Massive Pulmonary Embolism: A Case Report and Review of Literature

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CME INFORMATION

TARGET AUDIENCE

The July/August Clinical Case of the Month is intended for general practitioners, medicine subspecialists including cardiologists, hematologists, and pulmonary-critical care specialists, emergency medicine physicians, general surgeons, thoracic surgeons, and pathologists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. This case illustrates the clinical indications for thrombolysis in cases of massive pulmonary emboli (PE) as well as provides a framework for the discussion modalities used to assess the severity of PE. Finally, this case helps us to understand the pathophysiological mechanisms of right ventricular dysfunction secondary to PE and the role of cardiac troponins in patients with PE. Estimated time to complete this activity is one (1) hour.

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

DISCLOSURE

Drs. Jarreau, Hanna, Rodriguez, Martinez, and Mr. Romero have nothing to disclose.

Dr. Lopez discloses that he is a member of the *Journal* Board of Trustees. He is also on the *Journal* Editorial Board.

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CASE PRESENTATION

A 63-year-old man presented to the emergency department complaining of severe shortness of breath that began abruptly when he bent over to pick up some papers. He reported that as he reached down he suddenly was not able to catch his breath, felt lightheaded, and collapsed to the floor without any loss of consciousness. Associated symptoms included chest pain and diaphoresis. One week prior to this event, the patient reported that he began to notice pain and swelling in his right calf; otherwise his review of systems was negative. He had no significant past medical history. Social history was significant for a 50 pack per year smoking history and alcohol consumption of approximately one bottle of wine daily for many years. His mother had a history of phlebitis. The patient denied taking any medications and had no known drug allergies.

His vital signs upon arrival of emergency medical services were a palpable systolic blood pressure of 50 mmHg, a heart rate of 134 beats per minute, a respiratory rate of 40 per minute with an oxygen saturation of 80% breathing air. On arrival to the emergency department, his oxygen saturation was to 95% on a 100% non-rebreather facemask. He was pale, diaphoretic, and unable to speak in full sentences. His jugular veins were distended to the angle of the jaw while the patient was sitting upright at 90 degrees and was later measured at approximately 20 cm. Cardiac exam demonstrated tachycardia, a fixed wide of the second heart sound, the presence of a third heart sound at the left lower sternal border, and a right ventricular heave. Pulmonary findings consisted of bilateral crackles at the bases. His extremities were cool and cyanotic with weak peripheral pulses.

The initial electrocardiogram showed sinus tachycardia at a rate of 129 per minute, right bundle branch block with a QRS duration of 151 msec, right axis deviation of 110 degrees, and diffuse ST-segment depression and T-wave inversion (Figure 1). His arterial blood gas showed pH 7.16, pCO2 of

