Treat the Clot!

Why you should be using direct thrombolysis and thrombectomy in treating pulmonary embolism.

BY RENAN UFLACKER, MD

Venous thromboembolism includes deep venous thrombosis and pulmonary embolism (PE), and it is the third most common cardiovascular disease and a leading cause of death in the US.[1,2] The true incidence of PE is not known, but it is estimated that there are more than 600,000 cases annually in the US alone.[1] There are several risk factors for development of PE.[3,4] The immediate mortality rate related to PE is less than 8% when the condition is recognized and treated correctly. Of the 70% of patients in whom the diagnosis is not made, the mortality rate approaches 30%.[1,5,6] If appropriate therapy is initiated, mortality may decrease, but the overall mortality associated with PE has not significantly changed in the past 30 years.[7] Rapid reestablishment of pulmonary arterial flow is paramount to overcome the acute hemodynamic dysfunction and reduce the high mortality rate.[8]

Pulmonary arteriography is still the gold standard in diagnosing pulmonary emboli, but several other imaging modalities and laboratory tests have been used to diag-

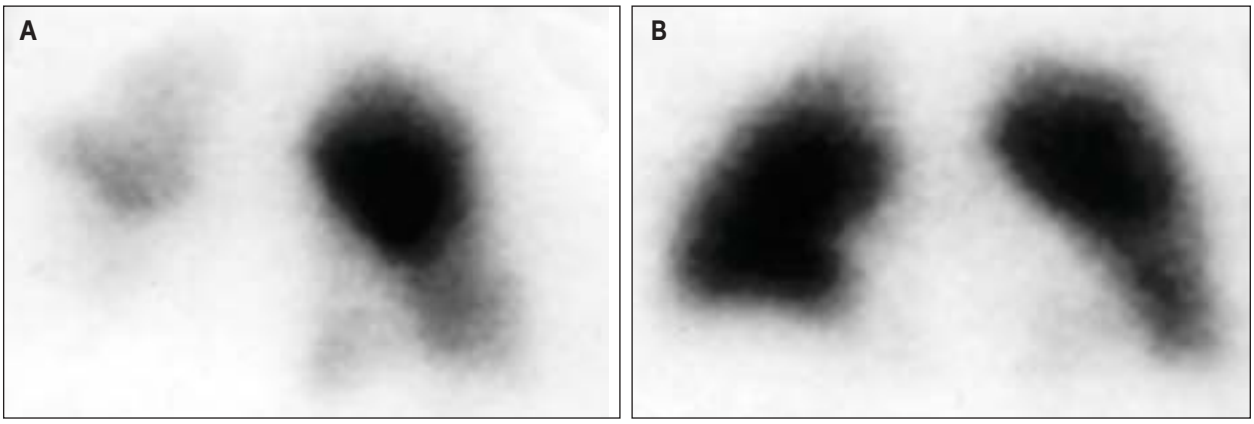

Figure 1. A female patient with massive pelvic vein thrombosis and pulmonary thromboembolism. A pulmonary perfusion scan showed massive occlusion of the right pulmonary artery flow and significant reduction of left lower lobe perfusion (A). Bilateral femoral vein infusion of urokinase at 100,000 IU/h for 12 hours cleared the pelvic veins (not shown). Follow-up lung perfusion scan showed remarkable improvement 24 hours after the infusion started (B).

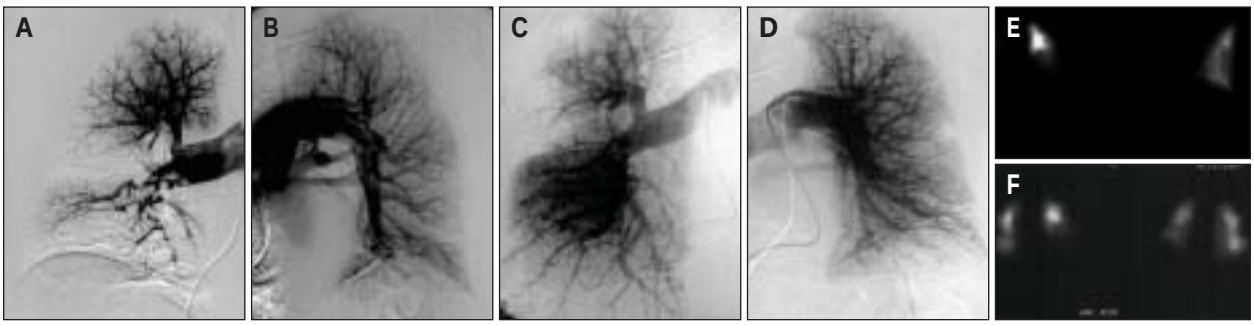

Figure 2. A patient with massive PE presented with syncope. A massive PE of the right pulmonary artery with a large thrombus occluded most of the artery, sparing just a portion of the right upper lobe (A). Left pulmonary angiogram showed large filling defect in the main left pulmonary artery (B). Catheter-directed thrombolytic therapy was performed. The catheter was wedged into the main thrombus in the right pulmonary artery and urokinase was started at 100,000 IU/h for 36 hours, with alternating catheterization of the left pulmonary artery for 12 hours. Posttreatment pulmonary angiography showed significant improvement of the pulmonary artery circulation in both lungs (C, D). The patient experienced dramatic recovery of the symptoms and reduction of pulmonary artery pressures. Pre- and posttreatment lung perfusion scans showed marked improvement of right lung perfusion (E, F). Note some improvement on the left lower lobe.

