Endovascular Therapy for Acute Pulmonary Embolism

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ABSTRACT

Acute pulmonary embolism (PE) is the third most common cause of death among hospitalized patients. Treatment escalation beyond anticoagulation therapy is necessary in patients with massive PE (defined by hemodynamic shock) as well as in many patients with submassive PE (defined by right ventricular strain). The best current evidence suggests that modern catheter-directed therapy to achieve rapid central clot debulking should be considered as an early or first-line treatment option for patients with acute massive PE; and emerging evidence suggests a catheter-directed thrombolytic infusion should be considered as adjunctive therapy for many patients with acute submassive PE. This article reviews the current approach to endovascular therapy for acute PE in the context of appropriate diagnosis, risk stratification, and management of acute massive and acute submassive PE.

ABBREVIATIONS

ART = AngioJet Rheolytic Thrombectomy, BNP = B-type natriuretic peptide, CDT = catheter-directed therapy, DVT = deep vein thrombosis, ELISA = enzyme-linked immunosorbent assay, FDA = Food and Drug Administration, IV = intravenous, LV = left ventricular, PE = pulmonary embolism, RV = right ventricular, TPA = tissue plasminogen activator

Acute massive pulmonary embolism (PE), defined as hemodynamic shock from acute PE, is a common life-threatening condition and represents the most serious manifestation along the spectrum of venous thromboembolic disease. In the United States, an estimated 530,000 cases of symptomatic PE occur annually (1); and approximately 300,000 people die every year from acute PE (2). The mortality rate can exceed 58% in patients with acute PE presenting with hemodynamic shock (3), and most of these deaths occur within 1 hour of presentation (4). Indeed, acute PE is believed to be the third most common cause of death among hospitalized patients (5), and, with an aging population, the number of people with PE is expected to increase. For these reasons, the United States Surgeon General issued a Call to Action in 2008 recognizing venous thromboembolism as a major public health problem (6). The present article reviews clinical PE assessment and the rationale for performing catheter-directed therapy (CDT) as life-saving treatment for patients with massive PE and as adjunctive thrombolytic treatment for patients with critical right heart strain from submassive PE.

PATHOPHYSIOLOGY OF ACUTE PULMONARY EMBOLISM

To identify appropriate candidates for endovascular treatment, the interventionalist must be familiar with the clinical diagnosis of acute PE and understand the underlying pathophysiology of acute PE. Life-threatening acute PE results whenever the combination of embolism size and underlying cardiopulmonary status interact to produce hemodynamic instability (4). The pathophysiology of PE consists of direct physical obstruction of the pulmonary arteries, hypoxemic vasoconstriction, and release of potent pulmonary arterial vasoconstrictors, which further increase pulmonary vascular resistance and right ventricular (RV) afterload. Acute RV pressure overload may result in RV hypokinesis and dilation, tricuspid regurgitation, and ultimately, RV failure. RV pressure overload may also result in increased wall stress and ischemia by increasing myocardial oxygen demand while simultaneously limiting its supply. Ultimately, cardiac failure from acute PE results from a combination of the increased wall stress and cardiac ischemia that compromise RV function and impair left ventricular (LV) output, resulting in life-threatening hemodynamic shock (4) (Fig 1)

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W.T.K. is a paid consultant for, and serves on the advisory board of, Veniti Medical (St. Louis, Missouri), which is unrelated to the present research.

Figure 2 and Table 2 are available online at www.jvir.org.

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The presence of submassive PE, but it is not sensitive stratification in patients with established PE to help deter-
elevated troponin level is most commonly used in risk
strain causing leakage of enzyme from RV myocytes. An
detectable within the bloodstream when there is enough RV
clot burden is significant enough to overwhelm the patient’s
underlying cardiopulmonary reserve. The enzyme becomes

(7). Depending on the underlying cardiopulmonary reserve,
the condition of patients with acute PE may deteriorate over
the course of several hours to days, and they may develop
systemic arterial hypotension, cardiogenic shock, and cardiac
arrest. Because of the risk of sudden death, these critically ill
patients should be quickly identified as candidates for rapid
endovascular treatment as a life-saving procedure.

**CLINICAL PRESENTATION OF ACUTE PULMONARY EMBOLISM**

Patients with acute PE often present with dyspnea or chest
pain, which may be sudden in onset or evolve over a period
days to weeks. If pulmonary infarction occurs, patients may
also experience pleuritic chest pain with hemoptysis.
Additionally, there are many nonspecific signs and symp-
toms including tachypnea, tachycardia, palpitations, light-
headedness, fever, cough, wheezing, and rales. These find-
ings may or may not be associated with symptoms of acute
deep vein thrombosis (DVT), and the amount of peripheral
clot burden may evolve silently and then present as symp-
tomatic or even fatal PE. The possibility of massive PE
should be considered in patients who have a sudden onset
of near-syncope or syncope, hypotension, extreme hypox-
emia, electromechanical dissociation, or cardiac arrest (2).

