Epidemiology, Pathophysiology, and Natural History of Pulmonary Embolism

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Abstract

Keywords

- Pulmonary Embolism
- venous thromboembolism
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- interventional radiology

Pulmonary embolism (PE) is a common and potentially deadly form of venous thromboembolic disease. It is the third most common cause of cardiovascular death and is associated with multiple inherited and acquired risk factors as well as advanced age. The prognosis from PE depends on the degree of obstruction and hemodynamic effects of PE and understanding the pathophysiology helps in risk-stratifying patients and determining treatment. Though the natural history of thrombus is resolution, a subset of patients have chronic residual thrombus, contributing to the post-PE syndrome.

Objectives: Upon completion of this article, the reader will be able to identify the disease burden of pulmonary embolism, as well as the progression of the disease with and without treatment, and potential for long-term disability.

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Pulmonary embolism (PE) and deep venous thrombosis (DVT) exist on the spectrum of venous thromboembolic disease (VTE). PE results when thrombus migrates from the venous circulation to the pulmonary vasculature and lodges in the pulmonary arterial system. The clinical presentation of acute PE ranges from asymptomatic and incidentally discovered to massive PE causing immediate death. This review focuses on the epidemiology, risk factors, pathophysiology, and natural history of PE.

Epidemiology

Venous thromboembolism is a major worldwide burden of disease with ~10 million cases per year and an associated substantial morbidity and mortality.1 The true incidence of PE is unknown, but in the United States, it is estimated that nearly a third of hospitalized patients are at risk of developing VTE and up to 600,000 cases of VTE are diagnosed per year with 100,000 deaths related to these diseases.2,3 In the United States, the estimated incidence of diagnosed VTE is 117 per 100,000, but the true incidence is likely to be more as these diseases are frequently undiagnosed or diagnosed only at autopsy.4–6 Based on a review of national

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inpatient data, the number of admissions for PE increased from nearly 60,000 in 1993 (23 per 100,000) to more than 202,000 in 2012 (65 per 100,000). Despite the increased incidence of PE, there was a decreased incidence of massive PE and hospital mortality over the same time period. Comorbidities associated with PE are also increasing (aging population and medical comorbidities), but the increased incidence in the face of decreased mortality likely reflects increased use of more sensitive CT angiography for diagnosis rather than a true change in prevalence.\(^7\)\(^-\)\(^10\)

VTE disproportionately affects the older population and incidence rates of VTE in those older than 70 years are three times higher than those aged 45 to 69 years, which again are three times higher than those aged 20 to 44 years.\(^3\)\(^1\) This age-related increase in incidence in VTE is largely attributed to a disproportionate increase in PE burden.\(^4\)\(^7\) The reported incidence of VTE is inconsistent with regard to gender, though several studies suggest higher incidence in males.\(^4\)\(^12\)

Between 5 and 10% of in-hospital deaths are a direct result of PE.\(^13\) In the United States, PE is responsible for 100,000 deaths per year, though deaths from diagnosed PE have been decreasing.\(^12\)\(^14\) Nevertheless, VTE is associated with significant mortality. The case fatality rate of a VTE event is \(~10\%\) at 30 days, which increases to 15% within 3 months, with a further increase up to 20% by 1 year.\(^11\)\(^12\)\(^15\)

**Risk Factors**

In the mid-19th century, Rudolph Virchow identified the triad of risk factors that contribute to thrombosis—stasis of blood flow, vascular endothelial damage, and hypercoagulability. All VTE risk factors reflect these underlying pathophysiologic processes and generally patients who experience VTE have at least one risk factor.\(^16\) Risk factors can be divided into inherited and acquired factors (see Table 1).

**Inherited Risk Factors**

There are several genetic conditions known to increase the risk of VTE including factor V Leiden, prothrombin gene mutation (G20210-A), antithrombin deficiency, protein C deficiency, and protein S deficiency. Deficiencies in protein C, protein S, and antithrombin are relatively infrequent but potent, and they can confer a 5- to 10-fold increase in venous thrombosis in those affected.\(^17\)\(^-\)\(^19\) Factor V Leiden is a more common mutation leading to hypercoagulability, and it is associated with a 5-fold increased risk of VTE with heterozygotes and a 10-fold risk with homozygotes.\(^20\) Finally, the prothrombin gene mutation can be detected in 7% of patients with VTE and increases the risk of thrombosis threefold.\(^21\)

<table>
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<th>Inherited risk factors</th>
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<td>Factor V Leiden</td>
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<td>Prothrombin gene mutation</td>
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**Acquired Risk Factors**

