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Pulmonary embolism

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The clinical spectrum of pulmonary embolism (PE) ranges from small, incidental thrombosis to massive PE associated with sudden death due to cardiogenic shock. Pulmonary arterial obstruction and platelet secretion of vasoactive agents elevate pulmonary vascular resistance. Increased alveolar dead space impairs gas exchange, and stimulation of irritant receptors causes alveolar hyperventilation. Reflex bronchoconstriction augments airway resistance, and lung edema decreases pulmonary compliance.[1] Elevation in right ventricular pressure can cause an increase in right ventricular wall tension with consequent right ventricular dilatation, dysfunction, and ischemia.

Epidemiology

The incidence of venous thromboembolism is approximately 1 in 1,000 per year.[2] More than 250,000 patients are hospitalized annually in the United States with PE or deep venous thrombosis (DVT). One-third of patients suffer recurrent episodes. For each 10-year increase in age, the incidence of venous thrombosis doubles.

PE continues to have a surprisingly high mortality rate. In our recent experience with the largest (2,454 consecutive hospitalized patients) PE registry ever undertaken, the International Cooperative Pulmonary Embolism Registry (ICOPER),[3] the 3-month mortality rate was 17.5%. PE itself, not cancer, was the principal cause of death.

ICOPER enrolled all PE patients consecutively diagnosed at participating hospitals. In contrast, the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) registry suggested a benign prognosis if PE is promptly recognized.[4] In PIOPED, the overall 3-month mortality rate was about 15%, but only 1 of 10 deaths was ascribed to PE. Cancer, the leading cause of death, accounted for 35% of mortalities. Although these findings might at first glance suggest that mortality from PE itself is rare, patients eligible for PIOPED had to be healthy enough to undergo bilateral pulmonary angiography. Thus, PIOPED patients were probably not as ill as the ordinary PE patient encountered in routine clinical practice and enrolled in ICOPER.

Right ventricular dysfunction and mortality

Four PE registries have demonstrated that right ventricular hypokinesis predicts an adverse clinical outcome.

Although fewer than 5% of ICOPER patients presented in cardiogenic shock, right ventricular hypokinesis as assessed by echocardiography occurred in about 40% of patients with normal systemic

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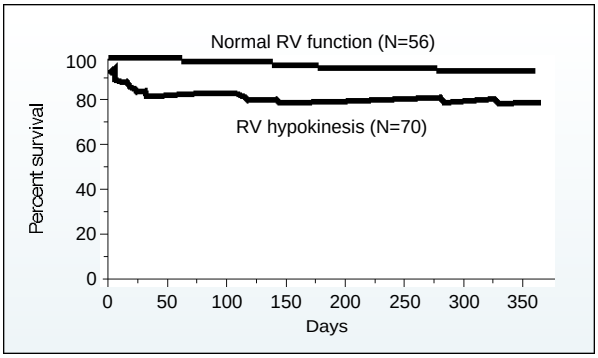
Figure 1: One-year survival in PE patients with normal and depressed right ventricular function on echocardiography.



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arterial pressure. Right ventricular hypokinesis was associated with a doubling of the mortality rate at 14 days and with a 1.5 times higher mortality rate at 3 months.

In a registry from the Karolinska Hospital, 126 consecutive PE patients underwent echocardiography on the day of initial PE diagnosis.[5] The overall one-year mortality rate was 15%. However, among those with right ventricular dysfunction, the mortality rate at one year was threefold higher than for patients with normal right ventricular function (Figure 1). Similar findings were observed in Kasper's registry of 317 patients with clinically suspected PE.[6]

The much larger Management Strategy and Prognosis of Pulmonary Embolism registry (MAPPET) enrolled 1,001 patients with PE and right ventricular dysfunction.[7] As with cases in the other registries, the mortality rate increased as right heart failure worsened.

