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# Pulmonary Embolism

## Winning the Game of Hide and Seek

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### Overview:

Pulmonary Embolism (pulmonary thromboembolism, pulmonary embolus or emboli, PE) is the third most common cause of death in the United States. It is a condition of which a venous blood clot, referred to as venous thromboembolism or VTE, gets lodged in a vessel of the pulmonary vasculature blocking blood flow to the lung segments distal to that point. This causes a sudden V/Q (ventilation/perfusion) mismatch, deoxygenation, pulmonary instability, and hemodynamic instability. Even in today's world of advanced medical technology PE remains a leading cause of sudden unexpected death (commonly referred to as "Sudden Death Syndrome" or "sudden cardiac death"), second only to coronary artery disease.

Pulmonary Embolism is not a disease. Rather, it is an often fatal complication of a much larger problem. Close to 90% of the patients who suffer from PE's are found to have VTE (*venous thromboembolism*) elsewhere in the body. Most of the time they are in the legs, a condition known as DVT's or deep vein thrombosis. 60% of all DVT's are in the legs and 80% of all leg DVT's start in the calf veins. Keeping these numbers aside understand that VTE or DVT can occur anywhere in the body. They are caused by one or more of three elements known as *Virchow's Triad*; hemostasis, hypercoagulability,

and vessel wall damage. Any one of these elements can trigger the coagulation cascade – a very complex chain of chemical reactions that results in the formation of a thrombus.

Diagnosing and effectively treating a pulmonary embolus can be one of the most challenging tasks in emergency medicine. A young, and otherwise healthy, patient with a pulmonary embolus (PE) can present to the Emergency Department with something as vague as mild shortness of breath, and be dead an hour later. Was something done wrong? Did the hospital staff miss something? Was the ER Physician negligent in looking for a cause of shortness of breath? I think not. More often than not PE's are very difficult to diagnose. In fact, PE's are only found in about 60% of the cases of which they are suspected, even with the most experienced medical staff. That makes them one of the greatest hide-n-seek killers of our time.

What normally happens when a patient presents complaining of mild shortness of breath is the usual battery of tests for such a complaint. A chest X-Ray is ordered. Blood tests looking for cell counts, cardiac enzymes, and arterial blood gases are done. Some physicians might even order a standard chest CT looking for things that are obvious, yet not so obvious. These are very good things to do but none of them will reveal a pulmonary embolus. The hardest part of treating a pulmonary embolus is finding it. It is therefore of utmost importance to suspect PE whenever a patient has a complaint of shortness of breath and a clear chest film.

It takes a special combination of several different tests combined with a PE probability scoring method (such as the Wells score), along with the evaluation of risk factors and presentation to have the best possible odds in accurately diagnosing a pulmonary embolism. The medical community is continually researching for better ways to reach this goal. I have researched the medical literature and compiled information on the most current combination of tests and information to obtain the best possible outcome in the never ending quest to accurately diagnose and treat a pulmonary embolism.

## **Incidence:**

Pulmonary embolism (PE) poses a great challenge to even the most experienced physicians. With over 650,000 cases, and almost 150,000 deaths annually, the effective diagnosis and treatment of

pulmonary embolism is of extreme importance. It is the second leading cause of sudden unexpected death in all age groups. Approximately 60% of all fatal PE's are not diagnosed until autopsy because they are very difficult to find even when signs and symptoms are not so vague. In most fatal cases pulmonary embolism isn't even considered, even when classic signs and symptoms are documented. There are several studies that show 60% of patients who die in the hospital have pulmonary embolism.

Most PE's come from DVT's (deep vein thrombosis), and more than 50% of the patients who have DVT's have PE's but most of them have no signs or symptoms. Even in today's modern medical world only about 20% – 40% of patients who have PE's have been diagnosed with them.

### **Risk Factors:**

There are many risk factors for pulmonary embolism, but most come from a venous thromboembolism elsewhere in the body, usually in the legs. In fact almost 70% of all PE patients have DVT's in the legs, and more than half of them are in the calf veins. Some studies suggest that nearly all PE's and DVT's are the result of an underlying hypercoagulable condition and that other causes are merely thromboembolic triggers for an unbalanced system. Hypercoagulable conditions can be acquired or congenital. The most common congenital risk factor is an activated Protein-C resistance (due mainly to a genetic mutation of factor V known as Factor-V Leyden), followed closely by Protein-C deficiency, Protein-S Deficiency, and antithrombin-III deficiency. Many of these conditions are often active complications of autoimmune disease, which is also far too often difficult to diagnose and treat.

