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Management of Acute Pulmonary Embolism: Anticipating and Responding to Complexity

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Stem Case and Key Questions Content

A 71-year-old 55 kg male is admitted to the surgical intensive care unit (SICU) following a left hemicolectomy for a sigmoid colon carcinoma, under general endotracheal anesthesia.
Past Medical History: One year ago, the patient was diagnosed with a prostatic cancer. He completed a successful course of radiation therapy 3 months prior to the current procedure. The patient has a history of hypertension that was well controlled on hydrochlorothiazide and smoking (pack year index: 20). Five years ago, the patient underwent a left total hip arthroplasty complicated by the development of a deep vein thrombosis for which he received a 6-months course of warfarin.

The patient's preoperative echocardiogram shows an ejection fraction of 55%, and moderate left ventricular hypertrophy. Preoperative electrocardiogram shows non-specific T-wave changes and normal sinus rhythm. Pertinent preoperative chemistry is: hematocrit of 40%, serum creatinine of 1.2 mg/dl, and an International Normalized Ratio (INR) of 1.2.
Intraoperatively, a left radial arterial line catheter and a right internal jugular central venous catheter are placed under ultrasound guidance. The surgical procedure is significant for a total blood loss of 2.5 liters due to an inadvertent injury to the inferior mesenteric artery. The patient is fluid-resuscitated in the form of 7 units of packed red blood cells, and 4 units of fresh frozen plasma. Additionally, the patient receives 3 liters of Lactated Ringer's solution. Total urine output is 750 ml.

An intra-operative blood gas shows the following: PH: 7.21, PaCO2: 37, PaO2: 83, HCO3: 17, BE: -8 (FIO2= 0.8). The procedure lasts for 4.5 hours. Based on massive Intraoperative resuscitation and ongoing acidemia, a decision is made to transfer the patient to the SICU with the endotracheal tube in place. Twenty-four hours later, and after clearance of acidemia, the patient is successfully extubated.

Over the course of 3 hours after extubation, the patient develops shortness of breath, and chest pain. The pulse oximeter reading shows a decline from 98 to 86%, and the blood pressure is 80/60.

1. Discuss the differential diagnosis of an acute hypoxemia and hypotension?

2. In the light of the above history, what is the most likely diagnosis?

3. What tests would you perform to confirm your diagnosis?

4. What is the mechanism of hypoxemia in this patient?

The patient's trachea was successfully intubated, and mechanical ventilation was begun. 500 ml of Lactated Ringers were administered over 15 minutes. A chest X-ray was performed, and a complete blood count, coagulation panel, arterial blood gas (ABG) and a bilateral upper and lower extremity duplex ultrasonography were ordered.

5. The ABG showed: PH7.32/ PaCO2 35 mm Hg/ PaO2 58/ Hco3 23/-1 (FIO2= 1). Interpret these results. Provide a differential diagnosis.

6. Discuss the utility of obtaining an EKG in this patient's management.

7. If troponin levels were drawn in this case, predict what they might be.

8. An echocardiogram is ordered and shows a right ventricular transverse diameter that is equal to left ventricular transverse diameter. What is your interpretation?

9. Serum creatinine rises to 2.2 mg/dl; discuss the utility of ordering a CT angiography (CTA) to rule out an acute PE under this circumstance. Indicate any further action, if any. Defend your answer.

10. Would you start a thrombolytic on this patent? Why or why not? Defend your answer.

11. What would be the indications of surgical pulmonary embolectomy in this case?

12. What pressor would you choose to support the circulation pending definitive action? Your response should include a rationale that focuses on desired physiologic and pharmacologic effects.

13. Discuss the utility of a pulmonary artery catheter to monitor pulmonary vascular pressures in this case.

14. Pulmonary artery pressures were 52/38, mean 42 mm Hg, what would you do next?

15. Discuss the utility of placing an inferior vena caval filter in this patient. Your response should include a rationale that focuses on the risks and benefits both short and long term.

16. Discuss the long-term anti-coagulation management of this patient. Your discussion should include the interaction between anti-coagulation and IVC filter.

17. The official diagnosis of this patient was 'submassive pulmonary embolism'. How different is 'submassive' from 'massive'? Are there any differences in management?