Risk factors for developing PE

Since genetic predisposition explains only about one-fifth of PE cases, identification of potentially modifiable environmental risk factors is critical. In the Nurses' Health Study,[8] the highest rates of PE were observed among nurses 60 years of age or older who were obese. Heavy cigarette smoking and high blood pressure were also identified as risk factors for PE (Table 1). However, no association was observed with high cholesterol or diabetes.

Table 1: Environmental risk factors for PE in the Nurses'Health Study

Variable	Multivariate Relative Risk (95% CI)
Current cigarette smoking	
1-14/day	0.8 (0.5-1.4)
15-24/day	1.1 (0.7-1.6)
25-34/day	1.8 (1.2-2.9)
≥35/day	2.1 (1.2-3.6)
High blood pressure	1.5 (1.2-2.0)

Adapted with permission from Goldhaber et al.[8]

Table 2: Causes of maternal death among pregnancies resulting in live birth, United States, 1979-1986

Cause of death	Number (%)
Pulmonary embolism	370 (27.1%)
Pregnancy-induced hypertension	307 (22.5%)
Hemorrhage	249 (18.3%)
Other	218 (16.0%)
Infection	101 (7.4%)
Anesthesia complications	65 (4.8%)
Cardiomyopathy	53 (3.9%)
Total	1,363 (100%)

Adapted with permission from Koonin et al.[9]

Pregnancy

From 1979–1986, there were 2,726 pregnancy-associated deaths reported in the United States.[9] For women whose pregnancies resulted in a live birth, thrombotic PE was the leading cause of death (Table 2).

Oral contraceptives

Most users take second-generation oral contraceptives, which triple the risk of venous thromboembolism compared with that for nonusers (Table 3). "Third-generation" oral contraceptives contain desogestrel, gestodene, or norgestimate as the progesterone (in combination with low-dose estrogen) and attenuate the androgenic side effects of acne and hirsutism. Unfortunately, the relative risk of venous thromboembolism appears to double for those taking third-generation compared with second-generation oral contraceptives.[10–12] However, the absolute risk is low despite the high relative risk.

Postmenopausal hormone replacement therapy

The conventional teaching has been that hormone replacement therapy does not predispose to PE because the estrogen content of postmenopausal hormones is trivial compared with that of oral contraceptives. However, data from three recent studies indicate that hormone replacement therapy doubles the risk of venous thromboembolism (Table 4).[13–15] The risk is higher near the start of therapy than after chronic use.

Cancer

Neoplastic cells can generate thrombin or stimulate mononuclear cells to synthesize procoagulants.[16] Occasion-

Table 3: Venous thromboembolic disease among oral contraceptive users taking low-dose estrogen formulation

Generation of OC	Relative risk	95% confidence interval
Second	3.61	(2.53 to 5.13)
Third	7.36	(4.20 to 12.90)

Adapted with permission from World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception.[10]

Table 4: Hormone replacement therapy and oral contraceptives

Variable	Absolute risk (woman-years)	Multivariate relative risk (95% CI)
Never HRT (postmenopausal women)	8.3 per 100,000	1.0
Current HRT	14 per 100,000	2.1 (1.2to 3.8)

Adapted with permission from Grodstein et al.[15]

ally, previously unsuspected cancer will be diagnosed in patients with newly established venous thrombosis.[17] Adenocarcinomas of breast, pancreas, ovary, and lung are most commonly associated with PE.

Surgery

Surgery predisposes to PE, and this susceptibility persists postoperatively for up to one month.[18,19] Thus, the risk of delayed postoperative PE must be considered when devising optimal strategies to prevent venous thromboembolism.

