

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

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

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

PE is a common cardiovascular and cardiopulmonary illness with an incidence in the United States that exceeds 1 per 1000 and a mortality rate >15% in the first 3 months after diagnosis.¹ This makes PE possibly as deadly an illness as acute myocardial infarction. Nevertheless, the lay public has not been well educated about PE. Consequently, early detection and prompt presentation for medical evaluation have lagged far behind the public awareness of acute coronary syndromes and stroke. Although discussion of the etiology of PE has classically focused on acquired and inherited causes of hypercoagulability, there is also an association between atherosclerotic disease and spontaneous venous thrombosis.²

The most common reversible risk factor for PE is obesity, an increasing pandemic in our society. Other common reversible risk factors include cigarette smoking and hypertension. Nevertheless, public fascination with PE has centered on long-haul air travel, a rare cause of venous thromboembolism.³ PE also occurs in the context of illness attributable to surgery, trauma, immobilization, cancer,⁴ oral contraceptives,⁵ pregnancy, and postmenopausal hormone replacement therapy,⁶ as well as medical conditions such as pneumonia and congestive heart failure. Genetic predisposition to venous thrombosis is being increasingly recognized,⁷ and twin studies have demonstrated the important contribution of an inherited prothrombotic state.⁸ Increased levels of clotting factors and activation peptides contribute to the risk of PE. Deficiencies of anticoagulant factors also increase thrombotic risk.⁹

Pathophysiology

Hemodynamics

The hemodynamic response to PE depends on the size of the embolus, coexistent cardiopulmonary disease, and neurohumoral effects.¹⁰ Hemodynamic decompensation occurs not only because of physical obstruction of blood flow but also because of the release of humoral factors, such as serotonin from platelets, thrombin from plasma, and histamine from tissue.

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

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

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

From the Cardiovascular Division (S.Z.G.), Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass, and the Department of Medicine (C.G.E.), Pulmonary and Critical Care Division, LDS Hospital and University of Utah School of Medicine, Salt Lake City, Utah.

Dr Goldhaber has served as a consultant for Aventis, Pfizer, AstraZeneca, Bayer, Paion, and Procter and Gamble. Dr Elliott has served as a consultant for Aventis, Pfizer, AstraZeneca, Actelion, and Encysive.

This is Part I of a 2-part article. Part II will appear in the December 9, 2003, issue of *Circulation*.

Correspondence to Samuel Z. Goldhaber, MD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115. E-mail goldhaber@partners.org

(*Circulation*. 2003;108:2726-2729.)

© 2003 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000097829.89204.0C

TABLE 1. Gas Exchange Definitions and Equations

Anatomic dead space	Breathed gas that does not enter gas exchange units of the lung
Physiological dead space	Ventilation to gas exchange units exceeds flow of venous blood through pulmonary capillaries; V/Q ratio exceeds 1.0
Total dead space volume (V_d)	Sum of anatomic and physiologic dead space
Alveolar volume (V_a)	Gas volume that effectively eliminates carbon dioxide = tidal volume (V_t) – total dead space volume (V_d)
Alveolar ventilation (\dot{V}_A)	$(V_a) \times$ breathing rate
Minute ventilation (\dot{V}_E)	$(V_t) \times$ breathing rate
Dead space ventilation (\dot{V}_D)	$(V_d) \times$ breathing rate
Alveolar ventilation (\dot{V}_A)	$\dot{V}_E - \dot{V}_D$
Partial pressure of CO_2 dissolved in arterial blood (P_{aCO_2})	Proportional to CO_2 produced (\dot{V}_{CO_2}) divided by alveolar ventilation (\dot{V}_A) = $(\dot{V}_{CO_2}/\dot{V}_A) \times K$, where K = constant of proportionality
Partial pressure of O_2 dissolved in arterial blood	P_{aO_2}
Atmospheric P_{O_2}	$P_{B_{O_2}} = (\text{total gas pressure}) \times (\text{fractional concentration of } O_2)$
Alveolar P_{O_2}	$P_{A_{O_2}}$
Water vapor pressure at 37°C	47 mm Hg
Respiratory gas exchange ratio	$(CO_2 \text{ produced}/O_2 \text{ consumed}) = 0.8$
Alveolar pressure of CO_2	$P_{A_{CO_2}} = (P_{a_{CO_2}}/0.8)$
Partial pressure of O_2 in the alveolae ($P_{A_{O_2}}$)	$(P_{B_{O_2}} - 47 \text{ mm Hg}) \times (\text{fractional concentration of } O_2) - (P_{a_{CO_2}}/0.8)$
Alveolar to arterial O_2 tension gradient	$P_{A_{O_2}} - P_{a_{O_2}}$