Model Discussion Content

Acute pulmonary embolism is a ubiquitous and potentially fatal condition in hospitalized patients. It is estimated that 600,000 episodes occur each year in the US resulting in 100,000 to 200,000 deaths [1].

Pulmonary venous thrombo-embolism commonly arises from deep venous thrombi in the calf veins. The latter has the potential to propagate to more proximal veins including and above the popliteal veins from which, they are more likely to embolize [2].

In acute PE, the mechanism of ventilation-perfusion mismatch is both mechanical; as a result of obstruction by the embolus and humoral; via the release of vasoactive mediators such as serotonin that lead to pulmonary arteriolar constriction with secondary right ventricular strain, dilatation, dysfunction and eventually failure [2].

Diagnosing acute PE can be challenging since many common conditions in critically ill patients have similar clinical presentation. The differential diagnosis in our patient encompasses acute lung injury due to massive blood transfusion, pneumothorax secondary to central venous catheter placement, pulmonary edema secondary to acute myocardial infarction, new onset pneumonia as well as acute pulmonary embolism. Failure to timely diagnose and treat any of these conditions can lead to fatal consequences.

Multiple clinical scoring systems [3] (Table1) were developed in order to raise clinical suspicion of an acute PE. Based on Wells and Geneva clinical criteria[4], our patient's criteria fit to a high probability of an acute PE: age older than 65, recent surgery, recent cancer, immobilization, presence of DVT, and tachycardia.

The next step in diagnosing PE is to evaluate the patient for signs of hemodynamic instability (a systolic blood pressure 40 mmHg in the absence of other causes) [5]. Hemodynamically stable patients with a high clinical probability of PE should undergo a multi-detector computerized tomography (CT) to confirm the diagnosis. Patients who are too unstable to be transferred to a radiology suite to undergo a multi-detector CT should be immediately placed on therapeutic doses of intravenous heparin. They should then undergo an echocardiographic examination to check for right ventricular dysfunction suggestive of a PE-induced acute right ventricular pressure overload. Our patient was hemodynamically unstable based on his BP and he was not a suitable candidate to undergo a multidetector CT without a delay. Also, his serum creatinine was elevated, representing a relative contraindication for computerized tomographic angiography (CTA). Multidetector CT is 97% sensitive for the diagnosing PE [6]. Once the diagnosis is confirmed, an elective echocardiography should be performed to rule out signs of right ventricular dysfunction, which correlates with prognosis.

The third step in managing an acute PE is risk-stratification. It is crucial to distinguish between massive, sub-massive and non-massive PE since the prognosis and treatment vary drastically (Table 2). Patients with massive PE manifested by shock and sustained not otherwise-explained hypotension have a high mortality [7] and are candidates for both anticoagulation and thrombolysis [5]. Patients with non-massive pulmonary embolism are not in shock and show no signs of right ventricular strain or of myocardial necrosis. They are candidates for therapeutic anticoagulation only (thrombolysis not indicated) and have a lower mortality. Patients with submassive PE are those who are hemodynamically stable but have signs of right ventricular dysfunction or myocardial necrosis. The management of these patients is controversial in terms

of whether to add thrombolysis to anticoagulation. Prognostically, signs of right ventricular dysfunction and myocardial necrosis are associated with poor prognosis. An S1, Q3, T3 pattern, a P- wave pulmonale, a right axis deviation and a right bundle-branch block, are all electrocardiographic signs of right ventricular dysfunction suggestive of massive rather than smaller pulmonary emboli. An increase in the diameter of the right ventricle in relation to that of the left ventricle predicts adverse short term outcomes in terms of in-hospital death, mortality at 30 days and at 3 months [8]. Elevated serum troponins are associated with a 9.4 times more risk of death from PE [9]. Therefore, serum troponins could be elevated in acute pulmonary embolism due to right ventricular myocardial necrosis that is not precipitated by an acute coronary syndrome.

