

## Submassive Pulmonary Embolism Where's the Tipping Point?

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### Foreword

Information about a real patient is presented in stages (bold-face type) to expert clinicians (Drs Louis J. Dell'Italia and David C. McGiffin) who respond to the information, sharing his or her reasoning with the reader (regular type). A discussion by the authors follows.

**A 67-year-old black woman presents to the emergency department with a 1-day history of dyspnea, which began the previous morning initially with moderate exertion now progressing to dyspnea at rest. She denies chest pain, cough, palpitations, nausea, diaphoresis, lower extremity swelling, paroxysmal nocturnal dyspnea, orthopnea, presyncope, or syncope. Her medical history is notable for hypertension, diabetes mellitus, and hypothyroidism. Her medications include metoprolol tartrate 12.5 mg twice daily, metformin 1000 mg twice daily, levothyroxine 25 µg daily, and estradiol 1 mg daily for symptomatic management of hot flashes. She lives alone and is a retired schoolteacher. She does not smoke, drink alcohol, or use illicit drugs. Family history is not significant. Travel history is notable for round-trip plane flight from Alabama to Utah, arriving home 2 days previously.**

**On physical examination her temperature is 98.4°F, pulse is 94 beats/min, blood pressure is 112/55 mm Hg in the right arm, 110/58 mm Hg in the left arm, respiratory rate 26 breaths/min, and oxygen saturation 90% on room air. She is an obese black woman (body mass index 32 kg/m<sup>2</sup>) in mild distress secondary to shortness of breath. Jugular venous pressure is estimated at 14 cm H<sub>2</sub>O. Lungs are clear to auscultation. The heart rhythm is regular with a normal S1 and S2. No murmurs, rubs, or gallops are appreciated. Peripheral pulses are brisk and symmetrical with trace pretibial pitting edema. Abdominal examination is benign.**

*Dr Louis J. Dell'Italia:* This patient presents with a 24-hour history of dyspnea progressing from symptoms with exertion to now occurring at rest. Probable causes for this presenting complaint often involve serious cardiopulmonary pathology. The history and physical examination is helpful in narrowing the differential and raises particular concern for

acute pulmonary thromboembolism (PE). Certain risk factors increase suspicion for venous thrombosis in this patient, including obesity, hormone replacement therapy, and recent plane flight. However, air travel less than 6 hours is associated with a very low incidence of venous thromboembolism and therefore does not represent an identifiable risk factor for thrombosis.<sup>1</sup> Rapid onset dyspnea at rest or exertion, as with this case, is the most common presenting symptom for acute PE.<sup>2</sup>

Currently the patient appears hemodynamically stable, although β-blockade may blunt a tachycardic response. Coupled with the history is an examination that is remarkable for an obvious elevation of the jugular venous pressure with clear lung fields, suggestive of right heart failure. Combined with sudden dyspnea and hypoxia, these findings strongly suggest the diagnosis of acute PE. It would be prudent to evaluate for deep vein thrombosis by assessing for symptoms of calf or thigh pain and examining the lower extremities for asymmetry, tenderness, or a palpable cord.

Given the broad differential diagnosis for this presentation, initial workup should include basic laboratory data, arterial blood gas, ECG, and chest x-ray. The Wells score<sup>3</sup> and revised Geneva score<sup>4</sup> may be used to calculate the clinical probability of PE (Table 1). In patients with low to intermediate clinical probability of PE, D-dimer measurement is a useful tool to determine further management. A D-dimer level below the exclusion threshold (<500 µg/L when using a quantitative ELISA assay) is highly sensitive in ruling out acute venous thromboembolism, whereas D-dimer values above the threshold warrant further evaluation. It should be noted that D-dimer testing is not indicated in patients with high clinical probability of PE, because a normal value does not reliably rule out PE in this population.

The dichotomized Wells score indicates a likely probability for PE in this patient based on recent immobilization and the absence of a more probable diagnosis. Likely probability for PE warrants more definitive testing with either computed tomography (CT) pulmonary angiography or ventilation-perfusion scanning. Empirical systemic anticoagulation should also be considered, particularly if more definitive diagnostic testing is not immediately available.

