Pulmonary Vascular Diseases

Gene G. Ryerson, MD, FCCP

Objectives:

1. To review the management of pulmonary embolism (PE).
2. To describe the risk factors and epidemiology of VTE.
3. To provide alternative approaches to the diagnosis of VTE.
4. What causes secondary pulmonary hypertension?
5. What are the steps in the diagnosis of primary pulmonary hypertension?
6. What is the recommended therapy for primary pulmonary hypertension?

Key words: anticoagulation; hypercoaguable state; pulmonary embolism; thrombolytic therapy; venous thrombosis, pulmonary hypertension

Pulmonary Embolism

Risk Factors

Risk factors associated with VTE include prolonged immobility or paralysis; prior VTE; cancer; major surgery (particularly operations involving the abdomen, pelvis, and lower extremities); obesity; pregnancy; varicose veins; congestive heart failure; cor pulmonale; myocardial infarction; stroke; fractures of the pelvis, hip, or leg; indwelling femoral vein catheters; and inflammatory bowel disease. Additionally, a number of congenital and acquired hypercoagulable states predispose to VTE. These include activated protein C resistance (factor V Leiden mutation); antithrombin III deficiency (as can occur with the nephrotic syndrome); protein C deficiency; protein S deficiency; dysfibrinogenemia; disorders of plasminogen and plasminogen activation; antiphospholipid antibodies and lupus anticoagulant; heparin-induced thrombocytopenia; hyperhomocystinemia; myeloproliferative disorders such as polycythemia vera; estrogen use; and hyperviscosity syndromes.

Many patients may present with multiple risk factors for VTE that can further increase their likelihood for the development of this complication. Examples include the elderly patient with congestive heart who sustains a hip fracture and the patient with a myeloproliferative disorder undergoing major surgery.

Pathogenesis

Virchow's triad of venous stasis, endothelial vascular injury, and hypercoagulability explains how various processes can interact to overcome antithrombotic defenses resulting in VTE. Vascular stasis predisposes to VTE by allowing activated coagulation factors to remain undiluted and in contact with vascular endothelium. Vascular trauma or injury, to include the presence of indwelling catheters, presumably initiates thrombosis through the release of tissue factors that activate coagulation proteins. Hypercoagulability refers to abnormal fibrinolytic system pathways or acquired and congenital deficiencies or functional abnormalities that predispose to VTE.

The incidence of cancer is slightly increased in a first episode of DVT or PE compared to control subjects (11% vs 9%) and (6% vs 5%). Pancreas, liver, ovary, brain, and metastatic disease account for most of these. Trousseau first described the association between certain cancers and hypercoagulability in 1872. This hypercoagulability relates to the effects of tumor cells on thrombin generation and fibrinolysis, as well as to tumor-derived activators of factor X. Since these tumors are most commonly incurable, an exhaustive evaluation for underlying malignancy, apart from routine history and physical examination, is not recommended.

DVT

PE usually arises from the deep venous system of the body as a complication of DVT. DVT usually begins in the lower extremities, although occasional thrombi form in pelvic veins, renal veins, upper extremity veins, and the right heart. Most thrombi originate in the soleal veins of the calf, often at sites of decreased blood flow such as valve cusps or bifurcations. The majority of calf thrombi resolve spontaneously, and PE is uncommon. About 20% to 30% of DVTs propagate to the popliteal, femoral, or iliac veins. An additional 10% to 20% of all DVTs begin in proximal veins without prior calf involvement. Iliofemoral thromboses appear to be the source of most clinically apparent pulmonary emboli.

The occurrence of DVT can be self-limited with resolution of the clot in most cases, embolization resulting in PE, and/or venous insufficiency of the lower extremity and the accompanying stasis changes resulting in varicose veins. Therefore, the prevention of DVT will prevent these complications. Risk factors for the occurrence of DVT can be grouped under three general categories (Table 1). Patients with these risk factors should receive prophylaxis treatment to prevent the complications associated with DVT.

Detection of DVT

The clinical diagnosis of DVT of the lower extremity is insensitive and nonspecific. When the classic signs and symptoms of thrombophlebitis are present, only 45% of patients are found to have DVT by venography. Therefore, objective tests have been developed for the detection of DVT (Table 2). Serially negative impedance plethysmography or Doppler-ultrasound excludes the diagnosis of DVT, and anticoagulation can be safely avoided.

The management of patients with clinically suspected PE, a nondiagnostic ventilation/perfusion lung scan ($\dot{V}/\dot{Q}$ scan), and no evidence of DVT is problematic. In selected patients with adequate cardiopulmonary reserve, it appears to be possible to withhold anticoagulation therapy if serial noninvasive tests for DVT are negative. Hull and coworkers evaluated 627 patients with clinically suspected PE who had (1) abnormal, nondiagnostic $\dot{V}/\dot{Q}$ scans; (2) not taking anticoagulation; and (3) had serial noninvasive lower extremity tests for DVT which were negative. The occurrence of VTE was 1.9% in this group, comparable to the rates of 0.7% among patients with normal $\dot{V}/\dot{Q}$ scans who had anticoagulation therapy withheld.

Prevention of DVT/PE

The rationale for DVT and PE prophylaxis is based on the clinically silent nature of the disease and the high prevalence of DVT among hospitalized patients. There is added importance for prophylaxis when one considers that most patients who die of PE do so within 30 min of the acute event. The prevention strategy used for DVT and PE should be based on the patient's level of risk as suggested by the ACCP Consensus Conference on Antithrombotic Therapy.