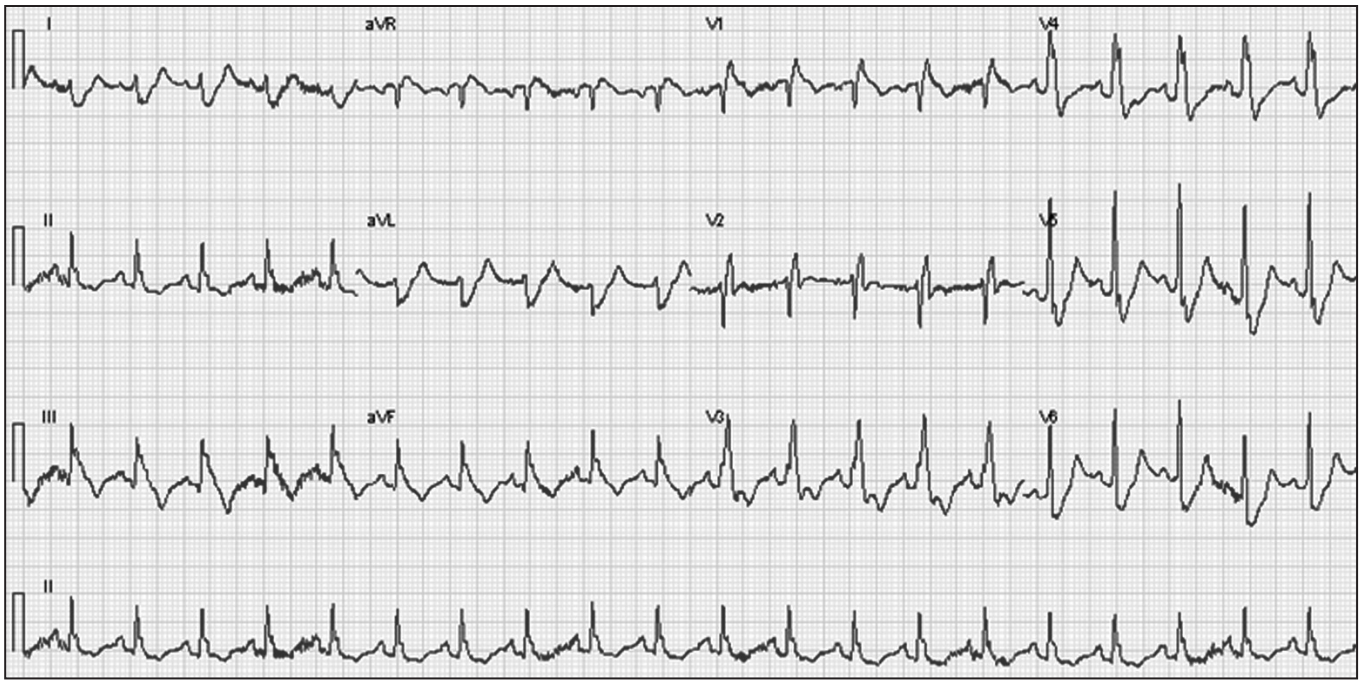

Figure 1. Initial electrocardiogram at presentation to the emergency room. Sinus tachycardia at rate of 129 beats per minute, right bundle branch block (QRS duration of 150 msec), right axis deviation (110 degrees), right ventricular hypertrophy, diffuse ST-segment depression, and T-wave inversion.

31 mm Hg, and pO2 of 58 mm Hg on 100% non-rebreather mask. Bedside echocardiogram demonstrated severe right ventricular (RV) dilation with signs of both RV pressure and volume overload, severe hypokinesis of the RV free wall and the ventricular septum, and good RV apical contraction. There was left ventricular (LV) cavity obliteration with no evidence of wall motion abnormality. Pulmonary artery pressure was estimated to be 50 mmHg (assuming right atrial pressure of 15 mmHg), and a minimal pericardial effusion was seen. A complete blood count, coagulation panel, and basic metabolic panel were normal.

The patient was immediately given normal saline and a loading dose of heparin intravenously for suspected pulmonary embolism. The patient's blood pressure failed to improve, so norepinephrine was initiated. A computed tomogram (CT) of the chest with pulmonary embolism protocol confirmed large bilateral pulmonary emboli with radiological evidence of RV strain (Figures 2-4), and a non-contrast CT of the head was negative for intracranial bleeding. Given the hemodynamic compromise resulting from the massive pulmonary embolism, the patient was given 100 mg of tissue plasminogen activator (tPA) IV over two hours. Approximately one hour after the infusion of thrombolytic therapy, the patient was weaned off norepinephrine.

By the next morning the patient's shortness of breath had resolved, and his oxygen saturation was >94% on breathing air. An electrocardiogram obtained 12 hours after admission showed a normal sinus rhythm, a rate of 83, a normal axis of 64 degrees, a normal QRS duration, and q waves in leads II, III, and aVF. Serial cardiac enzymes peaked on the second day of admission with a troponin I of 4.77 ng/mL (reference<0.04), CKMB of 15.8 (reference 0-5), CPK of 184 U/L (reference 5-220) suggesting myocardial damage from the right ventricular strain caused by the large pulmonary embolus.