Some biomarkers may offer useful clinical information.
Cardiac troponin levels may be elevated, particularly
in patients with acute massive or submassive PE in whom
clot burden is significant enough to overwhelm the patient’s
underlying cardiopulmonary reserve. The enzyme becomes
detectable within the bloodstream when there is enough RV
strain causing leakage of enzyme from RV myocytes. An
elevated troponin level is most commonly used in risk
stratification in patients with established PE to help deter-
mine the presence of submassive PE, but it is not sensitive

as a diagnostic tool when used alone (2). Elevations in
troponin can help clinicians suspect significant heart strain
and obtain necessary confirmatory imaging such as echo-
cardiography to specifically evaluate the degree of right
heart dysfunction. Elevations in plasma B-type natriuretic
peptide (BNP; formerly known as brain natriuretic peptide)
have been also been described in patients who have RV
dysfunction from acute PE; however, even though plasma
levels of BNP increase with ventricular stretching and may
suggest acute PE, these levels may also be elevated in
patients with congestive heart failure or various other con-
ditions that cause pulmonary hypertension (8). The d-dimer
test measures plasma levels of a specific derivative of
cross-linked fibrin to indicate possible presence of DVT
and/or PE. Although the enzyme-linked immunosorbent
assay (ELISA)–based d-dimer tests have superior sensitivity
(96%–98%), they must be interpreted together with
clinical presentation because the test alone is nonspecific
and may show a positive result in patients with cancer,
infection, injury, and underlying inflammatory conditions.
When an ELISA-based d-dimer test has negative findings in
patients with a low or moderate pretest probability, the
likelihood of DVT and PE is low, which precludes specific
imaging studies. However, in patients with a high pretest
probability for acute PE, imaging should be performed
instead of a screening d-dimer test (2).

**DIAGNOSTIC IMAGING OF ACUTE PULMONARY EMBOLISM**

Pulmonary angiography was once considered the gold stan-
dard for the diagnosis of PE, but it has largely been replaced
by the wide availability of cross-sectional imaging. Histori-
cally, many types of imaging studies have been used in diag-
nosing acute PE including ventilation/perfusion scanning,
magnetic resonance angiography, and computed tomographic
(CT) angiography. CT angiography is the preferred modality
and has proven to be advantageous because of its wide avail-
ability, superior speed, characterization of nonvascular struc-
tures, and detection of venous thrombosis. CT angiography
has the greatest sensitivity and specificity for detecting emboli
in the main, lobar, or segmental pulmonary arteries. System-
atic reviews and prospective randomized trials suggest that
outpatients with suspected PE and negative CT angiographic
studies have excellent outcomes without therapy (9).

If a patient has acute or chronic renal insufficiency and
contrast agent administration is undesirable, echocardiog-
raphy may be used to evaluate for right heart dysfunction as
an indication for underlying acute PE. The echocardiogram
can be obtained at bedside, and the study may reveal
findings that strongly support hemodynamically significant
PE (10), offering the potential to guide treatment escalation
to thrombolytic or endovascular therapy. Large emboli
moving from the heart to the lungs are occasionally con-
formed with this technique. In addition, intravascular ultra-
sonography (US) has also been used at the bedside to visualize central pulmonary emboli (11).

MEDICAL TREATMENT OF ACUTE MASSIVE PULMONARY EMBOLISM

Acute PE causing hemodynamic shock and instability is termed massive and requires prompt treatment. Among patients with acute PE, the diagnosis of massive PE hinges on the presence of systemic arterial hypotension (ie, systolic blood pressure < 90 mm Hg); therefore, anatomically large PE visualized on CT angiography in a hemodynamically stable patient is not considered massive PE and does not carry the same mortality risk. As the physiologic effect of massive PE is RV failure, which may compromise LV preload and lead to sudden death, saline fluid infusion for hypotension should be done with caution, and resuscitation with vasopressor therapy (eg, dopamine) should be initiated if hypotension persists. Oxygen supplementation, intubation, and mechanical ventilation are instituted as necessary for respiratory failure. Parenteral anticoagulation with low molecular weight heparin, the pentasaccharide fondaparinux, or standard unfractionated heparin should be initiated unless contraindicated. Although they are not thrombolytic, these drugs can allow the patient’s natural thrombolytic system to function unopposed, ultimately decreasing the thromboembolic burden (2). Anticoagulation clearly improves survival among patients with symptomatic PE, but the risk of recurrent, nonfatal venous thromboembolism is estimated to be 5%–10% during the first year after diagnosis (12). If the suspicion of massive PE is high, parenteral anticoagulation should be considered before imaging if the risk of bleeding is low (2). As patients with acute massive PE are in shock, treatment escalation beyond therapeutic anticoagulation is also required. From the interventionalist’s standpoint, the ability to initially anticoagulate a patient with PE not only influences the decision to offer inferior vena cava filtration in these patients, but it also helps to identify possible candidates who can tolerate escalation to systemic thrombolysis (ie, full-dose tissue plasminogen activator [TPA]) versus catheter-directed thrombolytic therapy (ie, no or low-dose local TPA). Current approved medical therapy for acute massive PE consists of systemic thrombolysis with 100 mg of TPA (alteplase; Genentech, South San Francisco, California) infused intravenously (IV) over a period of 2 hours (2), and the most widely accepted indication for thrombolytic therapy in these patients is cardiogenic shock from acute PE.