Table 1—*Risk Factors for Venous Thromboembolism*

Stasis	Endothelial Injury	Hypercoaguable State
Cor pulmonale	Trauma	Homocystinuria
Congestive heart failure	Orthopedic procedures	Polycythemia vera
Previous DVT	Sepsis	Underlying malignancy
Obesity	Intravascular catheter	Protein C and S deficiency
C-spine injury	Pancreatitis	Factor V Leiden
Pregnancy		Antithrombin III deficiency
		Oral contraceptives

Table 2—*Diagnostic Tests for DVT of the Lower Extremities*

Test	Invasiveness	Complications	Comments
Contrast venography	Most invasive	Phlebitis, allergic reactions, renal failure	Reference or gold standard
Radionuclide venography	Less invasive	Minimal	Sensitive for proximal DVT, not commonly used in clinical practice
Impedance plethysmography	Noninvasive	Minimal	Sensitive/specific for proximal DVT; limited in CHF setting and previous DVT
Real-time Doppler ultrasound	Noninvasive	Minimal	Sensitive/specific for proximal DVT, operator dependent
Fibrinogen scanning	Less invasive	Minimal	Sensitive for calf vein thrombosis, not commonly used in clinical practice

Low Risk Patients: These can be defined as individuals <40 years of age undergoing uncomplicated minor surgery with no clinical risk factors for VTE. Their risk of proximal DVT is 0.4%; clinical PE is 0.2%; and fatal PE is 0.002%. Therefore, no specific prophylaxis is recommended.

Moderate Risk Patients: Individuals undergoing any surgery (minor or major) between 40 and 60 years of age without additional risk factors; major surgery in patients <40 years; and minor surgery in patients with additional risk factors. Their risk of proximal DVT is 2 to 4%; clinical PE is 1 to 2%; and fatal PE is 0.1 to 0.4%. Recommended prophylaxis strategies include low-dose unfractionated heparin (LDUH) every 12 h, low molecular weight heparin (LMWH), intermittent pneumatic compression (IPC), and graded compression elastic stockings (ES).

High Risk Patients: This includes major surgery in patients >60 years without additional risk factors; major surgery in patients 40 to 60 years who have additional risk factors; patients with myocardial infarction, and medical patients with risk factors. Their risk of proximal DVT is 4 to 8%; clinical PE is 2 to 4%; and fatal PE is 0.4 to 1%. Recommended prophylaxis includes LDUH every 8 h, LMWH, and IPC.

Highest Risk Patients: Patients >40 years with prior VTE, malignant disease, or hypercoagulable state undergoing major surgery; patients with elective major lower extremity orthopedic surgery; hip fracture; stroke; multiple trauma; or acute spinal cord injury. Their risk of proximal DVT is 10 to 20%; clinical PE is 4 to 10%; and fatal PE is 1 to 5%. Recommended prophylaxis includes LMWH, oral anticoagulants, IPC (+LDUH or LMWH), and adjusted-dose heparin.

Natural History of PE

Resolution of PE with re-establishment of vascular patency begins almost immediately following PE. The National Institutes of Health trials demonstrated that with heparin therapy alone, resolution of pulmonary emboli occurred during the first several weeks after the event with 36% of the vascular defects resolving by day 5; 52% by day 14; 73% at 3 months, and 76% at 1 year. For patients who survive the initial event. Untreated pulmonary embolism has a mortality of nearly 30%. If treatment is initiated, mortality is less than 8%.

Diagnosis of PE

Clinical Suspicion: Clinical suspicion of PE should be based on a combination of factors including the presence or absence of identifiable risk factors (*eg*, recent surgery, obesity, prior VTE), symptoms (*eg*, dyspnea, pleuritic chest pain, hemoptysis), physical findings (*eg*, tachypnea), the results of basic laboratory studies (*eg*, hypoxemia), and the likely presence of alternative diagnoses (*eg*, asthma, pneumonia, congestive heart failure). The PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) investigators found that clinical suspicion clearly influenced the likelihood of PE. For example, pulmonary embolism was angiographically confirmed in 4% of patients with low-probability $\dot{V}/\dot{Q}$ scans and a low-probability clinical suspicion, 16% of patients with low-probability $\dot{V}/\dot{Q}$ scans and an intermediate clinical suspicion, and 40% of patients with a low-probability $\dot{V}/\dot{Q}$ scan and a high-probability clinical suspicion for PE.

Table 3—*Diagnostic Imaging Tests for PE*

Test	Invasiveness	Complications	Comments
Pulmonary angiogram	Most invasive	Allergic reactions, renal failure, cardiac complications	Reference or gold standard when properly performed
Angioscopy	Most invasive	Hemorrhage, endothelial injury	Most useful to evaluate chronic PE
$\dot{V}/\dot{Q}$ scan	Noninvasive	Respiratory distress uncommon	Equivocal when results are other than normal or high probability (>50% of scans)
CT	Noninvasive	Allergic reactions, renal failure	Newer machines able to image higher order pulmonary arteries
MRI	Noninvasive	Minimal	Also able to image higher order pulmonary arteries

V̇/Q̇ Scans: A normal perfusion scan provides compelling evidence against the diagnosis of PE. In one study of 515 consecutive patients with clinically suspected PE who had anticoagulation therapy withheld on the basis of a normal perfusion scan, only 3 had symptomatic VTE (1 PE) during a 3-month follow-up period.

Using PIOPED criteria, a high probability V̇/Q̇ lung scan accompanied with a high prescan clinical suspicion is associated with confirmed PE in more than 96% of the cases. Patients with a high probability V̇/Q̇ scan and a low or intermediate prescan clinical probability will likely warrant a confirmatory test. High probability V̇/Q̇ lung scans lack sensitivity for angiographically confirmed PE. In PIOPED, only 102 of 251 (41%) patients with angiographically confirmed PE had a high-probability V̇/Q̇ lung scan.

V̇/Q̇ scan patterns other than normal or high-probability will require additional diagnostic evaluation as suggested in Figure 1. These may include serial evaluation of the lower extremities with impedance plethysmography or Doppler ultrasound; pulmonary angiography; and CT or MRI (Table 3).

Pulmonary Angiography: Pulmonary angiography is considered the reference gold standard especially with subselective injection of contrast and the use of magnified views. A negative pulmonary angiogram with magnification appears to exclude clinically relevant PE based on two follow-up studies. Mortality of the procedure is less than 0.5% and morbidity is about 5% (usually due to catheter insertion and contrast reactions). Because of the expense and invasiveness of pulmonary angiography, alternative diagnostic algorithms have been sought.

