

Near-Fatal Pulmonary Embolism

LOUIS R. DEPALO, M.D.

Abstract

A case of a 79-year-old female admitted to the hospital with a hip fracture and suffering a near-fatal embolism, is presented. The article then reviews the epidemiology of deep venous thrombosis and pulmonary embolism in the setting of hip fracture and orthopedic surgery and outlines the diagnostic approach to a critically ill patient with pulmonary embolism. The use of thrombolysis as an adjunct to usual heparin therapy is examined, as are the potential benefits versus the absolute risks of thrombolysis. Finally, practical recommendations outlining a reasonable approach to this group of patients, based on available evidence, are proposed.

Key Words: Pulmonary embolism, thrombolytic therapy, echocardiography.

Case Presentation

A 79-YEAR-OLD FEMALE with a history of hypertension, diabetes, Parkinson's disease and colon cancer was admitted to the orthopedic service with a traumatic right femur fracture. The patient underwent an uneventful right hip reduction and internal fixation on the third hospital day. She received one dose of warfarin on the evening of the first postoperative day. The following evening the patient developed shortness of breath, and intravenous heparin was administered. But the patient continued in severe respiratory distress, responding only to noxious stimuli. Examination revealed blood pressure of 90/60 mm Hg, respiratory rate of 40/min, and regular heart rate of 90 beats per minute. Oxygen saturation with 100% oxygen by facemask was 90–95%. She had central cyanosis. There was no obvious jugular venous distention, and the mucus membranes were moist. Her pupils were equal and reactive to light, the heart was normal, and the lungs were clear bilaterally. Her extremities were cyanotic and cool, with thready pulses. There were no palpable lower

extremity venous cords or petechiae, and the surgical wound was clean and dry. Electrocardiogram revealed a regular sinus rhythm (rate of 83/min), a left axis deviation and a left anterior fascicular block unchanged from the admission tracing.

She deteriorated, becoming hemodynamically unstable with a palpable blood pressure of 60 mm Hg. She was treated with aggressive fluid resuscitation. Arterial blood gas analysis obtained while the patient was breathing 100% inspired oxygen revealed a pH of 7.38, carbon dioxide tension 24.7 mm Hg, and P_aO_2 of 82 mm Hg (100% saturation). Serum lactate, white blood count and creatinine were elevated. Serum creatine phosphokinase (CPK) and lactic dehydrogenase (LDH) were both markedly elevated, but creatine kinase MB band (CK-MB) was normal.

She remained hypotensive despite administration of 1.5 liters of normal saline. Oxygen saturation decreased and she appeared pre-terminal. A presumptive diagnosis of massive pulmonary embolism (PE) was made. The heparin drip was discontinued and tissue plasminogen activator (TPA) was administered as a 15-mg bolus, followed by an 85-mg infusion over 90 minutes. Within 30 minutes the oxygen saturation improved and blood pressure rose to 100/70, with overall improvement in the patient's clinical status. Ninety minutes following infusion of TPA, the arterial blood gas was $P_aO_2 = 166$ mm Hg. She was transferred to the med-

Address correspondence to Louis R. DePalo, M.D., F.C.C.P., Assistant Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Box 1232, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

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ical intensive care unit. By the next morning she was stable, breathing room air comfortably. Her chest radiograph showed cardiomegaly with no pulmonary infiltrates or effusions. Repeat hemoglobin revealed a significant drop (3 grams). She was transfused and heparin was withheld until her prothrombin time normalized and her partial prothrombin time was twice control value. A head computed tomography (CT) without contrast was obtained because of some residual confusion; no hemorrhage was seen. She returned to her nursing home.

Introduction

The object of life is not to be on the side of the majority, but to escape finding oneself in the ranks of the insane.