Treatment of acute PE is both definitive and supportive. Definitive treatment entails therapeutic anticoagulation using either unfractionated or low molecular weight heparin. Compared to un-fractionated heparin (UFH), low molecular weight heparin (LMWH) is associated with fewer incidences of embolic recurrence, less bleeding, and similar all-cause mortality in patients with non-massive PE [10]. Compared to UFH, LMWH has more predictable pharmacokinetics, does not require frequent monitoring, and is associated with less incidence of heparin-induced thrombocytopenia. Besides, LMWH has been shown to specifically decrease the risk of death in patients with DVT, compared to UFH [10]. Thrombolysis is reserved for patients with massive PE. Patients with submassive PE are a controversial group for using thrombolysis. Data from the recently completed EMPEROR trial [11] suggest that the mortality in patients with submassive PE treated with therapeutic anticoagulation is less than 3% with less additional mortality benefit from adjunctive thrombolysis. However, long-term outcomes in terms of right ventricular function and quality of life remain to be determined. Intravenous thrombolysis is associated with more rapid resolution of right ventricular dysfunction [12]. Hemodynamically unstable patients with contraindications for intravenous thrombolysis or with ineffective thrombolysis could be candidates for percutaneous thrombectomy or surgical embolectomy justified by the high mortality of hemodynamically unstable PE [13]. Surgical embolectomy may be performed off- cardiopulmonary bypass, with normo-thermia, and without cardioplegia or fibrillatory arrest. A hybrid procedure may be performed where catheter mechanical thrombectomy is combined with local infusion of thrombolytic agents such as tissue plasminogen activator. Hybrid techniques have been shown to improve the clinical success of mechanical thrombectomy [14]. Systemic thrombolysis increases the risk of bleeding and is mainly contraindicated in patients with intracranial disease, recent major surgery or trauma. The decision to proceed with surgical, catheter-based or hybrid procedures requires an interdisciplinary teamwork discussion, and should be performed in centers with facilities and expertise for such procedures.

Supportive treatment includes the use of inotropes and vasopressor to support cardiac function and to maintain peripheral tissue perfusion as well as mechanical ventilation to maintain oxygenation and ventilation. Placement of a pulmonary artery catheter (PAC) to monitor pulmonary artery pressures is not warranted, and may be risky in patients with acute PE. Placement of PAC may be associated with arrhythmias that may worsen the hemodynamic instability of patients in acute PE. Additionally, PAC carries the risk of dislodging a pulmonary embolus. Furthermore, information about pulmonary artery pressure and secondary right ventricular dysfunction can be obtained non-invasively by bedside echocardiography.
An ino-dilator such as milrinone would be an ideal drug to start in this situation. Milrinone is a phosphodiesterase-3 inhibitor that prevents the breakdown of the enzyme adenyl cyclase- the

enzyme that catalyzes the formation of cyclic adenosine monophosphate (cAMP) - thus increases intracellular calcium and hence cardiac inotropy. An increase in vascular smooth muscle c-AMP produces pulmonary and systemic vasodilation. It should be emphasized, however, that milrinone may be associated with systemic hypotension by virtue of its severe vasodilation leading to a reduction in coronary perfusion pressure and worsening of right ventricular ischemia by not meeting the increased demand of the strained right ventricle. Therefore, adding a vasopressor may be indicated to counter the severe vasodilator action of milrinone while maintaining its inotropic action.

Regarding vasopressors, vasopressin is more favorable than norepinephrine in the setting of elevated pulmonary artery pressure and secondary right ventricular failure. Vasopressin is not associated with an increase in the pulmonary vascular resistance, which could worsen right ventricular afterload. Selective pulmonary vasodilators such as inhaled prostacyclin could be used to produce pulmonary vasodilatation (via the production of cyclic adenosine monophosphate- cAMP) to lower PE-induced pulmonary hypertension. It also improves ventilation perfusion mismatch and hence improves gas exchange. It is less expensive and produces no toxic metabolites compared with nitric oxide [15].

Insertion of IVC filters is reserved for patients with a contraindication to anticoagulation, for recurrent thromboembolism while on anticoagulation and for patients in whom a recurrent PE would be fatal [5]. Although IVC filters are effective in reducing the incidence of acute pulmonary embolism, they increase the incidence of subsequent deep vein thrombosis. It therefore important to resume anticoagulation once its contraindication has resolved. Patients with long-term contraindication anticoagulation qualify for a permanent IVC filter. Our patient qualifies for a permanent IVC filter because of his poor cardiopulmonary reserve and the possibility of a fatal consequence of a future PE. I propose a three-legged approach for the diagnosis and

management of acute pulmonary embolism (Figure 1).