nose PE, including ventilation perfusion lung scanning, D-dimer, transthoracic and transesophageal echocardiography, magnetic resonance angiography, and contrast-enhanced, fast multislice spiral CT.[3,9] However, no single noninvasive test for PE is both sensitive and specific. Some tests are good for "ruling in" PE (eg, helical CT),[10,11] and some are good for "ruling out" PE (eg, D-dimer); others may able to do both but are often inconclusive (eg, V/Q lung scanning). Choosing which initial diagnostic test to use should take into account clinical assessment of the probability of PE and the patient characteristics that may influence test accuracy.[9] Cardiac Troponin T (cTnT) monitoring identifies the high-risk group of normotensive patients with acute severe PE.[12] A persistent increased cTnT level (>0.01 ng/mL) in patients with PE predicts a significant risk of a complicated clinical course and fatal outcome requiring a more aggressive treatment.

Traditional therapeutic options are anticoagulation, systemic thrombolysis, and surgical thrombectomy. More recently, multiple minimally invasive, but aggressive, procedures were introduced, which included catheter-directed thrombolysis, percutaneous embolectomy and embolus fragmentation techniques, pulmonary artery stent placement, or association of two or more of these techniques.[2,13-15] Successful management of acute massive PE requires prompt risk stratification and decisive, early intervention (Table 1). At least one of the described criteria must be present to justify more aggressive treatment.[14,16]

Despite the lack of information available, it may be appropriate to review the current techniques, protocols, and devices for the interventional management of massive PE, with emphasis on the percutaneous techniques.

ANTICOAGULATION

Initial intravenous administration of heparin is the therapy of choice to treat all forms of pulmonary thromboembolism. Heparin binds to and accelerates the activity of antithrombin III, prevents additional thrombus formation, and permits endogenous fibrinolytic mechanisms to lyse the clot that has already formed.

Heparin therapy, therefore, is directed more to the

TABLE 1. RISK STRATIFICATION AND INDICATIONS FOR AGGRESSIVE INTERVENTION TO TREAT MASSIVE PULMONARY EMBOLISM

Note. At least one of the following criteria must be present:

1. Arterial hypotension (<90 mm Hg systolic or drop of >40 mm Hg)
2. Cardiogenic shock with peripheral hypoperfusion and hypoxia
3. Circulatory collapse with need for cardiopulmonary resuscitation
4. Echocardiographic findings indicating right ventricular afterload stress and/or pulmonary hypertension
5. Diagnosis of precapillary pulmonary hypertension (mean PAP >20 mm Hg in presence of normal PAP occlusion pressures)
6. Widened arterial-alveolar O_2 gradient, >50 mm Hg
7. Clinically severe PE with a contraindication to anticoagulation or thrombolytic therapy.

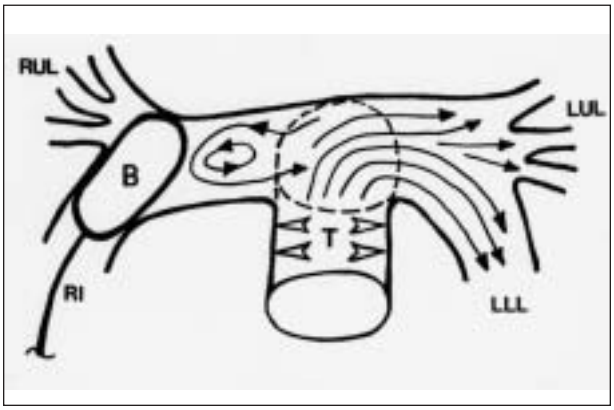

Figure 3. A schematic drawing of the flow model, showing vortex formation immediately proximal to the level of obstruction. Note that most of the fluid is washed into the nonoccluded left pulmonary artery and the vortex close to the occlusion, with only minimal flow of fluid making evanescent contact with an occluding embolus (B). RUL=right upper lobe, LUL=left upper lobe, LLL=left lower lobe, RI=right intermediate artery, T=pulmonary artery trunk, B=balloon.

source of the embolism rather than to treatment of the embolus located into the pulmonary artery. If the patient survives the initial PE episode and if no treatment is initiated, there is an 18% to 30% chance of recurrent lethal PE.[1,2,17-19]

In a 1960s landmark study comparing heparin versus placebo, Barritt and Jordan showed that none of 16 patients had recurrent PE (one associated death), whereas 52% of 19 patients receiving placebo had recurrent PE (five deaths).[6] In PE, an initial large IV heparin bolus of 10,000 to 20,000 units is recommended, followed by a more "standard" regimen of IV heparin at 1,000 units per hour, 2 to 4 hours after the bolus.[17] More recent evidence suggests that bleeding complications can be reduced with the use of low-molecular-weight heparin.[20-25]

Full anticoagulant protection with heparin should be maintained for 7 to 10 days. Oral anticoagulation should be started 3 or 4 days before the heparin is discontinued to allow a smooth transition between the two agents. Oral anticoagulants (warfarin 7.5 to 10 mg/day, or lower doses of 2 to 5 mg/day in smaller patients) are typically used for 3 to 6 months after the initial episode of PE, after heparin treatment, targeting an international normalized ratio (INR) range of 2 to 3. A recent publication by Ridker et al demonstrated that low-intensity warfarin prophylaxis, with a targeted INR of 1.5 to 2, is superior to placebo in preventing recurrent venous thromboembolism and effective for patients requiring more than 3 months of anticoagulation therapy.[26]