Marcus Aurelius

The use of thrombolytic therapy in the treatment of pulmonary embolism remains controversial. Contraindications include the immediate postoperative period, active bleeding, new neurological findings, and advanced age. Advocates of thrombolytic therapy for thromboembolic disease generally recommend some laboratory confirmation of the diagnosis prior to therapy. The decision to empirically treat this desperately ill, elderly patient with a history of hypertension, one day after hip surgery, was difficult. A therapeutic failure or life-threatening complication would certainly have occasioned a majority view that use of thrombolysis in this patient was unwise. Clinical acumen, an accurate risk-benefit analysis, and the courage to treat despite major contraindications led to an excellent clinical outcome.

Epidemiology

Despite advances in the diagnosis and treatment of deep venous thrombosis and pulmonary embolism (DVT-PE), only 260,000 of the projected 600,000 cases per year of DVT-PE are correctly diagnosed (1). This results in significant morbidity and mortality (30%) (2). Investigators (3) have documented readily identifiable risk factors that define patients and patient populations at high risk for venous thromboembolism. The top six risk factors are advanced age, obesity, history of previous DVT-PE, cancer, bedrest and major surgery. The patient in this report had at least three of these six risk factors and therefore a 50% likelihood of pulmonary embolism based on history alone (Table 1) (4).

TABLE 1

Proportion of Patients with Clinically Suspected DVT in Whom Diagnosis Was Confirmed by Objective Testing Increases with the Number of Risk Factors.

Number of DVT Risk Factors	Objectively Confirmed DVT(%)
0	11
1	24
2	36
3	50
4 or more	100

Data from Wheeler HB, Anderson FA, Cardullo PA, Jr, et al., modified with permission (4).

Considerable work has been done on attenuating the impact of risk factors in those patients at highest risk (5–7). Unfortunately, despite the longstanding evidence of the efficacy of various prophylactic agents, the adequacy of physician practices remains in question (8). Stasis, intimal injury and hypercoagulability (Virchow's triad) are the three underlying physiologic tenets that define risk for the development of DVT-PE. "Stasis" results from the supine position and the effects of general anesthesia that begin and can be readily identified within the operating theater (9, 10). "Intimal injury" results from mechanical trauma (ligatures, tourniquets, vessel traction) and humoral factors associated with stress (vasoactive amines), excessive free radical generation and anesthetic agents (11, 12). This constellation promotes "hypercoagulability" secondary to venous stasis and decreased clearance of activated clotting factors. Numerous clotting factors have been examined, including fibrinopeptide A, platelet factor 4, D-dimers, antithrombin III, prothrombin factor 4 tissue plasminogen activator inhibitor, and decreased plasmin activity (13). None of these factors, however, have arisen as either specific or sensitive assays to aid in identifying those surgical patients at greatest risk for the development of DVT-PE. Therefore, it is prudent for the practitioner to determine clinical risk factors, stratify overall risk and provide prophylaxis accordingly (14). Patients should be classified as having low, moderate, high or very high risk for developing DVT-PE (Table 2).

This patient had a traumatic hip fracture followed by orthopedic surgery. The American College of Chest Physicians Consensus Conference on Antithrombotic Therapy (5) strongly advocates prophylaxis for DVT-PE in this surgical group. Hip fractures have been shown to

TABLE 2
DVT and PE Risk Classification.

Risk Categories	Calf DVT(%)	Proximal DVT(%)	Fatal PE (%)
Low Age <40 years, minor surgery, no secondary risk factors*	2	<0.4	<0.002
Moderate Age >40 years, major surgery, no secondary risk factors*	10–20	4–8	0.1–0.4
High Age >40 years, major surgery, secondary risk factors age >60 years, major surgery, no risk factors	20–40	4–8	0.4–1
Very High age >40 years, major surgery, previous DVT, PE, cancer, hypercoagulable state, orthopedic surgery, multiple trauma, acute SCI	40–80	10–20	1–5

*Secondary risk factors: Obesity, varicose veins, estrogen use, malignancy, immobilization, and paralysis. SCI = spinal cord injury. Data from Clagett GP, Anderson FA, Jr, Geerts W, modified with permission (14).