The heparin drip was changed to a therapeutic dose of subcutaneous enoxaparin, and on hospital day two, oral warafin sodium was started. Both enoxaparin and warafin sodium were continued until the goal INR of 2.0-3.0 was reached. Lower extremity venous Doppler studies revealed an extensive thrombus in the superficial femoral vein of the right leg. A hypercoagulable work-up later revealed that the patient suffered from an inheritable protein S deficiency. The patient continued to improve clinically and was discharged home on hospital day five.

DISCUSSION

Pathophysiology

Pulmonary embolism (PE) ranges from incidental, clinically unimportant occurrences to causing sudden death. Virchow's triad of local trauma to the vessel wall, hypercoagulability, and stasis of blood leads to thrombus formation in the leg veins.[1]As thrombi form in the deep veins of the legs, pelvis, or arms, they may dislodge and embolize to the pulmonary arteries with potentially serious consequences. The most common sources of pulmonary emboli are the pelvic veins or deep veins of the thigh.[2] Pulmonary arterial obstruction by clot causes platelets to

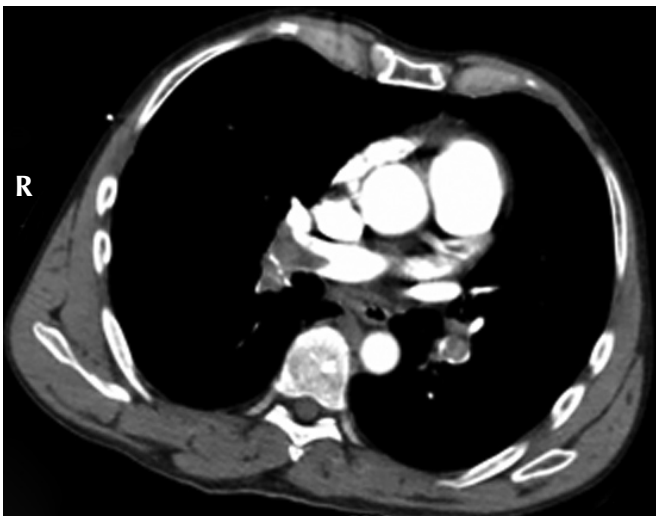

Figure 2. Axial computed tomographic pulmonary angiogram illustrating the large filling defect at the bifurcation of the main pulmonary artery as well as multiple subsegmental clots.

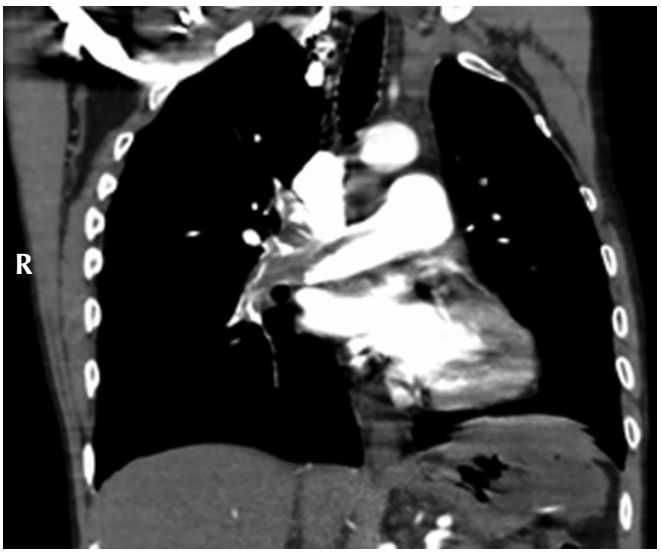

Figure 4. Coronal view of computed tomographic pulmonary angiogram showing a large saddle embolism at the bifurcation the main pulmonary artery.

release vasoactive agents such as serotonin which may lead to further elevation of pulmonary vascular resistance. This redistribution of blood flow increases alveolar dead space with a resultant ventilation/perfusion mismatch that impairs gas exchange.[3] As right ventricular afterload increases, tension rises in the right ventricular wall and may lead to dilatation, dysfunction, and ischemia of the right ventricle.[1]

Epidemiology

Venous thromboemboli are more common in men and increase in incidence with advancing age. According