SYSTEMIC THROMBOLYSIS

Because anticoagulant therapy does not treat the pulmonary embolus itself, several trials to lyse clots with IV infusion of thrombolytic agents have been attempted[28,29] and showed a more rapid lysis of PE and reduction in pulmonary hypertension with improvement in perfusion lung scans when compared with heparin alone (Figure 1). Whether these advantages result in an improved clinical outcome and outweigh the increased risk of bleeding complications is still unknown. More recent nonrandomized studies showed improvement of 1-year survival and pulmonary hemodynamics[27] in patients treated with thrombolytics. A larger multicenter registry designed to investigate current management strategies in patients with major but hemodynamically stable PE, compared thrombolytic treatment (using rt-PA, streptokinase, and urokinase) with heparin anticoagulation, showed reduced mortality (4.7% vs 11.1%), reduced recurrence of PE (7.7% vs 18.7%; *P*=.016), but a higher incidence of major bleeding complications (21.9% vs 7.8%).[15] A more recent study[28] presented a meta-analysis of 11 randomized and nonrandomized studies comparing thrombolysis and heparin, which showed a risk reduction of 41% and 40% in favor of thrombolysis for death and recurrence, respectively. There was a major bleeding rate of 12.9% in patients receiving thrombolysis and 8.6% in patients receiving heparin.[28]

Proposed thrombolytic regimes for PE are:[29-31]

• Streptokinase: 250,000 IU as a loading dose over 30 min-

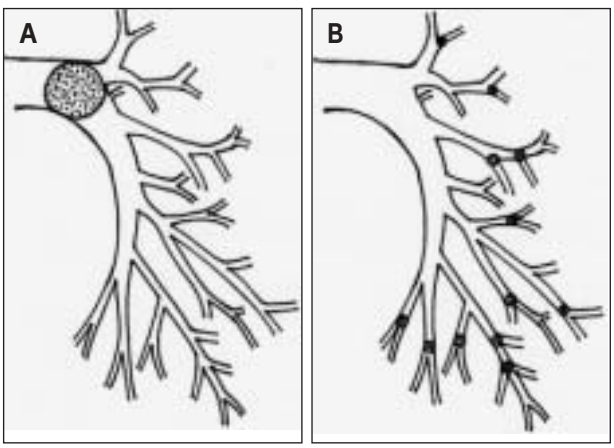

Figure 4. A schematic drawing demonstrating the effect of mechanical fragmentation of a total occlusive central thrombus in the pulmonary artery before (A) and after mechanical fragmentation and dispersion of the smaller clots into the peripheral branches of the pulmonary artery (B). Fragmentation and distal dispersion is likely to reduce pulmonary artery pressure and increase total pulmonary perfusion. Note that a number of peripheral branches of the pulmonary artery are open after fragmentation of the thrombus.

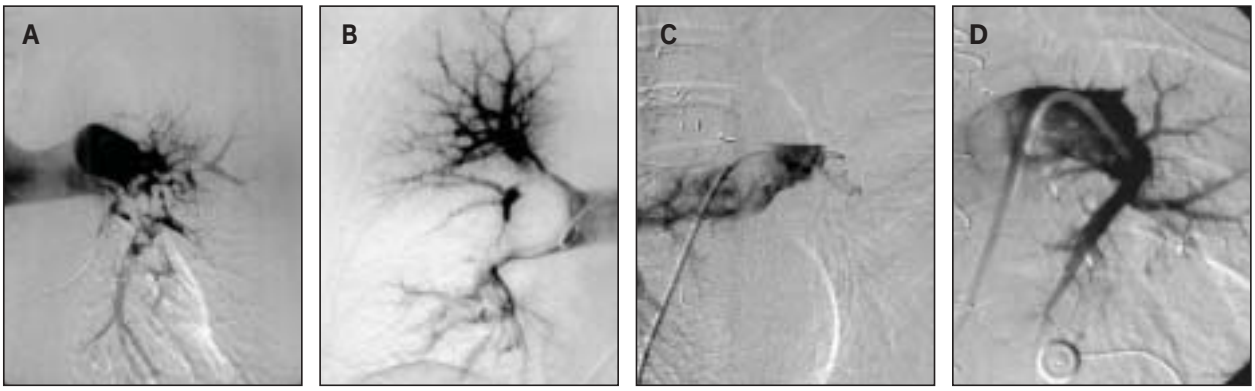

Figure 5. A type I pulmonary artery embolism showing a fragmented, recently embolized clot within the left pulmonary artery (A). A type II pulmonary artery embolism showing a large, recently embolized nonfragmented clot causing massive occlusion of the right pulmonary artery (B). A type III pulmonary artery embolism showing an old, organized clot within the left pulmonary artery, not responding to thrombolytic therapy (C) and barely responding to aggressive mechanical thrombectomy (D).

