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Pulmonary Embolism: Epidemiology, Patient Presentation, Diagnosis, and Treatment

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A B S T R A C T

Pulmonary embolism is a significant health concern, affecting mainly the adult and elderly population. The focus of this review article will be on the epidemiology, presentation, treatment, and outcomes of PE arising from deep venous thrombosis.

Introduction

Pulmonary embolism (PE) can be defined as a substance blocking the flow of blood within the pulmonary arterial vasculature which arises elsewhere in the body and travels via the bloodstream, technically making the term thromboembolism more accurate, but clinically the terms are freely interchanged. Approximately 90% of all pulmonary emboli arise from deep vein thrombosis of the lower extremities, although there are other less common causes such as fat embolism, air embolism, amniotic fluid, and foreign bodies from trauma and procedures (Bělohlávek et al., 2013).

PE ranks as the third most common cardiovascular disease after coronary artery disease and stroke (Bělohlávek et al., 2013). The overall annual incidence of PE is 0.6 per 1000. The incidence of PE is rare in the pediatric population at a rate of less than 1 out of 100,000 and relatively common after the age of 75 years at a rate of 1 out of 100 (Oger, 2000). Inpatients also have an increased risk of PE than the general population, estimated to occur in 1% of all hospital admissions (Bělohlávek et al., 2013).

It should be noted that the actual incidence of PE is likely significantly higher as autopsy studies have shown that a premortem diagnosis had occurred in only 30%-45% of patients, which suggests that PE is underdiagnosed and/or silent (Oger, 2000).

Those who suffer from an initial episode of PE are estimated to have a 30% chance of recurrence in the next 10 years, with the greatest risk in the first 2 years (Office of the Surgeon General (US); National Heart Lung and Blood Institute (US), 2008). The risk of recurrence is also higher when the thromboembolism is unprovoked.

The populations at greatest risk of PE include those who had recent trauma, had recent major surgery, are obese, are pregnant, underwent hormonal therapy, smoke, and have certain cancers (Office of the Surgeon General (US); National Heart Lung and Blood Institute (US), 2008).

Presentation

The most common symptoms associated with PE are dyspnea (85%), chest pain (50%), cough (20%), syncope (14%), and hemoptysis (7%) (Bělohlávek et al., 2013; Pineda et al., 2001). Other common signs are tachycardia and tachypnea.

Dyspnea onset is often sudden, although it can present as worsening shortness of breath on exertion. The pain is commonly described as sharp and occasionally provoked with inspiration. Many of these symptoms can overlap with a cardiac or aortic etiology, and therefore, diagnosis is not always straightforward.

Although the most common origin of PE is dislodged lower extremity deep vein thrombosis, signs and symptoms of concurrent lower extremity deep vein thrombosis are surprisingly uncommon, seen in only 3% of those with PE (Miniati et al., 2012).

In severe cases, embolic burden is large enough to cause hypotension, shock, and cardiac arrest.

Diagnosis

The diagnosis of a PE is achieved through clinical evaluation, laboratory testing, electrocardiogram (EKG), radiologic examinations, and echocardiography. There are also several scoring systems

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to assess the likelihood of PE, with the Wells criteria being the most commonly taught scoring system, which are not regularly used in day-to-day practice. Figure 1 summarizes the Wells criteria and allows for clinical risk stratification for patients at risk for PE (Wells et al., 1997). Figure 2 summarizes various clinical conditions that increase the relative risk of PE as described by the British Thoracic Society.

Laboratory testing

The most common laboratory tests used to aid in the diagnosis of PE include brain natriuretic peptide (BNP), troponin, and, the most important, D-Dimer tests.

D-Dimer is a small protein that is present in the blood when degradation of a clot occurs with fibrinolysis. D-dimer is most useful in patients with low to moderate risk of PE. It has been shown that a negative D-dimer (<80 ng/mL), in patients with a Wells score of 4 or less (low to moderate risk), has a negative predictive value of 98.5%, essentially excluding the possibility of PE (Geersing et al., 2012). If the patient is at high risk for PE, then it is reasonable to forgo D-dimer testing and move on to other tests.

BNP and troponin both indirectly test for cardiac dysfunction, which can be secondary to PE, although both are fairly insensitive and nonspecific. BNP is released by cardiomyocytes when there is stretching of the atrium, and a positive test is only 60% sensitive and 62% specific for the diagnosis of PE (Söhne et al., 2006). Troponin is associated with any type of myocyte damage, not limited to infarct, and can be elevated in 50% of patients with PE (Konstantinides, 2005). Because BNP and troponin have lower sensitivity and specificity for PE, they are more useful for stratification of adverse outcomes and death, which is beyond the scope of this review.