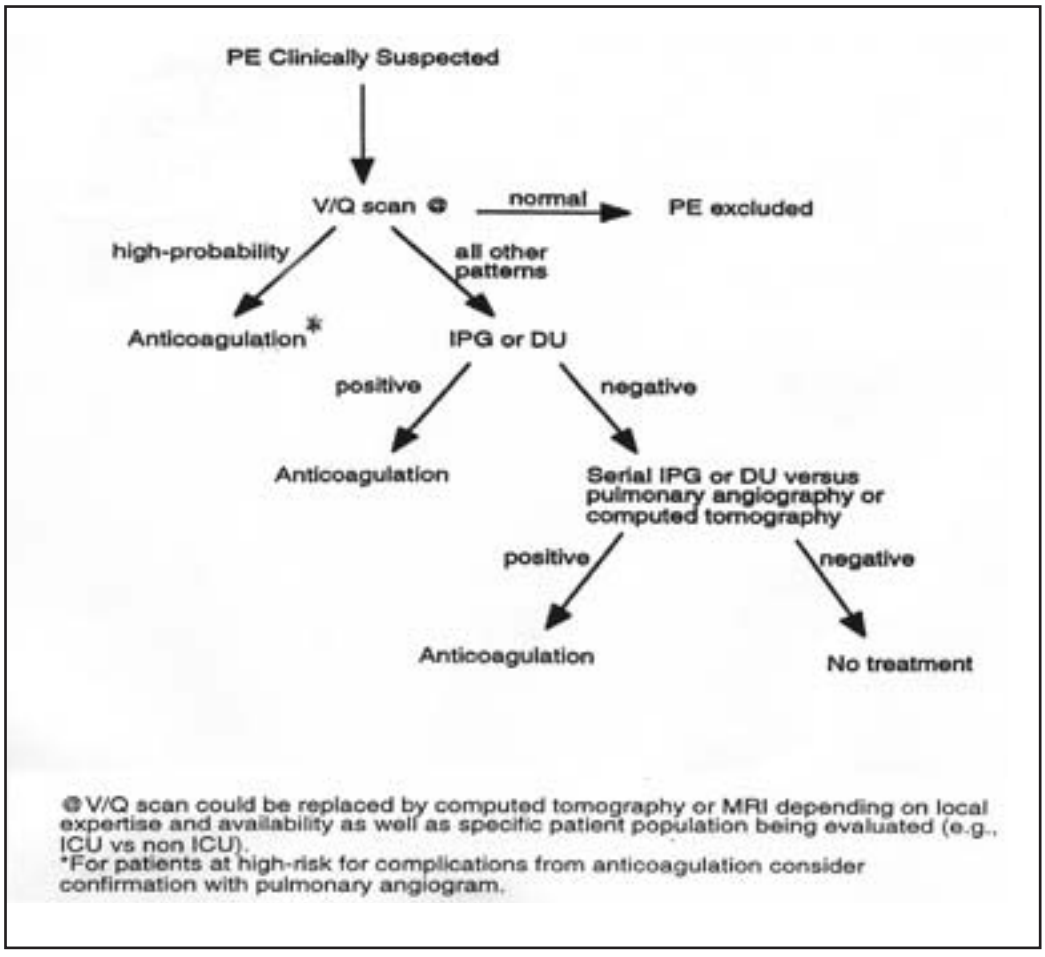

Figure 1. Algorithm for the evaluation of clinically suspected PE. PE=pulmonary embolism; IPG=impedance plethysmography; DU=Doppler ultrasound; IVC=inferior vena cava.
Modified from Kollef, MH. Pulmonary embolism. In: ACCP Pulmonary Board Review 2000-2001. Northbrook, IL: ACCP, 575-586.

Computed Tomography: Spiral CT angiography of the pulmonary circulation has recently emerged as a potential useful diagnostic method for the evaluation of PE. As a minimally invasive examination, this technique is becoming widely available and has replaced the use of conventional pulmonary angiography in some centers. However, its use in detecting more peripheral pulmonary emboli is unproven. Such small clots may not be important physiologically, but their detection may be important markers for future VTE. Several analyses suggest that CT may be a more cost-effective initial test for suspected PE, as compared with the $\dot{V}/\dot{Q}$ lung scan, due to its greater sensitivity for PE and ability to identify alternative diagnoses to PE.

Magnetic Resonance Angiography: Use of magnetic resonance angiography is still in the initial testing phases for PE. However, the initial results are promising especially with gadolinium enhancement of the vasculature. A major limitation of the study is the need for an experienced radiologist to interpret the study. In addition, breath holds of 20 to 30 s are now required for lung imaging which limits the efficacy of the test in acute PE. Newer scanners may reduce the need for breath holds beyond 10 to 15 s.

D-dimer: D-dimer is a plasmin-desired degradation product of cross-linked fibrin whose levels are elevated in the plasma of patients with acute thrombosis and other prothrombotic or inflammatory states.11-13 Numerous commercial quantitative and semiquantitative assays of D-dimer are available that have been shown useful for the exclusion of VTE.

A D-dimer level below 500 mg/mL using a rapid enzyme-linked immunospecific assay technique or a negative bedside whole-blood agglutination technique may be useful in excluding the diagnosis of acute VTE. An alternative diagnostic approach to PE involves obtaining sequential combination of the following procedures: clinical assessment, D-dimer measurement, lower extremity evaluation with impedance plethysmography or Doppler ultrasound, and lung scan or CT. This type of integrated approach may rule out PE in the majority of outpatients with suspected PE. D-dimer alone will exclude PE in about 30% of outpatients at low cost. Such a stepwise approach may be useful because only 20 to 35% of patients with clinically suspected PE have actual disease.

