Pulmonary Embolism Treatment Strategies

Using risk stratification to determine which therapeutic intervention is right for your acute pulmonary embolism patient.

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Pulmonary embolism (PE) is a common but serious disease encountered in both inpatient and outpatient settings. Certain issues still remain controversial for the clinician concerning the diagnosis, risk assessment, and therapeutic decisions of PE, which must be made quickly. The reported mortality rate without treatment is approximately 30%, which is lowered to 4% to 8% when treated.[1-4] Nevertheless, the clinical severity of acute PE can be highly variable and requires careful evaluation on a case-by-case basis.

Although massive and mild PE presentations won't lead to extended discussions between clinicians in terms of the treatment strategy, the management of submassive PE, as well as cases with high clot burden but no demonstrable right ventricular (RV) failure, are topics debated daily in health care systems around the world. Moreover, local (catheter-based) interventions are still evolving in an attempt to limit the potential, although infrequent, deleterious consequences of systemic thrombolysis.

Once the diagnosis of PE is made, or if there is a high clinical suspicion, anticoagulation should be started if the bleeding risk is deemed low while further case analysis is underway.[1,4] Therapeutic anticoagulation with weight-based subcutaneous low-molecular-weight heparin or fondaparinux can be initiated in accordance with the patient's renal function.[1] Standard unfractionated heparin remains an option, and when bleeding risk is higher, it may be preferred based upon its short action and reversibility. In October 2012, oral rivaroxaban was also approved by the US Food and Drug Administration (FDA) for patients with acute deep venous thrombosis (DVT) and acute PE. This is the first oral agent to be approved in the US since warfarin was approved nearly 60 years ago.

RISK STRATIFICATION

A crucial issue in acute PE treatment is how to risk stratify patients (ie, how to translate the status of the RV and overall severity of the PE event into meaningful treatment decisions). Undoubtedly, RV status correlates directly with cardiogenic shock and mortality.[3-7] Accurate, detailed assessment of RV function has been problematic, and it is feasible that different measures of RV size or function are associated with different prognoses. Several tools have been proposed so far. One rapid technique is to simply measure the chamber proportions on computed tomography (CT); an RV/left ventricular (LV) ratio ≥ 1 suggests RV dysfunction.

However, echocardiography performed by an expert operator can provide more detailed information. A significantly enlarged and/or hypokinetic RV with an interventricular septum that compromises filling of the left ventricle, potentially leading to systemic hypotension, raises concern.[7]

More accessible markers of RV compromise are elevated levels of brain natriuretic peptide (BNP), pro-BNP, and cardiac troponins (both T and I).[8,9] A meta-analysis of 1,985 PE patients from 20 studies showed that any elevation of the troponin level (microinfarction) confers a fivefold increase in short-term mortality.[9] Troponin levels appear to predict outcomes not only for PE patients in shock but also for those who are hemodynamically stable at presentation.[9]

MASSIVE PE

In the setting of PE and hemodynamic instability, and in the absence of absolute contraindications, most clinicians will agree to initiate systemic thrombolytics.[1,7] Although physiologically attractive, and clinical experience has supported this approach, no clinical trial has

conclusively demonstrated that it improves mortality (with statistical significance) more than anticoagulation therapy alone.[1-4] Nevertheless, given the high mortality rate of this subgroup, a treatment arm not offering thrombolytics would not be considered ethical by most clinicians. Hence, the American College of Chest Physicians consensus (published in February 2012) states that "in patients with acute PE associated with hypotension (eg, systolic BP < 90 mm Hg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (grade 2C)."[1]

Numerous thrombolytic agents and regimens have been directly compared in randomized trials, but no superiority of any over the other has been established.[2,5,6] Recombinant tissue-type plasminogen activator (tPA, alteplase), streptokinase, and recombinant human urokinase are the best studied thrombolytic agents for the treatment of acute PE. Streptokinase is the least expensive but the most commonly associated with adverse effects, including allergic reactions and hypotension. Newer agents approved for acute coronary syndromes, such as tenecteplase and reteplase, have not been approved for use in patients with acute PE.[2,5,10]

