Acute Pulmonary Embolism: Part I
Epidemiology, Pathophysiology, and Diagnosis

Samuel Z. Goldhaber, MD; C. Gregory Elliott, MD

This New Frontiers article reviews the epidemiology, pathophysiology, diagnosis, treatment, and prevention of pulmonary embolism (PE) in 2 parts. In this first section we summarize the mechanisms of right ventricular dysfunction, arterial hypoxemia, and other abnormalities of gas exchange. For diagnosis, we streamline and expedite the work-up. For the second part we provide a contemporary approach to risk stratification to determine which patients may warrant intervention beyond use of heparin and warfarin alone. We conclude with an overview of contemporary concepts in optimizing prophylaxis.

PE is a common cardiovascular and cardiopulmonary illness with an incidence in the United States that exceeds 1 per 1000 and a mortality rate >15% in the first 3 months after diagnosis. This makes PE possibly as deadly an illness as acute myocardial infarction. Nevertheless, the lay public has not been well educated about PE. Consequently, early detection and prompt presentation for medical evaluation have lagged far behind the public awareness of acute coronary syndromes and stroke. Although discussion of the etiology of PE has classically focused on acquired and inherited causes of hypercoagulability, there is also an association between atherosclerotic disease and spontaneous venous thrombosis.

The most common reversible risk factor for PE is obesity, an increasing pandemic in our society. Other common reversible risk factors include cigarette smoking and hypertension. Nevertheless, public fascination with PE has centered on long-haul air travel, a rare cause of venous thromboembolism. PE also occurs in the context of illness attributable to surgery, trauma, immobilization, cancer, oral contraceptives, pregnancy, and postmenopausal hormone replacement therapy, as well as medical conditions such as pneumonia and congestive heart failure. Genetic predisposition to venous thrombosis is being increasingly recognized, and twin studies have demonstrated the important contribution of an inherited prothrombotic state. Increased levels of clotting factors and activation peptides contribute to the risk of PE. Deficiencies of anticoagulant factors also increase thrombotic risk.

Pathophysiology

Hemodynamics

The hemodynamic response to PE depends on the size of the embolus, coexistent cardiopulmonary disease, and neurohumoral effects. Hemodynamic decompensation occurs not only because of physical obstruction of blood flow but also because of the release of humoral factors, such as serotonin from platelets, thrombin from plasma, and histamine from tissue.

Acute PE increases pulmonary vascular resistance, partly attributable to hypoxic vasoconstriction. In patients without prior cardiopulmonary disease, the mean pulmonary artery pressure can double to approximately 40 mm Hg. An additional doubling of pulmonary artery pressure may occur in patients with prior pulmonary hypertension. Under extreme circumstances in patients with chronic thromboembolic pulmonary hypertension, the pulmonary arterial pressure can exceed the systemic arterial pressure.

Increased right ventricular afterload can cause right ventricular dilatation, hypokinesia, tricuspid regurgitation with annular dilatation of the tricuspid valve, and ultimately right ventricular failure. While this pathological process evolves, most patients maintain a normal systemic arterial pressure for 12 to 48 hours and may give the impression of being hemodynamically stable. Then, often abruptly, pressor-resistant systemic arterial hypotension and cardiac arrest may ensue.

Right ventricular enlargement attributable to pressure overload causes a leftward shift of the interventricular septum, which is a manifestation of interventricular dependence. Right ventricular contraction continues even after the left ventricle starts relaxing at end-systole. The interventricular septum flattens during systole and then bulges toward the left ventricle, with paradoxical septal motion that distorts the normally circular left ventricular cavity. There is diastolic left ventricular impairment, attributable to septal displacement, reduced left ventricular distensibility, and impaired left ventricular filling during diastole. Left atrial contraction has a greater than normal contribution to left ventricular filling,
TABLE 1. Gas Exchange Definitions and Equations

