

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

THE USE OF THROMBOLYTICS IN THE INTENSIVE CARE UNIT FOR PULMONARY EMBOLISM

SUMMARY

The role of thrombolytic agents in the management of massive pulmonary embolism (PE) is not well established. Alteplase (recombinant tissue-plasminogen activator; rt-PA), streptokinase, and urokinase effectively restore pulmonary blood flow when administered by the intravenous or intrapulmonary route. They have not been shown to improve mortality or long-term outcome and are associated with a significant risk of bleeding. Thrombolytics should be reserved for patients with massive PE and evidence of cardiac dysfunction who have a low risk of bleeding. Intrapulmonary administration has not been consistently shown to be superior to intravenous dosing. Administration of thrombolytics in the intensive care unit setting should be reserved for patients who are not stable for transport to the interventional radiology suite. Given the allergic reactions associated with streptokinase and long infusion duration of both streptokinase and urokinase, rt-PA is a reasonable first-line thrombolytic.

RECOMMENDATIONS

- **Level 1**
 - **Heparin is the drug of choice for PE (regardless of whether thrombolytics are used) if:**
 - **No contraindications are present AND**
 - **The anticipated benefit outweighs the risk in patients at high risk for bleeding**
- **Level 2**
 - **End-tidal carbon dioxide (ETCO₂) measurements may be used to assess the efficacy of thrombolytic therapy**
- **Level 3**
 - **Consider intrapulmonary thrombolytics when urgent restoration of pulmonary blood flow is necessary.**
 - **ICU thrombolytics should be reserved for patients who meet the following criteria:**
 - **Massive PE AND**
 - **Evidence of cardiac dysfunction AND**
 - **Low bleeding risk AND**
 - **Transfer to interventional radiology is not feasible**
 - **Consider consultation with interventional radiology for mechanical intervention and/or possible thrombolysis.**
 - **Fibrinogen levels may be used to monitor thrombolytic therapy.**
 - **Rescue embolectomy should be considered for failed thrombolysis and evidence of continued cardiac dysfunction.**

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

INTRODUCTION

The role of thrombolytic agents in the treatment of PE is not well established. Thrombolytics clearly restore pulmonary perfusion more rapidly than heparin alone and are associated with early hemodynamic improvement and reversal of right ventricular dysfunction. Improvements in mortality and long-term pulmonary artery patency, however, have not been consistently demonstrated. The major disadvantage of thrombolytic therapy is serious bleeding, including intracranial hemorrhage. Heparin remains the cornerstone of therapy and thrombolytics are generally reserved for patients who are hemodynamically unstable and have a low risk of bleeding (1). Intravenous administration is the FDA-approved route of drug delivery for rt-PA, evaluated in several studies. The theoretical benefits of local administration include rapid achievement of peak concentrations at the thrombus and a decreased risk of systemic bleeding complications.

LITERATURE REVIEW

The safety and efficacy of intravenous versus intrapulmonary rt-PA were evaluated in a multicenter European study of patients with massive bilateral PE (2). After diagnosis was confirmed by pulmonary angiography, intravenous (n=15) or intrapulmonary (n=19) rt-PA was given as a 10mg bolus followed by 20mg/hour over the first 2 hours. All patients received an intravenous bolus of 5000 IU heparin followed by a continuous infusion of 1000 IU/hour. Follow-up pulmonary angiography was performed at the end of the 2-hour infusion period. If massive PE was present, a second infusion of 50mg rt-PA was given over 5 hours by the same route. Following rt-PA infusion, both groups had significant improvements in mean pulmonary arterial pressure and pulmonary angiographic severity score. Intrapulmonary infusion did not offer a significant benefit over the intravenous route of administration. Forty-seven percent (16/34) developed some degree of bleeding, primarily at puncture and/or surgical sites. (Class I)

Clot fragmentation combined with local fibrinolysis was performed in five patients with massive PE (3). All were fully heparinized during and after angiography. Local thrombolysis was achieved with an initial dose of 50-100mg rt-PA (a bolus of 14-20mg via the pulmonary artery after clot fragmentation, followed by an intrapulmonary infusion over 2-5 hours through a pigtail catheter). Pulmonary artery pressure significantly decreased following clot fragmentation and fibrinolysis. All patients' survived and clinical improvement was noted within 24 hours. Bleeding complications occurred in 4/5 patients. Two experienced minor bleeding at the puncture site and 2 developed groin and retroperitoneal hematomas. Anticoagulation with heparin followed by coumadin was continued. (Class III)

Four patients with massive PE were treated by thrombus fragmentation followed by local administration of rt-PA (4). One patient received a low-dose regimen and is not discussed further. Following thrombus fragmentation, a bolus dose of 10-50mg was administered into the main pulmonary artery or into the major branches of the right and left pulmonary arteries. A continuous infusion of 10mg/hr was then initiated for 14-18 hours via the main pulmonary artery. Heparin was administered at 1000 U/hr throughout thrombus fragmentation, rt-PA infusion, and until full anticoagulation with warfarin was achieved. All patients survived and their clinical condition was improved at the 24-hour assessment point. There were no hemorrhagic complications during or after rt-PA infusion. (Class III)