RATIONALE FOR ENDOVASCULAR TREATMENT OF MASSIVE PULMONARY EMBOLISM

Although IV TPA is indicated for treatment of acute massive PE, many patients cannot receive systemic thrombolysis due to contraindications, and even when patients with acute PE are prescreened for absolute contraindications, the rate of major hemorrhage from systemic thrombolytic administration is approximately 20%, including a 3%–5% risk of hemorrhagic stroke (3,13). Furthermore, there may be insufficient time in the acute setting to infuse full-dose IV thrombolytic agent. For these patients, CDT with no or low-dose local TPA should be considered if available (12,14), and the decision should be made as part of a multidisciplinary discussion involving the interventionalist and the patient’s medical team. Specific indications for the use of CDT for acute PE have been published (Table 1), and these should be used as guidelines to select candidates for endovascular therapy. The American College of Chest Physicians currently recommends that CDT be considered in selected highly compromised patients with PE who are unable to receive thrombolytic therapy because of bleeding risk (11), but global meta-analytic data have also demonstrated that CDT can be considered as a first-line treatment option in lieu of IV TPA (14).

In patients who are candidates for all treatment options, CDT can also be used in stepwise fashion to escalate treatment after failure of initial or ongoing systemic TPA (16). In some instances, it may be desirable to initiate IV TPA while simultaneously activating the interventional team to perform CDT. For example, in select patients who are in extremis from PE and deemed candidates for any thrombolytic treatment, some clinicians may desire to initiate urgent “medical” treatment in the form of IV thrombolytic agent as a bridge to escalation “surgical” treatment with CDT. When used in this fashion, IV TPA could also be less risky. For instance, the amount of IV thrombolytic agent could be reduced by at least 50% (from the standard 100-mg TPA dose infused over 2 hours) if catheter intervention is initiated promptly, allowing discontinuation of IV TPA within 30–60 minutes in patients who are candidates for systemic TPA (17).

In a meta-analysis of 594 patients with acute massive PE treated with modern CDT, clinical success was achieved in 86.5% (Fig 2; available online at www.jvir.org) (14), with success defined as the stabilization of hemodynamics,

Table 1. Indications for Aggressive Intervention to Treat Massive PE

<table>
<thead>
<tr>
<th>At least one of the following criteria must be present:</th>
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<tr>
<td>1. Arterial hypotension (&lt; 90 mm Hg systolic or decrease of &gt; 40 mm Hg)</td>
</tr>
<tr>
<td>2. Cardiogenic shock with peripheral hypoperfusion and hypoxia</td>
</tr>
<tr>
<td>3. Circulatory collapse with need for cardiopulmonary resuscitation (ie, syncope)</td>
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Note.—PE = pulmonary embolism. Reprinted with permission from reference 15.
Figure 3. Pulmonary angiography in a 57-year-old woman in shock from acute bilateral massive PE. Initial right (a) and left (b) pulmonary angiograms show near-complete obstruction. Pulmonary artery pressure was 73/18 mm Hg. Final right (c) and left (d) images after suction thrombectomy and catheter-directed thrombolytic agent injection into each main descending pulmonary artery. Pulmonary artery pressure was reduced to 36/16 mm Hg. (Images courtesy of Daniel Y. Sze.)
resolution of hypoxia, and survival to hospital discharge (14). In the same study, 96% of patients received CDT as the first adjunct to heparin with no previous systemic TPA infusion, and 33% of cases were initiated with mechanical treatment alone without local thrombolytic infusion (14). When injected locally, the required dose of TPA is likely to be lower compared with a full-dose systemic TPA infusion (16), and there is less risk for bleeding. Indeed, the rate of major complications from modern CDT has proven to be only 2.4% (14).

ENDOVASCULAR TECHNIQUES FOR MASSIVE PULMONARY EMBOLISM

Modern CDT for massive PE has been defined according to the following criteria: use of low-profile catheters and devices (≤ 10 F), catheter-directed mechanical fragmentation and/or aspiration of emboli with existing low-profile catheters, and intraclot thrombolytic agent injection if a local drug is infused (14). Therefore, a variety of devices can be used to treat PE successfully as long as they meet these criteria for modern CDT. Depending on anticipated bleeding risk, CDT may be performed with no or low-dose local TPA injection. The goal of all these techniques is rapid central clot debulking to relieve life-threatening heart strain and immediately improve pulmonary perfusion (Figs 3, 4). Catheter intervention is important not only for creating an immediate flow channel through the obstruction, but also for exposing a greater surface area of thrombus to the effects of locally infused thrombolytic drug. If local thrombolysis is performed without intraclot drug injection, and if the thrombolytic agent is instead infused proximal to the target embolus, as performed in older studies, there is little added benefit compared to systemic IV infusion (18).