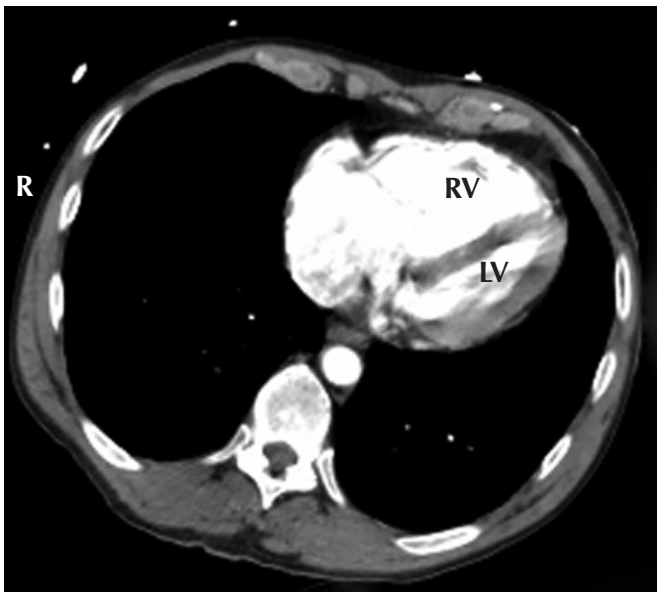

Figure 3. Axial computed tomographic pulmonary angiogram showing severe dilation of the right ventricle (RV). Measurement of the RV at the level of the tricuspid valve compared to the measurement of the left ventricle (LV) at the level of the mitral valve gives a RV:LV ratio of 3.

to *Silverstein et al*, each 10-year increase in age results in a doubling of the incidence of PE.[4] Estimates are more than 600,000 episodes of pulmonary embolism occur each year in the United States, resulting in 100,000 to 200,000 deaths.[5] The mortality rate for untreated PE is as high as 30%.[2] Right-sided heart failure is the usual cause of death from PE, and right ventricular dysfunction serves as a crucially important warning for a possible adverse outcome.[6] The mortality rate at one year is three times higher in patients with right ventricular dysfunction compared to those with normal right ventricular function. Chronic pulmonary hypertension affects approximately 4% of patients within two years after a first episode of symptomatic PE.[7]

Diagnosis

In patients considered for thrombolytic therapy, the diagnosis of PE should be based on a high probability ventilation-perfusion scan or a positive spiral chest CT. Frequently, however, patients considered for thrombolysis are hemodynamically unstable and cannot undergo either imaging modality. In such cases, the diagnosis must be based on clinical evaluation supplemented by indirect evidence of PE.[8] Dyspnea is the most frequent symptom of pulmonary embolism, and tachypnea is the most frequent sign. Syncope, hypotension, or cyanosis usually indicates a massive pulmonary embolism.[9] On physical examination, findings of right ventricular dysfunction include bulging neck veins with prominent *v* waves, a left parasternal lift, an accentuated pulmonic component of the second heart sound, and a systolic murmur at the left lower sternal border that increases in intensity during inspiration.[9]

A bedside transthoracic or transesophageal echocardiogram (TEE) can be used to demonstrate signs of right ventricular pressure overload, and right ventricular hypokinesis and/or dilatation. The McConnell sign of PE is normal apical motion of the right ventricle despite hypokinesis of its free wall.[10] Also, a bedside echocardiogram may eliminate other causes of shock, such as myocardial infarction, cardiac tamponade, and aortic dissection. On occasion, large central emboli may be visualized using TEE. In the absence of underlying cardiopulmonary disease, pulmonary artery pressure is a useful indicator of the severity of the acute PE and of the patient's overall prognosis.[2] The presence of right ventricular hypertrophy (>5-6 mm) helps differentiate from acute chronic right ventricular dysfunction. A pulmonary arterial systolic pressure greater than 60 mmHg cannot be generated by an acutely failing right ventricle, and pressures higher than this suggest some degree of chronicity.

Table 1. Findings suggesting massive acute pulmonary embolism.

