Management of Submassive Pulmonary Embolism
Gregory Piazza, MD; Samuel Z. Goldhaber, MD

Case presentation: A 58-year-old woman with a history of cigarette smoking, chronic obstructive pulmonary disease, and recent intensive care unit admission for pneumonia presented with sudden onset of right-sided chest discomfort and dyspnea. On physical examination, she was tachycardic (heart rate 110 beats per minute), normotensive (blood pressure of 128/72 mm Hg), tachypneic (24 breaths per minute), and hypoxemic (oxygen saturation 88% on room air). She had jugular venous distension to the angle of her mandible, a grade 2/6 holosystolic murmur that increased to grade 3/6 with inspiration at the left lower sternal border, lung fields clear to auscultation bilaterally, and mild symmetrical lower-extremity edema. The ECG was notable for sinus tachycardia and T-wave inversions across the anterior precordium. Laboratory evaluation was remarkable for a D-dimer level of 1104 ng/mL (normal ≤500 ng/mL) and a cardiac troponin I level of 1.4 ng/mL (normal <0.1 ng/mL). Contrast-enhanced chest computed tomography demonstrated thrombus that filled the right main pulmonary artery and moderate right ventricular (RV) enlargement (RV-to-left ventricular [LV] dimension ratio=1.2). Bedside transthoracic echocardiography documented moderately severe RV hypokinesis, moderate tricuspid regurgitation, and an estimated pulmonary artery systolic pressure of 55 mm Hg. These clinical, laboratory, and imaging findings established the diagnosis of submassive pulmonary embolism (PE). The principal management question was whether to treat with anticoagulation alone (a “watch and wait” strategy) or to administer fibrinolysis immediately.

Overview
Venous thromboembolism is the third most common cardiovascular disorder after myocardial infarction and stroke.1 The mortality rate for acute PE exceeds 15% in the first 3 months after diagnosis and surpasses that of myocardial infarction.2 Death most commonly results from progressive RV failure that culminates in cardiovascular collapse.3 Survivors of acute PE remain at risk for chronic thromboembolic pulmonary hypertension.4

Acute PE represents a spectrum of clinical syndromes with a variety of prognostic implications. Patients with acute PE who have normal systemic arterial pressure and preserved RV function have an excellent prognosis with therapeutic anticoagulation alone. In contrast, patients with massive PE present with syncope, systemic arterial hypotension, cardiogenic shock, or cardiac arrest and have an increased risk of adverse outcomes, including death.5 Normotensive patients with acute PE and evidence of RV dysfunction are classified as having submassive PE, constitute a large population at increased risk for adverse events, and warrant consultation from cardiovascular medicine specialists.6 Although advanced therapy with fibrinolysis is considered a life-saving intervention in massive PE, it remains controversial in patients with submassive PE.7

Patients with submassive PE can be identified by the presence of RV dysfunction detected on physical examination, electrocardiography, cardiac biomarkers, echocardiography, and chest computed tomography. Physical examination findings of tachycardia, elevated jugular venous pressure, right parasternal heave, accentuated sound of pulmonary valve closure (P2), and hepatomegaly suggest RV dysfunction. The ECG 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.8 Incomplete or complete right bundle-branch block, T-wave inversions in leads V1

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through $V_a$, and the combination of an S wave in lead I, Q wave in lead III, and T-wave inversion in lead III (S1Q3T3) signify RV strain.9

Elevations in cardiac biomarkers, including troponin, brain-type natriuretic peptide, and heart-type fatty acid–binding protein, are associated with RV dysfunction and can noninvasively identify patients with submassive PE. Normotensive patients with acute PE and elevations in levels of cardiac troponins and brain-type natriuretic peptide demonstrate increased short-term mortality and risk of adverse outcomes.10,11 Patients with acute PE and normal heart-type fatty acid–binding protein levels have an excellent prognosis, whereas those with increased levels (≥6 ng/mL) have a higher rate of adverse events, including hemodynamic collapse, respiratory failure, cardiac arrest, and death.12,13

Echocardiography is the best imaging study to detect RV dysfunction in the setting of acute PE. Characteristic echocardiographic findings in patients with submassive PE include RV hypokinesis and dilatation, 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 >2.6 m/s, and loss of inspiratory collapse of the inferior vena cava (IVC).14 Regional RV dysfunction with severe free-wall hypokinesia and apical sparing (McConnell sign) is a specific finding in acute PE.15 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.16 Echocardiography is warranted to identify RV dysfunction in patients with acute PE and clinical evidence of RV failure or elevated levels of cardiac biomarkers.3 A simple 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 1).17

### Submassive PE

Submassive PE can also be diagnosed when RV enlargement on chest computed tomography, defined by an RV-to-LV diameter ratio >0.9, is observed.18 RV enlargement on chest computed tomography predicts increased 30-day mortality in patients with acute PE.18,19 Detection of RV enlargement by chest computed tomography is especially convenient for diagnosis of submassive PE, because it uses data acquired during the initial diagnostic scan.