The evidence suggests that shorter infusions (eg, ≤ 2 hours) achieve more rapid clot lysis and are associated with lower rates of bleeding than longer ones (eg, 12 hours).[1] Thus, tPA has been recommended as the preferred thrombolytic agent due to its short infusion time.[1,7] The FDA advises stopping anticoagulation during tPA infusion and restarting it after the infusion when the activated partial thromboplastin time is < 80 seconds. However, in many other countries, heparin infusion is continued during thrombolytic therapy.[7]

SUBMASSIVE PE

A more challenging dilemma lies with the patient who is hemodynamically stable but has abnormal RV function, and thus, is at high risk of deterioration, according to several studies. The decision of whether to proceed to systemic thrombolysis versus local interventions or simply anticoagulation must be carefully made at the bedside with assessment and consideration of clot burden (see *Indications and Contraindications for Thrombolysis* sidebar). This assessment would include vital signs, presence/degree of RV dysfunction, extent of emboli by CT or ventilation perfusion scan, biomarkers, oxygenation, and residual DVT.[7] In addition, potential contraindications to thrombolytics, associated comorbidities, center expertise, and patient preferences should be taken into consideration.

Konstantinides et al demonstrated that patients who received tPA were significantly less likely to deteriorate clinically than those who received placebo (11% vs 25%).[10] No mortality difference could be demonstrated, but there was a high rate of rescue thrombolysis in the placebo group.

The most feared complication is intracranial bleeding, although this seems rare when a careful risk assessment has been undertaken (similar to myocardial infarction). In the ICOPER registry, intracranial bleeding occurred in 3% of the 304 patients who received thrombolytic therapy compared with 0.3% in the placebo group, suggesting that the risk is not only increased

INDICATIONS AND CONTRAINDICATIONS FOR THROMBOLYSIS

Indications for Thrombolysis

Absolute

- Systemic hypotension (< 90 mm Hg systolic or decrease of > 40 mm Hg)[a]
- Circulatory collapse with need for cardiopulmonary resuscitation (ie, syncope)

Consideration

- RV dysfunction (echocardiography, biomarkers) alone or judged to have adverse prognosis
- High clot burden by CT angiography or ventilation perfusion scan
- Concomitant DVT

Contraindications to Thrombolysis

Absolute

- Previous intracranial hemorrhage
- Known structural intracranial cerebrovascular disease
- Malignant intracranial neoplasm
- Ischemic stroke within 3 months
- Suspected aortic dissection
- Active bleeding or bleeding diathesis
- Recent surgery in spinal canal or brain
- Recent head trauma

Relative

- Older than 75 years
- Recent but inactive bleeding
- Pregnancy
- Severe, uncontrolled hypertension

[a]*Persistent hypotension and concomitant evidence of decompensation should be considered. For example, a drop from a baseline of 98 mm Hg systolic to 88 mm Hg systolic in an otherwise stable patient with PE may not merit aggressive therapy.*

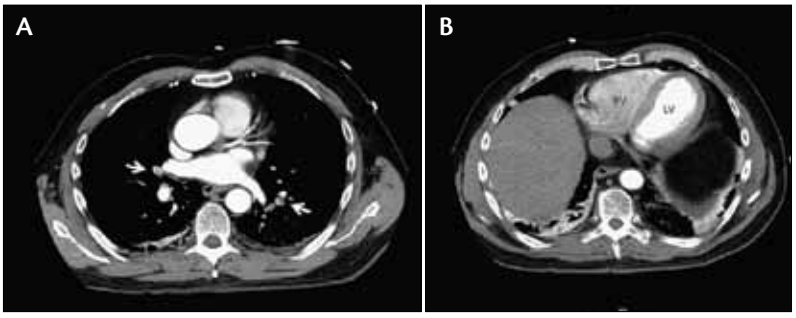

Figure 1. Bilateral PE predominantly affecting distal lobar vessels and segmental pulmonary arteries (A, arrows). The RV is in the upper limits of normal size, with no septal bowing (B). The LV is normal as confirmed on echocardiography. The blood pressure was normal. The BNP and troponin findings were negative, and the oxygen requirement was 4 L/min. The patient was successfully anticoagulated.