Electrocardiogram	Echocardiogram	Contrast computed tomogram short axis views
*T-wave inversion V1-V3 (right ventricular strain pattern)	Right ventricular dilation	Visualization of a large clot burden in the pulmonary arteries
S wave in lead I, Q wave and T-wave inversion in lead III	Paradoxical septal motion	Increased diameter of superior and inferior venae cavae and pulmonary artery
Right axis deviation of > 90° or indeterminate axis	Right ventricular hypokinesis sparing the apex	Large clot burden in the pelvis or legs
Right bundle branch block Right ventricular hypertrophy	Pulmonary artery hypertension (< 60 mmHg) without right ventricular hypertrophy	Right/left ventricular diameter ratio > 1
P pulmonale	Right atrial enlargement	Leftward septal bowing
Atrial flutter/ fibrillation	Severe tricuspid regurgitation	

**The most common finding reflecting severity.*

While the electrocardiogram and the echocardiogram (Table 1) have long been used to assess PE, several computed tomographic criteria recently have been validated in the assessment of the severity of PE. This allows a single test, namely the spiral CT, to establish the diagnosis and assess the severity of PE.[11] The short-axis of the right and left ventricles on the axial CT should be measured (at the levels of the tricuspid and the mitral valves respectively), in order to calculate a right ventricular to left ventricular diameter ratio (RV/LV). A RV/LV ratio of more than one and a leftward septal bowing on the chest CT have a sensitivity of 78%-92% and a specificity of 100% for the detection of right ventricular dysfunction when compared to echocardiographic findings.[12] The diameters of the superior vena cava and the azygos vein, as well as the diameter of the pulmonary artery also may be used as signs of pressure overload related to a severe PE.

In addition, elevated cardiac biomarkers such as cardiac troponin and brain naturetic peptide (BNP) have well established diagnostic and prognostic roles.[13] In RV failure secondary to massive PE, cardiac troponins are thought to be elevated secondary to RV ischemia or microinfarctions resulting from increased wall tension, metabolic demand, and reduced coronary perfusion with or without atherosclerosis.[13]

The myocardium synthesizes and secretes BNP as a result of increased RV shear stress caused by the acute PE. In general, the cutoff values for troponins in PE prognostication are identical to those for the diagnosis of myocardial ischemia. However, the BNP cutoff values are usually lower than those used for congestive heart failure. In patients with acute PE, elevated cardiac biomarkers may suggest the presence of RV failure and help to identify this high risk population.[13]

Treatment

Heparin constitutes the cornerstone of management of PE. It accelerates the action of antithrombin III, thereby preventing additional thrombus formation and permitting endogenous fibrinolysis to dissolve some of the clot.[14] Thrombolysis can be lifesaving in patients with massive pulmonary embolism, cardiogenic shock, or overt hemodynamic instability. Thrombolytic agents accelerate the lysis of the PE.[15] Currently, the Food and Drug Administration (FDA) recommends thrombolysis for the treatment of "massive pulmonary embolism."[6] "Massive" universally indicates cardiogenic shock secondary to PE, but also can suggest profound hypoxemia or impending respiratory failure.[16] Several studies have shown the physiological benefits of thrombolytics in cases of PE such as improvement in hemodynamics, oxygenation, and a lower incidence of early PE recurrence, but they have not shown a clear long-term mortality benefit.[16,17] According to the results of Phase 1 of the Urokinase Pulmonary Embolism Trial, hemodynamically stable patients treated with anticoagulation alone have similar outcomes as those treated with thrombolytics. Importantly, the difference in the degree

of clot resolution between the two groups progressively decreases after 24 hours, such that both treatment groups have no difference in clot burden at five or 14 days or even several months.[18]

A controversial issue is the administration of thrombolytics to patients with "submassive" PE, defined as right ventricular dysfunction associated with preserved systemic arterial pressure.[19] Right ventricular hypokinesis in the presence of normal systemic arterial pressure predicts an adverse clinical outcome.[1]Among the patients who underwent echocardiography, a finding of right ventricular hypokinesis was associated with a doubling of the mortality rate at 14 days and with a rate at three months that was 1.5 times that in patients without hypokinesis.[20] In the Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET) of 1001 patients with pulmonary embolism and right ventricular dysfunction,[21] the mortality rate increased as right ventricular failure worsened. Multivariate analysis of the patients in the MAPPET registry suggested that those who were initially treated with thrombolysis plus anticoagulation had better clinical outcomes than those who were initially treated with anticoagulation alone.[21] Proponents of the expanded criteria for thrombolysis claim a potential survival advantage, fewer recurrences of PE (through the dissolution of the clot at its venous origin) and long term prevention of pulmonary hypertension with improved quality of life.[6]