### Pathophysiology

Direct physical obstruction of the pulmonary arteries, hypoxemic vasoconstriction, and release of potent pulmonary arterial vasoconstrictors increase pulmonary vascular resistance and RV afterload. Acute RV pressure overload may result in RV hypokinesis and dilation, tricuspid regurgitation, and ultimately, RV failure. Patients with submassive PE may deteriorate over the course of several hours to days and develop systemic arterial hypotension, cardiogenic shock, and cardiac arrest. Elevated diastolic pressure causes deviation of the interventricular septum toward the LV and impairs LV filling. An abnormal transmitral flow pattern on Doppler echocardiography may be observed because left atrial contraction, represented by the A wave on transmitral Doppler, makes a greater contribution to LV diastole than passive filling, signified by the E wave. RV pressure overload may also result in increased wall stress and ischemia by increasing myocardial oxygen demand while simultaneously limiting its supply (Figure 1). Severe mismatch between myocardial oxygen demand and supply may lead to RV infarction.

A combination of ventilation-to-perfusion mismatch, increases in total dead space, and right-to-left shunting explains the majority of gas-exchange abnormalities observed in patients with acute PE. Arterial hypoxemia and an increased alveolar-arterial oxygen gradient are the most commonly noted abnormalities of gas exchange. Hyperventilation, especially in patients with normal baseline pulmonary function, may result in hypocapnea and respiratory alkalosis.

### Management

Anticoagulation remains the cornerstone of therapy. Current options for advanced therapy include fibrinolysis, catheter-assisted embolectomy, surgical embolectomy, and IVC filter insertion (Figure 2). The decision to select advanced therapy for submassive PE or to maintain anticoagulation alone must be individualized because of a paucity of trials to help guide management.

### Fibrinolysis

Fibrinolysis functions as a “medical embolectomy” and, when successful, will rapidly reverse hemodynamic compromise and gas-exchange derangements. In patients with submassive PE, fibrinolysis relieves RV pressure overload and may avert impending hemodynamic collapse and death due to progressive RV failure. Fibrinolytic therapy may reduce the likelihood of developing chronic thromboembolic pulmonary hypertension.20 The 2008 American College of Chest Physicians’ guidelines include fibrinolysis as an option for patients with submassive PE who are judged to

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**Table 1. Illustrations of Risk Stratification for Acute PE**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Clinical Appearance</th>
<th>Vital Signs</th>
<th>Cardiac Biomarkers</th>
<th>RV Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Appears well</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal RV size and function</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Appears well</td>
<td>Normal</td>
<td>Elevated</td>
<td>Moderate RV dysfunction</td>
</tr>
<tr>
<td>High</td>
<td>Appears III</td>
<td>Transient or sustained hypotension</td>
<td>Elevated</td>
<td>Severe RV dysfunction</td>
</tr>
</tbody>
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have a low risk of bleeding (grade 2B). Patients with a low risk of bleeding have normal renal function, are not frail, and are not receiving dual-antiplatelet therapy.

The Management Strategies and Prognosis of Pulmonary Embolism Trial-3 (MAPPET-3) randomized 256 patients with submassive PE to receive recombinant tissue plasminogen activator (tPA) 100 mg over a 2-hour period followed by unfractionated heparin infusion or placebo plus heparin anticoagulation. Compared with heparin anticoagulation alone, fibrinolysis re-
sulted in a significant reduction in the primary study end point of in-hospital death or clinical deterioration that required escalation of therapy (defined as catecholamine infusion, rescue fibrinolysis, mechanical ventilation, cardiopulmonary resuscitation, or emergency surgical embolectomy).22 The difference was largely attributable to a higher frequency of open-label fibrinolysis due to “clinical deterioration” as determined by the treating clinician.22

In a prospective study of 200 patients with submassive PE, echocardiography was performed at the time of diagnosis and after 6 months to determine the frequency of pulmonary hypertension.20 Estimated pulmonary artery systolic pressure at 6 months increased in 27% of patients receiving heparin alone, and nearly half of these patients were moderately symptomatic.20 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.20 Estimated pulmonary artery systolic pressure at follow-up did not increase in any of the patients treated with tPA.20

The Pulmonary Embolism International Thrombolysis Trial (PEITHO) is a large randomized controlled trial that began in 2007. The investigators plan to enroll 1000 patients in 12 countries to evaluate a primary clinical end point has approved tPA 100 mg administered within several days of acute PE. Although the efficacy of fibrinolysis is inversely proportional to the duration of symptoms, effective fibrinolysis can be observed up to 2 weeks after an acute event.24,25 Patients with more anatomically extensive PE achieve a greater response to fibrinolysis than those with smaller and peripherally located thrombi.25 On the basis of available data, local catheter-directed delivery of the fibrinolytic agent directly into the pulmonary artery does not appear to improve efficacy or safety. Therefore, peripherally administered fibrinolytic therapy is ordi