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**Table 1. Scoring Systems to Assess Probability of Suspected PE**

Wells		Revised Geneva	
Previous PE or DVT	1.5	Age > 65	1
Heart rate > 100 beats per minute	1.5	Previous PE or DVT	3
Recent surgery or immobilization	1.5	Surgery or lower limb fracture within 1 mo	2
Clinical signs of DVT	3	Active malignancy	2
PE most likely diagnosis	3	Unilateral leg pain	3
Hemoptysis	1	Hemoptysis	2
Cancer	1	Heart rate 75–94 beats per minute	3
		Heart rate $\geq$ 95 beats per minute	5
		Pain on deep leg vein palpation and unilateral edema	4
		<2 low risk, 2–6 intermediate risk, $\geq$ 6 high risk	

0–1 low risk, 2–6 intermediate risk,  $\geq$  7 high risk.  
For the dichotomized rule <4 is unlikely and  $\geq$ 4 is likely.

DVT indicates deep vein thrombosis; and PE, pulmonary thromboembolism.

**Complete blood count and chemistry panel are within normal limits. The ECG shows sinus rhythm, right bundle-branch block, and a S1Q3T3 pattern (Figure 1). Chest x-ray is normal. CT pulmonary angiography demonstrates central saddle pulmonary embolus with a large pulmonary thromboembolus burden involving the main, segmental, and subsegmental pulmonary arteries bilaterally (Figure 2).**

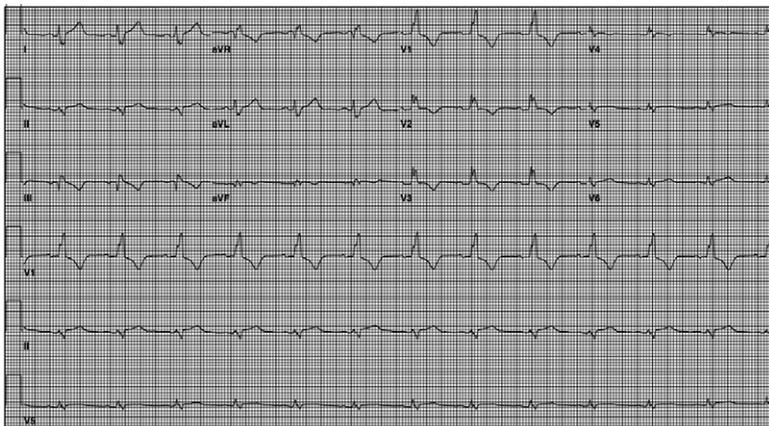
*Dr Dell'Italia:* The diagnosis of acute PE has been established; however, to optimize management for this patient she should be further risk stratified. Contemporary guidelines have specifically defined the stratification of acute PE into 3 categories, low risk, submassive, or massive (Table 2), which not only provides important prognostic information but also is central to the subsequent management strategy.<sup>5</sup>

In this case, the absence of sustained hypotension (systolic blood pressure <90 mmHg for 15 minutes or requiring inotropic support) or a patient in extremis precludes the diagnosis of massive PE. Acute PE without systemic hypotension (systolic blood pressure >90 mmHg) can be classified as low-risk or submassive, with submassive PE being defined by the presence of right ventricular (RV) dysfunction or myocardial necrosis.<sup>5</sup>

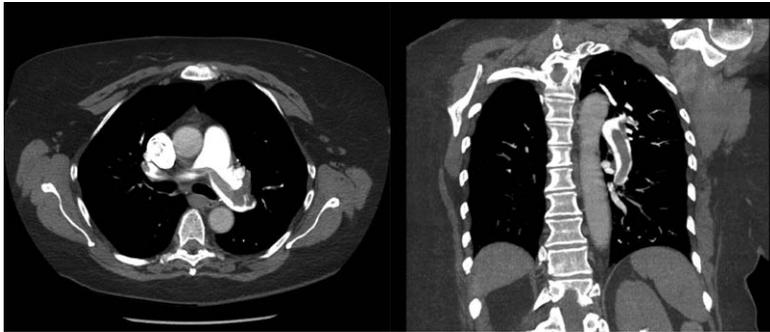
Embolization of thrombus to the pulmonary arteries results in acutely increased vascular resistance as a result of obstruction to flow, hypoxemic vasoconstriction, and release of