utes followed by 100,000 IU/h.[23]
- Urokinase: 2,000 IU/lb loading dose over 10 minutes followed by 2,000 IU/lb/h for 12 to 24 hours.[23]
- rt-PA: 100-mg continuous peripheral IV infusion over 2 hours or 50 mg/2 h plus an additional 40 mg/4 h if necessary[34] or 100 mg IV over 7 hours.[32]
- Heparin: 5,000 IU bolus followed by 1,000 IU/h (in association with the previously mentioned regimens), or weight-based heparin dosing nomogram, heparin 100 IU/kg/h.[33]

CATHETER-DIRECTED THROMBOLYSIS

Catheter-directed thrombolytic therapy with intrapulmonary artery infusion of thrombolytic drugs is an alternative technique advocated by many investigators,[34-36] and is intended to accelerate clot lyses and achieve more rapid reperfusion of the pulmonary circulation. The technique requires positioning of the catheter via femoral access wedged within the pulmonary artery clot, with injection of a bolus of thrombolytic drug followed by continuous infusion for 12 to 24 hours (Figure 2). Systemic heparinization is also used in association with thrombolytic therapy. In 1988, Verstraete et al[32] published the results of a multicenter, comparative study between peripheral IV and intrapulmonary treatment of acute massive PE with rt-PA (100 mg over a 7-hour period), and indicated that the intrapulmonary infusion of rt-PA does not offer significant benefit over the IV route. It also suggested that a prolonged infusion of rt-PA over 7 hours is superior to a single infusion of 50 mg over a 2-hour period. However, more recent evidence suggests that the systemic infusion of thrombolytics does not produce significant lyses due to poor contact of the drug with the clot in the occluded branch of the pulmonary artery (Figure 3).[37]

Proposed catheter-directed intrapulmonary thrombolytic regimens for PE are:[32,34-39]
- Urokinase: Infusion of 250,000 IU/h mixed with 2,000 IU of heparin over 2 hours followed by an infusion of 100,000 IU/h of urokinase for 12 to 24 hours.
- rt-PA: Bolus of 10 mg followed by 20 mg/h over 2 hours (total of 50 mg), or 100 mg over 7 hours, or a bolus of 20 mg followed by mechanical fragmentation and 80 mg over a period of 2 hours (total of 100 mg).[12]
- Heparin: Infusion of 1,000 IU/h keeping the PTT at 1.5 to 2.5 times the upper normal limits.

PERCUTANEOUS EMBOLECTOMY, CATHETER FRAGMENTATION, AND THROMBECTOMY

Frequently, the comorbid conditions that make patients poor thrombolysis candidates may also make them unsuitable for an open surgical approach.[40] Fortunately, when thrombolytic therapy fails or is contraindicated, the nonsurgical, less-invasive option available for this group of patients with massive PE is percutaneous embolectomy and thrombectomy using some of the current thrombectomy mechanical devices. Mechanisms of action and experimental and clinical outcomes have been extensively discussed in the literature.[41,42] Some of the techniques available do not totally eliminate the clots, but rather break down the thrombus in smaller fragments that will migrate peripherally in the pulmonary artery circulation, opening up the main pulmonary artery and improving perfusion (Figure 4).[43]

The rationale for using these devices in the pulmonary circulation is based on the rapid relief of central obstruction. The fact that the cross-sectional area of the distal arterioles is more than four times that of the central circulation and that the volume of the peripheral pulmonary circulatory bed is approximately two times that of the central pul-

monary arteries suggests that the redistribution of larger central clots into the peripheral pulmonary arteries may acutely improve cardiopulmonary hemodynamics, with significant increase in total pulmonary blood flow and right ventricular function.[38,44-46] The action of the thrombectomy devices may be facilitated in certain circumstances by softening of the thrombus mass by thrombolytic therapy, helping to speed up the debulking and fragmentation of the occlusive clots.[38] Fragmentation can, and should, be used as a complement to thrombolytic therapy. Fragmentation of the clot exposes fresh surfaces for endogenous urokinase and infused thrombolytic drugs to further break down the emboli (Table 2).[47]

It is common knowledge that the currently available thrombolytic therapy, mechanical thrombectomy, and fragmentation devices are more useful and successful when dealing with fresher thrombus. Three weeks is, in general, the age limit of thrombus when considering the option of a mechanical or rheolytic thrombectomy device. Based on the history, angiographic findings, outcomes, and follow-up of patients undergoing pulmonary thrombectomy with the Helix Clot Buster Thrombectomy System, or ATD (ev3, Plymouth, MN), three groups of patients have been identified.[15] Type I patients, with fresh clots that have recently embolized, should respond well to mechanical thrombectomy with increased peripheral flow and oxygenation (Figure 5A). Type II patients, with old, more organized clots that have recently embolized, respond less effectively to thrombectomy, and although more residual clots are likely to remain, there is a good chance for improvement of pulmonary flow (Figure 5B). Type III patients, with a history of old, organized, chronic PE with recent worsening secondary to recurrent PE, do not respond well to the effects of mechanical thrombectomy (Figure 5C and D).

AngioJet

The AngioJet (Possis Medical, Minneapolis, MN) uses the Bernoulli principle to perform thrombectomy, but it is different in design from other devices. The AngioJet is a double-lumen system ranging in diameter from 4 F to 6 F. The smaller lumen is made of fine metal tubing that conducts the high-pressure, high-velocity stream of saline fluid. The metal tubing makes a circle (ring) at the tip of the end hole of the catheter, and the jet is oriented backward, in the direction of the main lumen of the catheter shaft, creating a low-pressure area promoting fragmentation and evacuation of the clots (Figure 6). The catheter can be advanced over the wire, allowing for precise placement in the desired vessel,[41,44] which is advantageous when used in the pulmonary circulation.