Factor V Leiden

Activated protein C (APC) is a potent endogenous anticoagulant that prolongs the activated partial thromboplastin time when added to plasma. Resistance to APC is usually inherited as an autosomal dominant trait[20] and is due to a single amino acid point mutation (adenine for guanine) in the gene coding for coagulation factor V; this mutation is called factor V Leiden.[21] Glutamine replaces arginine at position 506, thereby making factor V more difficult for APC to cleave and inactivate.[22]

In the Physicians' Health Study,[23] the relative risk of venous thrombosis with factor V Leiden was 2.7. Within the United States,[24] the Leiden mutation was most frequent in Caucasians (5.3%) and was detected less frequently in Hispanic Americans (2.2%), African Americans (1.2%), Native Americans (1.2%), and Asian Americans (0.45%). According to the Physicians' Health Study database,[25] factor V Leiden was 8-fold more common in men older than 70 years with venous thrombosis compared with those younger than 50 years. Factor V Leiden also appears to increase the risk of recurrent PE after discontinuation of anticoagulant therapy.[26]

Hyperhomocysteinemia

There is a two- to threefold increased risk of DVT in patients with plasma hyperhomocysteinemia.[27,28] In the Physicians'Health Study,[29] hyperhomocysteinemia tripled the risk of idiopathic venous thrombosis, and factor V Leiden doubled the risk of venous thrombosis. However, combined hyperhomocysteinemia and factor V Leiden increased the risk almost tenfold.

Table 5: Differential diagnosis of PE

- Pneumonia, asthma, COPD exacerbation, bronchitis, lung cancer
- Myocardial infarction
- Costochondritis, "viral syndrome,"anxiety
- Dissection of the aorta
- Pericardial tamponade
- Lung cancer
- Primary pulmonary hypertension
- Rib fracture or pneumothorax
- Musculoskeletal pain

Antiphospholipid antibody syndrome and lupus anticoagulant

This acquired abnormality might be associated with an increased risk of venous thrombosis, recurrent spontaneous miscarriage, stroke, or pulmonary hypertension.[30]

Deficiencies of endogenous coagulation proteins

Since deficiencies of antithrombin III, protein C, and protein S are rare, they should not be sought during routine work-up for hypercoagulability. In one cohort with venous thrombosis, antithrombin III deficiency was identified in 1% of patients, and protein C or S deficiencies were identified in 3% and 2%, respectively.[31]

Diagnosis

PE, known as "the great masquerader,"can accompany or mimic other cardiopulmonary illnesses. Its differential diagnosis is extensive (Table 5). Dyspnea, syncope, or cyanosis usually indicate a massive PE, but pleuritic pain, cough, or hemoptysis often suggest a small embolism located distally near the pleura. Many patients with massive PE preserve adequate systemic arterial pressure until immediately before their demise. Their physical findings can include bulging neck veins with V waves, a left parasternal lift, an accentuated pulmonic component of the second heart sound, and a systolic murmur at the left lower sternal border that increases in intensity during inspiration.

The most frequent electrocardiographic abnormality is T-wave inversion in the anterior chest leads, V1-V4.[32] New onset right bundle branch block or atrial fibrillation is far less common. The rarely-seen pattern of S in lead I, Q in lead III, and T-wave inversion in lead III is associated with PE.

Although the chest X-ray is often normal, specific findings can include focal oligemia (Westermark's sign), a peripheral wedge-shaped density above the diaphragm (Hampton's hump), or an enlarged right descending pulmonary artery (Palla's sign).

Arterial blood gases of patients with suspected PE cannot accurately discriminate between those who require further

investigation and those in whom no further work-up is required.[34] However, the plasma D-dimer ELISA is at times a useful screening test because, even with PE, there is usually some endogenous (although clinically ineffective) fibrinolysis. When plasmin digests cross-linked fibrin from the PE that has formed, D-dimers are released into the plasma and can be recognized by commercially available monoclonal antibodies. A D-dimer ELISA >500 ng/mL is abnormal and is present in more than 90% of patients with PE. Conversely, a normal D-dimer ELISA provides reassurance in more than 90% of cases that PE is not present. Unfortunately, the D-dimer ELISA lacks specificity and is elevated following surgery and in patients with myocardial infarction, pneumonia, heart failure, and cancer. Therefore, this test is most helpful when used to screen patients who present to the Emergency Department or office without other systemic illness.[35]