All risk factors of venous thromboembolism, including DVT and PE, have present one or more of the three elements known as Virchow's Triad. 1) hemostasis, 2) hypercoagulability, and 3) vessel wall damage. Basically, anything that has a tendency interrupt or slow down the flow of blood in the vessels, cause the blood to coagulate faster than normal, or that causes damage to the blood vessel walls will increase the risk of forming a venous thromboembolism. Following is a list of some of the more common risk factors:

## **Risk Factors of Pulmonary Embolism:**

### **1. Transient Risk Factors:**

- a. Recent trauma
- b. Fracture
- c. Recent surgical intervention (Especially gynecological surgery)
- d. Hospitalization
- e. Pregnancy (or in the post-partum period)
- f. Oral contraceptives
- g. Hormone replacement therapy
- h. Obesity
- i. IV drug abuse
- j. Lengthy air travel (3-hours or longer. This is sometimes referred to as ‘Economy-Class Syndrome)

### **2. Permanent Risk Factors:**

- a. Fibrinogen abnormality
- b. Activated Protein-C resistance
- c. Deficiency in;
  - i. Antithrombin
  - ii. Protein-C
  - iii. Protein-S
- d. Mutation of;
  - i. Factor-V Leiden gene
  - ii. Prothrombin gene
- e. Thrombocytosis
- f. Thrombocytopenia (including heparin induced thrombocytopenia)
- g. Prior history of PE or DVT
- h. Presence of lupus anticoagulants
- i. Hemolytic anemia
- j. Active malignancy
- k. Immobilization from chronic illness
- l. Two or more first-degree relatives with venous thromboembolism
- m. Blood type-A: (Blood type-A is associated with lower levels of antithrombin-III and higher levels of factor-VIII than other blood types. This risk primarily affects women in their child bearing ages. Women who are of reproductive age and who have blood type-A have a four times more likely to have a venous thromboembolism).

### **3. Idiopathic Pulmonary Embolism**

## **Pathophysiology of a Thrombus:**

Blood clot formation involves a very complicated cascade of chemical reactions that are necessary to maintain balance within this very active system. Under normal circumstances most of this system is actively balanced. Within the venous system microthrombi are continually being formed and

thrombolysed (broken down) over and over until conditions are met that require the sustained formation of a blood clot, or *thrombus*. A break in a vessel wall, for example, will start activating some of the blood clotting factors that are otherwise passive. This causes an imbalance in the system and ultimately a thrombus is formed at that site. An imbalance in any part of this cascade will result in abnormal blood clotting in either direction, causing blood clots to form either too slowly or too quickly. As long as conditions remain in a normal state the coagulation/anticoagulation balance continues to be actively passive.

Under normal circumstances a blood clot is a response to a break in a vessel wall. Collagen and von Willebrand factor are normally within the endothelium of the vessel wall. When there is a break in the vessel wall they are exposed to blood flow, they become activated and attract platelets, and platelets begin to stick to the broken edges of the vessel wall. Once platelets adhere to the surface they release a chemical that attracts more platelets and a platelet plug is formed. This reaction is referred to as platelet aggregation. Sometimes this is enough to repair the damage to the vessel wall, but if not there is another cascade of reactions that takes place. It is the protein based system called the coagulation cascade.

Sometimes there is an imbalance that causes clots to be formed too quickly, or when they're not even needed. It is becoming more and more evident that this is the case most of the time with victims of venous thromboembolism, whether they're DVT's or PE's. Almost all patients who are diagnosed with PE's are found to have DVT's in the legs. All blood clots will eventually dissolve, a process called thrombolysis. As thrombolysis takes place a small piece of that thrombus will sometimes break free, becoming an embolus, and float "down-stream" until it lodges in a smaller vessel, usually in the lungs. The size of that embolus will be directly proportional to the severity of the symptoms.

### **Diagnostic Strategies:**

Diagnosing a pulmonary embolism remains one of the great challenges of medicine, even in the light of today's advanced medical technology and education. Nuclear scans and other advanced imaging techniques have certainly made it easier to see PE's but they're not fail proof. Also, before a physician scans for PE he/she must first suspect PE. That in itself is a challenge because most of the time PE's present with only vague and non-specific signs and symptoms. The Physician overseeing the case should

suspect PE early on with any patient who presents with unexplained shortness of breath and/or chest pain in conjunction with a clear chest X-Ray. Over time this practice would hopefully lead to a decrease in PE mortality because most fatal PE’s are those that were never found.