Electrocardiography

The EKG findings of PE are nonspecific and mostly secondary signs of right heart strain, which will only be seen if there is a moderate to large PE burden, and therefore, the absence of such findings does not exclude the possibility of PE. The classic EKG pattern is a prominent S wave in lead I, Q wave in lead III, and inverted T wave in lead III, which is known as a S1Q3T3 pattern. Other EKG findings of PE are tachycardia, right axis deviation, right bundle branch block, or atrial fibrillation. An EKG example of the S1Q3T3 pattern is demonstrated on Figure 3.

Echocardiography

Transthoracic echocardiography (TTE) is useful for evaluation if there is evidence of right heart strain, which would be seen with a moderate to large PE burden. These findings consist of right ventricle hypokinesis, right ventricle enlargement, leftward bowing of the interventricular septum, or in rare occurrences, thrombus within the right atrium/ventricle.

Transesophageal echocardiography has the ability to detect central pulmonary emboli with a sensitivity of 81% and specificity of 97% in patients in whom there is a high suspicion of PE and signs of right heart strain are seen on TTE (Pruszczyk et al., 2001). This is rarely the preferred method for confirmation of PE in clinical practice as it is fairly invasive and will not exclude more peripheral PE.

Radiologic and nuclear medicine examinations

The common imaging examinations performed in patients who may have PE are the chest radiography, computed topographic angiography of the chest, and ventilation-perfusion nuclear scintigraphy.

Predictor	Score
Clinical signs/symptoms of DVT	+3
Alternative diagnosis is less likely	+3
Heart rate >100	+1.5
Immobile x 3 days OR surgery in last 4 weeks	+1.5
Previous DVT/PE	+1.5
Hemoptysis	+1
Malignancy, active or treated in last 6 mo	+1
Total	**__ /12**
Risk of PE	**Total Score**
Low (3%)	1
Moderate (28%)	2-6
High (78%)	>6

Figure 1. Wells scoring for pulmonary embolism (Wells et al., 1997). DVT, deep vein thrombosis; PE, pulmonary embolism.

Radiography

The chest radiograph will be performed on nearly all patients presenting with any cardiopulmonary-related symptom. Most chest radiographs in patients with PE will have normal or nonspecific findings such as atelectasis, airspace opacities, or pleural fluid. The classic radiologic findings are the Westermark sign and Hampton hump. The Westermark sign is a region of relative lucency due to focal oligemia (reduced blood volume) caused by the more proximal embolism and is portrayed in Figure 4. The Hampton hump is a wedge-shaped airspace opacity with tip tapering centrally due to pulmonary infarction, demonstrated in Figure 5.

Computed tomographic angiography

Computed tomographic angiography (CTA) of the pulmonary arteries is the gold standard for detecting PE. This is accomplished by outlining the clots (filling defects) within the pulmonary vasculature by dense contrast, either by timing the scan after the injection or tracking the bolus and scanning when the main pulmonary artery reaches a certain predetermined level of attenuation (measured in Hounsfield units). Figure 6 demonstrates a large pulmonary embolism burden on computed angiography with clot present within the left and right pulmonary arteries and saddle embolism.

The positive predictive value for detecting a main or lobar PE is 97%, segmental 68%, and subsegmental 25% (Lewis, 2007). This shows that CTA is far from perfect when it comes to detecting smaller and more distal clot. There are many reasons why small clots can be missed, which include respiratory motion, poor bolus timing, uncooperative patients, artifact, and lung parenchymal disease.

Another important consideration is that CTA requires the administration of iodinated contrast, which is contraindicated in patients with severe contrast allergies, such as anaphylaxis, and has a relative contraindication in patients with decreased kidney

Major Risk factors (RR 5-20)	Minor Risk factors (RR 2-4)
Post operative state: Major abdominal/pelvic surgery, joint replacement, post-op ICU	**Cardiovascular:** congenital heart disease, heart failure, superficial venous thrombosis, central venous line
Obstetrics: late pregnancy, caesarian	**Hormonal**: estrogen use for hormone replacement or contraception
Malignancies: abdominal/pelvic, advanced metastatic disease	**Miscellaneous**: COPD, long distance travel, obesity, inflammatory bowel disease, chronic dialysis, nephritic syndrome, paroxysmal nocturnal hemoglobinuria, myeloproliferative disease
Limited mobility: Elderly and hospitalization	
Lower limb afflictions: Fractures, extensive varicose veins	
Miscellaneous: History of PE	

Figure 2. Table adapted from the British Thoracic Society risk factors for venous thromboembolism (British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group, 2003). ICU, intensive care unit; PE, pulmonary embolism; COPD, chronic obstructive pulmonary disease.