Although the presence of DVT can generally be used as a surrogate for PE, a major caveat is that a normal leg imaging test cannot exclude PE if clinical suspicion is moderately high. In a series of 41 PE patients who underwent both pulmonary angiography and bilateral contrast venography of the legs, 12 had negative leg venograms despite positive pulmonary angiograms.[36]

Unfortunately, even the high-probability lung scan is surprisingly insensitive, and in PIOPED it identified only 41% of patients with PE.[37] In the majority of patients with PE, the lung scan is nondiagnostic despite complex revisions of PIOPED diagnostic criteria.[38] Ventilation scanning rarely clarifies the interpretation of perfusion lung scans.[39] Furthermore, in the presence of high clinical suspicion for PE, the "low-probability" lung scan is a potentially lethal reading[40] because the term "low probability" can convey a false sense of security to the physician; this should be more accurately categorized as "nondiagnostic."[41]

Spiral chest CT scanning with contrast is a new diagnostic approach best suited for identifying PE in the proximal pulmonary vascular tree.[42] Another promising new technology is gadolinium-enhanced magnetic resonance pulmonary angiography,[43] which can display the anatomy of the pulmonary arteries as well as provide an assessment of right ventricular wall motion.

Transthoracic echocardiography is particularly useful in critically ill patients with suspected PE[44] and can help identify conditions that mimic PE such as myocardial infarction, dissection of the aorta, or pericardial tamponade. The thrombus itself is rarely visualized. Signs of right ventricular pressure overload include right ventricular dilatation, right ventricular hypokinesis, pulmonary arterial hypertension as assessed by Doppler, interventricular septal flattening and displacement into the left ventricle, and impaired left ventricular relaxation with a "D-shaped" left ventricle in cross-section. Detection of right ventricular hypertrophy suggests that the process is chronic, subacute, or acute superimposed upon chronic. The McConnell sign appears to be specific for acute PE and is a pattern of regional right ventricular dysfunction in which right ventricular apical wall motion remains normal despite hypokinesis of the right ventricular free wall. A "hinge point" is observed at the border of the mid-apical free wall and the apex (Figures 2, 3).[45]

Figure 2: Schematic diagram of the apical 4-chamber view from a transthoracic 2-dimensional echocardiogram.Qualitative wall motion scores were assigned at 4 locations of the right ventricular free wall (shaded areas). LV = left ventricle; RV = right ventricle.