Surgery and trauma are known to increase the risk of VTE. Orthopedic surgery in particular confers a higher risk with half of patients undergoing elective hip or knee replacement developing VTE without prophylaxis.\(^22\) Similarly, patients with traumatic hip fractures are at higher risk for VTE both preoperatively and postoperatively.\(^23\)\(^24\) The increased risk is mediated by immobility during and after the surgery as well as by direct venous injury and inflammation during surgery. Pharmacologic thromboprophylaxis is preferred over mechanical thromboprophylaxis and reduces the incidence of DVT and PE in the postoperative period.\(^25\) Active malignancy, associated with the production of procoagulant substances, increases the risk of VTE sevenfold.\(^26\) In a large population study of both solid and hematologic malignancies, nearly 2% of patients were diagnosed with VTE within 2 years of their cancer diagnosis, with the highest rates of VTE seen with metastatic disease and particularly with pancreatic and colon cancer.\(^27\) Additionally, patients with high-grade tumors are at higher risk compared with those with low-grade tumors.\(^28\) The risk of VTE is highest soon after diagnosis or after the initiation of treatment, and importantly, the risk diminishes when cancer is in remission.\(^27\)\(^29\)

Increased risk of VTE mediated primarily by stasis has been documented in patients with hospitalization, joint fixation, and prolonged travel. Recent hospitalization is noted in more than half of patients with VTE with up to two-thirds of posthospitalization VTE occurring within the first month following hospitalization and the remainder over the next 3 months.\(^30\)\(^31\) Joint immobility due to orthopedic injury in the absence of surgical management also increases the risk of VTE twofold compared with controls over a 72-hour period.\(^32\)

Travel is an often cited yet relatively uncommon causal factor for VTE with an estimated incidence of 4.8 cases of PE per million travelers flying over 10,000 km.\(^33\) There is a direct relationship between the frequency of occurrence, the distance, and duration traveled.\(^34\)\(^35\)

A natural hypercoagulable state exists in pregnancy to decrease the risk of hemorrhage during childbirth. This is mediated by an increase in factors VII, VIII, X, von Willebrand factor, and fibrinogen, along with a decrease in protein S with an acquired activated protein C resistance.\(^16\)\(^37\) The rate of VTE increases 4- to 5-fold during pregnancy with a 20-fold increase in 3 months following delivery.\(^3\)\(^38\) DVT is four times as common as PE, and PE occurs more often postpartum.\(^39\)\(^40\)

The risk of VTE while on estrogen containing oral contraceptives increases three- to fourfold.\(^41\) The risk is highest in the first year of use (especially the first 3 months), but it does not increase thereafter and is eliminated with cessation of therapy.\(^42\) A similar increase in risk occurs with postmenopausal hormone replacement therapy.\(^43\)
Age-related changes to the balance between anticoagu-
lants and procoagulants mediate an increased propensity for 
VTE with age. There is an increase in VTE starting in the 
fourth and fifth decades with a marked increase in those 
older than 60 years. This is confounded by decreasing 
mobility and higher rates of malignancy, obesity, and other 
comorbidities with increasing age.

There is a linear relationship between body mass index  
(BMI) and VTE, and patients with severe obesity (BMI ≥ 35) 
have a sixfold higher risk of VTE compared with those of  
normal weight. Interestingly while the incidence of PE  
is higher in obese patients, the mortality is paradoxically lower  
than in nonobese patients. It remains unclear whether this  
is due to increased body fat and an increased activity of the  
endocannabinoid system exerting a protective effect or due  
to another mechanism.

Antiphospholipid syndrome is characterized by recurrent  
venous or arterial thrombosis with DVT and PE being the most  
frequent manifestation occurring in one-third of patients. 
The risk of VTE is 5 to 8% higher in patients who carry lupus  
anticoagulant or anti-β2-glycoprotein I antibodies.

Atherosclerosis and arterial disease may be related to  
increased risk of VTE mediated by increased platelet activa-
tion and coagulation pathway. Patients with atherosclerosis  
have an increased risk of VTE, but this relationship is  
confounded by common comorbidities such as smoking, 
obesity, diabetes, hyperlipidemia, and hypertension.

In addition to the risk factors discussed earlier, a prior VTE  
event increases the risk for a recurrent event. Recurrence  
rates over a 5-year period can be 25% or higher in patients  
with unprovoked or idiopathic events.