Acute Pulmonary Embolism
Post Discussion Quiz
1. Which of the following clinical pictures BEST describes a sub-massive acute PE?
BP HR Serum Troponins TTE
a. 90/50 110 0.04 Normal RV
b. 95/45 105 0.2 Normal RV
c. 85/35 110 0.2 Dilated RV
d 89/50 120 0.6 Hypokinetic RV free wall
e. 96/55 120 100
b. Recent surgery
c. ET CO_2 less than 35
d. PaO_2 less than 47
e. Mild calf edema and tenderness on palpation
3. Which of the following pressures is most likely to be elevated in an acute PE?
a. Aortic systolic pressure
b. Left ventricular end diastolic pressure
c. Pulmonary venous pressure
d. Intracranial pressure
e. Pulmonary artery systolic pressure

4. Compared to low molecular weight heparin, un-fractionated heparin is associated with a higher incidence of heparin-induced thrombocytopenia.
a. False
b. True
5. 86-year-old male admitted to the ICU S/P right hip replacement for an inter-trochanteric hip fracture that resulted from a fall. His past medical history is significant of cancer and DVT. The following is his clinical picture:
Vitals: BP: 85/40, HR: 100, RR: 35, P/E: Diaphoresis, labs: BNP > 20,000, Troponins T 0.05, Hb 7.6, BUN: 44, serum creatinine: 1.1, TTE: Severe TR, severely dilated hypokinetic RV, estimated PASP: 64/33.
Which of the following is/are the MOST appropriate vasoactive therapy?
a. Milrinone + norepinephrine
b. Dobutamine + Epinephrine
c. Epinephrine + Milrinone + isopreternol
d. Vasopressin
e. Milrinone + vasopressin
6. Which of the following is the most appropriate treatment of an acute massive PE?
a. Low molecular weight heparin only
b. Un-fractionated heparin only
c. Un-fractionated heparin + low molecular weight heparin
d. Alteplase only
e. Un-fractionated heparin + alteplase
7. A permanent IVC filter would be MOST appropriate for which of the following patients?
a. 86-year-old male S/P acute massive PE
b. 90-year-old male S/P fall & acute PE
c. 35-year-old female with protein C deficiency S/P submassive PE
d. 30-year-old male with DVT S/P knee arthroscopy
e. 48-year- old female with autoimmune thrombocytopenia S/P hysterectomy
8. Mechanisms of hypoxemia in acute PE are best explained as,
a. Mechanical
b. Humoral
c. Hormonal
d. Humoral + mechanical
e. All of the above
9. 55-year-old male S/P coiling of an intracranial aneurysm develops an acute massive PE. The patient has a history of recurrent DVTs.
Which of the following is the most appropriate therapy?
a. Placement of an IVC filter
b. Surgical thrombectomy on cardiopulmonary bypass
c. IV alteplase
d. Catheter-based thrombectomy
10. A hybrid technique means,
a. Use of low molecular weight heparin together with oral anticoagulant
b. Use of surgical embolectomy with catheter thrombectomy
c. Use of surgical embolectomy with local thrombolysis
d. Use of catheter thrombectomy with local thrombolysis

Table 1. Scoring System for Clinical Suspicion of Acute pulmonary Embolism (3)	
Variable	**Score**
Wells Scoring System	
Clinical signs of DVT	3
Alternative diagnosis less likely	3
Pulse greater than 100	1.5
Immobilization or surgery in previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1
Malignancy	1
Geneva Scoring System	
Age 60-79 ≥80	 1 2
Previous DVT/PE	3
Recent surgery	3
Pulse>100	1
PaC02 in mm Hg <36 36-39	 2 1
Pa02 in mm Hg <48.7 48-59 60-71 72-82	 4 3 2 1
CXR Platelike atelectasis Elevated hemidiaphragm	 1 1

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