The treatment of massive PE is a potential application for this device, and it has been used successfully in an animal model and in a number of clinical cases, as recently reported in the literature,[48,49] including clots centrally located in the pulmonary artery. Koning et al reported improvement of the pulmonary pressure in one of two patients, but the procedures were long and large amounts of mixed saline and blood were retrieved, requiring interruption of the procedure.[48] As is the case with the other hydrodynamic systems, this device is likely to be more successful in patients

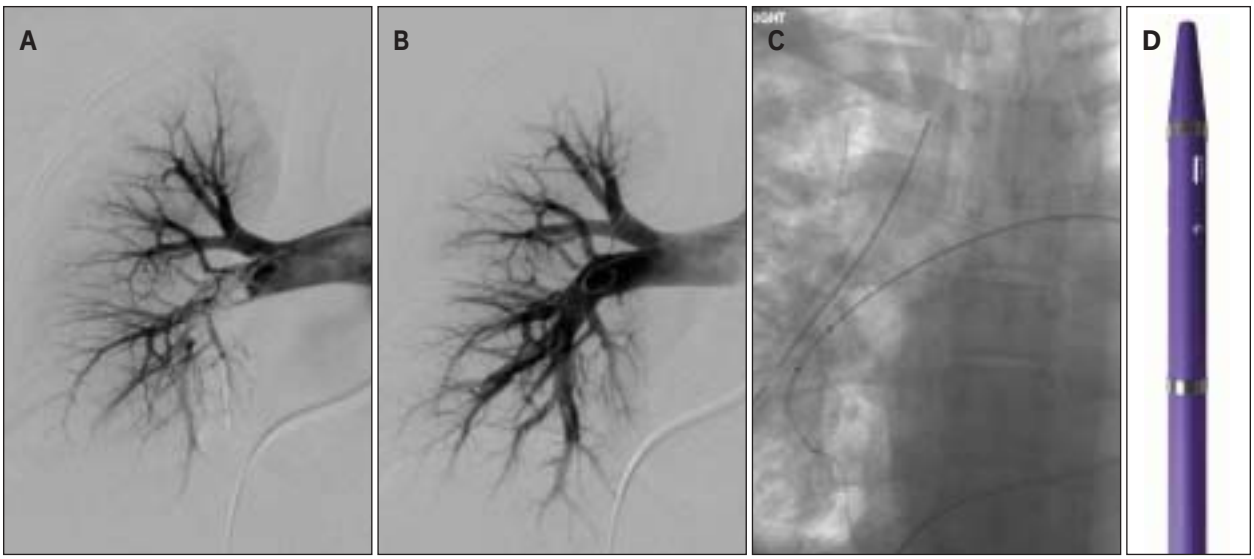

Figure 6. Severe PE in a female patient with a number of other clinical problems. Embolism of the right pulmonary artery (A). Pulmonary angiogram after AngioJet thrombectomy (B). The procedure was followed with urokinase infusion for approximately 24 hours. Use of the AngioJet device during the procedure within the right pulmonary artery (C). A newer version of the AngioJet device (D).

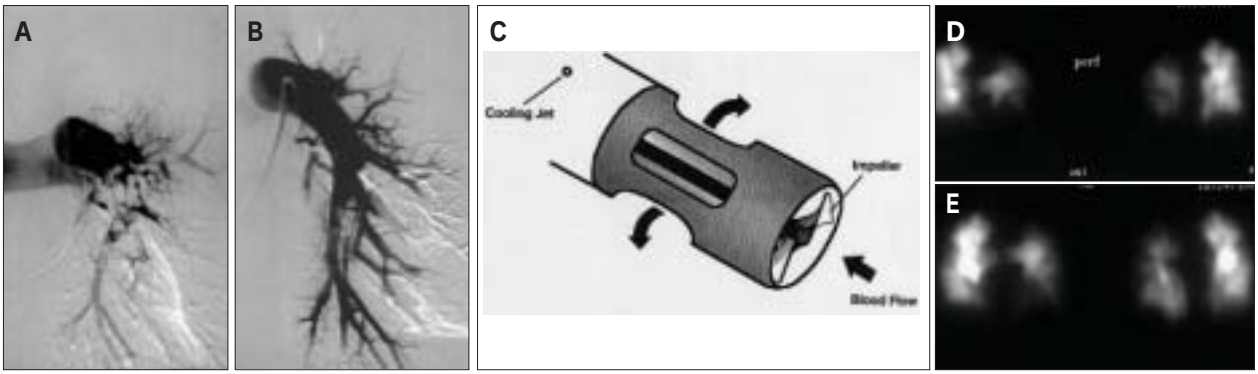

Figure 7. A pulmonary angiogram showed massive PE occluding the left main pulmonary artery. Mechanical thrombectomy was indicated in this case due to recent neurologic surgery. The Helix device was used through a 10-F guiding catheter (A). A postthrombectomy pulmonary arteriogram showed improved patency in the main pulmonary artery and improved lung perfusion (B). A schematic drawing of the distal tip of the 8-F Helix device (C). A recessed impeller is driven by a drive shaft at high speed within a 5-mm metal capsule. An initial positive perfusion scan shows bilateral PE that is massive on the left side (D). A follow-up perfusion scan shows improved perfusion in the left lung, mostly appreciated in the posterior view (E).