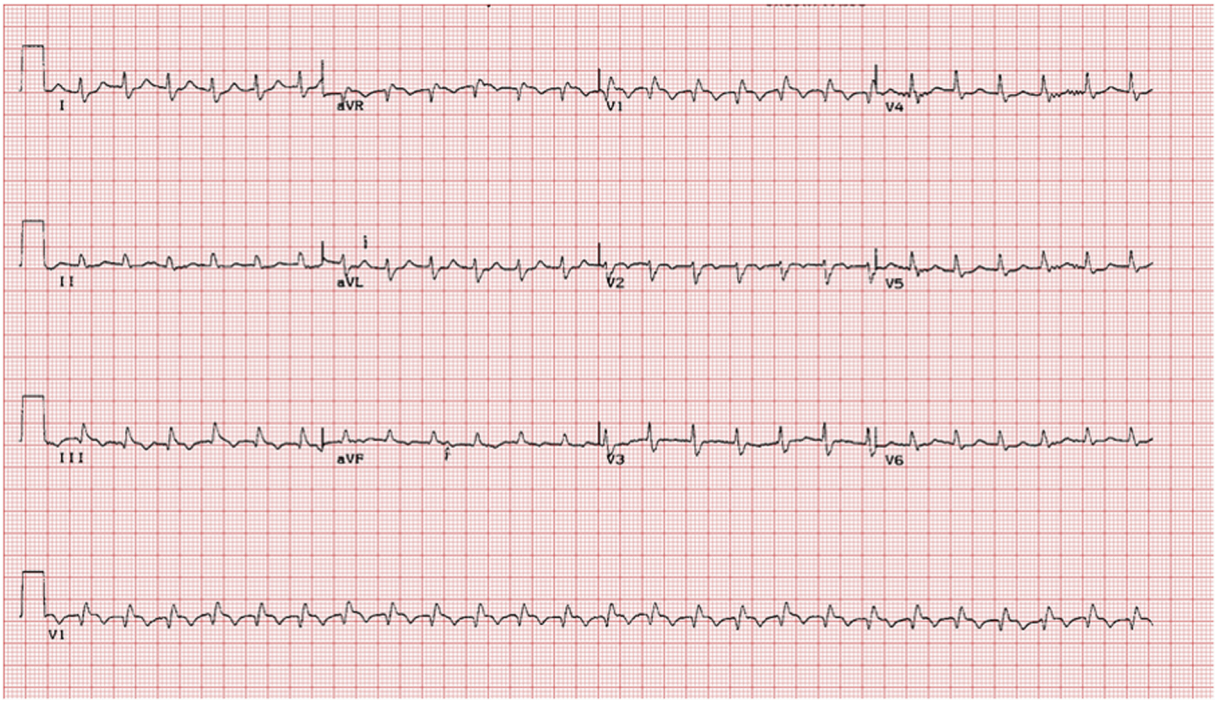

Figure 3. S1Q3T3 pattern, which can be seen with PE. PE, pulmonary embolism.

function and pregnancy. Premedication with steroids and diphenhydramine is an option in patients with mild to moderate allergies, but this requires several hours to take effect, which is usually not ideal in patients in whom PE is suspected.

Nuclear medicine ventilation-perfusion scintigraphy (V/Q)

The V/Q scan is an older method for evaluation of PE, although it is commonly used when there is contraindication to computed tomography contrast. The test is performed in two parts. The perfusion portion involves injection of a radioactive material (technetium-99m microaggregated albumin), which are small particles that become lodged in the precapillary arterioles and can then be imaged using a gamma camera. The second part of the examination requires a cooperative patient who can inhale a radiotracer (Tc99-m diethylenetriamine pentaacetate (DTPA) or xenon), particles small enough to reach the distal bronchial tree and can then be imaged using a gamma camera. The ventilation portion of the examination can be omitted in critically ill patients, although this decreases the sensitivity and specificity of the examination.

The concept of V/Q scanning is that pulmonary emboli result in predictable patterns of decreased blood flow, which are reflected in the perfusion portion of the examination. The ventilation portion of the examination can help support the diagnosis of the embolism if there is aeration in the region of decreased blood flow (mismatch).