A major limitation of the use of D-dimer assays, especially among inpatients, is the lack of specificity. Several recent studies found that D-dimer assays are rarely negative in the presence of sepsis, recent surgery, liver disease, and malignancy. Therefore, they will primarily be used for their negative predictive value to rule out the diagnosis of VTE. The negative predictive value of D-dimer assays may also be lower among patients with cancer compared to those without malignancy.

Treatment of VTE

Heparin: It is generally accepted that a minimal level of heparin anticoagulation must be maintained to achieve an effective antithrombotic state. Additionally, inadequate anticoagulant therapy results in unacceptably higher rates of recurrent VTE. Therefore, an adequate dosing strategy for heparin in the setting of acute VTE is required. The most widely used test for monitoring heparin therapy is the activated partial thromboplastin time (APTT), which is a global anticoagulation test and does not measure heparin levels. Failure to achieve an adequate anticoagulation response with heparin (ie, APTT >1.5 times control) is associated with increased recurrence of VTE.

Body weight-based dosing of heparin has been employed as a method to achieve an adequate level of anticoagulation. This requires the administration of an initial bolus of heparin (80 IU/kg) followed by a continuous IV infusion (18 IU/kg/h). The APTT is usually checked 6 h after the start of the continuous heparin infusion. Adjustments in the heparin dosing are subsequently made based on the APTT results. Warfarin treatment can usually be started on day 1 or 2 after achieving an adequate level of anticoagulation. The platelet count should be monitored daily while the patient is receiving heparin to assess for heparin-induced thrombocytopenia.

LMWH: Although the continuous IV administration of unfractionated heparin is usually effective and safe, it usually requires hospitalization and frequent monitoring of the APTT. LMWH as initial treatment of VTE can be given without dose adjustments or laboratory monitoring. Therefore, some patients, those with uncomplicated DVT, can be managed as outpatients resulting in significant savings.

LMWH has a mean molecular weight of 4,000 to 5,000 in contrast to 15,000 for unfractionated heparin. Various randomized clinical trials have shown LMWH to be equivalent to IV unfractionated heparin therapy for the management of VTE, although most of the data are for DVT. Therefore, LMWH will probably replace the use of unfractionated heparin for the treatment of DVT. Many of the LMWHs do not require monitoring. Thrombocytopenia is less common than unfractionated heparin. Platelet counts should be checked at initiation of LHWH and between days 3 and 5.

Hirudin: Hirudin is a peptide that directly inhibits thrombin. Currently, the clinically available recombinant hirudin (lepirudin) is primarily used for patients with heparin-induced thrombocytopenia needing anticoagulation therapy.

Coumadin and Other Coumarin Derivatives: Coumadin acts by inhibiting the synthesis of four vitamin K-dependent clotting proteins (factors II, VII, IX, X) and at least two vitamin K-dependent anticoagulant factors (proteins C and S). Coumadin does not act immediately, requiring time for the coagulation factors in plasma to be cleared. Factor VII and protein C have the shortest half-lives. Therefore, a large loading dose of coumadin could tip the hemostatic balance towards procoagulation. Coumadin therapy is usually started on day 1 or 2 at a dose of 5 mg that prevents more than 5 to 7 days of heparin administration in most patients. The level of anticoagulation with coumadin is monitored using the international normalized ratio (INR) where values of 2.0 to 3.0 are effective for VTE.

Duration of anticoagulation with coumadin varies according to patients' risk for recurrent VTE. In general, patients with a first episode of VTE and a reversible risk factor (eg, trauma, surgical operation, and estrogen use) can be treated for 3 to 6 months. Patients with an idiopathic etiology and a first event will usually require 6 months of treatment. Recurrent VTE or a first event in the setting of cancer (until resolved), homozygous activated protein C resistance, presence of an antiphospholipid antibody, or deficiency of antithrombin III, protein C, or protein S will require lifelong treatment.

Thrombolytic Therapy: Thrombolytic therapy is approved for proximal DVT and massive PE. These agents dissolve thrombi by activating plasminogen to plasmin. Plasmin degrades fibrin to soluble peptides in the presence of a thrombus or hemostatic plug. Streptokinase, urokinase, and tissue plasminogen activator are approved for use in the United States. Thrombolytic treatment of DVT has been associated with decreased pain, swelling, loss of venous values, and a reduced incidence of postphlebitic syndrome. For PE, thrombolytic agents produce more rapid resolution of intravascular abnormalities demonstrated by either $\dot{V}/\dot{Q}$ lung scans or pulmonary angiography. However, no proven effect on mortality has yet been demonstrated.

Inferior Vena Cava (IVC) Interruption: IVC interruption is most commonly achieved with the use of an intravascular filter. These devices are primarily used in patients at high risk to bleed (*eg*, extensive trauma, cancer, knee or hip surgery). A randomized trial found that the use of an IVC filter reduced the rate of PE, had no effect on mortality, and was associated with a greater risk of recurrent DVT.

Surgical Embolectomy: This procedure should be reserved for patients with confirmed massive PE who are hemodynamically unstable and not candidates for thrombolysis. The high mortality rates associated with this procedure, especially if cardiopulmonary arrest has occurred, has resulted in a limited enthusiasm for its use.

Pulmonary Hypertension

Pulmonary hypertension is defined as a mean pulmonary artery pressure of >25 mmHg at rest or 30 mmHg during exercise. The associated pulmonary artery wedge pressure or left ventricular end diastolic pressure is normal at <12-15 mmHg. Pulmonary hypertension is classified as primary or secondary. The diagnosis of primary pulmonary hypertension (PPH) can be made only when secondary causes of pulmonary hypertension have been excluded. PPH was previously felt to be an uncommon disorder affecting females more commonly than males in the 20-40 age group. Clinical and histologic features of PPH have now been found within association with portal hypertension, immunodeficiency virus (HIV) infection, collagen vascular disease, and anoretic agents (Table 4). The use of appetite suppressant drugs for more than 3 months has been associated with more than a 30x increase in the risk of developing pulmonary hypertension. The WHO also suggests that other appetite stimulants such as amphetamines may have a very likely causative role in pulmonary hy-

pertension (Table 5). A genetic susceptibility may also play an important role in the development of PPH. Some patients appear to have an autosomal dominant pattern of inheritance.