pulmonary artery vasoconstrictors. RV hypokinesia and dilation may then occur as a result of acute RV pressure overload, the degree of which is largely a function of PE size and underlying cardiopulmonary reserve. Within the setting of an acutely unyielding pericardium this can lead to shifting of the interventricular septum and a decrease in left ventricular filling and preload. The probability of RV systolic dysfunction increases when  $\geq$ 30% of the pulmonary vascular cross-sectional area has flow impairment secondary to PE.<sup>6</sup> Additionally, RV ischemia may occur due to acutely increased ventricular wall stress as a result of dilatation of the thin RV free wall and increased myocardial oxygen demand. In this case, the elevated jugular venous pressure suggests a right ventricle that has reached its preload reserve, and further increases in the impedance to RV ejection may result in hypotension.

Several techniques have been used to identify the presence of RV dysfunction in acute PE, either directly or indirectly. Among these, ECG changes including sinus tachycardia, new-onset atrial arrhythmias, new right bundle-branch block (complete or incomplete), Qr pattern in V1, S1Q3T3 pattern, negative T waves and ST segment changes in V1 through V4 have been shown to correlate with worse short-term prognosis in acute PE. The presence of new complete or incomplete right bundle-branch block, anteroseptal ST segment changes, or anteroseptal T-wave inversion satisfies the guideline criteria for RV dysfunction.<sup>5</sup> Biomarkers, specifically brain natriuretic



**Figure 1.** ECG depicting right bundle-branch block and S1Q3T3 pattern.



**Figure 2.** CT pulmonary angiogram depicting large central saddle pulmonary embolus extending into the bilateral pulmonary arteries.

peptide (BNP) and troponin, may be valuable in further defining this patient's risk. Elevated BNP (>90 pg/mL) and N-terminal pro-BNP (>500 pg/mL) are used as surrogate markers of RV dysfunction and predict increased short-term mortality in acute PE.<sup>5</sup> Evidence of myocardial necrosis (troponin I >0.4 ng/mL or troponin T >0.1 ng/mL) also differentiates low-risk from submassive PE and is associated with adverse prognosis.<sup>5</sup>

Methods of directly evaluating RV dysfunction include echocardiography and CT pulmonary angiography. CT scans should be routinely reviewed to assess for the presence of RV dilation. Using the 4-chamber view, dilation is present if the RV diameter to left ventricular diameter ratio is >0.9 by either echocardiogram or CT scan. An RV diameter to left ventricular diameter ratio >0.9 in the 4-chamber view portends adverse events and worse outcomes.<sup>5</sup>

**Table 2. Classification of Acute Pulmonary Embolism\***

Massive	Sustained hypotension (systolic BP <90 mm Hg for 15 min or requiring inotropic support) -or- Pulselessness -or- Sustained heart rate < 40 BPM with signs/symptoms of shock
Submassive	Systolic BP > 90 mm Hg and RV dysfunction or myocardial necrosis defined by: RV dilation (apical 4-chamber RV diameter divided by LV diameter > 0.9) or RV systolic dysfunction on echocardiography -or- RV dilation (4-chamber RV diameter divided by LV diameter > 0.9) on CT -or- Elevation of BNP (> 90 pg/mL), or N-terminal pro-BNP (> 500 pg/mL) -or- EKG changes (new complete or incomplete right bundle-branch block, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion) -or- Elevation of troponin I (> 0.4 ng/mL) or troponin T (> 0.1 ng/mL)
Low risk	Absence of the markers of adverse prognosis that define massive or submassive PE

BNP indicates brain natriuretic peptide; BP, blood pressure; BPM, beats per minute; CT, computed tomography; EKG, electrocardiography; LV, left ventricular; PE, pulmonary embolism; and RV, right ventricular.

\*Adapted from the American Heart Association Scientific Statement on Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension.<sup>5</sup>

Systemic anticoagulation should be initiated, with current options including unfractionated heparin, low-molecular-weight heparin, or fondaparinux. In high-risk patients, an advantage of initial therapy with intravenous unfractionated heparin is that it can be discontinued rapidly if more aggressive therapies are proposed. Obtaining biomarkers and directly evaluating for RV dysfunction will help further risk stratify this patient and evaluate the need for additional therapy.