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

As right ventricular wall stress increases, cardiac ischemia may develop, because increased right ventricular pressure compresses the right coronary artery, diminishes subendocardial perfusion, and limits myocardial oxygen supply.¹¹ Right ventricular microinfarction leads to elevations of troponin,¹² and right ventricular overload causes elevations of both pro-B-type natriuretic peptide¹³ and B-type natriuretic peptide.^{14,15}

Gas Exchange

Acute PE impairs the efficient transfer of oxygen and carbon dioxide across the lung (Tables 1 and 2). Decreased arterial P_{O_2} (hypoxemia) and an increase in the alveolar-arterial

oxygen tension gradient are the most common gas exchange abnormalities. Total dead space increases. Ventilation and perfusion become mismatched, with blood flow from obstructed pulmonary arteries redirected to other gas exchange units. Shunting of venous blood into the systemic circulation may occur.

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

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

Hypoxemia

Several mechanisms explain the presence of arterial hypoxemia in the setting of acute PE. Mismatching of ventilation

TABLE 2. Potential Gas Exchange Abnormalities in Pulmonary Embolism

Decreased arterial P_{O_2}
Increased alveolar to arterial oxygen tension gradient ($P_{A_{O_2}} - P_{a_{O_2}}$)
Respiratory alkalosis
Low V/Q units: impaired oxygen transfer to pulmonary capillaries, with preserved blood flow to pulmonary capillaries; ratio of ventilation to perfusion is <1.0
Right-to-left shunting: no ventilation and venous blood enters systemic circulation
Increased anatomic dead space: breathed gas does not enter gas exchange units of the lung
Increased physiologic dead space: ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries; ratio of ventilation to perfusion >1.0
Increased total dead space: anatomic plus physiologic dead space
Decreased carbon monoxide diffusion

and perfusion is the most common cause of impaired pulmonary oxygen transfer.¹⁶ Unlike normal lungs, where ventilation is well matched to blood flow, PE causes redistribution of blood flow so that some lung gas exchange units have low ratios of ventilation to perfusion, whereas other lung units have excessively high ratios of ventilation to perfusion. Arterial hypoxemia occurs when venous blood flows through lung gas exchange units, where the ratio of ventilation to capillary blood flow is low. Atelectasis, caused by loss of surfactant and alveolar hemorrhage, also contributes to reduced ratios of ventilation to perfusion and arterial hypoxemia.