In one large randomized trial by *Konstantinides et al,*[19] 256 hemodynamically stable patients with PE complicated by any degree of pulmonary hypertension and/or echocardiographic findings of right ventricular dilatation and/or electrocardiographic signs of right ventricular strain were randomized to receive heparin plus placebo or heparin plus alteplase. The alteplase group had less need for escalation of therapy (10.2% vs 24.6%, p=0.004) defined as the need to use rescue thrombolytics, vasopressors, or mechanical ventilation for respiratory failure. There was no significant difference in the mortality risk. This could be partly explained by the use of rescue thrombolytics in 23% of the patients assigned to the heparin plus placebo group. Another nonrandomized trial by *Konstantinides et al*[22] which included 719 hemodynamically stable patients with evidence of right ventricular dysfunction or pulmonary hypertension showed a survival benefit in those who were initially treated with thrombolysis plus heparin compared to those initially treated with heparin therapy alone (mortality 4.7% vs 11.1%) and a lower incidence of recurrent PE (7.7% vs 18.7%).[1,22]

CONCLUSION

Pulmonary emboli are potentially life threatening occurrences associated with significant morbidity and mortality both in the early and late stages.[2] There are a variety of diagnostic tools that maximize our ability to detect PE and enable better prognostication. Right ventricular dysfunction and the release of cardiac biomarkers are associated with more adverse events.[23] Patients treated with thrombolytic therapy show rapid improvement of right ventricular function and pulmonary perfusion which may lead to a lower rate of early recurrent PE and a decrease the late sequela of chronic pulmonary hypertension.

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CME QUESTIONS

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Choose the answer that is most correct for each question.

1. All of the following are true concerning pulmonary embolism (PE) except?
   a. The mortality rate for untreated pulmonary embolism (PE) is as high as 30%.
   b. The most common source of pulmonary emboli is from the popliteal veins.
   c. Chronic pulmonary hypertension affects approximately 4% of patients within two years after the first symptomatic PE.
   d. Syncope, hypotension, or cyanosis usually indicates a massive PE.
   e. The mortality rate is three times higher if right ventricular dysfunction is present.

2. All of the following findings suggest the presence of right ventricular dysfunction and have prognostic roles in the assessment the severity of PE except?
   a. Right ventricular to left ventricular (RV:LV) ratio of greater than one with septal bowing seen on axial slices of a contrast computed tomographic study.
   b. Elevated pulmonary artery pressures in the absence of underlying cardiopulmonary disease.
   c. The presence of elevated cardiac biomarkers.
   d. Indeterminate ventilation-perfusion scan.
   e. The echocardiographic finding of regional right ventricular dysfunction in which apical wall motion remains normal despite hypokinesis of the free wall.

3. Which of the following is not true regarding the use of thrombolytic therapy in the treatment of PE?
   a. Thrombolytic agents accelerate the lysis of the PE and help to decrease the late sequela of chronic pulmonary hypertension.
   b. Patients treated with thrombolytic therapy show rapid improvement of hemodynamics and oxygenation and have a lower incidence of early PE recurrence.
   c. Thrombolytic agents are FDA approved for the treatment of PE associated with hemodynamic compromise, profound hypoxemia, or impending respiratory failure.
   d. There is a clear long-term mortality benefit in using thrombolytic agents.
   e. Administering thrombolytic agents to all patients showing signs of RV dysfunction is a controversial issue.

4. True/False:
   Cardiac troponins and brain naturetic peptide (BNP) are released secondary to RV ischemia/infarction resulting from increased wall tension, shear stress, and metabolic demand and reduced coronary perfusion with or without atherosclerosis?