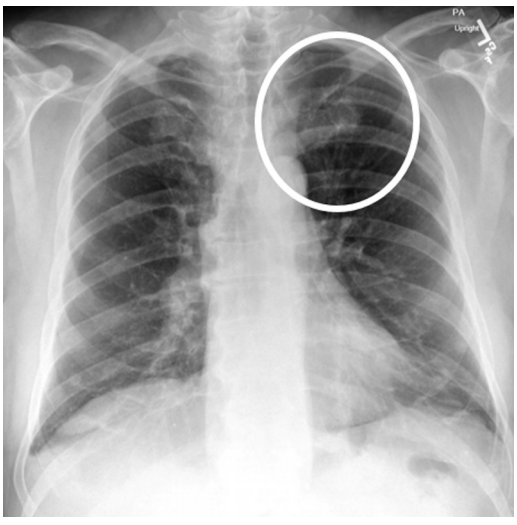

Figure 4. Westermark sign. The frontal chest radiograph shows a relative lucency of the left upper lung due to focal oligemia (circle) from a more proximal left-sided pulmonary embolism.

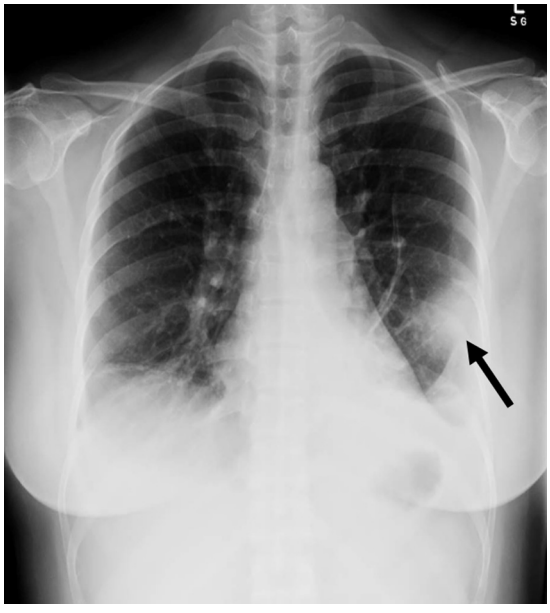

Figure 5. Hampton's hump. The frontal chest radiograph reveals a wedge-shaped opacity in the left lower lung (arrow), which is the result of a pulmonary infarct.

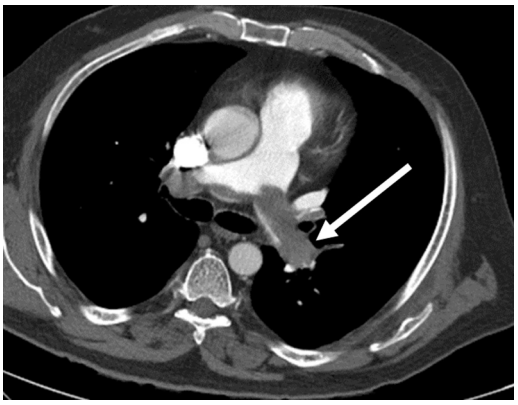

Figure 6. Computed angiography of the pulmonary arteries reveals extensive emboli within the left and right pulmonary arteries including saddle emboli (arrow).

If the areas of decreased ventilation and perfusion match, then it is unlikely to be the result of an embolism and is more likely to be a parenchyma disease, such as atelectasis, pneumonia, or a mass. This is due to the normal physiology of the lung where any area of decreased aeration results in shunting of blood away from that region. Figure 7 demonstrates a V/Q scan with high probability of pulmonary embolism as there are 2 wedge shaped segmental areas of decreased perfusion relative to ventilation.

The positive and negative predictive values of a V/Q scan are 85% and 96%, respectively, which are comparable to those of CTA (Lavorini et al., 2013). The main limitations of V/Q scanning are the limited availability of radiotracers after hours and decreased comfort level and familiarity of both the radiologist and ordering physician with the test, especially if the ventilation portion has been omitted.

Treatment

Treatment is based on the severity, which is generally classified as massive (high risk), submassive (intermediate risk), or non-massive (low risk). Massive PE is defined by systolic blood pressure less than 90 mmHg, heart rate < 40 BPM, or pulselessness (Sekhri et al., 2012). Submassive PE is defined by myocardial necrosis, reflected in troponin or BNP abnormalities or right ventricular (RV) strain, and stable hemodynamics. RV strain can be evaluated by CTA, echocardiography, or EKG. RV strain on computed tomography is defined as right ventricle being at least 0.9 times as large as the left ventricle, flattening/leftward bowing of the interventricular septum, contrast reflux into the inferior vena cava/hepatic veins, and pulmonary trunk diameter greater than that of the aorta (Reed & Shishehbor, 2015). An example of RV strain is demonstrated on Figure 8 with enlargement of the right ventricle and flattening of the interventricular septum. Echocardiography can evaluate the