Meneveau et al compared rescue surgical embolectomy and repeat thrombolysis in patients who did not respond to thrombolysis. A prospective single-center registry revealed 40 patients who did not respond to thrombolysis within the first 36 hours. Fourteen were treated by rescue surgical embolectomy and 26 by repeat thrombolysis. There was a trend toward higher mortality in the medical group (10/26) vs. the surgical group (1/14). There were significantly more recurrent PEs in the repeat thrombolysis group (35% vs. 0%, respectively). While there was no significant difference in the number of bleeding complications between the two groups (four each), all four bleeding episodes in the repeat fibrinolysis group were fatal. Rescue embolectomy was recommended for patients with persistent RV dysfunction following initial thrombolysis (14).

The use of continuous end-tidal carbon dioxide tension (ETCO₂) monitoring to assess the efficacy of thrombolytic therapy for acute massive PE was evaluated (5). Twelve consecutive patients with confirmed PE requiring mechanical ventilation and thrombolytic therapy were included. ETCO₂ levels

were lower in nonsurvivors than survivors (12.3 ± 1.3 versus 20 ± 5.3 mmHg; $p=0.08$). There were significant increases in cardiac index and $\text{PaO}_2/\text{FiO}_2$ and significant decreases in MPAP and ADCO_2 in the ten survivors following thrombolytic therapy. When individual patients were analyzed, the change in ETCO_2 was highly correlated with changes in MPAP ($r^2=0.79-0.98$; $p<0.001$) and ADCO_2 ($r^2=0.77-0.98$; $p<0.001$). (Class II)

The effects of heparin plus alteplase versus heparin plus placebo for the treatment of acute submassive PE were evaluated in a prospective, randomized trial (6). Two hundred fifty six patients with right ventricular dysfunction or pulmonary hypertension, without hemodynamic instability, were included. Alteplase was administered as a 10mg bolus, followed by 90mg intravenously over 2 hours. The incidence of the combined primary endpoint (in-hospital mortality plus clinical deterioration requiring escalation of treatment) was significantly higher in the heparin/placebo group (24.6% versus 11%; $p=0.006$). However, when assessed individually, there was no significant difference in in-hospital mortality between groups. No significant difference in the secondary endpoints of recurrent PE, major bleeding, or ischemic stroke were found. Of note, the trial has been critiqued due to the low incidence of major bleeding in the heparin/alteplase group (0.8%) (7). (Class I)

While there is still little data to support the routine use of thrombolytics in normotensive patients with submassive PE, recent diagnostic advancements reveal a subset of patients that may benefit from thrombolysis in this setting. A recent review by Konstantinides suggests the need for risk stratification of normotensive patients with PE, to identify a subset of patients that may carry an intermediate mortality risk, often associated with development of right ventricular (RV) failure. Increasing experience with echocardiography, and helical CT has improved the ability to detect RV dysfunction by non-invasive means. Echo findings of RV enlargement, hypokinesis of the free wall, leftward septal shift, and evidence of pulmonary hypertension are suggestive of RV dysfunction, and may carry a 2-3 fold increased risk of death (12, 13) (Class III).

CT findings of RV enlargement defined by a right/left ventricular dimension ratio >0.9 were found to independently predict 30-day PE related mortality (12). This trend was equivalent to echocardiographic findings in a recent registry evaluation by Fremont et al. 950 patients with acute PE underwent echocardiographic assessment upon hospital admission, including measurement of RV/LV ratios. While sensitivity (72%) and specificity (58%) values were less than overwhelming, for predicting in hospital mortality, RV/LV ratio ≥ 0.9 was found to be an independent predictive factor (OR, 2.66; $p=0.01$) (15). RV hypokinesis was also found to be an independent predictor of early death among normotensive (SBP >90) patients with PE. Evaluation of ICOPER (International Cooperative Pulmonary Embolism Registry) data revealed a 17% 30-day mortality associated with RV hypokinesis despite preserved SBP (16).

Cardiac biomarkers such as Troponin I, brain natriuretic peptide and Heart-type FABP (H-FABP) may identify those patients with early or developing myocardial cell damage possibly related to PE. Kline et al evaluated 8 biomarkers and found BNP and Troponin to demonstrate modest, but significant prognostic accuracy for prognostic significance in detecting RV hypokinesis in the setting of submassive PE (17). While these biomarkers have low specificity and positive predictive value for PE-related mortality, when considered in conjunction with the aforementioned imaging findings they may prove useful in identifying candidates for thrombolytic therapy prior to the development of hemodynamic instability. (Class III)

Table I: Dosing Information

Thrombolytic Regimens for the Treatment of Pulmonary Embolism		
Thrombolytic	IV	Intrapulmonary (Not FDA-approved)
Alteplase (Recombinant tissue-plasminogen activator; rt-PA;Activase [®])	100mg over 2 hours	10mg bolus over 10 minutes and re-evaluate need for continuation; may proceed with 20 mg/hr for 2 hours if necessary (2,8)
Streptokinase [®] (Streptase [®])	250,000 units over 30 minutes, followed by 100,000 units/hour for 24 hours	100,000 units/hr (9-11)
Urokinase [®] (Abbokinase [®])	4,400 units/kg over 10 minutes, followed by 4,400 units/kg/hour for 12 hours	Variable