with fresher thrombus that is more peripherally located in the pulmonary circulation. The use of the AngioJet device in other vascular beds, such as the portal vein and for transjugular intrahepatic portosystemic (TIPS) shunt recanalization has been occasionally related to the occurrence of severe bradyarrhythmia, type III heart block, possibly related to adenosine liberated from hemolyzed red cells acting on the atrioventricular node.[50] Hyperkalemia causing ST segment elevations has also been described.[50] Personally, we have observed bradyarrhythmia in a neonate when using the AngioJet device in the inferior vena cava, but without ST segment elevation. To the best of our knowledge, this problem has not been reported during the use of the AngioJet in the pulmonary circulation, but based on personal communications, it may happen but has not been associated with long-term sequelae.

Helix

The Helix thrombectomy device is a 120-cm-long, 7- or 8-F reinforced polyurethane catheter with a distal metal tip (can) housing an impeller mounted on a drive shaft. The metal can has three side ports behind the impeller used for recirculation of the particles. The high speed of the impeller creates a vortex inside the vessel, pulling the clots toward the impeller, which recirculates and pulverizes the fresh clots, creating a fluid with smaller particles. The system is propelled by an air turbine that can generate up to 150,000 rpm at a pressure of 50 psi. Infusion of saline through the catheter lubricates the shaft and cools off the system. There is a distal side port in the polyurethane catheter that allows for contrast injection to improve visualization of the clots during thrombectomy.

The access into the pulmonary artery is achieved through a 10-F, 95-cm-long guiding catheter. The guiding catheter is advanced into the clot, and the Helix is introduced through the catheter and activated at full speed. The device should be used in a slow, back-and-forth motion. As the smaller clots migrate peripherally, the Helix and guiding catheter system is advanced to treat smaller clots. The multipurpose of the shape of the guiding catheter allows some degree of steerability. Pulmonary pressures should be measured before and after the thrombectomy. Initial experience with the Helix device showed clinical improvement in a limited group of patients, with reduction of the respiratory symptoms and improvement of hypotension (Figure 7).[15] This device is known to be more effective in fresher clots, and in its current design, presents significant difficulty in steerability, requiring a guiding catheter for positioning within the pulmonary artery. A 7-F, 27% more powerful device recently became available, but it had not been extensively tested in the pulmonary circulation at the time this article went to press.

PE MANAGEMENT OVERVIEW

Successful management of acute massive PE requires prompt risk stratification and decisive, early intervention (Table 1).[40] Typically, clinically undetected right heart failure worsens with time, causing dependence on pressors, and may lead to unremitting cardiogenic shock. If, at this point, thrombolysis or surgical embolectomy is considered for treatment, the likelihood of a good outcome is very slim.[40] Despite adequate anticoagulation, right ventricular dysfunction is still a severe life-threatening condition.

When high-risk PE patients are identified, adequate anticoagulation should be instituted, and the patients need to be screened for pharmacologic thrombolysis. Thrombolysis offers the chance of clot removal without the risks and mor-

TABLE 2. THROMBECTOMY AND EMBOLECTOMY DEVICES AND TREATMENT

DEVICES

- Thrombolizer and Modified Impeller Catheter, Angiocor, Buenos Aires, Argentina
- Arrow-Trerotola Percutaneous Thrombolytic Device, Arrow International, Reading, PA
- Greenfield Embolectomy Device, Boston Scientific Corporation, Natick, MA
- Oasis (S.E.T.) Catheter, Boston Scientific Corporation, Natick, MA
- Rotatable Pigtail Catheter, Cook Incorporated, Bloomington, IN
- Hydrolyser Hydrodynamic Thrombectomy Catheter, Cordis Endovascular, Miami, FL
- Amplatz Thrombectomy Device, ev3, Plymouth, MN
- AngioJet Rheolytic Thrombectomy Catheter, Possis Medical, Minneapolis, MN
- Rotarex Catheter, Straub Medical AG, Wangs, Switzerland
- Lang Percutaneous Pulmonary Thrombectomy Device, (custom-made device)

PROCEDURES

- Balloon Angioplasty for Clot Fragmentation
- Pulmonary Artery Stent Placement
- Catheter-Directed Thrombolysis

bidity of surgical embolectomy, however, thrombolytic therapy is not without risks and careful evaluation is necessary. There is increased risk of major bleeding, including the possibility of intracranial hemorrhage. However, thrombolytic therapy also offers the opportunity of dissolution of more peripheral clots in the pulmonary circulation. Verstraete et al compared the recanalization effects of intrapulmonary versus IV infusion of rt-PA and showed that transcatheter intrapulmonary delivery does not offer a significant benefit over the IV route. These findings resulted in a loss of interest in the technique.[32]