**Pathogenesis and Pathophysiology**

**Pathogenesis**

Most PEs originate as thrombi in the deep veins of the lower  
extremities. The site of thrombosis is most frequently in the  
calf veins, then femoropopliteal veins, and less frequently in  
the iliac veins. Thrombosis begins in areas of decreased  
flow such as valve cusps and bifurcations and then propa-
gates due to local hypercoagulability caused by hypoxia and  
hepatoconcentration. A smaller percentage of emboli  
arises from upper extremity veins and are typically asso-
ciated with central venous catheters, intracardiac devices  
such as pacemakers and defibrillators, and malignancy or  
activity-related venous trauma. Pelvic vein DVTs can also  
cause pulmonary emboli, but they are generally associated  
with a predisposing factor such as pelvic infection, pelvic  
surgery, or pregnancy. Lower extremity central DVTs are  
most likely to embolize and cause PE (15–32% of the time),  
whereas upper extremity DVTs cause PE only 6% of the  
time. Calf vein DVTs rarely embolize to the lungs, but one-
third can extend into the central veins and subsequently  
have the potential to embolize.

Emboli detach from their point of origin and travel through  
the systemic venous system, through the right sided chambers  
of the heart, and lodge in the pulmonary arterial system. The  
physiologic and clinical consequences of PE vary ranging from  
asymptomatic to hemodynamic collapse and death. PE con-
tributes to gas exchange abnormalities and hypoxemia, but it is  
predominantly the hemodynamic consequences of PE that are  
responsible for increased morbidity and mortality. An under-
standing of the pulmonary pathophysiology of PE is important  
in risk-stratifying patients to determine treatment with anti-
coagulation alone or consideration for catheter-directed ther-
apies (thrombolytics or mechanical thrombectomy), systemic  
thrombolytics, or surgical intervention.

**Hypoxemia and Gas Exchange**

Though a normal partial arterial pressure of oxygen (PaO₂)  
does not exclude PE, hypoxemia is the most common physio-
logic consequence of acute PE. The most common mechanisms of hypoxemia are ventilation-perfusion inequalities and shunt. There is redistribution of cardiac output and blood flow from obstructed regions of the vascular bed to uninvolved areas of the pulmonary vascular bed. This results in areas of low ratios of ventilation to perfusion in some lung gas exchange units and areas of high ratios of ventilation to perfusion in other units. Shunting can be due to intrapulmonary or intracardiac causes. Areas that retain blood flow but no ventilation such as atelectasis due to loss of surfactant or areas of pulmonary hemorrhage or infarct can contribute to shunt. Elevated right atrial pressures in setting of acute PE can open a patent foramen ovale and cause right-to-left intracar-
diac shunting. Low mixed venous saturation can also contrib-
ute to hypoxemia. Massive PE can cause reduced cardiac  
output leading to a low mixed venous oxygen saturation  
(SVO₂). A low SVO₂ coupled with VQ mismatch from the PE  
can exacerbate hypoxemia. One mechanism relates to areas  
of high flow (low V/Q units) in non obstructed areas. The  
abnormally desaturated venous blood will not have enough  
time to oxygenate as it passes through the alveolar capillaries  
in these low VQ units. Vascular obstruction leads to  
increased dead space because lung units continue to be  
ventilated despite reduced or absent perfusion. Though  
increased dead space is expected to impair the elimination  
of carbon dioxide, hypercapnia in acute PE is rare because  
medullary receptors sense the increase in partial pressure of  
carbon dioxide and increase minute ventilation. Most patients  
with PE therefore have a respiratory alkalosis.

**Hemodynamics**

The cardiac and hemodynamic effects relate to the size  
and location of emboli and the presence or absence of underlying  
cardiopulmonary disease (CPD). As opposed to clot burden,  
acute PEs are categorized according to hemodynamic effect,  
with a focus on the effects of right ventricular (RV) physio-
logy (see Fig. 1). Nonmassive PE patients are those who are  
normotensive with normal RV function. Massive PE implies  
hemodynamic instability from RV failure and submassive PE  
patients may clinically be normotensive but have evidence of  
RV dysfunction by echocardiography or CT imaging. These  
categories have risk implications with regard to morbidity  
and mortality and treatment choices.