There is no single blood test or exam that can determine if a PE is present and, as suggested earlier, it is much easier and safer to rule out a PE than it is to diagnose one. Either way it takes a combination of clinical tools to achieve the best outcome. If PE is suspected then calculating the clinical probability score right away would be a huge benefit. The most commonly used are the *Wells Score* (Table-1) and the *Revised Geneva Score* (Table-2). However, it must be known that neither one of these scores alone are sufficient because much of the criteria of these scoring systems are based on the Physicians

<b>Wells PE Probability Score</b>	
<b>Clinically Suspected DVT</b>	3.0
<b>Alternate Diagnosis Less Likely Than PE</b>	3.0
<b>Tachycardia (Heart Rate &gt;100 b/m)</b>	1.5
<b>Surgery / Immobilization in the Past 4 Weeks</b>	1.5
<b>History of DVT or PE</b>	1.5
<b>Hemoptysis</b>	1.0
<b>Malignancy (or treatment within 6 months)</b>	1.0
<ul style="list-style-type: none"> <li>• <b>Score &gt;6.0 = High Probability (59%)</b></li> <li>• <b>Score 2.0 – 6.0 = Moderate Probability (29%)</b></li> <li>• <b>Score &lt; 2.0 = Low Probability (15%)</b></li> </ul> <p><b>Alternate Scoring Method:</b></p> <ul style="list-style-type: none"> <li>• <b>Score ≥ 4.5 = PE Likely. Consider Diagnostic Imaging</b></li> <li>• <b>Score &lt; 4.5 = PE unlikely. D-Dimer to rule out</b></li> </ul>	

subjective opinion. A clinical probability score must be calculated in conjunction with, at the very least, a D-Dimer assay. A clinical probability score in conjunction with D-Dimer assay and advanced imaging techniques, such as a high-resolution Multi-Detector CTPA (Computed Topography Pulmonary Angiography), tend to have the best outcome.

***D-Dimer Assay:***

The D-Dimer assay is an important test to perform but it is more used to rule out PE rather than diagnose one. This is because the D-Dimer assay is not specific to pulmonary embolism. A positive result, or rather an increased D-Dimer value, tells the physician that there is a high level of fibrin degradation fragments in the blood. Fibrin degradation fragments are the result of thrombolysis. Because there are always microthrombi being formed and thrombolysed, as part of the normal balance of the coagulation cascade, there is always a low level of fibrin degradation fragments. An increased level indicates that

<b>Revised Geneva Score – PE Probability</b>	
Age 65 Years or Older	1 points
Previous VTE (DVT or PE)	3 points
Surgery or Fracture Within 1 Month	2 points
Active Malignant condition	2 points
Unilateral lower limb pain	3 points
Hemoptysis	2 points
Heart Rate: 75 – 94	3 points
Heart Rate: 95 or higher	5 points
Pain on deep palpation of lower limb, and unilateral edema	4 points
<b>Total:</b>	
<b>0 – 3 = 8% low probability</b> <b>4 – 10 = 28% intermediate probability</b> <b>11 or higher = 74% high probability</b>	

there is a significant thrombus that is actively being broken down, or thrombolysed, somewhere in the body. It does not indicate the location of the thrombus, just that one exists.

The results of a D-Dimer are also skewed by the presence of several conditions. In addition to the presence of a thrombus of unknown origin and location the D-Dimer levels can be elevated due to DIC, liver disease, some cancers, heart disease, and even pregnancy. For this reason is it impossible to diagnose a PE based on an elevated

D-Dimer, but a normal D-Dimer level is certainly an indicator that there are no acute conditions or disease processes that would cause an abnormal formation and breakdown of a thrombus.

### **High-Resolution Multi-Detector CTPA:**

Once the physician suspects PE, and receives an elevated D-Dimer level in conjunction with an intermediate or high probability score, diagnostic imaging becomes the next step and will often be used as the final diagnostic decision tool. There are many opinions on the subject of diagnostic imaging for the purpose of diagnosing a PE. In the medical literature a high-resolution multi-detector computed tomography pulmonary angiogram (MD-CTPA) seems to be the *golden nugget*. While it's not conclusive 100% of the time the MD-CTPA is the most sensitive imaging exam to date for diagnosing pulmonary embolism, in addition to having the ability to show other existing disease states or conditions. The downside of this exam is the increased risk of contrast related kidney damage, and a risk of cancer secondary to radiation exposure.

### **Ventilation/Perfusion Nuclear Scan:**

The “very close” second runner up is the ventilation/perfusion scan (V/Q Scan), which is a nuclear imaging scan that uses radioisotopes to compare the ventilation of the lungs against the perfusion of the lungs. This scanning technique is most often used to try to find PE's but use with caution. This scan is a

better tool for ruling OUT a PE than it is to diagnose one. Other factors to ponder when choosing diagnostic strategies are the facts that the V/Q scan is a very slow imaging technique, sometimes taking up to an hour to complete, and the reality that the V/Q scan exposes the patient to a much higher dose of radiation than does the superior High-Resolution MD-CTPA.