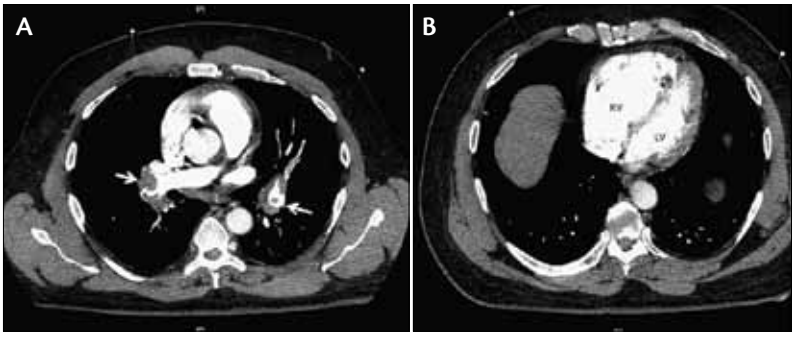

Figure 2. Extensive bilateral PE (A, arrows). Severely enlarged RV with septal bowing compromised the LV (B). The brain natriuretic peptide level was three times the upper limits of normal, and the troponin I was five times the upper limits of normal. The patient required 80% oxygen by facemask to keep the O_2 saturation above 90%. The patient's blood pressure was 100/52 mm Hg, although the heart rate was 130/min. Thrombolytic therapy (tPA) was given intravenously at 100 mg for this submassive PE with excellent results. There was no significant bleeding.

but also that the "real-life" risk may be higher than in randomized clinical trials.[3]

It is anticipated that more definitive evidence will be available after the conclusion of the PEITHO international multicenter study, which is comparing thrombolysis with tenecteplase plus anticoagulation versus anticoagulation alone in this subgroup of patients.[11] Many clinicians have concerns that aggressive approaches to acute PE are underutilized.[12,13] Risk stratification is crucial for decision making in acute PE (Figures 1 and 2), although more data for submassive PE are needed.

PULMONARY EMBOLECTOMY

Embolectomy approaches, via surgery or transcatheter procedures, still have a somewhat unclear role. According to the data from the Nationwide Inpatient Sample register from 1998 to 2008, 72,230 patients presented with unstable PE, and of these, only 1.2% underwent open pulmonary embolectomy, and 0.3% underwent catheter-tip embolectomy.[14] Nevertheless, with accumulating experience with newer catheter devices communicating favorable outcomes (albeit without randomized trial data) and the concerns of adverse effects of systemic thrombolysis, there has been more interest in these interventions.[15]

There are certain clinical settings in which the local management of thrombus presents as an appealing alternative: massive PE in patients with formal contraindications to thrombolytics, critical conditions that must be reversed immediately, less severe presentations with RV dysfunction, and as an escalation therapy when systemic thrombolysis has failed.

SURGICAL EMBOLECTOMY

Experience with surgical embolectomy showing high mortality rates (approximately 27%) has dampened enthusiasm for this approach.[14] However, more recently, some centers have liberalized their criteria for acute pulmonary embolectomy and have operated on patients with preserved systemic arterial pressure presenting with anatomically extensive PE and concomitant RV dysfunction.[16] A published series of 47 consecutive patients meeting such criteria who underwent surgical pulmonary embolectomy (requiring cardiopulmonary bypass but under normothermic conditions and avoiding cardioplegic arrest) showed a 96% survival rate at 27 months of follow-up.[16] This high survival rate (also shown in other modern series) was attributed to the multidisciplinary approach, rapid diagnosis (including risk stratification), and probably the most important factor, improved and immediate surgical technique.[16]

CATHETER-BASED TECHNIQUES

The modern catheter-based techniques include mechanical fragmentation and/or aspiration of emboli (including rheolytic thrombectomy) with or without intraembolic thrombolytic injection (exposing a greater

thrombus area surface to the drug's effect), as opposed to simply proximal drug infusion to the thrombus, which offered no benefit over systemic delivery.[15,17]