**Treatment with unfractionated heparin is initiated and the patient is admitted to the medical intensive care unit. Review of the CT scan shows RV to left ventricular ratio of 1.3. The troponin I is 1.2 ng/mL (normal <0.4 ng/mL) and BNP is 260 pg/mL (normal <90 pg/mL). Clinically, the patient continues to be tachypneic, requiring supplemental oxygen via nasal cannula at 6 L/min. The systolic blood pressure ranges from approximately 90 to 110 mm Hg and heart rate 100 to 120 beats/min.**

*Dr David C. McGiffin:* Although the use of aggressive therapies such as thrombolysis for massive PE is widely accepted as first line treatment, therapy for submassive PE remains controversial. Evidence of RV dysfunction and necrosis as well as tenuous hemodynamics place this patient at increased risk of mortality, therefore consideration of a more aggressive treatment approach is not unreasonable. In patients without contraindications, current guidelines state thrombolytic therapy may be considered in patients with acute submassive PE with systolic blood pressure <90 mm Hg at any time or shock index >1.0 (as distinct from the sustained hypotension that is required for the designation of massive), respiratory failure (SaO<sub>2</sub><95% with Borg score>8, altered mental status, or appearance of suffering), or moderate to severe RV strain (Class IIb recommendation).<sup>5</sup> Some centers have reported the use of surgical embolectomy for hemodynamically stable patients with significant RV dysfunction, citing the significant bleeding risk associated with systemic thrombolysis. The results of this approach have been good with acceptable risk, however such practice currently is limited to experienced centers.

A further option is percutaneous catheter-directed therapy, which represents a growing field in the treatment of acute PE. Various percutaneous catheter-based techniques have been described, including thrombus fragmentation, rheolytic thrombectomy, suction thrombectomy, rotational thrombectomy, catheter-directed thrombolysis, and ultrasound-enhanced thrombolysis.<sup>7,8</sup> Pharmacomechanical therapy is a commonly used strategy where a mechanical catheter intervention

technique is combined with local administration of low-dose thrombolytics. Because of risk of pulmonary artery perforation, catheter-based therapy is limited to embolus located in the main and large lower lobe segmental pulmonary arteries. Catheter-based interventions can be rapidly instituted and are minimally invasive, making it an attractive option for high-risk patients with contraindications to systemic thrombolysis, which may be present in as many as 50% of patients with PE. Although catheter-based therapies for acute PE have not been rigorously studied, a systemic review and meta-analysis of 594 patients with massive PE demonstrated a pooled clinical success rate of 86.5%, and risk of minor and major procedural complication 7.9 and 2.4% respectively.<sup>9</sup> In this case the large saddle PE is anatomically suitable for catheter-based therapy, and therefore this may be a viable therapeutic option at experienced centers, particularly if the patient's condition were to deteriorate further.

The decision to pursue aggressive therapies in the setting of submassive PE depends on clinician assessment of PE severity using both clinical judgment and objective measures of prognosis balanced against the risk of therapy. Although echocardiography is not specifically required to determine the presence of RV dysfunction, we routinely obtain an echocardiogram before the institution of aggressive therapy for submassive PE, not only to serve as a baseline for response to treatment but to evaluate for the presence of a patent foramen ovale or free-floating right atrial thrombus that may alter management strategy.

**A transthoracic echocardiogram is obtained, showing a large mobile wormlike thrombus in the right atrium, which prolapses into the right ventricle during diastole (Figure 3). The right ventricle is markedly dilated, with severe hypokinesis of the ventricular free wall sparing the apex (McConnell's sign) and an estimated pulmonary artery pressure of 52 mm Hg (Movies I and II in the online-only Data Supplement).**

*Dr McGiffin:* The presence of a concomitant free-floating right heart thrombus noted on the echocardiogram must be factored into the therapeutic planning because of its potential to embolize and further increase RV impedance to ejection. Free-floating right heart thrombi are infrequent, occurring in ≈4% of patients evaluated with echocardiography in the setting of diagnosed PE.<sup>10</sup> Free-floating right heart thrombi are nearly always associated with PE (98%) and represent a medical emergency, with associated mortality reported as high as 21% within the first day of diagnosis.<sup>11</sup>

Treatment with heparin alone may not be adequate for patients with free-floating right heart thrombi and PE, even if the patient appears clinically stable.<sup>10</sup> The International Cooperative Pulmonary Embolism Registry (ICOPER) demonstrates a markedly higher 14-day mortality (23.5% versus 8%) in patients with PE and free-floating right heart thrombi treated with heparin alone versus those patients without free-floating right heart thrombi. Thus, in addition to anticoagulation, management in this scenario necessitates consideration of a more aggressive treatment strategy.