Despite this controversy regarding the efficacy of peripheral versus intrapulmonary thrombolytic therapy, recent experimental evidence *in vitro* and *in vivo* suggests that when there is a massive pulmonary occlusion by an embolus, there is formation of a vortex proximal to the occluding embolus, and any fluids infused proximal to the pulmonary artery occlusion will make only evanescent contact with the edge of the thrombus, and the fluid is washed into the nonoccluded ipsilateral and contralateral pulmonary arteries (Figure 3).[37] After embolus fragmentation, the infused fluid is carried completely into the formerly occluded artery. These flow studies possibly explain why thrombolytic agents administered via a catheter positioned adjacent to the embolus may have no more effect than systemically infused agents. The enhanced local effect, observed in other vascular territories, is precluded by the rapid washout into the nonoccluded pulmonary arteries followed by systemic dilution of the drug. Catheter fragmentation followed by intrapulmonary thrombolytic infusion is an adequate, and in our opinion, underused technique to achieve rapid resolution of the thrombus, improving hemodynamic conditions in most patients. Simple fragmentation with an angiographic catheter may be very beneficial. The use of larger angioplasty balloons for clot fragmentation is also a simple and immediately available technique to most budgets and angiographic laboratories.[38] As discussed previously, the association of fragmentation, mechanical thrombectomy, and thrombolytic therapy is desirable for potentially improving outcomes. In fact, it is likely that most of the devices will be more effective if thrombolytic therapy is used in association with the thrombectomy device. There are, however, situations that make patients unsuitable for thrombolysis, either systemic or intrapulmonary.

SUMMARY

For high-risk PE patients who are unsuitable for pharmacologic thrombolysis or open embolectomy, modern catheter thrombectomy technology may be employed. In acute massive PE, the main purpose of the treatment

should be the rapid restoration of the pulmonary blood flow to increase pulmonary perfusion, improve oxygenation, and reduce pulmonary pressure and cardiac failure. When thrombolysis is contraindicated or inadvisable, mechanical intervention using some of the available devices should be considered. The advent of more aggressive interventional treatments and techniques for the management of massive PE has a tremendous potential for saving lives. Nevertheless, the new technology that became available in the last few years requires the close participation of a skilled interventional radiologist as member of the interdisciplinary team in charge of identifying and treating those patients. The development and implementation of protocols for treating massive PE, tailored for each institution, is mandatory and may improve outcomes, saving patients' lives. However, no easy or final solution is currently available for the management of the difficult problems faced when treating patients with massive PE, and it is likely that the new devices and the available thrombolytic techniques will be used in association, rather than individually. ■

Renan Uflacker, MD, is Professor of Radiology and Director, Division of Vascular and Interventional Radiology, Department of Radiology, Medical University of South Carolina, Charleston, South Carolina. He has disclosed that he has no financial interest in any product or manufacturer mentioned herein. Dr. Uflacker may be reached at (843) 792-6160; uflacker@musc.edu.

