted CT scan of the head if the neurologic findings change.
9. Measure partial thromboplastin time every 2 to 4 h. Restart heparin drip (without a bolus) when measurement is < 2.5 times the control value.

*Adapted from Arcasoy and Kreit3 and Goldhaber.10

### Summary

Thrombolytic therapy has been demonstrated to improve angiographic and hemodynamic abnormalities in acute PE. Nevertheless, a statistically significant reduction in mortality or recurrent VTE has not been demonstrated. This lesson outlined the available evidence supporting the present recommendation for thrombolytic therapy in massive PE with hypotension.
The evidence for thrombolytic therapy in submassive or "hemodynamically stable" PE is less conclusive. In this clinical setting, a large, multicenter, controlled clinical trial will be required to demonstrate a reduced mortality with thrombolytic therapy. Because of the low case-fatality rate for acute PE, approximately 1,000 patients will be required to demonstrate a statistically significant reduction in mortality. For example, the Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico (GISSI-1) trial, utilizing thrombolytic therapy in acute myocardial infarction, enrolled 11,712 patients to demonstrate a reduction in mortality with thrombolytic therapy. For acute PE, an endeavor of this proportion will require a unified, multicenter effort that has yet to materialize.

Recent clinical trials suggest that a subset of patients may be at high risk for recurrent VTE or death in the setting of submassive PE. Early in the hospital course, these patients demonstrate significant or progressive RV dysfunction. RV dyskinesis or dysfunction can be assessed noninvasively with a transthoracic echocardiogram. This technique may help "risk-stratify" these patients into a higher mortality group despite stable hemodynamics. Thrombolytic therapy in these patients may have a role, as supported by the studies discussed in this review. For now, the decision to use thrombolytic therapy for submassive PE must be individualized for each patient by carefully weighing the advantages, disadvantages, and contraindications. Until further studies confirm the available preliminary data, exact guidelines for this clinical scenario cannot be proposed.

References


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