Pathogenesis

Patients with PPH probably sustain a vascular injury, leading to either a decrease in endothelium-derived vasodilators (nitric oxide, prostacyclin) or an increase in vasoconstrictors (endothelin 1, thromboxane, serotonin). Vasoconstriction and medial hypertrophy occur early in the course, followed by the hallmark pathologic changes of intimal hyperplasia and fibrosis, *in situ* thrombosis, and plexogenic arteriopathy. The plexogenic lesion is an aneurismal dilatation of an artery distal to an area of obstruction; the dilated segment is filled with a mesh of endothelium-lined microchannels. Veno-occlusive disease, with intimal proliferation and fibrosis of the pulmonary veins and venules, occurs in <10% of cases.

Table 4—*Risk Factors for Primary Pulmonary Hypertension*

Drugs and Toxins
Definite causal relationship
Aminorex
Fenfluramine
Dexfenfluramine
Toxic rapeseed oil
Very likely causal relationship
Amphetamines
L-Tryptophan
Possible causal relationship
Meta-amphetamines
Cocaine
Chemotherapeutic agents
Unlikely causal relationship
Antidepressants
Oral contraceptives
Estrogen therapy
Cigarette smoking
Demographic factors and medical conditions
Definite causal relationship
Gender
Possible causal relationship
Pregnancy
Systemic hypertension
Unlikely causal relationship
Obesity
Diseases
Definite causal relationship
HIV infection
Very likely causal relationship
Portal hypertension and/or liver disease
Collagen vascular diseases
Congenital systemic-to-pulmonary cardiac shunts
Possible causal relationship
Thyroid disorders

Adapted from Rich S, ed. Executive summary from the World Symposium on Primary Pulmonary Hypertension 1998.

Table 5—*World Health Organization's Diagnostic Classification of Pulmonary Hypertension*

Pulmonary arterial hypertension
Primary pulmonary hypertension
Sporadic disorder
Familial disorder
Related conditions
Collagen vascular disease
Congenital systemic-to-pulmonary shunt
Portal hypertension
HIV infection
Drugs and toxins
Anorectic agents (appetite suppressants)
Others
Persistent pulmonary hypertension of the newborn
Others
Pulmonary venous hypertension
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease
Extrinsic compression of central pulmonary veins
Fibrosing mediastinitis
Adenopathy and/or tumors
Pulmonary veno-occlusive disease
Others
Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitudes
Neonatal lung disease
Alveolar-capillary dysplasia
Others
Pulmonary hypertension resulting from chronic thrombotic and/or embolic disease
Thromboembolic obstruction of proximal pulmonary arteries
Obstruction of distal pulmonary arteries
Pulmonary embolism (thrombus, tumors, ova and/or parasites foreign material)
In-situ thrombosis
Sickle cell disease
Pulmonary hypertension resulting from disorders directly affecting the pulmonary vasculature
Inflammatory conditions
Schistosomiasis
Sarcoidosis
Others
Pulmonary capillary hemangiomatosis

Adapted from Rich S, ed. Executive summary from the World Symposium on Primary Pulmonary Hypertension 1998.

Clinical Features

Pulmonary hypertension frequently presents with nonspecific symptoms (Table 6). The most common symptoms are dyspnea on exertion, fatigue, and syncope, resulting from reduced cardiac output during activity. Patients may also occasionally present with anginal-like chest pain with normal coronary arteries. This chest pain may reflect right ventricular ischemia. Hemoptysis as a consequence of pulmonary vascular rupture is rare but may be a catastrophic event. Raynaud's phenomenon is seen in approximately 2% of patients with primary pulmonary hypertension, but is a frequent finding in cases of pulmonary hypertension associated with connective tissue diseases such as scleroderma. Physical examination is nonspecific, but may give clues to a secondary cause of pulmonary hypertension. With more advanced disease, the physical exam reveals signs of right ventricular dysfunction. The electrocardiogram most often reveals right atrial or right ventricular hypertrophy and right axis deviation. The chest roentgenograph shows an enlarged cardiac silhouette consistent with right ventricular hypertrophy, with enlarged pulmonary arteries.

Diagnostic Approach—Primary vs Secondary Pulmonary Hypertension

Most patients with pulmonary hypertension are discovered to have an underlying etiology. Therefore, secondary causes of pulmonary hypertension should be thoroughly investigated. Patients with symptoms, signs, ECG, or radiologic abnormalities suggestive of pulmonary hypertension should undergo a systematic evaluation. Transthoracic echocardiography can quantify the approximate degree of pulmonary hypertension and also assess left ventricular systolic and diastolic function, as well as valvular abnormalities.

Table 6—*Signs and Symptoms of Pulmonary Hypertension*

Signs	Symptoms
Jugular vein distention	Dyspnea on exertion
Prominent right ventricular heave	Fatigue
Accentuated pulmonic valve component (P_2)	Syncope
Right-sided third heart sound (S_3)	Anginal chest pain
Tricuspid insufficiency murmur	Hemoptysis
Hepatomegaly	Raynaud's phenomenon
Peripheral edema	

Contrast enhanced transthoracic echocardiography can detect a clinically significant atrial septal defect. Arterial blood gas analysis may detect hypoxemia as a cause of pulmonary hypertension. If resting room air blood gases are within normal limits and nocturnal oxygen desaturation is suspected, overnight oximetry should be performed. Approximately 20% of chronic obstructive pulmonary disease patients with normal resting room air arterial oxygen tensions may have nocturnal oxygen desaturation, even without the presence of sleep apnea. Pulmonary function tests should evaluate for the presence of an obstructive or restrictive ventilatory defect. In chronic obstructive pulmonary disease, pulmonary hypertension is unlikely to occur until the FEV_1 decreases below 50% of predicted. In addition, restrictive lung disease also requires a severe defect. If the cause of pulmonary hypertension is still unexplained, patients should undergo ventilation perfusion lung scan to exclude chronic thromboembolic disease. In primary pulmonary hyper tension, the ventilation perfusion lung scan is normal or may reveal patchy subsegmental abnormalities. Further testing to rule out secondary causes of pulmonary hypertension include antinuclear antibodies for connective tissue diseases, rheumatoid factor, and antineutrophil cytoplasmic autoantibody for possible vasculitis. Patient should also undergo HIV testing and liver function tests for possible portopulmonary hypertension. It is recommended that high resolution CT also be performed to evaluate the lung parenchyma and mediastinum, especially when pulmonary function tests and chest radiographs are nondiagnostic.