Although various catheter-based devices exist, only scant evidence-based literature is available for each of them, and the majority consists of observational studies. Early studies proved that a simple vacuum suction catheter technique could be effective, but it was a number of years before there was renewed interest in catheter-based techniques.[18] One of the most commonly used methods nowadays is the rotating pigtail fragmentation catheter, which usually needs adjunctive aspiration due to distal clot embolization.[17] Another technique utilizes the AngioJet rheolytic device (Bayer Radiology & Interventional, Indianola, PA), which provides mechanical thrombolysis and concomitant thrombolytic injection.[19,20] However, adverse events including hemolysis may occur. The use of ultrasound to enhance thrombolytic permeation of large emboli has been successfully utilized. The EkoSonic ultrasound-accelerated catheter (Ekos Corporation, Bothell, WA) is being studied in both retrospective nonrandomized and prospective randomized clinical trials to this end.[21,22]

A novel and promising approach is the AngioVac aspiration system (Vortex Medical, Inc., recently acquired by AngioDynamics, Latham, NY), which is composed of an extracorporeal bypass circuit that facilitates drainage, filtration, and reinfusion of blood cleared from unwanted clot material.[23] Already approved by the FDA, this technique appears to have promise as an aggressive technique to treat very large emboli, although few data have been published to date.

Data regarding the effectiveness of each therapy are limited. No system has yet been proven to be superior to the others. Therefore, whether surgical or catheter-based embolectomy is chosen depends upon the availability of resources and the institution's expertise.

INFERIOR VENA CAVA FILTER PLACEMENT

Despite of the almost complete lack of randomized controlled trials on acute PE, the use of inferior vena cava filters for classic indications is deeply entrenched in clinical practice. The option of filter retrieval (with safe and successful removal after at least 1 year) appears to have contributed to the increased frequency of their placement. In the PREPIC randomized trial, filter placement was evaluated as an adjunct to anticoagulant therapy in 400 patients with acute DVT who were deemed to be at high risk for acute PE.[24] After 8 years of follow-up, several conclusions could be reached: although filters did not affect total mortality (risk ratio, 0.95 at 8 years), the rate of recurrent PE (symptomatic plus asymptomatic) was reduced at 12 days (1.1% vs 4.8%; $P = .03$) and at 8 years (6.2% vs 15.1%; $P = .008$).[25] Nevertheless, filters increased DVT at 2 years (20.8% vs 11.6%; $P = .02$).

The American College of Chest Physicians and American Heart Association guidelines recommend inferior vena cava filter placement in patients with contraindications to anticoagulation, major bleeding complications during anticoagulation, and recurrent embolism while on therapeutic anticoagulation.[1,7] Filters are sometimes placed in cases of massive PE, when it is believed that additional emboli might be lethal, either with or without thrombolytic therapy; however, this indication is not based on prospective clinical trial data.

CONCLUSION

Over the past 2 decades, considerable progress in technology and clinical research methods have led to advances in the diagnosis, treatment, and prevention of acute venous thromboembolism. Published guidelines are useful but are limited by the existing evidence-based literature, so that controversies remain in regard to topics such as duration of anticoagulation, indications for placement and removal of inferior vena cava filters, and when and how to administer thrombolytic therapy.

This last question is a crucial one, particularly in the management of submassive PE. We recommend strong consideration for more aggressive therapy in certain hemodynamically stable patients, such as when RV size and function, biomarkers, clot burden (lungs and legs), and cardiovascular reserve suggest the potential for high mortality. There is no clear submassive PE subtype that indicates the clear need for therapy beyond anticoagulation, but the higher the clot burden, the more abnormal the RV and biomarkers, and the poorer the oxygenation, the lower the threshold should be for proceeding with an aggressive approach.