have a DVT-PE incidence of 40–45% with fatal pulmonary embolism occurring in as many as 6–10% of those who have surgical repair (15, 16). External pneumatic compression devices, warfarin sodium, adjusted dose unfractionated heparin (UFH) and low molecular weight heparin (LMWH) have all been shown to be more effective than low-dose heparin or no prophylaxis after elective hip surgery (17). External compression, though effective, needs to be utilized 23 hours per day and is not practical, given shortened hospital stays and early mobilization. In hip fracture repair, “preoperative” adjusted dose warfarin has been shown since 1959 (15) to result in reductions in incidence of both DVT (27% to 3%) and fatal PE (10% to 0%). The patient in this report received no preoperative prophylaxis; warfarin was administered only on the first postoperative day. The clinical risks for developing DVT-PE were considerable for this patient, and prophylaxis was inadequate.

Diagnostic Approach

The approach to the acutely ill patient with pulmonary embolism is essentially the same as for the general population, with certain caveats. The physician must balance the need to make a

quick and accurate diagnosis with providing prompt, life-saving treatment. Treatment is often begun prior to establishing a definitive diagnosis. Ventilation-perfusion scanning generally is still considered the procedure of first choice. However, disadvantages include low sensitivity (18), general unavailability “after hours,” and the fact that it is time consuming. Unstable patients (hypoxia, hemodynamics) may not be able to tolerate being transported to nuclear medicine departments for any extended interval of time.

The plasma D-dimer determination has received increasing interest as a screening test for DVT-PE, particularly when combined with clinical decision modeling and other diagnostic tests (19). However, the negative predictive value in patients clinically deemed to be at highest risk assessment for DVT-PE is not well known. Dynamic, contrast-enhanced, computerized tomographic angiography (spiral or helical CT) is a rapid, noninvasive means to diagnose patients with pulmonary embolism. Preliminary reports suggest good sensitivity and specificity with acceptable clinical outcomes (20–22). Departments of radiology routinely care for critically ill patients, and new, high-speed scanners allow for rapid scanning with single breath-holds that can even be performed in the ventilated patient.

The patient presented here is an example of the unstable patient for whom transportation is not feasible or safe, and for whom rapid, life-saving bedside decisions are mandatory. While some bedside diagnostic tests can be effective, portable perfusion scans are cumbersome and offer limited views; the diagnostic accuracy compared to traditional ventilation perfusion scanning is not well characterized. Bedside echocardiography is extremely valuable, both as a diagnostic tool and as a predictor of clinical outcomes (23, 24). Transthoracic echocardiography is simple, noninvasive and readily available, but subject to limitations of image quality and subjective interpretations. Transesophageal echocardiography is much more accurate in visualizing the right-sided cardiac chambers, providing accurate assessment of right ventricular pressure overload, hypokinesis and ventricular wall motion abnormalities. However, it is relatively invasive and requires an experienced operator. Echocardiography offers the additional advantage of confirming alternative diagnoses such as myocardial infarction, acute aortic dissection or pericardial tamponade (which can masquerade as an acute pulmonary embolus). Finally, for a patient with multiple medical problems who is desperately ill, and who has contraindications to anticoagulation therapy, pulmonary angiography may remain feasible, though often not practical. Pulmonary angiography in unstable patients is difficult, requiring expertise in critical care management and interventional radiology. Angiography can be combined with therapeutic interventions such as catheter directed thrombolysis and placement of a vena caval filter device. Newer, catheter-based techniques offer the hope of *in situ* lysis (angiojet) of acute clots.