Schmitz-Rode et al (19) demonstrated with in vitro and in vivo flow studies that an obstructing embolus causes proximal vortex formation that prevents a drug infused upstream from making rapid contact with the downstream embolus, and the eddy currents instead cause washout of thrombolytic agent into the nonobstructed pulmonary arteries (Fig 5). These flow studies emphasize the importance of direct intrathrombus injection as an adjunct to embolus fragmentation to achieve rapid and effective catheter-directed thrombolysis (19).

Several devices that meet the criteria for modern CDT have been used effectively (Table 2; available online at www.jvir.org) (14,16,20–53), but the most common technique currently used is rotating pigtail fragmentation (Fig 6) (23), which has been used alone or in combination with other methods in 70% of patients worldwide who have received CDT (14). Although pigtail clot fragmentation appears to effectively debulk proximal emboli, in some instances, it has resulted in distal embolization with pulmo-
nary artery pressure elevation, requiring adjunctive aspiration thrombectomy to complete treatment (54). Aspiration can be performed with virtually any end-hole catheter, such as an 8-F JR4 catheter (Cook, Bloomington, Indiana). Additional clot fragmentation may also be achieved with insertion and inflation of an angioplasty balloon sized smaller than the target arterial diameter. Thus, it is important to have adjunctive methods available to use in conjunction with pigtail rotation. The main advantage of the rotating pigtail is its wide availability and low cost relative to the mechanically driven thrombectomy devices.

The use of at least one mechanical device—the AngioJet Rheolytic Thrombectomy (ART) System (Possis, Minneapolis, Minnesota)—has been associated with relatively higher procedure-related complications, including bradycardia, heart block, hemoglobinuria, renal insufficiency, major hemoptysis, and procedure-related death. From an extensive meta-analysis (14), the highest complication rates occurred in the 68 patients who underwent CDT with the ART System, including 27 minor complications (40%) and 19 major complications (28%), with five procedure-related deaths (14). Interestingly, 76% of all major complications (19 of 25) recorded in the study were directly attributed to the ART System despite the fact that it was used in only a small percentage (11%) of the 594 patients evaluated (14). Conversely, the data indicate that most modern CDT (89%) has been performed worldwide with a high degree of safety and efficacy without the use of the ART System. Several deaths related to the ART System have been recorded in the US Food and Drug Administration FDA Manufacturer and User Facility Device Experience database (55). As a result, the FDA has issued a block-box warning on the device label (56). For all these reasons, unless the device can be improved, the ART System should probably by avoided as the initial mechanical option in future CDT protocols for acute massive PE (17,57).

The Helix Clot Buster (ev3, Plymouth, Minnesota), formerly known as the Amplatz thrombectomy device, is approved for use in dialysis grafts and native vessel dialysis fistulas, but it has been used on an off-label basis to treat acute PE. The device is a 75- or 120-cm-long, 7-F reinforced polyurethane catheter with a distal metal tip containing an impeller, which is connected to a drive shaft. The catheter is connected to an air-source turbine that generates as much as 140,000 rpm at pressures between 30 and 35 psi during operation (Fig 7). Although few data are available on the new version of this device for the treatment of PE, data from off-label use of the older 8-F version have been published in conjunction with the use of a 10-F guide catheter (20). The possibility of hemolytic complications exists, but, so far, the degree of such has not been shown to be clinically significant (20). Despite promising results for rapid thrombectomy, production of the Helix device is on hold by the manufacturer at the time of this writing, with possible plans for a product rerelease.

The search for an optimal thrombectomy catheter continues. A relatively new device, the Aspirex catheter (Straub, Wangs, Switzerland), has shown promising results for acute PE thrombectomy (21,58). The Aspirex catheter works on the principle of an Archimedes screw, which rotates within a catheter lumen. The metallic spiral is connected to an electric motor drive and control unit. Electronic activation of the spiral coil produces aspiration from the open catheter tip, transporting material down the catheter shaft and into a collecting system (Fig 8) (58). At the time of this writing, the Aspirex device is currently unavailable in the United States.

Figure 6. Photo diagram of the rotating pigtail method most commonly used to treat acute massive PE. (Reprinted with permission from Schmitz-Rode T, Janssens U, Duda SH, Erley CM, Günther RW. Massive pulmonary embolism: percutaneous emergency treatment by pigtail rotation catheter. J Am Coll Cardiol 2000; 36:375–380 [23].)

Figure 7. Photo of the Helix thrombectomy device. A recessed impeller is driven by a drive shaft at high speed (140,000 rpm), allowing thrombus to be aspirated through the tip, fragmented to smaller than 10 μm, and then expelled through the side ports (arrows). (Photograph of the Helix Clot Buster device reprinted with permission from ev3.)
States, but it is undergoing the evaluation process for FDA approval as a peripheral thrombectomy device. When it has been approved for use in the periphery, it will become available for off-label use to treat PE in the United States.