Table II: Absolute Contraindications to rt-PA

- Active internal bleeding
- History of cerebrovascular accident
- Intracranial or intraspinal surgery or trauma (\leq 2 months)
- Intracranial neoplasm
- Arteriovenous malformation or aneurysm
- Bleeding diathesis
- Severe uncontrolled hypertension

Table III: Relative Contraindications to rt-PA

The following conditions may increase the risk of bleeding and must be weighed against the anticipated benefits:

- Recent (\leq 10 days) major surgery
- Cerebrovascular disease
- Recent (\leq 10 days) GI or GU bleeding
- Recent (\leq 10 days) trauma
- Hypertension: $>$ 180 mmHg systolic or \geq 110 mmHg diastolic
- Likelihood of left heart thrombus (e.g., mitral stenosis with atrial fibrillation)
- Acute pericarditis
- Subacute bacterial endocarditis
- Hemostatic defects secondary to severe hepatic or renal disease
- Significant liver dysfunction
- Pregnancy
- Diabetic hemorrhagic retinopathy or other ophthalmic hemorrhaging
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- Advanced age (e.g., $>$ 75 years old)
- Patients currently receiving oral anticoagulants
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Table IV: Contraindications/Precautions to Heparin Therapy

- Hypersensitivity to heparin
- Active bleeding
- Severe thrombocytopenia
- Increased risk of hemorrhage, such as:
 - Selected traumatic injuries (i.e., severe liver laceration, intracranial hemorrhage, spinal cord injury)
 - Dissecting aneurysm
 - Treatment with drotrecogin alfa (activated) (Xigris™)
 - Hemophilia or other blood disorders
 - Epidural catheter
 - Subacute bacterial endocarditis
 - Uncontrolled hypertension

References

1. Hyers TM, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease. *Chest* 2001;119:176S-193S.
2. Verstraete M, Miller GAH, Bounameaux H, et al. Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. *Circulation* 1988;77(2):353-60.
3. Stock KW, Jacob AL, Schnabel KJ, et al. Massive pulmonary embolism: treatment with thrombus fragmentation and local fibrinolysis with recombinant human-tissue plasminogen activator. *Cardiovasc Intervent Radiol* 1997;20:364-8.
4. Murphy JM, Mulvihill N, Mulcahy D, et al. Percutaneous catheter and guidewire Fragmentation with local administration of recombinant tissue plasminogen activator as a treatment for massive pulmonary embolism. *Cardiovasc Intervent Radiol* 1997;20:364-8.
5. Wiegand UK, Kurowski V, Giannitsis E, et al. Effectiveness of end-tidal carbon dioxide tension for monitoring of thrombolytic therapy in acute pulmonary embolism. *Crit Care Med* 2000;28:3588-92.
6. Konstantinides S, Geibel A, Heusel G, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002;347:1143-50.
7. Goldhaber SZ. Thrombolysis for pulmonary embolism. *N Engl J Med* 2002;347:1131-2.
8. McEvoy GK, ed. AHFS Drug Information. Bethesda: American Society of Health-System Pharmacists, Inc.;2000.
9. Essop MR, Middlemost S, Skoularigis J, et al. Simultaneous mechanical clot fragmentation and pharmacologic thrombolysis in acute massive pulmonary embolism. *Am J Cardiol* 1992;69:427-30.
10. Krivec B, Voga G, Zuran I, et al. Diagnosis and treatment of shock due to massive pulmonary embolism. *Chest* 1997;112:1310-16.
11. Wong PS, Singh SP, Watson RD, et al. Management of pulmonary thrombo-embolism using catheter manipulation: a report of four cases and review of the literature. *Postgrad Med J*;75:737-41.
12. Zamanian RT, Gould MK. Effectiveness and cost effectiveness of thrombolysis in patient with acute pulmonary embolism. *Curr Opinion in Pulm Med* 2008; Vol.4 (5):422-426.
13. Konstantinides SV. Massive Pulmonary Embolism: What Level of Aggression? *Semin Respir Crit Care Med* 2008; 29:47-55.
14. Meneveau N, Seronde MF. Management of Unsuccessful Thrombolysis in Acute Massive Pulmonary Embolism. *Chest* 2008; 129: 1043-1049.
15. Fremont B, Pacouret, G, et al. Prognostic value of echocardiographic Right/Left ventricular End-diastolic diameter ration in Patients With acute Pulmonary embolism. *Chest* 2008; 133:358-362.
16. Kucher N, Rossi E, et al. Prognostic Role of Echocardiography Among Patients With Acute Pulmonary Embolism and a Systolic Arterial Pressure of 90mmHg or Higher. *Archives of Internal Medicine* 2005; 165: 1777-1781.
17. Kline JA, Zeitouni R, et al. Comparison of 8 biomarkers for prediction of right ventricular hypokinesia 6 months after submassive pulmonary embolism. *American Heart Journal* 2008; 156(2): 308-314.