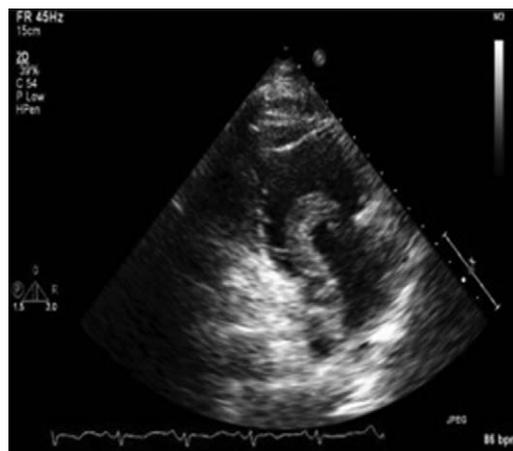
Two reasonable treatment options for submassive PE and free-floating right atrial thrombus include systemic

thrombolysis or surgical thromboembolectomy. Surgical thromboembolectomy is considered the classic treatment for removal of free-floating right atrial thrombus; however, there is no convincing evidence to definitively guide therapy in 1 direction. Ultimately, institutional experience and resources determine the treatment strategy.

**The patient is taken to the operating room and after median sternotomy cardiopulmonary bypass is established. The right atrium is opened with removal of a large free-floating thrombus measuring 12 cm in length. Bilateral pulmonary artery embolectomies are performed, with thrombus extracted from all segmental and subsegmental lobar branches by direct visualization (Figure 4). Immediately after the operation an inferior vena cava filter is placed. A transthoracic echocardiogram 5 days postoperatively demonstrates a RV ejection fraction of 0.50 and an estimated pulmonary artery pressure of 30 mm Hg.**

*Dr McGiffin:* Surgical thromboembolectomy may provide an effective treatment option for massive PE, high risk submassive PE with contraindication to thrombolytic therapy or in cases of therapeutic failure of thrombolytic therapy.<sup>12</sup> The operation is also well suited for patients requiring removal of right atrial thrombus. It is accepted practice to routinely place inferior vena cava filters after thromboembolectomy in an effort to prevent a potentially lethal recurrent PE. Recent data from a nationwide study of >3000 patients undergoing embolectomy for acute PE demonstrated markedly decreased case-fatality rates among patients who had placement of an inferior vena cava filter compared with those without.<sup>13</sup> The implanted inferior vena cava filter may be removed when the patient's hemodynamic status is stabilized and acute protection from a recurrent event is no longer needed.

**The patient is commenced on warfarin therapy and subsequent hypercoagulable workup demonstrates a positive anticardiolipin antibody that is confirmed 12 weeks later. Her hormone replacement therapy is stopped, and she will continue therapeutic anticoagulation indefinitely. She is doing well at 6-month follow-up with excellent**



**Figure 3.** Echocardiogram depicting free-floating right atrial thrombus prolapsing into the right ventricle.



**Figure 4.** Postoperative specimens of removed right atrial and pulmonary thrombus.

#### exercise tolerance and no significant limitations in physical activity.

*Dr Dell'Italia:* Obesity and hormone replacement therapy represent risk factors for venous thromboembolism in this patient.<sup>14</sup> Costly hypercoagulable workups are not routinely recommended after an initial thrombotic event, because the presence of a thrombophilic state does not often change management. Compared with idiopathic venous thromboembolism, most hypercoagulable conditions are not associated with an increased risk of recurrent thromboembolic events, and therefore duration of anticoagulation is not affected by a positive result.<sup>15</sup> An exception is the antiphospholipid syndrome; the most common acquired thrombophilia defined by thrombosis or pregnancy morbidity in the presence of circulating antiphospholipid antibodies. Confirmed persistence of antiphospholipid antibodies must be demonstrated at least 12 weeks after an initial positive result, because transiently elevated antiphospholipid antibodies can occur in normal individuals and in the setting of certain infections. The antiphospholipid syndrome is associated with high rates of recurrent thrombotic events, and therefore indefinite antithrombotic therapy is recommended after an initial thrombotic event.<sup>16</sup>

Recent trials have shown promising results using direct inhibitors of Factor Xa and thrombin in the treatment of acute venous thromboembolism.<sup>17,18</sup> These fixed-dose unmonitored oral medications provide an attractive alternative to current treatment options and may replace heparin and vitamin K antagonists as the favorable management strategy for venous thromboembolism in the future.