Recent studies of seemingly hemodynamically stable patients demonstrate a significant proportion of patients with echocardiographic evidence of right ventricular compromise and adverse clinical outcomes (24), despite appropriate standard care with unfractionated heparin (UFH). It has been suggested that, in this group of patients, thrombolytic therapy may result in fewer adverse events. The echocardiogram, therefore, aside from providing diagnostic information (e.g., pulmonary artery clot, isolated right ventricular pressure overload in high suspect cases), can aid in directing treatment beyond standard care. Deciding which patients with PE should have bedside echocardiography is difficult. While hemodynamically unstable patients are obvious candidates, Goldhaber has

demonstrated right ventricular dysfunction in patients without obvious hemodynamic instability (24). Studies have shown that patients with less than 30% perfusion defects, as defined on nuclear perfusion scan, do not have echocardiographic evidence of right ventricular dysfunction (25). Therefore, a perfusion scan with greater than 30% decrement in perfusion is a sensitive, though nonspecific, screen for determining who should receive bedside echocardiography.

Thrombolysis as an Adjunct to Standard Care?

Anticoagulation with UFH remains the treatment of choice for patients presenting with an acute pulmonary embolus (26–28). Heparin therapy prevents further clot deposition and allows for natural fibrinolysis of the existing clot. Heparin anticoagulation provides secondary prevention of recurrent PE but does not provide primary therapy (lysis) of the acute embolism. Despite appropriate UFH care, there are patients who experience recurrent pulmonary emboli and mortality (29, 30). The Urokinase Pulmonary Embolism Trial (UPET) revealed that 15% of patients with massive PE had two or more previous episodes, and 20% of treated patients were found to have signs of recurrent PE within the first two weeks (29, 30). Clearly a substantial population of patients remains at risk, and adjunct therapies should be considered.

Thrombolytic agents dissolve clots promptly (31), hasten pulmonary reperfusion, reverse right heart failure (24) and improve capillary blood volume (32). Table 3 outlines the FDA-approved thrombolytic regimens. Intravenous TPA, compared with the other thrombolytic agents streptokinase and urokinase, achieves a faster clot lysis with improved safety and better tolerance, and is the most convenient fibrinolytic to administer (33). Therapeutic goals for thrombolysis should include symptom relief, hemodynamic stability, improvement in

TABLE 3

FDA-Approved Thrombolytic Regimens for PE.

Streptokinase: 250,000 IU as a loading dose over 30 minutes, followed by 100,000 U/hr for 24 hours — approved in 1977
Rt-PA: 100 mg as a continuous peripheral intravenous infusion administered over 2 hours — approved in 1978
Urokinase*: 4400 IU/kg as a loading dose over 10 minutes, followed by 4400/kg/hr for 12–24 hours — approved in 1978

*Urokinase is presently unavailable for clinical use.

pulmonary reperfusion (normalization of V/Q mismatch), improvement in right ventricular function and decreased mortality. However, there has been no randomized controlled trial that demonstrates a mortality benefit favoring thrombolytic therapy for PE. This fact, however, needs to be put in both historical and statistical context. The use of thrombolytic therapy for myocardial infarction goes back several decades. Early experience focused on demonstrating surrogate markers of mortality. Specifically, evidence of reperfusion, including improvement in coronary angiograms, left ventricular function, and constraint of infarct size served as early signs of efficacy until the large controlled trials were able to demonstrate survival benefit. The largest prospective, controlled PE thrombolysis trials (24, 30) do not have sufficient sample power to detect small but clinically relevant improvement in mortality. Early trials of PE thrombolysis (29, 30), though of historical interest, have limited relevance in the era of modern thrombolytic therapies, as our agents and our understanding of risk factors and management of complications have evolved. In the absence of sufficiently powered randomized controlled trials, discussions of thrombolysis for PE have focused on surrogate markers presumed to be important in determining mortality. Specifically, improvement in oxygen requirements, V/Q scans, pulmonary angiograms, pulmonary artery pressure, right ventricular function, and decreased recurrent PEs have served as markers of therapeutic "efficacy." A recent trial (33) evaluated 719 hemodynamically stable PE patients with right ventricular dysfunction and reported a 30-day mortality of 11.1% in the heparin group versus 4.7% in the thrombolytic group ($p < 0.018$). There was a PE recurrence rate of 7.7% versus 18.7% in favor of the thrombolytic group ($p < 0.001$). These benefits must be counterbalanced by the inherent risks of thrombolysis to determine the ultimate clinical "effectiveness."

