**Pulmonary Embolism**

**MINICASES**

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**Summary**

**Pulmonary embolism (PE) is an important and potentially fatal disorder of the pulmonary vasculature and right ventricle. This minicase session will address the risk factors for PE, as well as the pathophysiology, clinical presentation, and principles of diagnosis and treatment of PE. Patient outcome depends on the interaction between the size of the thromboembolism and the patient’s underlying cardiopulmonary reserve.**

**Preparatory Instructions/Session Resources**

1. Session notes
   1. Relevant previous sessions in this course
      1. Functional anatomy of the pulmonary vasculature 2/6/18)
      2. Pulmonary Hypertension Large group and minicases 3/12/18
      3. Introduction to hemostasis (3/13/18)
      4. Thrombophilia and Anticoagulants (3/15/18)
   2. Relevant sessions from previous courses
      1. Foundations Pathology-5 – Endothelium, Hemostasis, and Thrombosis section on The Coagulation Cascade.
2. Required readings
   1. Weinberger Ch. 12 – Anatomic and Physiologic Aspects of the Pulmonary Vasculature--whole chapter. It’s short! (this is review from 3/12)
   2. Weinberger Ch. 13 – Pulmonary Embolism (skip section on treatment.)
   3. Session notes (below)
3. Assess your understanding of the preparatory material by completing THE READINESS ASSESSMENT on Learning Catalytics.
4. Consider these Thought Questions
   1. A typical arterial blood gas in patients with acute, submassive PE shows a widened Aa gradient, decreased PaCO2, and increased pH. By obstructing a pulmonary artery or arteriole, acute PE causes an abrupt increase in dead space. That is, the alveoli normally perfused by the blocked artery will now be ventilated but not perfused. How can you reconcile the abrupt increase in dead space with the typical blood gas?
   2. Pulmonary infarct is a relatively unusual complication of PE. The risk factor for pulmonary infarction are congestive heart failure (i.e. an increase in pulmonary venous pressure) and a smaller, more distal embolism. Explain these observations. Think about the dual blood supply to the lungs, the capillaries, and the venous drainage of the lungs to the left atrium.

*Session goals / objectives:*

1. Describe the anatomy of the pulmonary vasculature and the dual blood supply to the pulmonary parenchyma.
2. Describe the principles of imaging the pulmonary vasculature and how these principles relate to diagnosing pulmonary emboli.
3. Describe how the interaction between the size of a pulmonary embolism and the underlying cardiopulmonary reserve influences the clinical presentation of PE (i.e. PE “Syndromes”)
4. Describe the gas exchange abnormalities expected in patients with pulmonary emboli.
5. Pharmacology (This will be addressed in the Thrombophilia and Anticoagulants large group session on 3/15)—describe the mechanism of action of the following drugs:
   1. Heparins
      1. Standard heparin
      2. Low-molecular weight heparin (enoxaparin)
   2. Warfarin
   3. Factor Xa Inhibitor
      1. Direct oral anticoagulants (DOAC)
         1. Rivaroxaban
         2. Apixaban
      2. Fondaparinux
   4. Direct Thrombin inhibitors
      1. Argatroban (IV)
      2. Dabigatran (oral)

**Be able to define the following terms:**

*From earlier sessions*

Term 1 CTA chest

Term 2 D-dimer

*For this session*

Term 1 Ventilation-perfusion scan

*Why should you care?* Pulmonary embolism is a potentially life-threatening disorder. Prompt diagnosis and treatment are essential in decreasing the morbidity and mortality. Most commonly, it is not the existing pulmonary embolism that kills a patient; rather, it is the *next* pulmonary embolism from untreated thrombosis that is fatal. Unfortunately, the clinical presentation of patients with PE (dyspnea +/- chest pain) is non-specific and overlaps with many other less dangerous problems. Thus, PE is a notoriously missed diagnosis unless you have a high index of suspicion.

The clinical presentation of pulmonary emboli (PE) depends on the interaction of two factors: the size of the clot burden and the underlying cardiopulmonary reserve of the patient. If a thromboembolism causes a substantial obstruction of the pulmonary vasculature and significant increase in right ventricular afterload to which the right ventricle (RV) is unable to respond sufficiently, a patient will suffer acute RV failure. In simple terms, when a patient is unstable or dies directly related to PE, it is the result of right ventricular (RV) failure—that is, the RV is unable to generate enough pressure to overcome an acute increase in RV afterload. Thus, a small clot burden in a patient who has poor baseline RV function can lead to hemodynamic compromise, whereas a patient with a well-functioning RV can withstand a larger abrupt increase in afterload without failing.

In this section, a simplified outline to help you start thinking about PE pathophysiology, clinical presentation, diagnosis and treatment is presented. Just as dividing COPD into “pure” emphysema vs. “pure” chronic bronchitis is artificial—but helps us think about the disease—the “PE Syndromes” below present a straightforward framework to help you begin to understand PE pathophysiology.