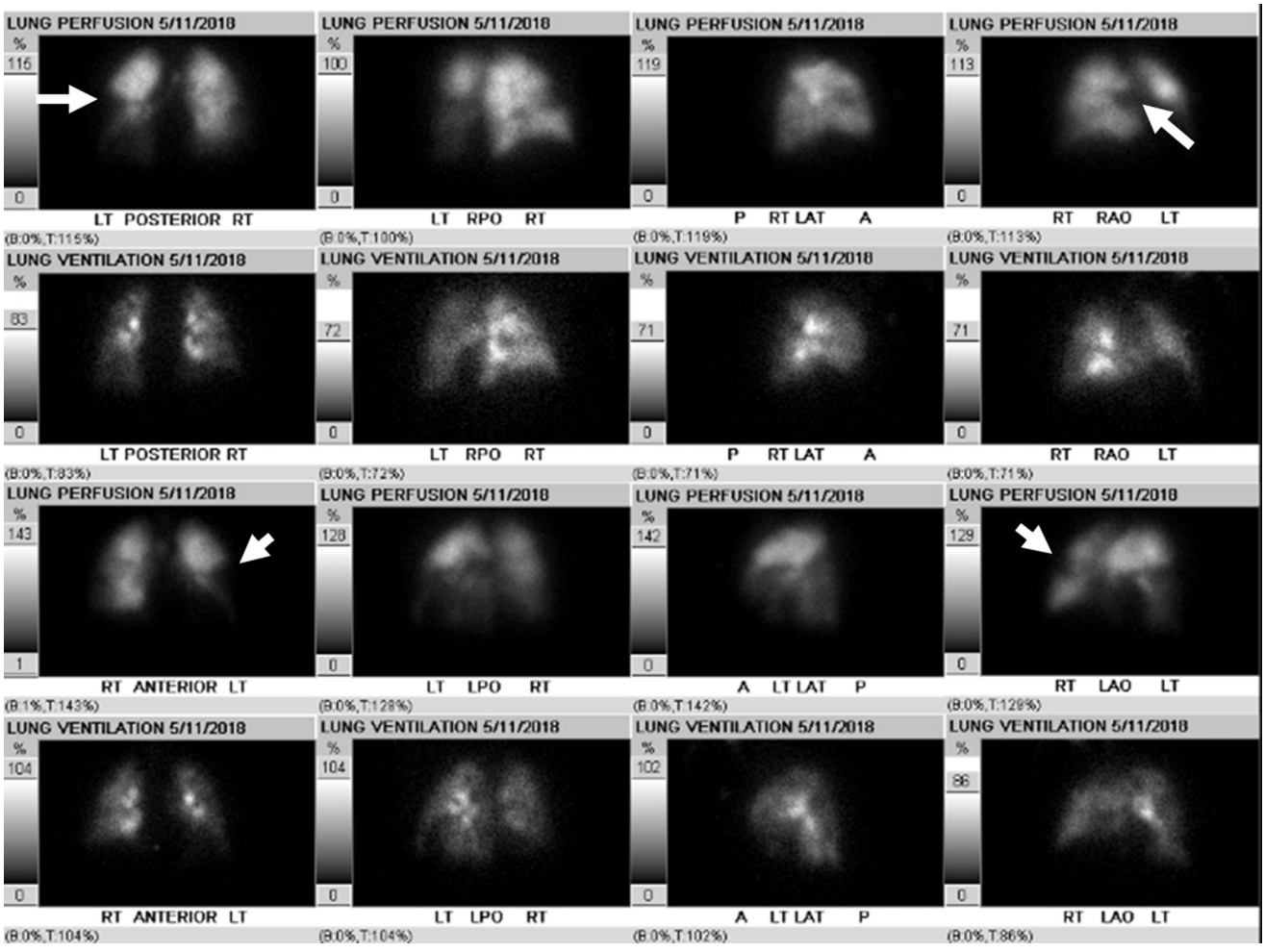

Figure 7. Ventilation-perfusion scintigraphy shows wedge-shaped lack of radiotracer uptake in the anterior segment of the right upper lobe and the superior segment of the left lower lobe (arrows), without matched defects in the ventilatory images. These findings are consistent with a high probability of pulmonary embolism.