<table>
<thead>
<tr>
<th>Definition</th>
<th>Formula/Equation</th>
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<tbody>
<tr>
<td>Anatomic dead space</td>
<td>Breathed gas that does not enter gas exchange units of the lung</td>
</tr>
<tr>
<td>Physiological dead space</td>
<td>Ventilation to gas exchange units exceeds flow of venous blood through pulmonary capillaries; V/Q ratio exceeds 1.0</td>
</tr>
<tr>
<td>Total dead space volume (Vd)</td>
<td>Sum of anatomic and physiologic dead space</td>
</tr>
<tr>
<td>Alveolar volume (Va)</td>
<td>Gas volume that effectively eliminates carbon dioxide =</td>
</tr>
<tr>
<td></td>
<td>[(V_a) \times \text{breathing rate}]</td>
</tr>
<tr>
<td>Alveolar ventilation (Va)</td>
<td>[(V_a) \times \text{breathing rate}]</td>
</tr>
<tr>
<td>Minute ventilation (Vt)</td>
<td>[(V_t) \times \text{breathing rate}]</td>
</tr>
<tr>
<td>Dead space ventilation (Vd)</td>
<td>[(V_t) \times \text{breathing rate}]</td>
</tr>
<tr>
<td>Alveolar ventilation (Vd)</td>
<td>[V_t - V_d]</td>
</tr>
<tr>
<td>Partial pressure of CO2 dissolved in arterial blood (Paco2)</td>
<td>Proportional to CO2 produced (VCO2) divided by alveolar ventilation (Vd) [K] = [(VCO2V_d) \times K]</td>
</tr>
<tr>
<td>Partial pressure of O2 dissolved in arterial blood</td>
<td>[PaO2]</td>
</tr>
<tr>
<td>Atmospheric PO2</td>
<td>[P_{A02} = (\text{total gas pressure}) \times (\text{fractional concentration of O2})]</td>
</tr>
<tr>
<td>Alveolar PO2</td>
<td>[PaO2]</td>
</tr>
<tr>
<td>Water vapor pressure at 37°C</td>
<td>47 mm Hg</td>
</tr>
<tr>
<td>Respiratory gas exchange ratio</td>
<td>[(\text{CO2 produced/O2 consumed}) = 0.8]</td>
</tr>
<tr>
<td>Alveolar pressure of CO2</td>
<td>[P_{A02} = \left(\frac{P_{A02}}{0.8}\right)]</td>
</tr>
<tr>
<td>Partial pressure of O2 in the alveolae (PA02)</td>
<td>[(PaO2 - 47 \text{ mm Hg}) \times (\text{fractional concentration of O2}) - (Paco2/0.8)]</td>
</tr>
<tr>
<td>Alveolar to arterial O2 tension gradient</td>
<td>[PaO2 - PaO2]</td>
</tr>
</tbody>
</table>

resulting in a prominent A wave on Doppler that is much higher than the E wave. 10

As right ventricular wall stress increases, cardiac ischemia may develop, because increased right ventricular pressure compresses the right coronary artery, diminishes subendocardial perfusion, and limits myocardial oxygen supply. 11 Right ventricular microinfarction leads to elevations of both pro-B-type natriuretic peptide 13 and B-type natriuretic peptide. 14, 15

Gas Exchange

Acute PE impairs the efficient transfer of oxygen and carbon dioxide across the lung (Tables 1 and 2). Decreased arterial PO2 (hypoxemia) and an increase in the alveolar-arterial oxygen tension gradient are the most common gas exchange abnormalities. Total dead space increases. Ventilation and perfusion become mismatched, with blood flow from obstructed pulmonary arteries redirected to other gas exchange units. Shunting of venous blood into the systemic circulation may occur.

Normal tidal volume includes both breathed gas that enters the gas exchange units (respiratory bronchioles, alveolar ducts, and alveolar sacs) and anatomic dead space. In normal lungs, ventilation and perfusion are well matched, and the ratio of ventilation to the gas exchange structures and blood flow to the pulmonary capillaries is approximately 1.0. Transfer of oxygen is impaired when alveolar ventilation to pulmonary capillaries is reduced relative to blood flow (low V/Q units); the ratio of ventilation to perfusion falls to <1.0. Right-to-left shunting occurs when there is no ventilation to perfused lung units or when venous blood bypasses the lungs and enters the systemic circulation.