**PE “Syndromes”:**

1. **Submassive or small PE leading to acute or subacute dyspnea—can also be asymptomatic**
   1. Most common presentation, but easy to miss. You must think about it!
   2. Most patients (~70%) will have dyspnea
   3. Other typical findings are\* (from the PIOPED study 1990)
      1. Dyspnea at rest or with exertion (73 percent)
      2. Pleuritic pain (44 percent)
      3. Cough (37 percent)
      4. Orthopnea (28 percent)
      5. Calf or thigh pain and/or swelling (44 percent)
      6. Hemoptysis (13 percent)
      7. \*Please note—you do *NOT* have to memorize these numbers—just appreciate that the presentation is often non-specific. Dyspnea occurs in most, but all of the other findings occur *<50% of the time.* Hemoptysis is actually fairly unusual.
   4. Small to moderate clot burden
   5. Hemodynamically *stable*
      1. Normal blood pressure, normal heart rate (or slight tachycardia)
      2. RV is coping with the relatively small increase in afterload.
   6. Diagnosis
      1. Screen with D-dimer
      2. Chest CT angiogram
      3. Ventilation-perfusion scan
   7. Treatment
      1. Prompt institution of anticoagulation is essential
      2. May start anticoagulants before actually confirming the diagnosis
2. **Pulmonary infarction** (This is really a subset of #1, but separated here to emphasize the pathophysiology.)
   1. Relatively unusual (15% of patients) due to the dual blood supply of the lung
   2. Risk factors for infarction in patients with PE:
      1. Congestive heart failure (why? See thought question)
      2. Occlusion of smaller, more distal vessel
   3. Often associated with hemoptysis
   4. Often appears as wedged shaped, pleural based density on chest x-ray or CT scan
      1. So called, “Hampton’s Hump” for those who like a little medical history. The sign was first described by Dr. Aubrey Otis Hampton who was Chief of Radiology at MGH in the 1940s.
   5. Diagnosis and Treatment is the same as #1
      1. Note-In most clinical scenarios, bleeding is at least a relative contraindication to anticoagulation. However, a small amount of hemoptysis due to PE is **NOT** contraindication for anticoagulation. (Why? See thought questions)
3. **Acute Massive PE**
   1. Least common, but easiest to understand.
   2. Large clot burden
   3. Presentation dominated by *shock*
      1. Hypotension, tachycardia
      2. Acute, abrupt increase in RV afterload causing RV failure
   4. High mortality
   5. Diagnosis
      1. Most often you are looking for signs of RV strain/failure
         1. Echo, biomarkers
   6. If patient survives to seek medical care:
      1. Anticoagulate
      2. Consider lytic therapy
      3. Consider thrombectomy (catheter-based or surgical)
4. **Chronic Thromboembolic Pulmonary Hypertension (CTEPH)**
   1. Chronic PE resulting in chronic pulmonary hypertension
   2. Results from recurrent thromboemboli entering the pulmonary circulation, getting “stuck”.” The fresh clot is stuck to vessel wall and eventually becomes covered with endothelium, and the vessel wall remodels. The obstruction of and increased vascular resistance in the pulmonary arteries are due to the remodeling—not due to fresh clot.
   3. Although thought to be stimulated by recurrent pulmonary thromboemboli, this is a different disease. CTEPH is a subset of pulmonary hypertension.

**PE: Pathophysiologic Consequences**

1. Hemodynamic
   1. As discussed above, the hemodynamic consequences depend on the interaction between clot burden and RV function.
   2. The “syndromes” above are over- simplified. Patients often present somewhere between hemodynamically stable and shock. You are then left to decide how aggressively to treat, and whether a patient should undergo thrombolysis.
   3. “Clot burden” is also an oversimplification. The pulmonary vasculature will undergo a variable degree of vasoconstriction after a PE. This is thought to be due to an imbalance between production of vasodilators (primarily nitric oxide) and vasoconstrictors (primarily endothelin-1) by the injured endothelium.
2. Gas Exchange
   1. If the only effect on gas exchange was due to an acute occlusion of a pulmonary artery, the only consequence would be an acute increase in dead space. There should be no effect on oxygenation (unless the increase in dead space is so large that the PaCO2 increased.) (Think about this a little bit before moving on…)
   2. The typical blood gas in a small to medium sized PE is a decreased PaCO2 (i.e. Hyperventilation) and a widened Aa gradient. These findings result from:
      1. An increase in alveolar ventilation—that is, the patient is able to increase total ventilation enough to overcome any increase in dead space.
      2. Increased V/Q mismatch due to release of vasoactive and “bronchoactive” mediators:
         1. Primarily from Clot (platelets)
            1. Thromboxane A2
            2. Serotonin
         2. Primarily from injured endothelium
            1. Endothelin-1
            2. ⇓ Nitric Oxide
      3. Some degree of shunt may occur due to
         1. Surfactant dysfunction within 24 hrs leading to atelectasis in the lung segment distal to the clot.