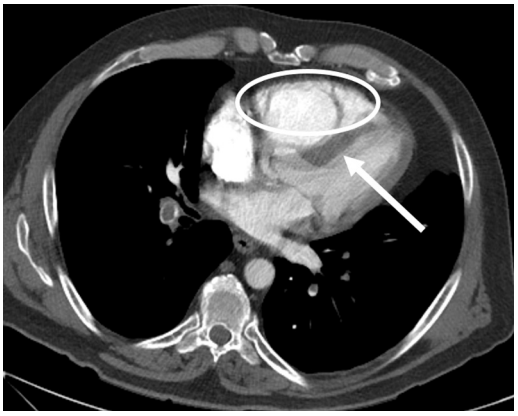

Figure 8. CTA of the pulmonary arteries in the same patient shown in Figure 6. There is evidence of right heart strain, with the RV (oval) being more than 0.9 times the diameter of the LV and flattening or S-shaped intraventricular septum (arrow). CTA, computed tomographic angiography; RV, right ventricle; LV, left ventricle.

size of the right ventricle and hypokinesis. EKG can show signs of RV strain with a new right bundle branch block, anteroseptal ST changes, or anteroseptal T wave inversion. A patient with low risk of PE is hemodynamically stable, with no myocardial necrosis or evidence of RV strain; however, hypoxia may be present.

Low-risk PE

Standard of care for a low-risk PE is anticoagulation starting with weight-based low-molecular-weight heparin or fondaparinux, with a 3- to 5-day bridge to warfarin or one of the novel anticoagulants, such as rivaroxaban or dabigatran. Anticoagulation is continued for 3 months in provoked episodes of PE, and then risk and benefits of treatment are reassessed. If the PE is unprovoked, then anticoagulation treatment may be continued indefinitely (Sekhri et al., 2012).

Intermediate-risk PE

Treatment of the intermediate-risk group has the most variation, with most physicians leaning toward more conservative management via anticoagulation over systemic thrombolysis due to perceived risk of bleeding (Reed & Shishehbor, 2015). In certain clinical scenarios, catheter-directed interventions may be used due to increased adverse outcomes associated with prolonged RV dysfunction.

High-risk PE

An early diagnosis of massive PE is imperative as 50% of patients die within 30 min, 70% die within 1 h, and more than 85% die within 6 h of the onset of symptoms (Sekhri et al., 2012). Given this high acuity of massive PE, early identification of patient instability is imperative.

Patients suspected to have massive PE should be stabilized hemodynamically and treated with systemic thrombolysis if there is no history of intracranial bleed, brain vascular malformation, malignant brain neoplasm, ischemic stroke in last 3 months, active bleeding, recent neurological surgery, or aortic dissection. Approved thrombolytic agents are alteplase, urokinase, or streptokinase. Alteplase is given as a continuous infusion over 2 hours, whereas urokinase and streptokinase are given as a bolus, followed by 24-hour infusion (Sekhri et al., 2012). The patient is at significantly increased risk of bleeding during the 24 hours after the initiation of systemic thrombolytics, and therefore, neurological assessment and blood pressure checks are recommended every 15 minutes for the first 2 hours after initiation, every 30 minutes for the next 6 hours, and then hourly until 24 hours after initiation (Powers et al., 2018). Figure 9 demonstrates a coronal CTA which reveals bilateral PE in a patient with persistent hypotension after attempted fluid resuscitation, classifying the PE as massive.

Catheter-directed interventions

If there is contraindication for systemic thrombolytics or if systemic treatment has failed, then catheter-based interventions should be considered. There are dozens of types of catheter-directed treatment systems with three basic categories such as clot removal, clot fragmentation, and catheter-directed thrombolysis. The choice of catheter-directed intervention is determined by operator preference/comfort and clinical scenario. Figure 10 demonstrates catheter directed angiography of the pulmonary arteries with digital subtraction revealing central filling defects following systemic thrombolysis, with is an indication for catheter-directed intervention.