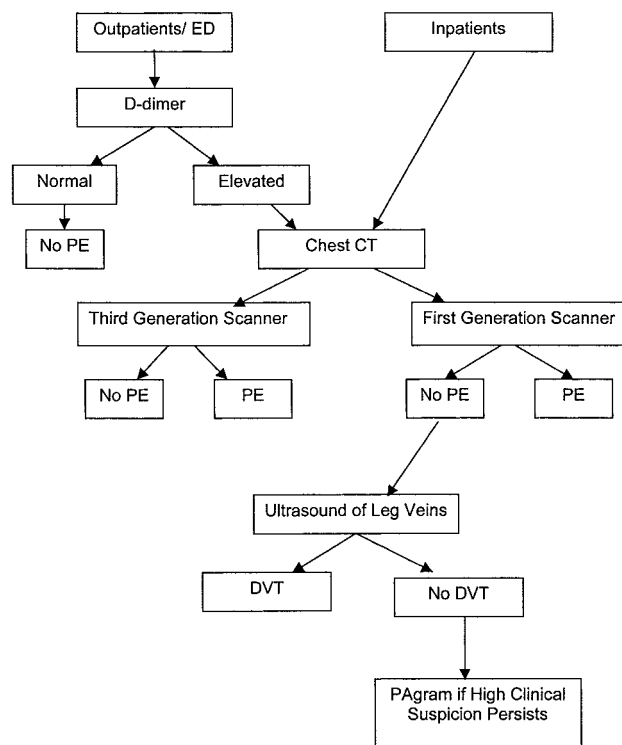
A shunt exists when venous blood enters the systemic arterial system without passing through ventilated gas exchange units of the lung. The failure of supplemental oxygen to correct arterial hypoxemia accompanying acute PE often reflects the existence of right to left shunting of venous blood through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

A low pressure of oxygen in venous blood also may contribute to arterial hypoxemia when PE causes right ventricular failure. Low cardiac output leads to increased extraction of oxygen in the tissues, thereby decreasing the partial pressure of oxygen in venous blood below normal levels. Venous blood with an abnormally low P_{O_2} amplifies the effect of low ventilation to perfusion ratios when it passes through diseased lung gas exchange units to the systemic circulation. In contrast, arterial oxygen content is not affected by low venous P_{O_2} when the lungs are normal and ratios of ventilation to blood flow in the lung gas exchange units are approximately 1.0.

Other Gas Exchange Abnormalities

In patients with acute PE, total dead space increases because lung units continue to be ventilated despite diminished or absent perfusion. Complete obstruction of a pulmonary artery by an embolus causes an increase in anatomic dead space. In contrast, incomplete obstruction of a pulmonary artery increases physiological dead space, ie, ratios of ventilation to perfusion increase. Increased dead space impairs the efficient elimination of carbon dioxide. However, medullary chemoreceptors sense any increase in arterial PCO_2 , and they will increase the total minute ventilation, thereby lowering the arterial PCO_2 to normal and often below normal. Thus, most patients with PE present with a lower than normal arterial PCO_2 and respiratory alkalosis because of an increased total minute ventilation. Limited data suggest that the increased total minute ventilation occurs because of reflex stimulation of irritant and juxta capillary sensors in the lung.

In the setting of acute PE, hypercapnia reflects massive embolism accompanied by marked increases in both ana-



Proposed diagnostic strategy.

tomically and physiologically dead space. The alveolar volume of each tidal breath is severely reduced, and the ventilatory muscles are unable to sustain the marked increase of minute ventilation needed to maintain normal arterial P_{aCO_2} . Treatment with positive pressure ventilation and paralysis allow reduction of carbon dioxide production and resting of the ventilatory muscles until definitive therapy relieves thromboembolic obstruction and increases the alveolar volume of each tidal breath.

The single-breath carbon monoxide diffusion capacity (DLCO) is a well standardized and sensitive technique that screens for abnormal pulmonary gas exchange by measuring the rate of carbon monoxide uptake.¹⁷ Although the DLCO is often reduced in patients with PE, many other pulmonary disorders also cause abnormal reductions of DLCO.