With regard to catheter-based embolectomy procedures, it is still impossible to clearly specify precise recommendations for use. Nor is it possible to determine the superiority of a particular technique due to the lack of comparative and randomized trial data. However, it appears reasonable to consider one of these procedures in patients with proven massive PE and hemodynamic instability, especially when thrombolytic therapy has failed or is contraindicated. The use of filters in massive PE and for certain submassive PE patients should be based on very sound clinical judgment. More clinical trials should still be conducted. ■

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1. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis. 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e419S-494S.
2. Thabut G, Thabut D, Myers RP, et al. Thrombolytic therapy of pulmonary embolism: a meta-analysis. J Am Coll Cardiol. 2002;40:1660-1667.
3. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;353:1386-1389.
4. Ruíz-Giménez N, Suárez C, González R, et al. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE registry. Thromb Haemost. 2008;100:26-31.
5. Dong B, Jirong Y, Liu G, et al. Thrombolytic therapy for pulmonary embolism. Cochrane Database Syst Rev. 2006;CD004437.
6. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation. 2004;110:744-749.
7. Jaff MR. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011;123:1788-1830.
8. Kostrubiec M, Pruszczyk P, Bochowicz A, et al. Biomarker-based risk assessment model in acute pulmonary embolism. Eur Heart. J 2005,26:2166-2172.
9. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation. 2007;116:427-433.
10. Konstantinides S, Tiede N, Geibel A, et al. Comparison of alteplase versus heparin for resolution of major pulmonary embolism. Am J Cardiol. 1998;82:966-970.
11. PEITHO Pulmonary Embolism Thrombolysis Study. Clinicaltrials.gov website. Available at: http://clinicaltrials.gov/ct2/show/NCT00639743. Accessed November 10, 2012.
12. Stein PD, Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused. Am J of Med. 2012;125:465-470.
13. Tapson VF. What will it take to initiate a move toward a more aggressive therapeutic approach to venous thromboembolism? Am J Med. 2008;121(11 suppl 1):S20-S27.
14. Kilic A, Shah AS, Conte JV, Yuh DD. Nationwide outcomes of surgical embolectomy for acute pulmonary embolism. J Thorac Cardiovasc Surg. In press.
15. Kuo WT, Gould MK, Louie JD. Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. J Vasc Interv Radiol. 2009;20:1431-1440.
16. Leacche M, Unic D, Goldhaber SZ, et al. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. J Thorac Cardiovasc Surg. 2005;129:1018-1023.
17. Tapson VF. Interventional therapies for venous thromboembolism: vena caval interruption, surgical embolectomy, and catheter-directed interventions. Clin Chest Med. 2010;31:771-781.
18. Greenfield LJ, Kimmell GO, McCurdy WC 3rd. Transvenous removal of pulmonary emboli by vacuum-cup catheter technique. J Surg Res. 1969;9:347-352.
19. Siablis D, Karnabatidis D, Katsanos K, et al. AngioJet rheolytic thrombectomy versus local intrapulmonary thrombolysis in massive pulmonary embolism: a retrospective data analysis. J Endovasc Ther. 2005;12,206-214.
20. Margheri M, Vittori G, Vecchio S, et al. Early and long-term clinical results of AngioJet rheolytic thrombectomy in patients with acute pulmonary embolism. Am J Cardiol. 2008;101:252-258.
21. Engelhardt TC, Taylor AJ, Simprini LA, Kucher N. Catheter-directed ultrasound-accelerated thrombolysis for the treatment of acute pulmonary embolism. Thromb Res. 2011;128:149-154.
22. A prospective, single-arm, multi-center trial of EkoSonic Endovascular System and Activase for treatment of acute pulmonary embolism (PE) (SEATTLE II). Clinicaltrials.gov website. Available at: http://www.clinicaltrials.gov/ct2/show/NCT01513759. Accessed November 10, 2012.
23. Todoran TM, Sobieszczyk PS, Levy MS, et al. Percutaneous extraction of right atrial mass using using the Angiovac aspiration system. J Vasc Interv Radiol. 2011;22:1345-1347.
24. Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis: Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. N Engl J Med. 1998;338:409-415.
25. Decousus H; PREPIC Study Group. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC randomized study. Circulation. 2005;112:416-422.