Regardless of the catheter-based technique initiated to treat acute PE, some believe hemodynamic improvement with resolution of shock should be used as guidance to conclude initial mechanical debulking regardless of angiographic results when treating massive PE (59). However, if the patient can tolerate additional thrombolysis, consideration can be made to treating the residual clot with a prolonged or overnight catheter-directed thrombolytic infusion, especially if there is residual elevation of PA pressures with right heart strain and the PE has been “downstaged” from massive to submassive PE (see below). Based on a global meta-analysis (14), an extended thrombolytic infusion was performed via catheter in approximately 60% of patients worldwide for treatment of residual submassive PE after initial CDT was used to resolve hemodynamic shock from acute massive PE. A possible advantage to performing a thorough thrombolytic infusion with further clot reduction and good angiographic result is the potential for reducing the risk of chronic PE formation and chronic pulmonary hypertension, as data on thrombolytic therapy have suggested it may reduce the likelihood of developing chronic thromboembolic pulmonary hypertension (see below).

**DIAGNOSIS OF SUBMASSIVE PULMONARY EMBOLISM AND RATIONALE FOR TREATMENT ESCALATION**

To identify potential candidates for endovascular treatment of less severe PE, the interventionalist must be familiar with the clinical diagnosis of submassive PE (ie, acute PE causing right heart strain without systemic hypotension) and the rationale for offering endovascular therapy. Although the diagnosis of submassive PE follows a similar workup to the evaluation of massive PE, these patients do not present with systemic arterial hypotension, and particular attention must be made to detecting the presence of right heart strain, which clinches the diagnosis of submassive PE. The identification of right heart strain allows risk stratification for possible treatment escalation beyond anticoagulation in normotensive patients with PE. Echocardiography is the best imaging study to detect RV dysfunction in the setting of acute PE. Characteristic echocardiographic findings in
Table 3. Risk Score for 30-Day Adverse Events in Acute PE

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered mental state*</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>10</td>
</tr>
<tr>
<td>Cardiogenic shock on admission</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>6</td>
</tr>
<tr>
<td>BNP (ng/L)</td>
<td></td>
</tr>
<tr>
<td>&lt; 100</td>
<td>0</td>
</tr>
<tr>
<td>100–249</td>
<td>1</td>
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<tr>
<td>250–499</td>
<td>2</td>
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<tr>
<td>500–999</td>
<td>4</td>
</tr>
<tr>
<td>≥ 1,000</td>
<td>8</td>
</tr>
<tr>
<td>RV/LV ratio on echocardiography</td>
<td></td>
</tr>
<tr>
<td>0.2–0.49</td>
<td>0</td>
</tr>
<tr>
<td>0.5–0.74</td>
<td>3</td>
</tr>
<tr>
<td>0.75–1.00</td>
<td>5</td>
</tr>
<tr>
<td>1.00–1.25</td>
<td>8</td>
</tr>
<tr>
<td>≥ 1.25</td>
<td>11</td>
</tr>
</tbody>
</table>

Note.—The calculated prognostic score can be used as a bedside tool. Range of total score, 0–41. The points assigned correspond to the following risk classes: 6 = class I, low risk; 7–17 = class II, intermediate risk; and 18 = class III, high risk. The classification correlates with the following 30-day risk of adverse events (death, secondary cardiogenic shock, recurrent venous thromboembolism): class I, low risk (predicted risk < 5% or score < 7); class II, intermediate risk (predicted risk 5%–30% or score 7–17); and class III, high risk (predicted risk 30% or score 18). BNP = B-type natriuretic peptide, LV = left ventricular, PE = pulmonary embolism, RV = right ventricular. Reprinted with permission from reference 62.

* Altered mental state was defined as disorientation, stupor, or coma.

patients with submassive PE include RV hypokinesis and dilation, interventricular septal flattening and paradoxical motion toward the LV, abnormal transmitral Doppler flow profile, tricuspid regurgitation, pulmonary hypertension as identified by a peak tricuspid regurgitant jet velocity greater than 2.6 m/s, and loss of inspiratory collapse of the inferior vena cava (60). An RV-to-LV end-diastolic diameter ratio of 0.9 or greater, assessed in the left parasternal long-axis view or the subcostal view, is an independent predictor of hospital mortality (61). A score based on clinical parameters, echocardiographic findings, and cardiac biomarkers can be used to stratify patients with acute PE according to risk of adverse outcomes (Table 3) (62). Detection of RV enlargement by chest CT angiography is especially convenient for diagnosis of submassive PE, because it uses data acquired during the initial diagnostic scan. Submassive PE can be diagnosed when RV enlargement on chest CT, defined by an RV-to-LV diameter ratio greater than 0.9, is observed (63); and RV enlargement on chest CT angiography also predicts increased 30-day mortality in patients with acute PE (63,64). Furthermore, even if shock and death do not ensue, survivors of acute submassive PE remain at risk for developing chronic PE and thromboembolic pulmonary hypertension (65).