Diagnosis

To diagnose PE, one must think of PE as a diagnostic possibility. The clinical setting, combined with a focused history and physical examination, often provides helpful hints. The ECG and chest x-ray may rapidly identify alternative diagnoses, especially myocardial infarction and pneumonia, respectively. Arterial blood gas measurements have proved disappointing. Normal values of the alveolar-arterial oxygen gradient do not exclude acute PE¹⁸; hypoxemia discriminates poorly between those who do and do not have acute PE.¹⁹

Prompt and accurate diagnosis of PE is facilitated by a clinical evaluation that assesses the probability of PE and makes appropriate use of the plasma D-dimer ELISA and chest CT scanning (Figure).²⁰ Wells et al²¹ developed a simple clinical model to predict the likelihood of PE. Their

scoring system has a maximum of 12.5 points, based on 7 variables: 3 points each for clinical evidence of deep vein thrombosis and an alternative diagnosis being less likely than PE, 1.5 points each for heart rate >100 per minute, immobilization/surgery within 4 weeks, and previous deep vein thrombosis/PE, and 1 point each for hemoptysis or cancer. A score of <2 points makes PE low probability (2% likelihood), and a score of >6 points makes PE high probability (50% likelihood). In a consecutive cohort of patients suspected of PE, almost half had a low probability score.

The D-dimer is elevated in almost all patients with PE because of endogenous albeit ineffective fibrinolysis, which causes plasmin to digest some of the fibrin clot and release D-dimers into the systemic circulation. Among patients presenting to the Emergency Department at Brigham and Women's Hospital, normal D-dimer ELISA levels have a high negative predictive value for PE regardless of clinical probability.²² Of 1109 consecutive D-dimer assays among patients suspected of PE, 547 were normal. Only 2 of 547 had PE despite a normal D-dimer. In this cohort, the sensitivity of the D-dimer for acute PE was 96.4%, and the negative predictive value was 99.6%. By incorporating the D-dimer ELISA into the diagnostic algorithm, fewer chest CT scans will be needed, resulting in improved diagnostic efficiency and cost reduction. However, these findings do not pertain to inpatients suspected of PE.

In acute PE, the fibrinogen level decreases, probably because of activation of endogenous fibrinolysis. As the fibrinogen level declines, the D-dimer level increases. In the future, a high ratio of D-dimer to fibrinogen may help to rule in acute PE.²³

Chest CT scanning has become the preferred imaging modality.^{20,24} In the absence of PE, the chest CT may yield a previously unsuspected reason for symptoms mimicking PE, such as pneumonia or interstitial fibrosis that were not apparent on the chest radiograph. Lung scanning is being used less frequently because its results are often equivocal. Lung scanning nevertheless remains the first-line imaging study for patients with anaphylaxis to contrast agent, renal failure, or pregnancy, as well as in patients with prior PE diagnosed by lung scan.

Knowing the generation of chest CT scanner that is being used is crucial to interpreting the results of the imaging test. First-generation scanners have 5-mm resolution and may fail to detect one third of PEs, especially in the subsegmental pulmonary arteries.²⁵ However, third-generation scanners provide 1-mm resolution with a single breath hold. For institutions without third-generation scanners, a useful alternative strategy is venous ultrasonography of the legs when the chest CT scan shows no evidence of PE.²⁶