### Discussion

Deep vein thrombosis and its associated complication PE, collectively referred to as venous thromboembolism, represent the third most common cardiovascular disorder in the United States, with an estimated 900 000 incident or recurrent cases occurring annually.<sup>19</sup> PE is associated with poor prognosis, underlined by a case fatality of  $\approx 15\%$  in the first 3 months after diagnosis, greater than that of acute myocardial infarction.<sup>20</sup> Approximately one third of PE cases are fatal,<sup>19</sup> and nearly 25% of patients with PE present with sudden cardiac death.<sup>21</sup> Furthermore, for those surviving the initial event, prognosis

and quality of life may be markedly impaired with increased likelihood of developing long-term complications, such as RV dysfunction and pulmonary hypertension with associated exercise intolerance, fatigue, dyspnea, and shortened life expectancy.<sup>22</sup> It is imperative therefore to have management strategies in place for these patients that aim to improve both immediate and long-term prognosis.

Until recently, PE was classified into two groups, massive or nonmassive, based on the presence or absence of cardiogenic shock. Massive PE represents  $<5\%$  of patients presenting with acute PE,<sup>20</sup> and thus the remainder of patients were considered to be part of the same group with regard to therapeutic decision-making. Contemporary management, however, involves the identification of an intermediate high-risk group of patients with RV dysfunction and/or necrosis with preserved systemic arterial pressure, defined as submassive PE.<sup>5</sup> In massive PE, mortality has been reported as high as 50%,<sup>20</sup> and even greater for those requiring cardiopulmonary resuscitation, thus necessitating emergent aggressive intervention. Submassive PE presents more of a clinical dilemma, because patients are known to be at increased risk of worse outcomes, but therapeutic implications of aggressive therapy remain uncertain. Thrombolytic therapy for acute PE is not without risk, with analysis of 5 clinical trials for acute PE reporting a risk of intracranial hemorrhage of 1.9%<sup>23</sup> and the ICOPER data demonstrating the risk of intracranial hemorrhage to be  $\approx 3\%$ .<sup>20</sup> Furthermore, major bleeding has been reported to occur in up to 20% of patients receiving fibrinolysis for acute PE.<sup>24</sup> Therefore, some clinicians are hesitant to routinely prescribe such treatment to patients who appear to be hemodynamically stable, particularly in the face of a lack of definitive evidence.

Treatment with heparin alone, however, in a normotensive patient with acute PE and RV dysfunction remains a troubling proposition, and the argument for use of more aggressive therapy in patients with submassive PE is not without merit. At least 7 studies, totaling  $>600$  patients, have documented short-term mortality in normotensive patients with RV dysfunction as assessed by echocardiography or CT scan. A meta-analysis of available data calculated a relative risk of RV dysfunction for predicting death to be 2.4 (95% confidence interval, 1.3–4.4).<sup>25</sup> The presence of persistent RV dysfunction after acute PE is associated with higher rates of recurrent PE, deep vein thrombosis, and PE-related death.<sup>26</sup> Moreover, presence of myocardial necrosis in PE, as determined by elevation in troponin, is associated with significantly worse prognosis.<sup>27</sup> Taken together these findings highlight the vulnerability of patients with submassive PE. Counterintuitively, data from the 4 large PE registries suggest an overall low mortality (probably  $<3\%$ ) in submassive PE treated with anticoagulation alone.<sup>5</sup> However, when evaluating individual patients, registry analysis should be interpreted with caution, taking into account the inherent limitations of evaluating submassive PE as a single group. For example, a normotensive patient with mildly elevated BNP, and a normotensive patient with tachypnea, tachycardia, severe RV hypokinesis, and markedly elevated troponin, clearly represent different risk groups, despite each being classified as submassive.