**Diagnosis of PE**—

1. Screen with D-dimer testing
2. Chest computed tomographic angiography (CTA) most common diagnostic test.
3. Ventilation Perfusion Scan (VQ scan)
   1. used less frequently
   2. most commonly used in pregnant women given lower radiation dose compared with CTA.
4. Pulmonary Angiogram
   1. rarely used
   2. invasive, higher radiation dose

**Treatment of PE**

1. The most important concept is to *think of the diagnosis and treat quickly* to decrease the likelihood of another embolism!
2. Unless a patient is presenting with an acute massive PE, it is not the clot that is in the lungs that will cause mortality…it’s the clot still sitting in the veins waiting to embolize. Prompt anticoagulation decreases the risk of recurrent embolization and markedly decreases mortality.
3. Anticoagulant choice must be individualized for the patient.
4. Patients with a high risk of bleeding (brain tumor, recently post-op, etc.), may not be candidates for anticoagulation.
5. Anticoagulants (You should be familiar with the route of administration and mechanisms of action of these drugs.)
   1. Heparins
      1. Standard heparin
      2. Low-molecular weight heparin (enoxaparin)
   2. Warfarin (not appropriate for acute anticoagulation…why?)
   3. Factor Xa Inhibitor
      1. Direct oral anticoagulants (DOAC)
         1. Rivaroxaban
         2. Apixaban
      2. Fondaparinux
   4. Direct Thrombin inhibitors
      1. Argatroban (IV)
      2. Dabigatran (oral)

**Minicase I**

**Part I**

Ayse Katenay is a healthy 29 year old woman. Ms. Katenay is traveling from California to Boston on a seven hour plane flight where she is presenting at a conference on Native American Health. Two weeks prior to the trip, she suffered a rock-climbing accident and tibial fracture involving the articular surface of her distal femur. She is in a long-leg cast. For the last few days prior to the trip, her leg has been more swollen and uncomfortable. She considered staying home, but this was an important presentation for her. The night before her trip, she was so busy putting last minute touches on her talk that she skipped dinner. She also got up late, and had no time for breakfast.

During the flight, her leg became more uncomfortable, and she experienced some funny chest pains and felt a little short of breath and anxious. She decided she was just nervous about her presentation.

You happen to be sitting next to Ayse on the plane. You check her pulse—it is strong, HR = 110, RR = 20. You notice that her foot is quite swollen below the cast. You remember your fabulous Homeostasis I course and think about what you would do if she was your patient in the Emergency Department.

**Question 1. Describe a screening blood test could be used to help guide further evaluation in a patient with possible deep venous thrombosis and/or pulmonary embolism.? Would this be appropriate for Ms. Katenay?**

**Question 2. *IF* you were seeing her in the ED, what would you do next?**

You are quite worried about Ayse, and recommend she go to the Emergency Room as soon as she lands. You offer to accompany her.

During the descent, Ayse has the abrupt onset of severe dyspnea and distress. She is having trouble talking and looks like she might pass out. You check her pulse again. HR = 138 but now hard to feel. You check her carotid pulse, and it is also barely palpable. You ring the call button for the Flight Attendant and clearly state:

“Please get some oxygen immediately. I am a physician in training. She is having a medical emergency. The plane needs to land as soon as possible, and an ambulance needs to be waiting to take this patient to the hospital. ”

**Question 3. What is the role of the physician/health care professional in the non-clinical setting?**

The plane is met on the tarmac at Logan and Ms. Katenay is brought to the ED by ambulance. A large bore IV is started, and she receives a liter of normal saline before reaching the ED. The EMTs obtained the following additional information: She is in a long cast immobilizing her knee. She takes oral contraceptives but no other medications. She does not smoke.

In the Emergency room a focused physical exam is performed:

She is in marked respiratory distress.

VS: RR 26, BP 92/64, HR 110, SaO2 97% on supplemental oxygen

Chest: few crackles at right base.

Heart: neck veins are elevated at 12 cm, tachycardia, normal S1, S2 is split with a loud P2.

Extremities: right leg is normal, left leg is in long cast, visible part of the left foot appears swollen.

**Question 4. Summarize the case. What are the pertinent positives and negatives in her history and on physical exam? What is your next step?**

Intravenous saline is administered, and her blood pressure increases to 104/64, heart rate decreases to 98. She appears much more comfortable. Anticoagulation is started, and further studies are done.

**Question 5. A CTA confirms multiple large bilateral pulmonary emboli with some evidence of right heart strain. How do the size of pulmonary emboli and a patients underlying cardiopulmonary reserve interact to determine clinical presentation?**

**Question 6. Which anticoagulant(s) is/are most appropriate at this point? Why? (Please review the mechanism of action of the drugs listed in the objectives on your own.)**