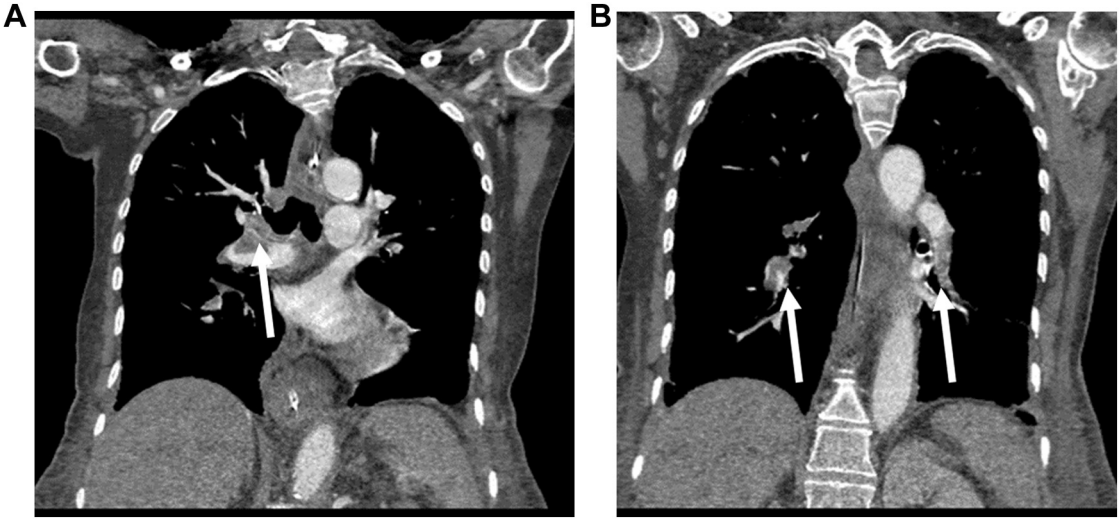

Figure 9. Coronal CTA images of the pulmonary arteries reveals bilateral PE (arrows) involving the right main pulmonary (A) and bilateral segmental PE (B) in a patient with persistent hypotension.

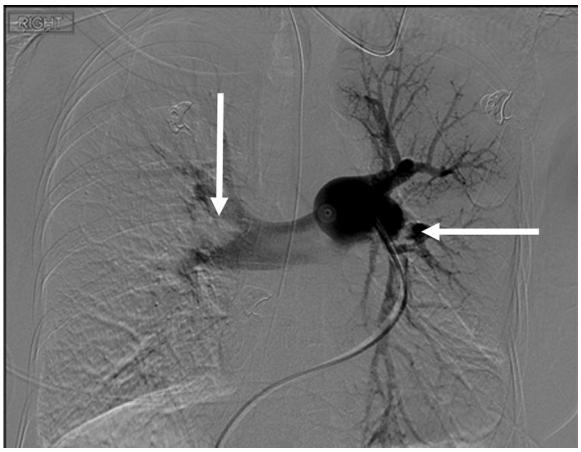

Figure 10. Digital subtraction angiography of the pulmonary arteries shows that the clot remains in the distal right pulmonary artery (arrow) and left lower lobar pulmonary artery (arrow).

Catheter-Directed Thrombolysis

This is a method to maximize the thrombolytic effects on the clot while minimizing the total dose of drug administered to reduce the bleeding risk. A catheter is directed into the pulmonary artery adjacent to the clot. Then, a loading dose of either urokinase or recombinant tissue plasminogen activator is given, followed by a continuous infusion for up to 24 hours (Fava, 2000). Figure 11 demonstrates fluoroscopic images of catheter-directed thrombolysis of the bilateral pulmonary arteries.

Catheter-Directed Fragmentation Thrombectomy

These devices fragment the clot into smaller pieces without removing the clot. The idea is that multiple small pulmonary emboli decrease pulmonary vascular resistance compared with a large central clot and increases the surface area of the clot for enzymatic breakdown (Basche et al., 1991).

Catheter-Directed Aspiration Thrombectomy

This method physically removed the clot via negative pressure systems either by simple syringe aspiration, catheter-directed suction cups, or negative pressure via a rotary motor.

Combination Fragmentation and Removal Catheter Techniques

This method is also known as rheolytic thrombectomy. These devices both remove and fragment clots but produce the unwanted side effect of hemolysis (Koning et al., 1997).

Surgical embolectomy

Surgical embolectomy is used as a last resort after other treatments have failed or if the patient is too unstable. Surgical embolectomy has a very high mortality rate of 29%, which increases to 58% in patients who require cardiopulmonary resuscitation (Gray et al., 1988).

Cardiopulmonary management in the unstable patient

Hypotension Management

Before invasive therapy, the patient should be stabilized hemodynamically. In case of nonspecific shock, 1-2 L of crystalloids is generally given. However, it has been shown that in a patient with known right ventricular dysfunction, this may actually accelerate right ventricular dysfunction (RVD) and ischemia; therefore, preference should be given to inotropes and vasopressors (Sekhri et al., 2012).