To date, Management Strategies and Prognosis of Pulmonary Embolism Trial-3 (MAPPET-3) is the largest published prospective, randomized trial that has evaluated the

effect of thrombolysis on outcomes in patients with submassive PE as defined by normal blood pressure and RV dysfunction.<sup>28</sup> Thrombolysis as compared with placebo was associated with improved clinical course, namely a significant reduction in need for escalation of therapy defined as use of vasopressors, cardiopulmonary resuscitation, mechanical ventilation, embolectomy, or rescue thrombolysis. The trial has been criticized, because mortality was low and not significantly different between treatment groups. Furthermore, results in favor of thrombolysis were largely attributed to more frequent administration of open-label thrombolysis to the heparin-only group as a result of subjectively determined clinical deterioration.

Several prospective studies of thrombolysis in submassive PE have shown a beneficial effect on surrogate end points, including improvement in RV function, RV systolic pressure, and symptomatic status.<sup>29,30</sup> Recently, published results of the MOPETT (MOderate Pulmonary Embolism Treated with Thrombolysis) trial suggest that administering a lower dose of tissue plasminogen activator—approximately half the standard dosing for PE—may safely decrease the development of pulmonary hypertension, recurrent PE, and shorten hospital stay in hemodynamically stable patients with symptomatic PE.<sup>31</sup> However, this small study requires verification in larger randomized trials before this strategy is adopted into routine practice.

Generally accepted indications for surgical thromboembolectomy in acute PE include massive PE with contraindication to thrombolysis and rescue for those remaining unstable after thrombolysis (Class IIa level of evidence C recommendation). Other clinical scenarios that warrant consideration for surgery include free-floating right atrial thrombus, as in the current case, or the presence of a patent foramen ovale, particularly in the setting of paradoxical embolus. Timely diagnosis, rapid triage, and patient selection are likely the key factors in optimizing outcomes of surgical embolectomy for acute PE, as reserving surgical intervention for those patients in extremis is associated with dismal outcomes. Recent reports of surgical thromboembolectomy for massive PE from experienced centers demonstrate encouraging results in this high-risk group of patients with intermediate-term survival ranging from 78% to 92%<sup>32–34</sup> and the bulk of deaths occurring in patients with need for preoperative cardiopulmonary resuscitation. Investigators from the Brigham and Women's Hospital further expanded the indication for surgical thromboembolectomy to include anatomically extensive PE and moderate to severe right ventricular dysfunction despite preserved hemodynamics, reporting a high survival rate of 89% in the initial series and an actuarial survival of 86% at 1 year in the entire cohort.<sup>35,36</sup> Taken together, these studies suggest that in centers with adequate resources and expertise, surgical thromboembolectomy may be included in the armamentarium of treatment options for patients presenting with acute PE. Furthermore, catheter-directed therapy is an area of growing interest that may present an effective clinical option with acceptable risk in the treatment of acute PE.

Although it is clear that acute PE patients with RV dysfunction and/or evidence of myocardial necrosis are at increased risk of poor outcomes, the submassive classification encompasses a wide spectrum of clinical presentations and

further investigation is required to better risk stratify this large group and identify those who would clearly benefit from aggressive therapies. Unfortunately, until the availability of high-quality, definitive, randomized, controlled data, the use of aggressive therapies such as thrombolysis for submassive PE will remain controversial. Current guideline recommendations are appropriately broad, and management of massive and submassive PE should ideally be on a case-by-case basis, using an experienced multidisciplinary team approach and prioritizing the bedside clinician's assessment of severity. Forthcoming results from trials investigating patients with submassive PE (Pulmonary Embolism Thrombolysis Study [PEITHO] NCT00639743 and Tenecteplase Or Placebo: Cardiopulmonary Outcomes At Three Months [TOPCOAT] NCT00680628) will hopefully help to resolve some of the therapeutic uncertainty regarding the management of these patients. The management of massive PE is considerably clearer than that in submassive PE, however in some patients with submassive PE the circulation is precarious, the compensatory mechanisms tenuous, and the potential for adverse outcomes is very real. When do we need to intervene? Defining the tipping point is the key to resolving the dilemma.

## Disclosures

None.

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