Before cardiac imaging is obtained, patients with submassive PE can be potentially identified by the presence of RV dysfunction detected on physical examination, electrocardiography, and assessment of cardiac biomarkers. Physical examination findings of tachycardia, elevated jugular venous pressure, right parasternal heave, accentuated sound of pulmonic valve closure (P2), and hepatomegaly suggest RV dysfunction. The electrocardiogram can provide a rapid and inexpensive indicator of RV strain and adds incremental prognostic value to echocardiographic findings of RV dysfunction in patients with submassive PE (66). Incomplete or complete right bundle-branch block, T-wave inversions in leads V1 through V4, and the combination of an S wave in lead I, Q wave in lead III, and T-wave inversion in lead II (ie, S1Q3T3) signify RV strain. Elevations in cardiac biomarkers, including troponin, BNP, and heart-type fatty acid binding protein, are associated with RV dysfunction and can help noninvasively identify patients with potential submassive PE (7). Furthermore, these help clinicians determine the need for confirmatory imaging such as echocardiography to better evaluate the degree of right heart dysfunction. The identification of submassive PE for treatment escalation is important because these normotensive patients with PE still exhibit increased short-term mortality and risk of adverse outcomes when the degree of heart strain results in elevations in levels of cardiac troponins and BNP (67,68). Furthermore, patients with acute PE and normal heart-type fatty acid–binding protein levels have an excellent prognosis, whereas those with increased levels (ie, ≥ 6 ng/mL) have a higher rate of adverse events including hemodynamic collapse, respiratory failure, cardiac arrest, and death (69,70).

**TREATMENT OF SUBMASSIVE PULMONARY EMBOLISM**

The use of systemic thrombolysis in submassive PE—that is, PE causing RV strain and hypokinesis without systemic hypotension—is still debated (71–73). The optimal protocol for treatment of acute submassive PE is still in evolution, but a proposed algorithm for the management of submassive PE has been published describing treatment escalation beyond anticoagulation (Fig 9) (7). Although IV TPA infusion (100 mg administered over a 2-hour period) is FDA-approved for acute massive PE, it is still considered to constitute off-label use when infused to treat submassive PE (7). Nevertheless, there is growing evidence that aggressive treatment of submassive PE is beneficial. The Management Strategies and Prognosis of Pulmonary Embolism
Trial 3 (41) randomized 256 patients with submassive PE to receive 100 mg of IV TPA over a 2-hour period followed by unfractionated heparin infusion versus placebo plus heparin anticoagulation. Compared with heparin anticoagulation alone, thrombolysis resulted in a significant reduction in the primary study endpoint of in-hospital death or clinical deterioration that required escalation of therapy (defined as catecholamine infusion, rescue thrombolysis, mechanical ventilation, cardiopulmonary resuscitation, or emergency surgical embolectomy) (73). The difference was largely attributable to a higher frequency of open-label thrombolysis (breaking randomized trial protocol to offer medically necessary thrombolysis) in the setting of clinical deterioration as determined by the treating clinician (73).

In a prospective study of 200 patients with submassive PE (65), echocardiography was performed at the time of diagnosis and after 6 months to determine the frequency of pulmonary hypertension between two groups—one group treated with heparin and another group treated with IV TPA and heparin. The median decrease in pulmonary artery systolic pressure was only 2 mm Hg in patients treated with heparin alone, compared with 22 mm Hg in those treated with TPA plus heparin (65). At 6 months, the pulmonary artery systolic pressure increased in 27% of patients who had received heparin alone, and nearly half these patients were moderately symptomatic (65). These data suggest that thrombolytic therapy may reduce the likelihood of developing chronic thromboembolic pulmonary hypertension (65).

However, the perpetual problem with systemic TPA infusion is the risk of bleeding, and it is estimated that half of all patients with acute PE have contraindications to systemic thrombolysis (7). Furthermore, even when patients with acute PE are carefully prescreened for absolute contraindications before IV tPA administration, the rate of major hemorrhage from systemic thrombolytic administration is still 20%, including a 3%–5% risk of hemorrhagic stroke (3,13). For patients who are not good candidates for systemic TPA, the next logical step to consider is catheter-directed intervention. That is why the incorporation of a CDT protocol (with targeted drug delivery and a lower overall thrombolytic agent dose) could further improve outcomes while reducing hemorrhagic risk in this submassive PE group. Indeed, when low-dose (ie, ≤ 30 mg) local TPA was administered to patients with acute massive PE—a group at higher risk for bleeding than those with submassive PE (13)—there were no major hemorrhagic complications (12,14).