The transfer of oxygen is a cascade with gas flowing from a high-pressure source (the atmosphere) to a lower-pressure destination (the mitochondria). The partial pressure of oxygen decreases as gas moves from the atmosphere to alveolae to arterial blood and finally to the tissues. The initial decrease in oxygen pressure occurs when air enters humid upper airways, where water vapor molecules reduce the partial pressure of oxygen. The diffusion of carbon dioxide from capillaries into gas exchange units additionally decreases alveolar oxygen pressure. The alveolar to arterial oxygen tension gradient represents the inefficiency of oxygen transfer across the lungs, often as the result of a decreased ratio of ventilation relative to perfusion in lung gas exchange units.

TABLE 2. Potential Gas Exchange Abnormalities in Pulmonary Embolism

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Decreased arterial PO2</td>
<td>Hypoxemia</td>
</tr>
<tr>
<td>Increased alveolar to arterial oxygen tension gradient (PAO2−PaO2)</td>
<td></td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td></td>
</tr>
<tr>
<td>Low V/Q units: impaired oxygen transfer to pulmonary capillaries, with preserved blood flow to pulmonary capillaries; ratio of ventilation to perfusion is &lt;1.0</td>
<td></td>
</tr>
<tr>
<td>Right-to-left shunting: no ventilation and venous blood enters systemic circulation</td>
<td></td>
</tr>
<tr>
<td>Increased anatomic dead space: breathed gas does not enter gas exchange units of the lung</td>
<td></td>
</tr>
<tr>
<td>Increased physiologic dead space: ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries; ratio of ventilation to perfusion &gt;1.0</td>
<td></td>
</tr>
<tr>
<td>Increased total dead space: anatomic plus physiologic dead space</td>
<td></td>
</tr>
<tr>
<td>Decreased carbon monoxide diffusion</td>
<td></td>
</tr>
</tbody>
</table>

Hypoxemia

Several mechanisms explain the presence of arterial hypoxemia in the setting of acute PE. Mismatching of ventilation...
and perfusion is the most common cause of impaired pulmonary oxygen transfer. Unlike normal lungs, where ventilation is well matched to blood flow, PE causes redistribution of blood flow so that some lung gas exchange units have low ratios of ventilation to perfusion, whereas other lung units have excessively high ratios of ventilation to perfusion. Arterial hypoxemia occurs when venous blood flows through lung gas exchange units, where the ratio of ventilation to capillary blood flow is low. Atelectasis, caused by loss of surfactant and alveolar hemorrhage, also contributes to reduced ratios of ventilation to perfusion and arterial hypoxemia.

A shunt exists when venous blood enters the systemic arterial system without passing through ventilated gas exchange units of the lung. The failure of supplemental oxygen to correct arterial hypoxemia accompanying acute PE often reflects the existence of right to left shunting of venous blood through the heart, the lungs, or both. In acute PE, intracardiac shunting usually occurs through a patent foramen ovale; right atrial pressure exceeds left atrial pressure, even if both pressures are normal. The application of positive end-expiratory pressure or continuous positive airway pressure may worsen intracardiac shunting, because positive airway pressure additionally increases pulmonary vascular resistance by increasing alveolar pressure and compressing pulmonary vessels. The resultant increased right atrial pressure exacerbates the right to left intracardiac shunt.

A low pressure of oxygen in venous blood also may contribute to arterial hypoxemia when PE causes right ventricular failure. Low cardiac output leads to increased extraction of oxygen in the tissues, thereby decreasing the partial pressure of oxygen in venous blood below normal levels. Venous blood with an abnormally low PO2 amplifies the effect of low ventilation to perfusion ratios when it passes through diseased lung gas exchange units to the systemic circulation. In contrast, arterial oxygen content is not affected by low venous PO2 when the lungs are normal and ratios of ventilation to blood flow in the lung gas exchange units are approximately 1.0.

**Other Gas Exchange Abnormalities**

In patients with acute PE, total dead space increases because lung units continue to be ventilated despite diminished or absent perfusion. Complete obstruction of a pulmonary artery by an embolus causes an increase in anatomic dead space. In contrast, incomplete obstruction of a pulmonary artery increases physiological dead space, ie, ratios of ventilation to perfusion increase. Increased dead space impairs the efficient elimination of carbon dioxide. However, medullary chemoreceptors sense any increase in arterial PCO2, and they will increase the total minute ventilation, thereby lowering the arterial PCO2 to normal and often below normal. Thus, most patients with PE present with a lower than normal arterial PCO2 and respiratory alkalosis because of an increased total minute ventilation. Limited data suggest that the increased total minute ventilation occurs because of reflex stimulation of irritant and juxta capillary sensors in the lung.

