Epidemiology, Pathophysiology, and Natural History of Pulmonary Embolism

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Abstract

Keywords
- Pulmonary Embolism
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- risk factors
- hemodynamics
- natural history
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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
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.

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. This age-related increase in incidence in VTE is largely attributed to a disproportionate increase in PE burden. The reported incidence of VTE is inconsistent with regard to gender, though several studies suggest higher incidence in males. Between 5 and 10% of in-hospital deaths are a direct result of PE. In the United States, PE is responsible for 100,000 deaths per year, though deaths from diagnosed PE have been decreasing. 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.

### 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. 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. Factor V Leiden is a more common mutation leading to the production of procoagulant substances, and it is associated with a 5-fold increased risk of VTE with heterozygotes and a 10-fold risk with homozygotes. Finally, the prothrombin gene mutation can be detected in 7% of patients with VTE and increases the risk of thrombosis threefold.

### 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. Similarly, patients with traumatic hip fractures are at higher risk for VTE both preoperatively and postoperatively. 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. Active malignancy, associated with the production of procoagulant substances, increases the risk of VTE sevenfold. 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. Additionally, patients with high-grade tumors are at higher risk compared with those with low-grade tumors. 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.

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. 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. 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. There is a direct relationship between the frequency of occurrence, the distance, and duration traveled.

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. The rate of VTE increases 4- to 5-fold during pregnancy with a 20-fold increase in 3 months following delivery. DVT is four times as common as PE, and PE occurs more often postpartum.

The risk of VTE while on estrogen containing oral contraceptives increases three- to fourfold. 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. A similar increase in risk occurs with postmenopausal hormone replacement therapy.

### Table 1 Risk factors for VTE

<table>
<thead>
<tr>
<th>Inherited risk factors</th>
<th>Acquired risk factors</th>
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<tr>
<td>Factor V Leiden</td>
<td>Trauma</td>
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<tr>
<td>Prothrombin gene mutation</td>
<td>Surgery</td>
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<td>Antithrombin deficiency</td>
<td>Malignancy</td>
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<td>Protein C deficiency</td>
<td>Peripartum state</td>
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<td>Protein S deficiency</td>
<td>Estrogen therapy</td>
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<td>Thrombophilia</td>
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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
hemoconcentration. A smaller percentage of emboli
arises from upper extremity veins and are typically associ-
ated with central venous catheters, intracardiac devices
such as pacemakers and defibrillators, and malignancy or
activity-related venous trauma. Pelvic vein DTVs 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 DTVs are
most likely to embolize and cause PE (15–32% of the time),
whereas upper extremity DTVs cause PE only 6% of the
time. Calf vein DTVs 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
contributes 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 antico-
agulation alone or consideration for catheter-directed ther-
api es (thrombolytics or mechanical thrombectomy), systemic
thrombolitics, 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 inequal-
ities 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 intrapulmo-
ary 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 con-
tribute to hypoxemia. Massive PE can cause reduced cardiac
output leading to a low mixed venous oxygen saturation
(SV02). A low SV02 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) physiol-
ogy (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). 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. 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 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 ~40 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 (Fig. 1).

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.

**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%, while those with low-risk PE and normal heart function have <1% mortality with anticoagulation. 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. Recurrence is also increased in those with associated congenital or acquired risk factors. 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. 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. 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 patients with PE is recognized. In particular, PE with hypoxic respiratory failure leads to respiratory decompensation and increased hospitalization rates. The increased PVR and RV pressure load lead to pulmonary hypertension and right heart strain. Both the cardiovascular consequences of obstruction with gas exchange abnormalities, mortality risk is due to the immediate morbidity and mortality caused by PE, in recent years the post-PE syndrome of functional limitation in the submassive population with the question of 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**

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Turet et al.


44 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


69 Jaff MR, McMurtry MS, Archer SL, et al; American Heart Association Council on Cardiovascular and Pulmonary Rehabilitation, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary
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