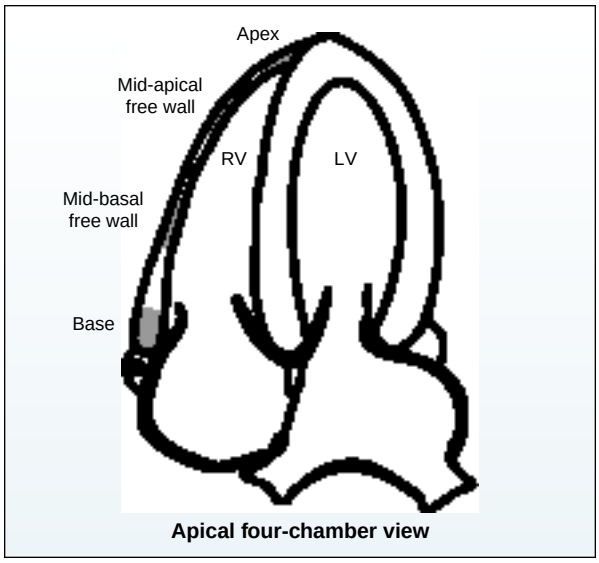

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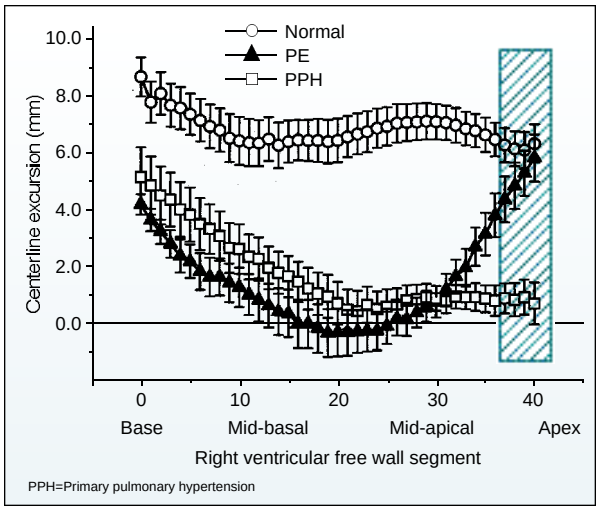
Figure 3: Segmental right ventricular free wall excursion (mean ± SEM) by centerline analysis as a function of right ventricular free wall segment. Centerline excursion in patients with acute pulmonary embolism (PE) was near normal at the apex (hatched area) but abnormal at the mid-free wall and base (p<0.02 vs normal). Centerline excursion in patients with primary pulmonary hypertension was reduced compared with normal subjects in all segments (p<0.03).



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Contrast pulmonary angiography remains the gold standard. It can generally be performed safely[46] and might resolve the dilemma of high clinical suspicion despite nondiagnostic lung scanning, normal venous ultrasonography, or normal echocardiography. It is especially worthwhile to undertake angiography in the presence of high clinical suspicion, nondiagnostic lung scanning, and a normal venous ultrasound of the legs.

Therapy

Heparin accelerates the action of antithrombin III, prevents additional thrombi from forming, and permits endogenous fibrinolysis to dissolve some of the PE clot. Heparin promotes endothelialization of thrombus and decreases the likelihood of its embolization from the venous wall. Patients suspected of PE should have expeditious and intensive anticoagulation therapy with heparin even while the diagnostic work-up is under way. A bolus (average 7,500 U) followed by a continuous infusion of unfractionated heparin (average 1,250 U/hour) usually rapidly produces a therapeutic activated partial thromboplastin time (aPTT) between 60 and 80 seconds. Heparin nomograms facilitate proper dosing.[47] Heparin without oral anticoagulation is used throughout pregnancy to manage PE.[48] Heparin is also employed in Trousseau's syndrome for both acute and chronic therapy, because oral anticoagulation usually fails to prevent recurrent thrombosis.[49] Recently, inpatient administration of low-molecular-weight heparin has been shown to be as safe and effective as administration of unfractionated heparin, even when treating hemodynamically stable PE.[50,51]

In patients with free-floating proximal DVT, inferior vena caval (IVC) filters appear to offer no advantage compared with anticoagulation alone.[52] Filters do not halt the thrombotic process and can cause massive leg edema due to caval thrombosis. In a randomized controlled trial of 400 DVT patients, IVC filters plus anticoagulation did not reduce mortality compared with anticoagulation alone.[53] However, an IVC filter is indicated for PE patients who present with active hemorrhage or recurrent PE despite intensive and prolonged anticoagulation.

Warfarin can safely be started immediately after obtaining a therapeutic PTT or heparin level. Loading warfarin does not shorten the usual five days needed to achieve adequate oral anticoagulation. An initial average dose of 5 mg usually suffices[54] except for small, debilitated, or elderly patients in whom a 2 mg dose is prudent, or for large, young, otherwise healthy patients in whom a 7.5 mg dose is reasonable. Although the target International Normalized Ratio (INR) is usually considered to be 2-3, it should generally be maintained close to the upper part of this range.