***Bilateral Lower-Extremity Venous Ultrasound:***

In cases where a HR-CTA and/or V/Q scan are not immediately available there are still other advanced exams to assist the physician in predicting the diagnosis of PE and start anticoagulation therapy. Whether or not a PE has been positively diagnosed a venous ultrasound of both lower extremities should be performed because close to 85% of all PE's start as DVT's of the legs, 50% of which are found in the calf veins.

The venous system is a low-pressure, low-flow return system that brings used blood back to the heart and lungs to offload the waste products such as carbon dioxide, and load up with fresh oxygen to be delivered to the body. In the leg veins, often due to simple gravity, blood flow is slowest and often gets trapped on the back side of the valve leaflets. When there is an imbalance in the coagulation/anticoagulation system a thrombus begins to form there. As the thrombus grows a piece sometimes breaks off, becoming an emboli, floats “downstream” with the flow of blood, and eventually gets lodged in the smaller vessels of the lungs. Often times, when there is a reasonable suspicion of PE, a positive D-Dimer and a venous ultrasound positive for DVT's, the diagnosis of PE can be made and anticoagulation can be started. This diagnostic strategy can save time because further diagnostic imaging is no longer needed, and potentially life-saving treatments can be started.

***Transthoracic or Transesophageal Echocardiogram:***

In cases where HR-CTA or V/Q scan is not immediately available some studies suggest looking for right ventricular dysfunction, another common finding in the presence of a significant pulmonary embolism. This is best accomplished by obtaining a transthoracic or transesophageal echocardiogram, or cardiac ultrasound. During these studies right ventricular hypertrophy may be noted in addition to right ventricular hypokinesis, and even ventricular septal ‘bowing’ toward the left ventricle. These defects are a direct result of backpressure or increased pulmonary vascular resistance that results from the blockage in



the pulmonary arterial tree. Emboli that block at least 25% of the pulmonary arterial tree will cause a pulmonary hypertension, and right ventricular dysfunction, eventually leading to right ventricular failure, hemodynamic imbalance and instability, and eventually death.

***$E_TCO^2/O^2$  Ratio:***

The most recent tool in the tool box is being studied as you read these words. It is believed that a segmental or larger pulmonary embolism will predictably decrease the ratio of exhaled carbon dioxide compared to exhaled oxygen. This is referred to as  $E_TCO^2/O^2$ , and the idea is that a segmental PE or larger significantly increases alveolar dead space, enough so that a ratio between exhaled carbon dioxide and oxygen can predict its presence. Until now there was really no good way to calculate alveolar dead space without obtaining an arterial blood sample. In a recent study it's been shown that patients in a moderate risk probability group (by Wells score or Revised Geneva score) patients with a D-Dimer of  $>499$  ng/mL and an  $E_TCO^2/O^2$  ratio of  $<0.28$  have a significantly higher probability of having a segmental or larger pulmonary embolism, such that anticoagulation can be started sparing the patient the radiation risks of diagnostic imaging by MD-CTPA or V/Q lung scanning. On the flip side patients in the same group with a  $E_TCO^2/O^2$  ratio of  $>0.45$  accurately predicted the absence of a segmental pulmonary embolism. Adding this exam to the diagnostic strategy tool box greatly increases diagnostic accuracy, improves patient outcome, and decreases unnecessary risk to the patient. The only downside to this new tool is the lack of equipment that makes the accurate measurement of exhaled carbon dioxide and oxygen in the same 7 – 8 breaths easy to obtain. Such devices do exist but they are not very commonly seen in the hospital setting.

***$P(a - E_T)CO^2$  (also called the  $CO^2$  diff):***

The weakest of all contenders in the fight against PE fatalities is commonly referred to as the  $CO^2$  diff. It is the difference the concentration of carbon dioxide in arterial blood and exhaled gas. The greater the alveolar dead space the greater the  $CO^2$  diff. This exam requires an arterial blood sample to be drawn while the patient is breathing through a  $CO^2$  monitor circuit measuring the  $E_TCO^2$ . There are several problems with the rationale of utilizing this exam. There are several conditions that can increase the  $CO^2$  diff including emphysema, certain acidotic states, and pregnancy just to name a few. Another observation is that it takes quite a significant PE to increase the  $CO^2$  diff enough to make a diagnosis of PE.

## Final Thoughts:

Medicine has definitely come a long way in the fight against PE fatalities. Advanced medical education and technology has made it possible to diagnose and treat significant pulmonary emboli with more accuracy, and less risk, than ever before. While it is true that the PE diagnostic toolbox continues to grow it is also true that these tools are only as good as physicians are PE conscious. A presentation of unexplained shortness of breath and/or chest pain accompanied with a clear chest X-Ray should always raise the suspicion of a pulmonary embolism, and a probability score should be established. The more PE's we find and treat the more lives we save. That alone is a good reason to keep looking.

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