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The US Food and Drug Administration has approved tPA 100 mg administered as a continuous intravenous infusion over a 2-hour period for treatment of acute massive PE. Nevertheless, tPA is often used off-label to treat submassive PE. All patients being considered for fibrinolysis should be screened carefully for contraindications that make the bleeding risk prohibitive. The most dreaded complication of fibrinolysis is intracranial hemorrhage. An analysis from the International Cooperative Pulmonary Embolism Registry (ICOPER) observed that the risk of intracranial hemorrhage may be as high as 3%.2 A study from a center with experience in fibrinolysis for acute PE reported that the overall major bleeding rate may approach 20%.21 Major contraindications to fibrinolysis include intracranial mass; cerebrovascular event or neurosurgery within the prior 2 months; history of intracranial hemorrhage; recent major trauma; active or recent respiratory tract, gastrointestinal, or genitourinary bleeding; severe uncontrolled hypertension; recent prolonged cardiopulmonary resuscitation; thrombocytopenia (<50 000 platelets/μL); acute pericarditis or pericardial effusion; ongoing suspicion of aortic dissection; and recent surgery, invasive procedure, or internal organ biopsy.

Table 2. How to Administer Fibrinolytic Therapy for Submassive PE

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Stop heparin infusion when issuing the order to administer fibrinolysis</td>
<td></td>
</tr>
<tr>
<td>2. Infuse recombinant tPA 100 mg over a 2-hour period with careful monitoring for bleeding complications, including neurological checks every 15 minutes during the infusion</td>
<td></td>
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<tr>
<td>3. Obtain immediate post-fibrinolytic infusion aPTT</td>
<td></td>
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</tbody>
</table>

aPTT indicates activated partial thromboplastin time.

the fibrinolytic infusion, the activated partial thromboplastin time should be checked. Unfractionated heparin infusion should be restarted without a bolus when the activated partial thromboplastin time is less than 80 seconds. If greater than 80 seconds, the activated partial thromboplastin time should be rechecked every 4 hours until it falls into the range at which heparin can be safely restarted.

Alternative Advanced Therapies

Alternatives to fibrinolysis may be considered when contraindications to fibrinolysis exist or when patients have failed to respond to an initial trial of fibrinolytic therapy. Approximately half of all patients with acute PE have contraindications to fibrinolysis. Alternative advanced therapies include catheter-assisted embolectomy, surgical embolectomy, and IVC filter insertion.

Catheter-assisted embolectomy is an emerging technique for advanced therapy when full-dose fibrinolysis has failed or is contraindicated.30,31 Catheter-assisted techniques, such as low-dose “local” fibrinolysis and thrombus fragmentation or aspiration, have the greatest success when applied to large, centrally located thrombi within the first 5 days of symptoms. The combination of local fibrinolysis with mechanical thrombec-
tomy is called “pharmacomechanical therapy.”

Surgical embolectomy requires a median sternotomy and cardiopulmonary bypass. Surgical embolectomy is most effective in patients with large, centrally located thrombi. Perioperative mortality for patients undergoing surgical embolectomy has declined over the last 2 decades.33 Surgical embolectomy has been shown to be a safe and effective technique in the treatment of acute PE when performed by experienced surgeons.34,35

IVC filter insertion should be considered in patients with submassive PE in whom fibrinolysis and embolectomy are contraindicated or unavailable. IVC filter insertion reduces the incidence of recurrent PE but has not been shown to lower long-term mortality.36 IVC filters do not halt ongoing thrombogenesis and appear to increase the risk of deep vein thrombosis.36

Retrievable IVC filters offer a safe and effective alternative to permanent filters and may be removed up to several months after insertion.37

Case Presentation (continued): The patient immediately received unfractionated heparin by intravenous bolus and then continuous infusion. After screening for contraindications to fibrinolysis was performed and after discussion with the patient and her family about their preferences, the decision was made to proceed with fibrinolysis for submassive PE. Our recommendation to proceed with fibrinolysis was predicated on a low risk of bleeding and an increased risk of death due to recurrent PE and RV failure with anticoagulation alone. Unfractionated heparin infusion was discontinued, and 100 mg of tPA was administered over a 2-hour period. The patient began having gingival oozing during tPA administration; this was managed with gauze packing. At approximately 1 hour into fibrinolysis, her chest pain and dyspnea abated. After completion of the fibrinolytic infusion and when the activated partial thromboplastin time was less than twice the upper limit of normal, unfractionated heparin infusion was restarted without a bolus as a “bridge” to anticoagulation with warfarin. At her 2-week office visit, the patient felt well and had no chest pain or shortness of breath. A follow-up transthoracic echocardiogram 6 weeks later demonstrated normal pulmonary artery systolic pressures and normal RV size and systolic function.

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Disclosures

None.

References


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