References

- Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet*. 1999;353:1386–1389.
- Prandoni P, Bilora F, Marchiori A, et al. An association between atherosclerosis and venous thrombosis. *N Engl J Med*. 2003;348:1435–1441.
- Lapostolle F, Surget V, Borron SW, et al. Severe pulmonary embolism associated with air travel. *N Engl J Med*. 2001;345:779–783.
- Schulman S, Lindmarker P. Incidence of cancer after prophylaxis with warfarin against recurrent venous thromboembolism: Duration of Anticoagulation Trial. *N Engl J Med*. 2000;342:1953–1958.
- Vandenbroucke JP, Rosing J, Bloemenkamp KW, et al. Oral contraceptives and the risk of venous thrombosis. *N Engl J Med*. 2001;344:1527–1535.
- Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288:321–333.
- Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. *N Engl J Med*. 2001;344:1222–1231.
- Rosendaal FR, Bovill EG. Heritability of clotting factors and the revival of the prothrombotic state. *Lancet*. 2002;359:638–639.
- Joffe HV, Goldhaber SZ. Laboratory thrombophilias and venous thromboembolism. *Vasc Med*. 2002;7:93–102.
- Goldhaber SZ. Echocardiography in the management of pulmonary embolism. *Ann Intern Med*. 2002;136:691–700.
- Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. *Chest*. 2002;121:877–905.
- Konstantinides S, Geibel A, Olschewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. *Circulation*. 2002;106:1263–1268.
- Kucher N, Printzen G, Doernhoefer T, et al. Low pro-brain natriuretic peptide levels predict benign clinical outcome in acute pulmonary embolism. *Circulation*. 2003;107:1576–1578.
- ten Wolde M, Tulevski II, Mulder JW, et al. Brain natriuretic peptide as a predictor of adverse outcome in patients with pulmonary embolism. *Circulation*. 2003;107:2082–2084.
- Kucher N, Printzen G, Goldhaber SZ. Prognostic role of BNP in acute pulmonary embolism. *Circulation*. 2003;107:2545–2547.
- Iti E, Nguyen S, Robin F, et al. Distribution of ventilation/perfusion ratios in pulmonary embolism: an adjunct to the interpretation of ventilation/perfusion lung scans. *J Nucl Med*. 2002;43:1596–1602.
- Crapo RO, Jensen RL, Wanger JS. Single-breath carbon monoxide diffusing capacity. *Clin Chest Med*. 2001;22:637–649.
- Stein PD, Goldhaber SZ, Henry JW. Alveolar-arterial oxygen gradient in the assessment of acute pulmonary embolism. *Chest*. 1995;107:139–143.
- Stein PD, Goldhaber SZ, Henry JW, et al. Arterial blood gas analysis in the assessment of suspected acute pulmonary embolism. *Chest*. 1996;109:78–81.
- British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. *Thorax*. 2003;58:470–483.
- Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost*. 2000;83:416–420.
- Dunn KL, Wolf JP, Dorfman DM, et al. Normal D-dimer levels in emergency department patients suspected of acute pulmonary embolism. *J Am Coll Cardiol*. 2002;40:1475–1478.
- Kucher N, Kohler HP, Dornhofer T, et al. Accuracy of d-dimer/fibrinogen ratio to predict pulmonary embolism: a prospective diagnostic study. *J Thromb Haemost*. 2003;1:708–713.
- van Strijen MJ, de Monye W, Schiereck J, et al for the Advances in New Technologies Evaluating the Localisation of Pulmonary Embolism Study Group. Single-detector helical computed tomography as the primary diagnostic test in suspected pulmonary embolism: a multicenter clinical management study of 510 patients. *Ann Intern Med*. 2003;138:307–314.
- Perrier A, Howarth N, Didier D, et al. Performance of helical computed tomography in unselected outpatients with suspected pulmonary embolism. *Ann Intern Med*. 2001;135:88–97.
- Musset D, Parent F, Meyer G, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. *Lancet*. 2002;360:1914–1920.

KEY WORDS: thrombosis ■ embolism ■ pulmonary heart disease ■ diagnosis

Acute Pulmonary Embolism: Part II Risk Stratification, Treatment, and Prevention

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

Pulmonary embolism (PE) presents with a wide clinical spectrum, from asymptomatic small PE to life-threatening major PE that causes hypotension and cardiogenic shock (Table). Traditionally, our risk assessment is done by *gestalt*. However, a more precise risk assessment can be obtained by using a formal clinical scoring system, such as the Geneva Prognostic Index.¹ The Geneva Prognostic Index uses an 8-point scoring system and identifies 6 predictors of adverse outcome: 2 points each for cancer and hypotension and 1 point each for heart failure, prior deep vein thrombosis (DVT), arterial hypoxemia, and ultrasound-proven DVT. As points accumulate, prognosis worsens. Remarkably, hypoxemia accounts for only 1 of 8 points.