Invasive Testing

Most authors recommend heart catheterization of both the right and left sides. Left-sided heart catheterization can evaluate for coronary artery disease, as well as measure left ventricular end diastolic pressure. Right heart catheterization measurements should include sequential oxygen saturation for the presence of an intracardiac shunt, pulmonary angiography for thromboembolic pulmonary hypertension, hemodynamic measurements including pulmonary artery pressures, pulmonary artery occlusion pressure, and cardiac index. Pulmonary hypertension is evaluated with short-acting vasodilators to determine vasodilator responsiveness. Intravenous epoprostenol,

intravenous adenosine, or inhaled nitric oxide are recommended. Although there is disagreement as to the precise definition of vasodilator response, a reduction in mean pulmonary artery pressure of 10 mmHg without a fall in cardiac output or systemic hypotension is significant. These patients are then given nifedipine or diltiazem while hemodynamic monitoring is continued. Immediate improvement in the pulmonary artery pressure indicates better than average prognosis.

Treatment of Primary Pulmonary Hypertension (PPH)

1. Anticoagulation: Patients with PPH should receive chronic anticoagulation therapy. Patients with this condition are prone to thromboembolism, in part due to reduced pulmonary artery blood flow, right ventricular dilatation, venous insufficiency, and inactivity. The range of anticoagulation that is recommended is an international normalized ratio of 1.5 to 2.5.
2. Inotropic Agents: There is no data on the chronic use of inotropic therapy for PPH. Some authors suggest using Digitalis since it may improve right ventricular function.
3. Calcium Channel Blockers: About 20% of patients with PPH have up to a 25% fall in pulmonary artery pressure during right heart catheterization, after administration of a selective pulmonary vasodilator such as prostacyclin, nitric oxide, or adenosine. In patients who exhibit evidence of an acute hemodynamic response to these agents, long-term treatment with orally administered calcium channel blockers in relatively high doses can produce a sustained hemodynamic response with reduction in pulmonary artery pressure and an increased cardiac output. This group of responders not only have improvement in symptoms in exercise tolerance but also increased survival. In patients who do not show reduction in pulmonary artery pressure (with administration of vasodilators) during right heart catheterization, it is not beneficial and potentially dangerous to initiate calcium channel blockers. Significant adverse effects include systemic hypotension, pulmonary edema, and right ventricular failure.
4. Prostaglandins:
   a. Continuous intravenous infusion of epoprostenol (prostacyclin) and iloprost (investigational - not available in the US): Epoprostenol is a potent, short-acting vasodilator and inhibitor of platelet aggregation. In addition, epoprostenol may affect pulmonary vascular remottling through additional mechanisms. The stable prostacyclin analog iloprost may suppress the production of connective tissue growth factor. Continuous infusion of epoprostenol has been shown to improve exercise capacity, quality of life, hemodynamics, and long-term survival in patients with Class 3 or 4 pulmonary hypertension (Table 7). Prostacyclin agemts are approved for treatment in patients with PPH who respond poorly to vasodilators during right heart catheterization and respond poorly to calcium channel blockers. Due to short half-life (3-5 minutes), this drug must be given by continuous intravenous infusion. The optimal dosing of epoprostenol remains undefined, but treatment is generally initiated as dose of 2-4 ng/kg/min, followed by dosing increments of 1-2 ng/kg/min until clinical improvement is shown or adverse effects are intolerable. These include flushing, headaches, jaw pain, flank pain, diarrhea, and nausea. More significant complications are related to the permanent

Table 7—*Functional Assessment of Patients with Pulmonary Hypertension*

Class 1:	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.
Class 2:	Patients with pulmonary hypertension resulting in slight limitation of physical activity. These patients are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class 3:	Patients with pulmonary hypertension resulting in marked limitation of physical activity. These patients are comfortable at rest, but less than ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
Class 4:	Patients with pulmonary hypertension resulting in inability to perform any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.

Modified from the New York Heart Association classification of patients with cardiac disease. Adapted from Rich S, ed. Executive summary from the World Symposium on Primary Pulmonary Hypertension1998.

central venous access that is required for administration. Randomized controlled trials with epoprostenol for other forms of pulmonary artery hypertension have been reported only in scleroderma. Although survival does not appear to be improved when compared to conventional therapy, patients receiving epoprostenol had significant improvement in hemodynamics and exercise capacity. Iloprost, a stable prostacyclin analog derivative, has a longer half-life of 20-30 minutes and may have some advantages over epoprostenol but limited studies have been reported. Intravenous prostaglandins are the first line of treatment for patients with pulmonary hypertension in New York Heart Association functional classes III and IV.

b. Subcutaneous treprostinil: This prostatcyclin analog is administered by continuous subcutaneous infusion by a mini-pump system that is used extensively for insulin administration. Pain at the local infusion site is exceedingly common and may necessitate discontinuation.
c. Oral Beraprost. Beraprost is an oral prostacyclin analog that has been reported to improve hemodynamics in pulmonary hypertension, but in uncontrolled studies. Beraprost may be a treatment alternative for patients with less severe pulmonary hypertension, primarily NYHA class II.
d. Inhaled iloprost (investigational – not available in the U.S.): Aerolized iloprost is an effective pulmonary vasodilator which may be more effective in decreasing pulmonary artery pressure and also increasing cardiac output than that seen with inhaled nitric oxide. Unfortunately, the relatively short duration of action is a drawback to this treatment. Inhaled iloprost requires 6-12 inhalations per day to maintain a clinical effect. At this time, inhaled iloprost may be considered in patients with NYHA class 3 disease.