Massive PE with cardiogenic shock and hypotension, as in the patient presented here, has a mortality approaching 100% (34). The risk-benefit ratio in this patient group clearly favors thrombolytic intervention. A study comparing heparin alone versus heparin plus thrombolysis with streptokinase in PE patients with cardiogenic shock clearly favored thrombolysis (34). In hemodynamically stable patients, the indications for thrombolysis are controversial. Italian investigators (35) reported the results of 36 patients with angiographically proven PE who

were randomized to receive either recombinant human-tissue-type plasminogen activator (rt-PA) or heparin alone. They document angiographic clot lysis and a decrease in pulmonary artery pressure, but obvious net clinical benefit. Goldhaber (36) demonstrated similar hemodynamic and angiographic improvement with a 57% increase in pulmonary perfusion and dramatic improvement in right ventricular function. This work motivated a relatively large, randomized, multicenter trial carried out at 13 American centers (24). This trial examined 101 hemodynamically stable patients who were randomized to receive rt-PA and heparin versus heparin alone. Baseline and follow-up echocardiograms were evaluated. No difference in mortality was noted. However, this study was only capable of demonstrating mortality benefits of greater than 15–20%; lesser reductions would not have been detected. Four-fifths of the enrolled patients were diagnosed by perfusion scans, one-fifth by angiography, dispelling the myth that angiograms are required before thrombolysis. Therapy with rt-PA followed by heparin provided striking improvement in right ventricular function and pulmonary perfusion compared with heparin alone (Table 4). With regard to right ventricular function, 39% of the rt-PA group improved and 2% worsened, compared to the heparin group, where only 17% improved and 17% worsened ($p < 0.005$). Notably, no clinical episodes of recurrent PE occurred among rt-PA patients, but there were five (two of them fatal) clinically suspected recurrent PEs within 14 days in the heparin alone group ($p < 0.06$). All five patients with recurrent PE had echocardiographic evidence of right ventricular hypokinesis. Goldhaber suggests that right ventricular hypokinesis predisposes to *in situ* thrombosis within the right ventricle, right atrium and caval system secondary to vascular congestion. Right ventricular hypokinesis may be a marker for larger peripheral clot burden, worse arterial oxygenation and a downward spiraling hemodynamic state. Whatever the mechanism, the finding of right ventricular hypokinesis clearly defines patients at high risk for clinical decline; these patients deserve consideration for thrombolytic therapy.

A Practical Approach

The figure outlines a diagnostic-therapeutic algorithm that is useful when considering an acutely ill patient with probable PE. Generally, confirmation of any diagnosis should

TABLE 4
Effects of TPA on Right Ventricular Function and Pulmonary Perfusion.

Right Ventricular Function	Worse	Improved	No Change
Heparin	17%*	17%*	66%
TPA	2%*	39%*	59%

Pulmonary Perfusion	Improved
Heparin	1.5%
TPA	14.6% **

(*p<0.005, **p<0.0001)

Data from Goldhaber SZ, Haire WD, Feldstein ML, et al., modified with permission (24).