1. Dalen JE, Alper JS. Natural history of pulmonary embolism. *Prog Cardiovasc Dis.* 1975;17:259-270.
2. Uflacker R. Interventional therapy for pulmonary embolism. *J Vasc Intervent Radiol.* 2001;12:147-164.
3. Brotman DJ, Jaffer A. "Coach class thrombosis": Is the risk real? What do we tell our patients? *Cleve Clin J Med.* 2002;69:832-837.
4. Lapostolle F, Surget V, Borron SW, et al. Severe pulmonary embolism associated with air travel. *N Engl J Med.* 2001;345:779-783.
5. Olin JW. Pulmonary embolism. *Rev Cardiovasc Med.* 2002;3:S68-S75.
6. Barrit DW, Jordan SE. Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. *Lancet.* 1960;1:1309-1312.
7. Elliot CG. Pulmonary physiology during pulmonary embolism. *Chest.* 1992;101(suppl):1635-1715.
8. Lilienfeld DE, Chan E, Ehland J, et al. Mortality from pulmonary embolism. *Prog Cardiovasc Dis.* 1975;17:259-270.
9. Kearon C. Diagnosis of pulmonary embolism. *CMAJ.* 2003;168:183-194.
10. Mastora I, Remy-Jardin M, Masson P, et al. Severity of acute pulmonary embolism: evaluation of a new spiral CT angiographic score in correlation with echocardiographic data. *Eur J Radiol.* 2003;13:29-35.
11. Haage P, Piroth W, Krombach G, et al. Pulmonary embolism: comparison of angiography with spiral CT, MRA and real-time MR imaging. *Am J Respir Crit Care Med.* 2002;167:729-734.
12. Pruszczyk P, Bochowicz A, Torbicki A, et al. Cardiac troponin T monitoring identifies high-risk group of normotensive patients with acute pulmonary embolism. *Chest.* 2003;123:1947-1952.
13. De Gregorio MA, Gimeno MJ, Mainar A, et al. Mechanical and enzymatic thrombolysis for massive pulmonary embolism. *J Vasc Intervent Radiol.* 2002;13:163-169.
14. Konstantinides S, Geibel A, Olschewski M, et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: results of a multicenter registry. *Circulation.* 1997;96:882-888.
15. Uflacker R, Strange C, Vujic I. Massive pulmonary embolism: preliminary results of treatment with the Amplatz thrombectomy device. *J Vasc Intervent Radiol.* 1996;7:519-528.
16. Moser KM. Pulmonary embolism. In: Braunwald E. Fauci A, Kasper D, et al (eds). Harrison's Principles of Internal Medicine. McGraw-Hill, Inc., New York: 2002;1214-1220.
17. Jones TK, Barnes RW, Greenfield LJ. Greenfield vena cava filter: rationale and current indications. *Ann Thorac Surg.* 1986;42:S48-S55.
18. Carson JL, Kelley MA, Duff A, et al. The clinical course of pulmonary embolism. *N Engl J Med.* 1993;326:1240-1245.
19. Hull RD, Raskob GE, Hirsh J, et al. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal-vein thrombosis. *N Engl J Med.* 1986;315:1109-1114.
20. Aguilar D, Goldhager SZ. Clinical uses of low-molecular-weight heparins. *Chest.* 1999;115:1418-1423.
21. Quader MA, Stump LS, Sumpio BE. Low molecular weight heparins: current use and indications. *J Am Coll Surg.* 1998;187:641-658.
22. Howard PA. Dalteparin: a low-molecular-weight heparin. *Ann Pharmacoth.* 1997;31:192-203.
23. Samama MM, Cohen AT, Darmon J-Y, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med.* 1999;341:793-800.
24. Haas SK. Treatment of deep venous thrombosis and pulmonary embolism: current recommendations. *Med Clin N Am.* 1998;82:495-510.
25. Ranze O, Ranze P, Magnani HN, et al. Heparin-induced thrombocytopenia in paediatric patients- a review of the literature and a new case treated with danaparoid sodium. *Eur J Pediatr.* 1999;158:S130-S133.
26. Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med.* 2003;348:1425-1434.
27. Schwarz F, Stehr H, Zimmerman R, et al. Sustained improvement of pulmonary hemodynamics in patients at rest and during exercise after thrombolytic therapy of massive pulmonary embolism. *Circulation.* 1985;71:117-123.
28. Agnelli G, Becattini C, Kirschstein T. Thrombolysis vs heparin in the treatment of pulmonary embolism: a clinical outcome-based meta-analysis. *Arch Intern Med.* 2002;162:2537-2541.
29. 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;347:1143-1150.
30. Gunn NA, Tierney LM. Letter to the editor. *N Engl J Med.* 2002;348:357-358.
31. Goldhaber SZ. Thrombolytic therapy for pulmonary embolism. *Semin Vasc Surg.* 1992;5:69-75.
32. 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;77:353-360.
33. Raschke RA, Reilly BM, Guidry JR, et al. The weight-based heparin dosing nomogram compared with a "standard of care" nomogram: a randomized controlled trial. *Ann Intern Med.* 1993;119:874-881.
34. Molina HE, Hunter DW, Yedlick JW, et al. Thrombolytic therapy for post operative pulmonary embolism. *Am J Surg.* 1992;163:375-381.
35. Gonzales-Juanatey JR, Valdes L, Amaro A, et al. Treatment of massive pulmonary thromboembolism with low intrapulmonary dosages of urokinase: short term angiographic and hemodynamic evolution. *Chest.* 1992;102:341-346.
36. Vujic I, Young JWR, Gobien RP, et al. Massive pulmonary embolism treatment with full heparinization and topical low-dose streptokinase. *Radiology.* 1983;148:671-675.
37. Schmitz-Rode T, Kilbinger M, Günther RW. Simulated flow pattern in massive pulmonary embolism: significance for selective intrapulmonary thrombolysis. *Cardiosvasc Intervent Radiol.* 1998:21:199-204.
38. Fava M, Loyola S, Flores P, et al. Mechanical fragmentation and pharmacologic thrombolysis in massive pulmonary embolism. *J Vasc Intervent Radiol.* 1997;8:261-266.
39. Goldhaber SZ, Markis JE, Meyrovitz MF, et al. Acute pulmonary embolism treated with tissue plasminogen activator. *Lancet.* 1986;886-889.
40. Goldhaber SZ. Integration of catheter thrombectomy into our armamentarium to treat acute pulmonary embolism. *Chest.* 1998;114;1237-1238.
41. Sharafuddin MJA, Hicks ME. Current status of percutaneous mechanical thrombectomy. Part I. General principles. *J Vasc Intervent Radiol.* 1997;8:911-921.
42. Sharafuddin MIA, Hicks ME. Current status of percutaneous mechanical thrombectomy. Part II. Devices and mechanisms of action. *J Vasc Intervent Radiol.* 1998;9:15-31.
43. Brady AJ, Crake T, Oakley CM. Percutaneous catheter fragmentation and distal dispersion of proximal pulmonary embolus. *Lancet.* 1991;338:1186-1189.
44. Handa K, Sasaki Y, Kiyonaga A, et al. Acute pulmonary thromboembolism treated successfully by balloon angioplasty: a case report. *Angiology.* 1988;8:775-778.
45. Girard P. Catheter fragmentation of pulmonary emboli. *Chest.* 1999;115:1759.
46. Timsit JF, Reynaud P, Meyer G, et al. Pulmonary embolectomy by catheter device in massive pulmonary embolism. *Chest.* 1991;100:655-658.
47. Oakley CM. Conservative management of pulmonary embolism. *Br J Surg.* 1968;55:801-805.
48. Koning R, Cribier A, Gerber L, et al. A new treatment for severe pulmonary embolism. *Circulation.* 1997;96:2498-2500.
49. Voigtlander T, Rupprecht HJ, Nowak B, et al. Clinical application of a new rheolytic thrombectomy catheter system for massive pulmonary embolism. *Catheter Cardiovasc Intervent.* 1999;47:91-96.
50. Fontaine AB, Borsa JJ, Hoffer EK, et al: Type III heart block with peripheral use of the Angiojet thrombectomy system. *J Vasc Intervent Radiol.* 2001;12:1223-1225.