5. Endothelin Receptor Antagonists (Bosentan): Bosentan is an orally active nonpeptide antagonist of endothelin receptors. Endothelin may play a significant role in the pathogenesis and evolution of pulmonary hypertension. As a potent vasoconstrictor, this substance may increase vascular tone and vascular hypertrophy in the pulmonary circulation, resulting in pulmonary hypertension. Bosentan, by blocking endothelin receptors, has been shown to increase exercise capacity and improve hemodynamics in patients with primary pulmonary hypertension.
6. Phosphodiestrerase Inhibitors: Phosphodiesterase (PDE) inhibitor sildenafil originally developed for the treatment of erectile dysfunction is an effective pulmonary vasodilator. Oral sildenafil protentiates and prolongs the vasodilatory effects of aerosolized iloprost. Case reports have suggested a long-term beneficial effect to sildenafil in primary pulmonary hypertension. At the present time, more trials are needed to document the effects of PDE-5/6 in pulmonary arterial hypertension.

Lung Transplantation

Lung Transplantation should be considered in some patients younger than 65 years old with primary pulmonary hypertension who fail to respond to medical management. Experience has shown that lung transplant recipients with primary pulmonary hypertension have survival rates at 73% at one year, 55% at three years, and 45% at five years. Obliterative bronchiolitis is a common complication in transplant patients with PPH. Recurrence of PPH after lung transplantation has not been reported in the transplanted lung. Acceptable results have been reported with heart-lung transplantation, bilateral lung transplantation, and single lung transplantation. There is no consensus which procedure is best.

Prognosis

The median duration of survival after the initial diagnosis of PPH is approximately 2.8 years. This survival rate can vary greatly. The use of anticoagulation appears to improve survival. Patients without evidence of right ventricular failure may survive more than ten years. Responders to calcium channel blockers have a 95% five year survival. NYHA classes III and IV treated patients with Epoprostenol which have a five year survival twice that of matched controls.

Acknowledgment: The section on "Pulmonary Embolism" is modified from Kollef, MH. Pulmonary embolism. In: ACCP Pulmonary Board Review 2000-2001. Northbrook, IL: ACCP, 575-586.

Annotated Bibliography

Agnelli G, Piovella F, Buoncristiani P, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. N Engl J Med 1998; 339:80-85

Enoxaparin combined with compression stockings was found to be more effective than compression stockings alone for the prevention of VTE after neurosurgery and did not cause excessive bleeding.

Arcasoy SM, Kreit JW. Thrombolytic therapy of pulmonary embolism: a comprehensive review of current evidence. Chest 1999; 115:1695-1707

Up-to-date review of the role of thrombolysis in VTE.

Clagett GP, Anderson FA, Geerts WH, et al. Prevention of venous thromboembolism. Chest 1998; 114:531S-560S

Evidence-based recommendations for the prevention of VTE.

De Monye W, Sanson BJ, Mac Gillavry MR, et al. Embolus location affects the sensitivity of a rapid quantitative D-dimer assay in the diagnosis of pulmonary embolism. Am J Respir Crit Care Med 2002; 165:345-348

D-dimer concentration and the accuracy of D-dimer assays are dependent on embolus location and smaller, subsegmental emboli may be missed when D-dimer assays are used as a sole test to exclude pulmonary embolism.

Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. N Engl J Med 1998; 338:409-415

In high-risk patients with proximal DVT, the initial beneficial effect of vena caval filters for the prevention of pulmonary embolism was counterbalanced by an excess of recurrent DVT, without any difference in mortality.

Douketis JD, Kearon C, Bates S, et al. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA 1998; 279:458-462

Among patients with symptomatic pulmonary embolism or DVT who are treated with anticoagulation for 3 months, fatal pulmonary embolism is rare during and following anticoagulant therapy. However, patients presenting with pulmonary embolism are more likely to die of recurrent pulmonary embolism than are patients presenting with DVT.

Gaine SP, Rubin LJ. Primary pulmonary hypertension. Lancet 1998; 352:719-725

Reviews the progress made in diagnosis and treatment of PPH over the past 20 years.

Ginsberg JS, Wells PS, Kearon C, et al. Sensitivity and specificity of a rapid whole-based assay for D-dimer in the diagnosis of pulmonary embolism. Ann Intern Med 1998; 129:1006-1011

Demonstrated that a normal semiquantitative measure of D-dimer is useful in excluding pulmonary embolism in patients with a low pretest probability of pulmonary embolism or a nondiagnostic lung scan.

Goldhaber SZ. Pulmonary embolism. N Engl J Med 1998; 339:93-104

State-of-the-art review on the topic of pulmonary embolism. Very good discussion of clinical approach to the problem of pulmonary embolism.

Goldhaber SZ, Grodstein F, Stampfer MJ, et al. A prospective study of risk factors for pulmonary embolism in women. JAMA 1997; 277:642-645

Obesity, cigarette smoking, and hypertension were associated with increased risk of pulmonary embolism in women. Control of these risk factors could decrease the risk of pulmonary embolism among women.

Hoeper MM, Galie N, Simonneau G, et al. New treatments for pulmonary arterial hypertension. Am J Respir Crit Care Med 2002; 265:1209-1216

This perspective describes the most recent developments in our understanding of the pathogenesis of PAH and how they relate to novel therapeutic approaches; summarizes the results of clinical trials on emerging new therapies; and provides our recommendations for a tailored therapeutic approach.

Hyers TA, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease. Chest 1998; 114:561S-578S

State-of-the-art review of medical treatment for VTE.

Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. Ann Intern Med 1998; 129:1044-1049

Venous ultrasonography is a very valuable test for the diagnosis and management of patients with suspected DVT or pulmonary embolism. However, the following factors reduce the positive predictive value of venous ultrasonography for acute thromboembolism: asymptomatic for DVT; low clinical suspicion for DVT; abnormality confined to a short segment of proximal vein; abnormality confined to calf veins; history of previous VTE; negative result of another test that is sensitive for DVT (such as D-dimer); and low prevalence of DVT in referral population. (With one or more of the above factors, venography or other testing should be considered to exclude the possibility of a false-positive test.)

Kearon C, Julian JA, Newman TE, et al. Noninvasive diagnosis of deep vein thrombosis. Ann Intern Med 1998; 128:663-677

Reviews literature emphasizing that patients with suspected DVT can usually be managed with noninvasive testing. However, if the results of this testing are nondiagnostic or are discordant with the clinical assessment, venography or

other confirmatory tests should be considered.

Konstsantinides S, Geibel A, Kapser W, et al. Patient foramen ovale is an important predictor of adverse outcome in patients with major pulmonary embolism. Circulation 1999; 97:1946-1951

In patients with major pulmonary embolism, echocardiography detection of a patent foramen ovale signifies a particularly high risk of death and arterial thromboembolic complications.

Konstantinides S, Geibel A, Olschewski M, et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: results of a multicenter registry. Circulation 1997; 96:882-888

This cohort study suggests that thrombolysis may favorably affect the clinical outcome of hemodynamically stable patients with major pulmonary embolism. It also suggests that echocardiographic criteria demonstrating abnormal right heart function may identify a cohort of patients at higher risk of mortality with hemodynamically stable pulmonary embolism.

Lee AY, Julian JA, Levine MN, et al. Clinical utility of a rapid whole-blood D-dimer assay in patients with cancer who present with suspected acute deep venous thrombosis. Ann Intern Med 1999; 131:417-423

A negative D-dimer test result in patients with cancer does not reliably exclude deep venous thrombosis because the negative predictive value of the test is significantly lower in these patients than in patients without cancer.

Mandel J, Mark EJ, Hales CA. Pulmonary veno-occlusive disease. Am J Respir Crit Care Med 2000; 162: 1964-1973

This review summarizes the current state of knowledge regarding PVOD.

McGoon MD. The assessment of pulmonary hypertension. Clin Chest Med 2001; 22:493-508

A diagnostic algorithm can guide the evaluation of pulmonary hypertension (PH). Symptomatic patients require evaluation to identify an aggressive therapeutic strategy to reduce symptoms, improve hemodynamics, and prolong survival.

Opinions regarding the diagnosis and management of venous thromboembolic disease: ACCP Consensus Committee on Pulmonary Embolism; American College of Chest Physicians. Chest 1998; 113:499-504

This expert group attempted to present the available data in support of specific issues related to the diagnosis and management of VTE, as well as to identify areas requiring further investigation.

Remy-Jardin M, Remy J. Spiral CT angiography of the pulmonary circulation. Radiology 1999; 212:615-636

A review of the utility of spiral computed tomography, including cost considerations for the evaluation of PE.

Ridker PM, Glynn RJ, Miletich JP, et al. Age-specific incidence rates of venous thromboembolism among heterozygous carriers of factor V Leiden mutation. Ann Intern Med 1997; 126:528-531

VTE risk increased by age and factor V Leiden carrier status. Therefore, the risk and pathogenesis of VTE involve acquired and genetic factors. Determination of factor V Leiden mutation status should not be limited to young patients as this increases the risk of VTE in older patients as well.

Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med 1999; 341:793-800

The prophylactic use of 40 mg of enoxaparin subcutaneously once per day safely and effectively reduces the risk of venous thromboembolism in patients with acute medical illnesses.

Schulman S, Granquvist S, Holmstrom M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. N Engl J Med 1997; 336:393-398

Prophylactic anticoagulation that was continued for an indefinite period after a second episode of venous thromboembolism was associated with a much lower rate of recurrence during 4 years of follow-up than treatment for 6 months. However, there was a trend toward a higher risk of major hemorrhage when anticoagulation was continued indefinitely.

Simmoneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism: the THESEE Study Group. N Engl J Med 1997; 337:663-669

Initial subcutaneous treatment with low-molecular-weight heparin (tinzaparin) appeared to be as effective and safe as IV unfractionated heparin in patients with acute pulmonary embolism.

Sorensen HT, Mellemkjaer L, Steffensen FH, et al. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. N Engl J Med 1998; 338:1169-1173

Among 15,348 patients with DVT and 11,305 patients with pulmonary embolism, there were 1,727 cases of cancer. The expected number of cancers was 1,372 based on national Danish statistics (observed to expected ratio 1.3 [95% CI 1.21 to 1.33]). Forty percent of patients with a diagnosis of cancer within 1 year of hospitalization for VTE had distant metastases at the time of diagnosis of cancer. The authors conclude that an aggressive search for hidden cancer in patients presenting with VTE is not warranted.

Swensen SJ, Sheedy PF, Ryu JH, et al. Outcomes after withholding anticoagulation from patients with suspected acute pulmonary embolism and negative computed tomographic findings: a cohort study. Mayo Clin Proc 2002; 77:130-138

Results showed that the incidence of overall deep venous thrombosis or pulmonary embolism or fatal pulmonary embolism among patients with suspected acute pulmonary embolism, negative CT results, and no other evidence of venous thromboembolism is low. Withholding anticoagulation in these patients appears to be safe.

Well PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med 1998; 129:997-1005

Among inpatients and outpatients with suspected pulmonary embolism, only 3 of 665 patients (0.5% [95% CI, 0.1% to 1.3%]) with low or moderate pretest probability and a non-high-probability $\dot{V}/\dot{Q}$ lung scan who were considered negative for pulmonary embolism had pulmonary embolism or DVT during a 90 day follow-up. These data suggest that the management of patients with suspected pulmonary embolism on the basis of pretest probability and results of $\dot{V}/\dot{Q}$ lung scanning is safe.

Notes