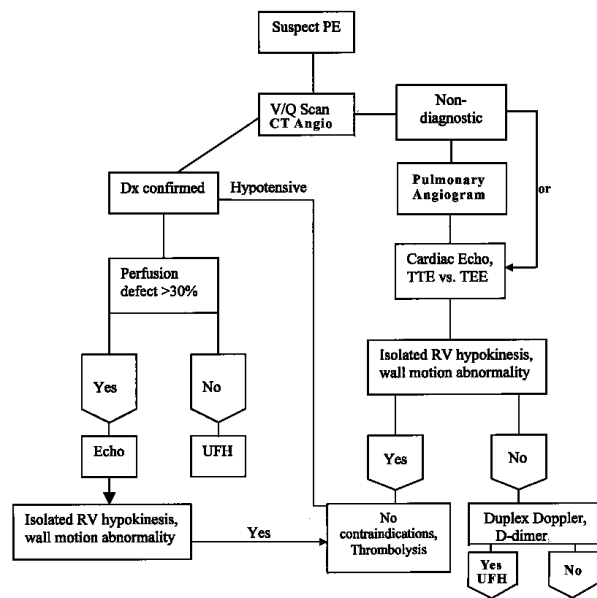


Figure. Strategy for evaluation of patients with pulmonary embolism for thrombolytic therapy. Echo = echocardiogram; RV = right ventricle; TTE = transthoracic echocardiogram; TEE = transesophageal echocardiogram; UFH = unfractionated heparin; V/Q scan = ventilation/perfusion scan (see text).

be encouraged. In hemodynamically stable patients, V/Q scanning can establish a diagnosis in about 25% of the patients who are ultimately confirmed to have a PE. CT angiography, which is less definitive with respect to quantifying the extent of any perfusion defect, also can be diagnostic in many patients. If the V/Q scan indicates a perfusion deficit greater than 30%, an echocardiogram should be done. A fraction of these patients will exhibit right ventricular dysfunction, and they will be at high risk for failure of standard heparin therapy. For this group of patients, the additional use of thrombolysis therapy should be considered.

Non-diagnostic V/Q scans remain problematic. Pulmonary angiography may be helpful in confirming the diagnosis in these patients. Stein et al. (37) maintain that invasive procedures such as pulmonary angiography in patients destined to receive thrombolytic therapy carry a significant risk of complications and that the risk of bleeding following thrombolytic therapy in patients with intermediate probability scans and high clinical suspicion (a high prevalence cohort) was less than the risks associated with pulmonary angiography. This study must be interpreted with caution, because it is a retrospective, population-based analysis of pooled data from PE and myocardial infarction patients. Finally, pulmonary angiography, though diagnostic, is difficult in “sick” patients and raises the complication rate of subsequent thrombolysis (37). In patients “too sick” to make a “definitive” diagnosis by pulmonary angiography, an echocardiogram may help to demonstrate acute right ventricular failure. With a high-risk patient for whom there is a strong clinical suspicion of PE, this documentation may be sufficient to proceed with thrombolytic therapy if there are no contraindications to thrombolysis. Contraindications are both absolute and relative. Evidence of active gastrointestinal bleeding, severe and uncontrolled hypertension, intracranial or intraspinal disease, recent (7–10 days) major surgery, and known bleeding diathesis are generally considered absolute contraindications. Other, more relative contraindications include a history of recent blunt or minor surgical trauma, advanced age, evidence for retinopathy, and drug allergy. However, our patient illustrates that even with those absolute “contraindications,” in special life-threatening situations thrombolysis is indicated. If the echocardiogram fails to show right ventricular hypokinesia, then a

duplex Doppler and D-dimer test may help to establish the diagnosis of PE and thereby support proceeding with heparin therapy. If these latter tests are non-diagnostic, then a decision to initiate anticoagulation must be made on clinical grounds.

Summary

Pulmonary embolism continues to result in excessive morbidity and mortality, particularly in the postoperative period. Identification of risk factors and appropriate DVT-PE prophylaxis based on risk stratification significantly reduce this morbidity and mortality. Life-threatening pulmonary embolism requires immediate recognition, heparin anticoagulation and consideration for thrombolytic therapy. Thrombolytic therapy offers hemodynamic improvement and improved gas exchange secondary to improvement in V/Q (reperfusion), and perhaps lowers the risk for recurrent pulmonary embolism and death. Definitive data demonstrating effectiveness awaits a large multicenter trial requiring more than 1,000 patients (to detect a 5% mortality benefit, assuming a 30% case fatality rate). Difficulty in rapidly and accurately attaining a diagnosis for acutely ill patients has limited the more general use of thrombolytic therapy. Two-dimensional echocardiograph offers accurate, valuable diagnostic information, identifies apparently hemodynamically stable patients at risk for recurrent pulmonary embolism and adverse clinical outcomes, and can be used to direct clinical decision making.

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