Physical examination, ECG, chest radiograph, CT scan, and echocardiogram² can provide evidence of right ventricular dysfunction, a key prognostic marker of high risk and increased major adverse clinical events. The most recent development in prognostication is the use of biomarkers^{2a} such as troponin elevation,³ which indicates right ventricular microinfarction, and elevations of pro-B-type natriuretic peptide⁴ and B-type natriuretic peptide, which indicate right ventricular overload.^{5,6}

On physical examination, general clinical appearance is useful, but young patients may appear deceptively well despite massive PE. Clues to right heart failure include distended jugular veins, an accentuated pulmonic heart sound, and a tricuspid regurgitation murmur.

The ECG may show a classic S1Q3T3 pattern but more often will demonstrate a less commonly recognized sign of right ventricular strain, T wave inversion in leads V₁ through V₄. New incomplete or complete right bundle-branch block is a very useful sign of right ventricular dysfunction. The chest radiograph may show enlarged pulmonary arteries, especially an enlarged right descending pulmonary artery, indicating pulmonary hypertension. Although the chest CT scan is performed primarily to detect or exclude PE, information about right ventricular dilatation can also be gleaned in the phase of the scan in which the right and left ventricles are imaged. If the right ventricle is as large as the left ventricle, then right ventricular dilatation attributable to right ventricular dysfunction can be confidently diagnosed.

The echocardiogram is a low-yield diagnostic tool in patients with PE, because it will usually be normal. However, in acutely ill patients, the echocardiogram is quite useful because it can often help differentiate right ventricular dysfunction typical for PE from other catastrophic illnesses, such as pericardial tamponade, dissection of the aorta, and acute myocardial infarction. Among patients in whom the diagnosis of PE is established, the echocardiogram provides rapid and accurate risk stratification. Moderate or severe right ventricular hypokinesis, pulmonary hypertension, a patent foramen ovale, and free-floating right-heart thrombus are markers for a high risk of death or recurrent PE.

Anticoagulation

When acute PE is considered likely, heparin anticoagulation should be begun while pursuing the diagnostic workup. Short-acting, intravenously administered unfractionated heparin is initiated with a bolus of 80 U/kg followed by a continuous infusion of 18 U/kg per hour.⁷ The target activated partial thromboplastin time is usually between 60 and 80 seconds. After discontinuing the infusion, the anticoagulant effect will quickly abate. This rapid reversibility is important for patients who may require thrombolysis or embolectomy.

For stable patients with PE, there is increasing interest in using weight-based dosing of low-molecular-weight heparin in lieu of unfractionated heparin. In the therapy of DVT, a meta-analysis indicated that low-molecular-weight heparin reduces mortality with no increase in bleeding compared with unfractionated heparin.⁸ A DVT trial using contrast venography showed that the low-molecular-weight heparin reviparin is more effective than unfractionated heparin in reducing the size of the thrombus.⁹ An alternative approach to anticoagulation is use of a long-term, low-molecular-weight heparin without oral anticoagulation.¹⁰ This strategy reduces the risk of recurrent venous thromboembolism in patients with cancer.¹¹ Monotherapy with low-molecular-weight heparin is also suitable for patients either intolerant of warfarin or unable to maintain therapeutic levels of warfarin. When heparin-induced thrombocytopenia complicates management, the intravenous direct thrombin inhibitors argatroban¹² and lepirudin¹³ can be used.

From the Cardiovascular Division (S.Z.G.), Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass, and the Department of Medicine (C.G.E.), Pulmonary and Critical Care Division, LDS Hospital and University of Utah School of Medicine, Salt Lake City, Utah.

Dr Goldhaber has served as a consultant for Aventis, Pfizer, AstraZeneca, Bayer, Paion, and Procter and Gamble. Dr Elliott served as a consultant for Aventis, Pfizer, AstraZeneca, Actelion, and Encysive.