When thrombus embolizes from the extremities and  
lodges in the pulmonary arterial vasculature, pulmonary
vascular resistance (PVR) increases due to both mechanical obstruction and release of vasoconstrictive substances from platelets (serotonin and thromboxane-A2), plasma (thrombin), and tissue (histamine and endothelin).\textsuperscript{71–73} The thin walled RV is accustomed to low pressure and cannot easily adapt to this increased afterload, which has effects on both RV and left ventricular (LV) function.\textsuperscript{74} If obstruction is mild, PVR and pulmonary artery pressure remain normal by recruiting and distending pulmonary vessels. At moderate levels of obstruction, pulmonary artery pressure remain normal by recruiting and distending pulmonary vessels. At moderate levels of obstruction, pulmonary artery pressure and right atrial pressure increase. Initially, RV stroke volume and cardiac output are maintained by an increase in heart rate and contractility. In patients without prior CPD, the maximal mean pulmonary artery pressure that can be generated even with $>50\%$ obstruction is $\sim40$ mm Hg. Obstruction much beyond this will precipitate RV failure. When the degree of obstruction exceeds 50 to 60%, the right heart dilates, RV wall tension increases, coronary perfusion pressure drops, RV ischemia and RV dysfunction develops, and cardiac output falls, leading to hypotension. Furthermore, the dilated RV impinges on the intraventricular septum and via interventricular dependences causes decreased LV diastolic filling and decreased LV cardiac output (\textit{\textsuperscript{–}Fig. 1}).\textsuperscript{75–77}

In patients without prior CPD, the degree of obstruction has a hyperbolic relationship to PVR and the hemodynamic manifestations of PE are related to embolism size. Patients with preexisting CPD have diminished pulmonary vascular reserve and a smaller degree of obstruction can lead to disproportionate increase in pulmonary artery pressure and hemodynamic instability.\textsuperscript{76}

**Natural History**

Prognosis from PE depends on the degree of obstruction and hemodynamic effects of PE. Those with massive PE may be at imminent risk of death with an estimated mortality of 25 to 65%, those with submassive PE have a mortality of 3 to 15%,\textsuperscript{58} while those with low-risk PE and normal heart function have $<1\%$ mortality with anticoagulation.\textsuperscript{25,78–80} The risk for recurrent VTE is estimated at 20 to 25% after 5 years in unselected cohorts, and higher than 25% in those without a clear provoking cause.\textsuperscript{53,81} Recurrence is also increased in those with associated congenital or acquired risk factors.\textsuperscript{82} There are potential long-term consequences of PE with regard to functional impairment especially for those with recurrent PE.

The natural history of thrombus is resolution over time. However, 15 to 30\% of patients have residual thrombus identified on lung scintigraphy 1 year after the initial event.\textsuperscript{83,84} Persistent thrombus can contribute to ongoing increased PVR and RV pressure load and have physiologic consequences leading to functional impairment and decreased quality of life. The "post-PE syndrome" is defined by dyspnea, exercise intolerance, and diminished quality of life in the setting of suboptimal cardiac function, pulmonary artery flow dynamics, or pulmonary gas exchange.\textsuperscript{85} The most severe manifestation of post-PE syndrome is chronic thromboembolic pulmonary hypertension (CTEPH), which
affects an estimated 1 to 5% of survivors of acute PE.\textsuperscript{86,87} Chronic thromboembolic disease (CTED) refers to persistent perfusion defects without pulmonary hypertension, and it is estimated that based on the incidence of acute PE in the United States, 35,000 people will have CTED and 1,250 will have CTEPH.\textsuperscript{85,88}

### Conclusion

The incidence of PE is increasing possibly due to overdiagnosis, and although mortality is falling, PE continues to be a common and a potentially fatal form of VTE. Inherited and acquired risk factors (particularly surgery and malignancy) increase the likelihood of VTE and PE. Though commonly a cause of gas exchange abnormalities, mortality risk is due to the cardiovascular consequences of obstruction with increasing PVR, RV pressure load, and dysfunction. Both the burden of PE and underlying cardiopulmonary status contribute to these hemodynamic consequences. In addition to the immediate morbidity and mortality caused by PE, in recent years the post–PE syndrome of functional limitation in association with ongoing cardiac and gas exchange dysfunction has received more attention and research is ongoing to determine who is at increased risk for these consequences especially in the submassive population with the question of benefits from early intervention to reduce clot burden.

### References

45 Silverstein RL, Bauer KA, Cushman M, Esmon CT, Ershler WB, Tracy RP. Venous thrombosis in the elderly: more questions than answers. Blood 2007;110(09):3097–3101

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74 Matthews JC, McLaughlin V. Acute right ventricular failure in the setting of acute pulmonary embolism or chronic pulmonary hypertension: a detailed review of the pathophysiology, diagnosis, and management. Curr Cardiol Rev 2008;4(01):49–59
75 McIntyre KM, Sasahara AA. Determinants of right ventricular function and hemodynamics after pulmonary embolism. Chest 1974;65(05):534–543
77 Lualdi JC, Goldhaber SZ. Right ventricular dysfunction after acute pulmonary embolism: pathophysiologic factors, detection, and therapeutic implications. Am Heart J 1995;130(06):1276–1282