If the patient has both hypotension and reduced cardiac output, preference should be placed on starting with a vasopressor agent (to avoid worsening hypotension) such as norepinephrine or epinephrine, and then if no improvement is observed, an ionotropic agent can be started (Piazza & Goldhaber, 2005). If the patient has reduced cardiac output but is normotensive, then inotropes such as dopamine, dobutamine, or milrinone can be provided (Piazza & Goldhaber, 2005).

Respiratory Management

Low-Flow Oxygen Delivery

Treatment of hypoxia can be initiated once the oxygen saturation is at 90% or lower (Fulmer & Snider, 1984). When starting oxygen therapy, it begins in a stepwise manner to reach the oxygen saturation goal. Nasal cannula is the first-line option and can provide 4-6 L per minute (LPM) at 30%-40% FiO2 (Miller & Faarc, 2018). A simple facemask is the next level providing 5-10 LPM at 40%-60% FiO2. A nonrebreather mask can provide even greater level of oxygenation at 8-10 LPM and up to 90% FiO2 (Miller & Faarc, 2018). The drawbacks of mask-type oxygen delivery are increased risk of

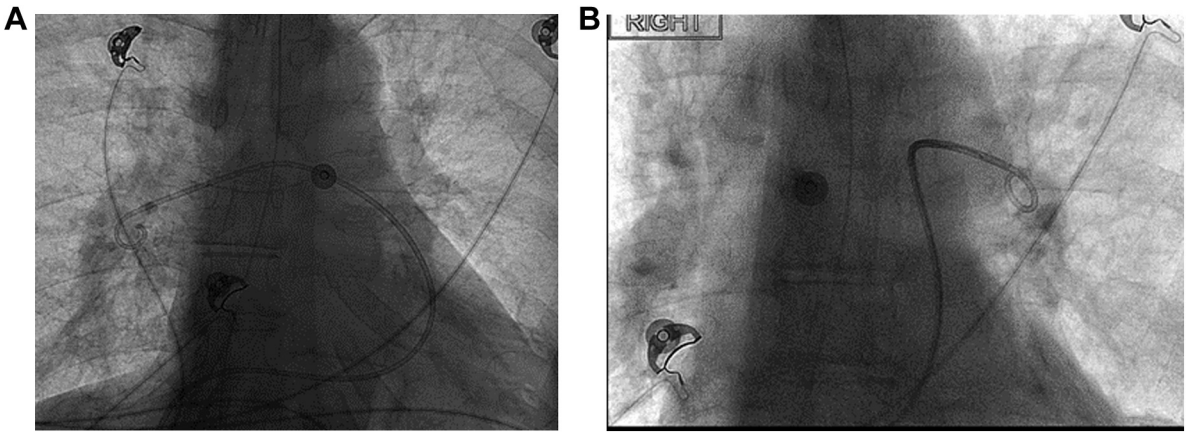

Figure 11. (A and B): Fluoroscopic images of the pigtail flush catheter placed within the distal right pulmonary artery where 6 mg of TPA was instilled and let dwell for 6-7 minutes. The same procedure was then performed on the left pulmonary artery but with 2 mg of tissue plasminogen activator (tPA) due to lesser clot burden. TPA, tissue plasminogen activator.

aspiration if the patient vomits, difficulty in patients with claustrophobia, and need for a tight seal in the nonrebreather.

High-flow oxygen delivery

High-flow methods are used to achieve consistent FiO2 and positive pressure ventilation or to prevent carbon dioxide retention. Options include the use of a venturi mask and the high-flow nasal cannula. Generally, these delivery methods are initiated in a higher level of care such as a step-down unit or intensive care unit.

Invasive forms of oxygen delivery

In case of severe refractory respiratory failure, the patient will require either intubation and/or extracorporal membrane oxygenation (ECMO). ECMO is generally reserved for reversible causes of respiratory failure, making it ideal for use in a patient with massive PE who does not have a significant underlying pulmonary disease. The downside to ECMO therapy is that the patient must be a candidate for full anticoagulation, and the risk for significant bleeding complications is seen in 35% of patients in whom the device is used (Weinberg et al., 2017).

Conclusion

PE is a fairly common occurrence, especially in the elderly and hospital population. Diagnosis requires a high clinical suspicion due to symptomatology overlapping with other cardiopulmonary etiologies. Workup consists of a combination of laboratory work and cardiac studies, with radiologic studies (mainly CTA) being the gold standard for PE confirmation. Treatment ranges from simple anticoagulation for low-risk PE to systemic thrombolysis, catheter-directed intervention, or even surgical embolectomy for high-risk PE. Overall, the care of patients with PE requires a multidisciplinary team consisting of interventional radiologists, cardiologists, internists, and cardiothoracic surgeons.

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