As these patients with submassive PE are in hemodynamically stable condition, rapid mechanical clot debulking may not be necessary. For these patients, an endovascular treatment regimen should involve image-guided catheter placement into thrombosed lobar arteries for prolonged or overnight thrombolytic infusion. This can be accomplished with a multiple–side hole catheter system such as the UniFuse system (AngioDynamics, Queensbury, New York), and TPA can be infused unilaterally or bilaterally at a total dose rate of 1.0–2.0 mg/h (ie, 0.5–1.0 mg/h through each catheter; Fig 10) depending on clot burden. Fibrinogen levels can be monitored particularly in those patients at greater risk of bleeding or if the infusion will be continued beyond 24 hours. When fibrinogen levels decrease to lower

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**Figure 9.** An algorithm for management of patients with submassive PE. According to the algorithm, CDT should be considered in particular when there are contraindications to systemic thrombolysis. (Reprinted with permission from Piazza G, Goldhaber SZ. Management of submassive pulmonary embolism. Circulation 2010; 122:1124–1129 [7].)
than 150–200 mg/dL, the infusion should be reduced, discontinued, or alternatively continued with transfusions of fresh frozen plasma if further thrombolysis is desired. Furthermore, newer modalities such as US-assisted catheter-directed thrombolysis have the potential to shorten the duration of infusion and lower the total dose of thrombo-

Figure 10. Images from a 29-year-old man with an episode of DVT 12 months before presentation with a 1-day history of right flank pain made worse with inspiration. He denied fever, chills, or dysuria, but described “heaviness” in his chest that made breathing difficult. His vital signs were as follows: blood pressure, 136/84 mm Hg; temperature, 98.2°F; 18 respirations per minute; and O₂ saturation, 96%. Results of an ELISA d-dimer test were elevated at 3,244 IU/L (normal range, 68–494 IU/L), and the patient was started on IV heparin. On the following day, he experienced worsening shortness of breath and could not lie flat. Echocardiography was performed, showing moderate to severe right heart strain. Treatment escalation beyond heparin anticoagulation was desired, and the interventional radiology service was consulted for possible CDT.

(a) Curved planar reformats from a chest CT angiogram show bilateral acute PE. (b–e) Right and left pulmonary angiograms were obtained to localize large thrombosed segments (arrows) for infusion catheter placement. (f) A central 8-F sheath was positioned with its tip in the main pulmonary artery (top arrows), and the mean pulmonary pressure transduced here was 51 mm Hg. Bilateral 5-F Unifuse catheters were placed (peripheral arrows), and TPA infusion was initiated at 0.5 mg/h through each catheter. (g,h) After 24 hours and 24 mg of TPA had been administered, a follow-up chest CT angiogram showed interval reduction of thrombus burden, and the mean pulmonary pressure transduced through the 8-F sheath was 22 mm Hg. Because the patient was still experiencing dyspnea and mild chest discomfort, the TPA infusions were continued. After 36 hours and 36 mg of TPA had been administered, the mean pulmonary pressure was reduced to 15 mm Hg, and the patient’s symptoms of chest pain and shortness of breath had resolved. The bilateral infusion catheters were removed at bedside, and a follow-up echocardiogram was obtained, which showed normal RV function. A subsequent hematologic workup revealed the patient to be heterozygous for both factor V Leiden and prothrombin 20210A mutation. The patient was prescribed lifelong therapeutic anticoagulation for prevention of further venous thromboembolism. (Available in color online at www.jvir.org.)
FUTURE DIRECTIONS

Further research on CDT for acute PE is needed to refine existing protocols and to evaluate long-term outcomes, particularly in patients with submassive PE. In 2010, the Society of Interventional Radiology endorsed reporting standards for the endovascular treatment of PE (75), and ongoing studies such as the multicenter Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis registry (PERFECT) (clinicaltrials.gov identifier NCT01097928) will strive to achieve these goals.

CONCLUSION

Rapid risk stratification by identifying patients with acute massive and acute submassive PE is essential in determining appropriate treatment escalation beyond anticoagulation. In the urgent clinical setting, the decision to escalate therapy should be made as part of a multidisciplinary discussion involving the interventionalist and the primary medical team. For patients with less severe or submassive PE, the use of endovascular treatment in the form of local thrombolytic drug infusion appears to be a promising option for reducing acute and chronic complications from PE while avoiding the bleeding risks from full-dose systemic thrombolysis. For patients in extremis from massive PE, emergent treatment escalation is necessary in the form of systemic thrombolysis, CDT, or combination therapy depending on the circumstance. If IV TPA is contraindicated or there is insufficient time for full-dose TPA, CDT may be the only viable treatment option. Indeed, at experienced centers, the use of modern CDT has proven to be a life-saving treatment in patients dying from acute massive PE. It is therefore recommended that all interventionalists understand the rationale for CDT and become familiar with initiating CDT as a life-saving endovascular procedure.

REFERENCES


The main diagnostic criterion for acute massive pulmonary embolism (PE) is:

- Saddle embolus compromising flow to both lungs.
- Presence of hemodynamic shock.
- Evidence of right ventricular strain.
- Pulmonary embolus that does not resolve with systemic thrombolysis.

Rationale for endovascular treatment of massive PE include all of the following EXCEPT:

- Even with well-selected patients, the risk of major hemorrhage from systemic thrombolysis is about 20%.
- Patients may not be able to tolerate waiting 2 hours for a complete systemic thrombolytic infusion.
- Currently, tissue plasminogen activator is not approved for systemic PE thrombolysis.
- Clinical success can be achieved in over 80% of patients.