Table 6: Prevention of venous thromboembolism

Condition	Prophylaxis strategy
General surgery	UFH 5,000 U BID/TID or Enoxaparin 40 mg SC q 24h or Dalteparin 2,500 or 5,000 U SC q24h
Total hip replacement	Warfarin (target INR 2.5) or IPC or Enoxaparin 30 mg SC BID or Danaparoid 750 U SC BID
Total knee replacement	Enoxaparin 30 mg SC BID or Ardeparin 50 U/ kg SC BID
General medical patient	GCS or IPC or UFH 5,000 U BID/ TID

GCS=graduated compression stockings
UFH=unfractionated heparin
IPC =intermittent pneumatic compression device

After an initial PE, six months of anticoagulation prevents far more recurrences than does six weeks.[55] Indefinite anticoagulation should be considered in patients with recurrent PE if their risk of major bleeding is low.[56] Whether patients with factor V Leiden and an initial PE should receive prolonged courses of anticoagulation remains sharply debated. Although there is consensus that thrombolysis can be lifesaving in patients with massive PE, controversy persists regarding its use in PE patients with stable systemic arterial pressure and right ventricular dysfunction. A randomized controlled trial[57] and multivariate analysis of a large German registry[58] suggest that—in patients with right ventricular dysfunction— thrombolysis might better lower the rate of recurrent PE compared with heparin therapy alone. However, the risk of major hemorrhage rises with increasing age and body mass index.[59] If aggressive intervention is warranted in the setting of failed or contraindicated thrombolysis, transvenous catheterization[60] or open surgical embolectomy[61] should be considered.

Prevention

Although no prophylaxis method is perfect, virtually all hospitalized patients at moderate or high risk should receive mechanical or pharmacological prophylaxis. Mechanical approaches include graduated compression stockings, intermittent pneumatic compression devices, or inferior vena caval filters. Foot pumps are also available for prophylaxis, but they have not been extensively investigated in rigorous clinical trials.

Pharmacologic methods include fixed low-dose subcutaneous unfractionated heparin ("miniheparin"), low-molecular-weight heparin, and warfarin. Miniheparin reduces the perioperative rate of fatal PE by two-thirds.[62] The typical dose is 5,000 U twice or three times daily. An initial injection is administered 2 hours before the skin incision, and miniheparin is continued until the patient is discharged and fully ambulatory.

Compared with minihe parin, low-molecular-weight heparins have superior bioavailability, require less frequent injections, and have reduced rates of heparin-induced thrombocytopenia.[63] At present, three low-molecular-weight heparins (enoxaparin, dalteparin, and ardeparin) and one heparinoid (danaparoid),[64] have received FDA approval for specific prophylaxis. Table 6 lists various prophylaxis strategies for venous thromboembolism.

Conclusion

The epidemiology, diagnosis, treatment, and prophylaxis of PE are rapidly advancing. There is now an increased understanding of inherited and environmental risks. Our array of diagnostic tools has expanded to include the plasma D-dimer ELISA, echocardiography, and spiral chest computed tomography with contrast. We have also gained a keen appreciation for the importance of risk stratification of our patients. The decision to administer thrombolysis or to undertake embolectomy might now depend upon the presence of right ventricular dysfunction even if systemic arterial pressure is maintained. The availability of low-molecular-weight heparins broadens our options for pharmacologic prophylaxis. Despite these advances, diagnostic suspicion and vigilance in prophylaxis remain our first line of defense.

Addendum

Criteria for inserting inferior vena caval filters include major bleeding that precludes anticoagulation or documented failure of intensive anticoagulation. Much more controversial is whether patients at high risk for PE who do not meet these strict criteria should receive filters. Accordingly, a French group undertook a multicentered trial of 400 patients with proximal deep venous thrombosis. They were randomized in a 2-by-2 factorial design to filter/no filter and to low-molecular-weight heparin (enoxaparin 1 mg/kg SC q 12h) or to continuous intravenous unfractionated heparin. Patients began warfarin on the fourth hospital day, and heparin was continuted until a stable INR of 2.0-3.0 was achieved. Anticoagulation continued for at least three months. Outcomes were assessed at 12 days and at two years.

At day 12, fewer patients (p=0.03) in the filter group (1.1%) had PE compared with the no filter group (4.8%), but by two years, recurrent PE and DVT occurred in 21% compared with 12%, respectively (p=0.02). Mortality rates were almost identical in the two groups. With respect to heparin,no differences in efficacy or safety were observed between low-molecular-weight and unfractionated heparin.

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