In the setting of acute PE, hypercapnia reflects massive embolism accompanied by marked increases in both anatomic and physiological dead space. The alveolar volume of each tidal breath is severely reduced, and the ventilatory muscles are unable to sustain the marked increase of minute ventilation needed to maintain normal arterial PaCO2. Treatment with positive pressure ventilation and paralysis allow reduction of carbon dioxide production and resting of the ventilatory muscles until definitive therapy relieves thromboembolic obstruction and increases the alveolar volume of each tidal breath.

The single-breath carbon monoxide diffusion capacity (DLCO) is a well standardized and sensitive technique that screens for abnormal pulmonary gas exchange by measuring the rate of carbon monoxide uptake. Although the DLCO is often reduced in patients with PE, many other pulmonary disorders also cause abnormal reductions of DLCO.

**Diagnosis**

To diagnose PE, one must think of PE as a diagnostic possibility. The clinical setting, combined with a focused history and physical examination, often provides helpful hints. The ECG and chest x-ray may rapidly identify alternative diagnoses, especially myocardial infarction and pneumonia, respectively. Arterial blood gas measurements have proved disappointing. Normal values of the alveolar-arterial oxygen gradient do not exclude acute PE; hypoxemia discriminates poorly between those who do and do not have acute PE.

Prompt and accurate diagnosis of PE is facilitated by a clinical evaluation that assesses the probability of PE and makes appropriate use of the plasma D-dimer ELISA and chest CT scanning (Figure). Wells et al11 developed a simple clinical model to predict the likelihood of PE. Their
scoring system has a maximum of 12.5 points, based on 7 variables: 3 points each for clinical evidence of deep vein thrombosis and an alternative diagnosis being less likely than PE, 1.5 points each for heart rate >100 per minute, immobilization/surgery within 4 weeks, and previous deep vein thrombosis/PE, and 1 point each for hemoptysis or cancer. A score of <2 points makes PE low probability (2% likelihood), and a score of >6 points makes PE high probability (50% likelihood). In a consecutive cohort of patients suspected of PE, almost half had a low probability score.

The D-dimer is elevated in almost all patients with PE because of endogenous albeit ineffective fibrinolysis, which causes plasmin to digest some of the fibrin clot and release D-dimers into the systemic circulation. Among patients presenting to the Emergency Department at Brigham and Women’s Hospital, normal D-dimer ELISA levels have a high negative predictive value for PE regardless of clinical probability. Of 1109 consecutive D-dimer assays among patients suspected of PE, 547 were normal. Only 2 of 547 had PE despite a normal D-dimer. In this cohort, the sensitivity of the D-dimer for acute PE was 96.4%, and the negative predictive value was 99.6%. By incorporating the D-dimer ELISA into the diagnostic algorithm, fewer chest CT scans will be needed, resulting in improved diagnostic efficiency and cost reduction. However, these findings do not pertain to patients suspected of PE.

In acute PE, the fibrinogen level decreases, probably because of activation of endogenous fibrinolysis. As the fibrinogen level declines, the D-dimer level increases. In the future, a high ratio of D-dimer to fibrinogen may help to rule in acute PE.

Chest CT scanning has become the preferred imaging modality. In the absence of PE, the chest CT may yield a previously unsuspected reason for symptoms mimicking PE, such as pneumonia or interstitial fibrosis that were not apparent on the chest radiograph. Lung scanning is being used less frequently because its results are often equivocal. Lung scanning nevertheless remains the first-line imaging study for patients with anaphylaxis to contrast agent, renal failure, or pregnancy, as well as in patients with prior PE diagnosed by lung scan.

Knowing the generation of chest CT scanner that is being used is crucial to interpreting the results of the imaging test. First-generation scanners have 5-mm resolution and may fail to detect one third of PEs, especially in the subsegmental pulmonary arteries. However, third-generation scanners provide 1-mm resolution with a single breath hold. For institutions without third-generation scanners, a useful alternative strategy is venous ultrasonography of the legs when the chest CT scan shows no evidence of PE.

References

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