With regard to techniques described for endovascular treatment of massive PE:

- The rotating pigtail is the most commonly reported technique, but it frequently requires adjunctive methods.
- Thrombolytic drug infusion proximal to the target embolus is just as effective as infusion within the thrombus.
- Of the techniques discussed, the AngioJet Rheo-lytic Thrombectomy device has the lowest complication rate.
- Hemodynamic improvement with resolution of shock is the most important criterion for a good long-term outcome.

4. Treatment of submassive PE:

- Is just as well accepted as treatment of acute massive PE.
- Has been shown to reduce in-hospital death and clinical deterioration.
- Requires rapid debulking to prevent permanent right ventricular dysfunction.
- Using catheter-directed techniques is more effective than systemic thrombolysis.
Review: Endovascular Therapy for Acute Pulmonary Embolism

Schmitz-Rode et al. 1998 (44) 0.60 (0.44, 0.97)
Schmitz-Rode et al. 2000 (45) 0.80 (0.56, 0.94)
Müller-Hulsbeck et al. 2001 (46) 0.00 (0.66, 1.00)
Prokubovsky et al. 2003 (47) 0.70 (0.46, 0.88)
Tajima et al. 2004 (48) 1.00 (0.86, 1.00)
Barbosa et al. 2008 (49) 0.90 (0.55, 1.00)
Brady et al. 1991 (50) 1.00 (0.29, 1.00)
Rafique et al. 1992 (51) 1.00 (0.48, 1.00)
Ufliacker et al. 1996 (23) 0.60 (0.15, 0.95)
Fava et al. 1997 (52) 0.88 (0.62, 0.98)
Stock et al. 1997 (53) 1.00 (0.48, 1.00)
Basche et al. 1997 (54) 0.60 (0.52, 0.96)
Hiramatsu et al. 1999 (55) 0.88 (0.47, 1.00)
Wong et al. 1999 (56) 0.75 (0.19, 0.99)
Murphy et al. 1999 (57) 1.00 (0.40, 1.00)
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Yoshida et al. 2006 (67) 0.88 (0.47, 1.00)
Li J-J et al. 2006 (68) 1.00 (0.78, 1.00)
Pieri and Agresti 2007 (69) 0.84 (0.78, 0.89)
Chauhan et al. 2007 (70) 0.67 (0.22, 0.96)
Krajina et al. 2007 (71) 0.40 (0.05, 0.85)
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Margheri et al. 2008 (73) 0.85 (0.62, 0.97)
Vecchio et al 2008 (74) 0.62 (0.32, 0.86)
Chen et al 2008 (75) 1.00 (0.87, 1.00)
Eid-Lidt et al. 2008 (25) 0.89 (0.65, 0.99)
Kuo et al. 2008 (15) 0.83 (0.52, 0.98)
Combined 0.865 (0.82, 0.90)
Figure 2. Forest plot shows clinical success rates from CDT and CIs from reported studies encompassing 594 patients with acute massive PE. The percentage of clinical success is denoted along the x axis. Extended lines represent 95% CIs. Squares are proportional to study weight. The width of the diamonds corresponds to the 95% CI for the pooled clinical success rate of 86.5%. (Reprinted from Kuo WT, Gould MK, Louie JD, Rosenberg JK, Sze DY, Hofmann LV. 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 [14].)
Table 2. Catheter-Directed Therapy for Massive Pulmonary Embolism in 594 Patients (14,16,20–53)

<table>
<thead>
<tr>
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<td>53 (36–71)</td>
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<td>12</td>
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</tr>
<tr>
<td><strong>Total (35 studies)</strong></td>
<td></td>
<td>594</td>
<td></td>
<td>53 (18–87)</td>
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Note.—AT = aspiration thrombectomy, ATD = Amplatz thrombectomy device (Microvena, White Bear Lake, Minnesota), BA = balloon fragmentation, DB = Dormia basket (Cook), G = Gensini (Cordis, Miami, Florida), Hy = Hydrolyser (Cordis), IC = infusion catheter, MC = multipurpose catheter, NA = not available, Oa = Oasis (Boston Scientific, Galway, Ireland), PF = pigtail catheter fragmentation, RT = rheolytic AngioJet thrombectomy (Possis), SR = Rotarex (Straub), WD = wire disruption. Reprinted with permission from reference 14.

* If different techniques were used among patients, the number of patient treated with each technique is indicated in parentheses.
† Pooled estimates from random-effects model, with 95% CIs in parentheses.
Table 2. Catheter-Directed Therapy for Massive Pulmonary Embolism in 594 Patients (14,16,20-53), Continued

<table>
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<tr>
<th>Technique*</th>
<th>During CDT</th>
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<th>Minor</th>
<th>Major</th>
<th>Clinical Success (%)</th>
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<tr>
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<td>0</td>
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<td>16</td>
<td>0</td>
<td>0</td>
<td>14/20 (70)</td>
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<td>0</td>
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<td>MC</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>0</td>
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</tr>
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<td>0</td>
<td>1</td>
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| — | 356/535 (67%) | 329/552 (60%) | 7.9% (5.0%–11.3%)† | 2.4% (1.9%–4.3%)† | 86.5% (82.2%–90.2%)† |