This is Part II of a 2-part article. Part I appeared in the December 2, 2003, issue of *Circulation* (*Circulation*. 2003;108:2726–2729).

Correspondence to Samuel Z. Goldhaber, MD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115. E-mail sgoldhaber@partners.org

(*Circulation*. 2003;108:2834-2838.)

© 2003 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

Risk Stratification

Clinical assessment

Gestalt

Geneva Prognostic Index

Right ventricular dysfunction

Clinical evaluation

Jugular venous distension

Tricuspid regurgitation murmur

Accentuated pulmonary heart sound

Electrocardiogram

T-wave inversion in leads V₁–V₄

New right bundle-branch block

S1Q3T3

Chest CT

Right ventricular enlargement relative to left ventricular size

Echocardiogram

Right ventricular dilatation

Right ventricular free wall hypokinesis; decreased right ventricular systolic function with increased right ventricular afterload and decreased right ventricular stroke work

Pulmonary hypertension with Doppler estimate of pulmonary artery systolic pressure

Impaired left ventricular diastolic filling, with leftward displacement of the interventricular septum; A/E ratio is >1

Biomarkers

Troponin (increased right ventricular end diastolic pressure impairs subendocardial perfusion, limits the coronary oxygen supply, and leads to right ventricular microinfarction)

Pro-B-type natriuretic peptide

B-type natriuretic peptide

Anatomy

"Saddle" or large proximal PE on CT scan

Inferior Vena Caval Filters

Inferior vena caval filters can be inserted percutaneously to prevent PE, but they do not halt the thrombotic process. They also serve as a nidus for recurrent venous thromboembolism.¹⁴ In a large California database, use of a filter was associated with a 2.6-fold increase in the likelihood of rehospitalization for venous thrombosis within 1 year of filter placement.¹⁵ The 2 principal indications are an absolute contraindication to anticoagulation and recurrent PE despite extended and therapeutic-level anticoagulation. Retrievable filters provide the option of temporary use.

Thrombolysis

Thrombolysis in PE has been hampered by a paucity of clinical trials. Therefore, guidelines for its use and data on efficacy and safety are far less precise than for acute myocardial infarction. There is a consensus to use thrombolysis in massive PE, but controversy arises because most patients who are potential candidates have preserved systemic arterial pressure with moderate or severe right ventricular dysfunction. The only contemporary Food and Drug Administration–approved agent is recombinant tissue

plasminogen activator (rt-PA), administered as a 100-mg continuous infusion over 2 hours without concomitant heparin. We withhold heparin because reocclusion does not seem to be a clinical problem during administration of thrombolysis.

In 1993, a multicentered United States trial randomized 101 hemodynamically stable patients to tissue plasminogen activator followed by heparin versus heparin alone.¹⁶ No clinical episodes of recurrent PE were observed among rt-PA patients, but there were 5 recurrences, including 2 fatalities, among heparin-alone patients within the ensuing 14 days ($P=0.06$). Right ventricular wall motion improved in more than twice as many rt-PA compared with heparin-alone patients. This improvement was accompanied by a decrease in right ventricular end diastolic area. The rapid reversal of right ventricular dysfunction provides a mechanism to explain potential reduction in mortality from PE.

In 2003, the Management strategies and Prognosis of Pulmonary Embolism-3 Trial (MAPPET-3) group compared rt-PA plus heparin and heparin alone in a double-blind trial of 256 PE patients with right ventricular dysfunction but without hypotension or shock.¹⁷ The primary end point was death or escalation of therapy, defined as the need for catecholamine infusion, open-label thrombolysis, endotracheal intubation, cardiopulmonary resuscitation, or emergency embolectomy. The primary end point occurred in 25% of patients treated with heparin alone compared with 10% of patients treated with rt-PA plus heparin ($P=0.006$). No intracranial hemorrhage occurred. However, in the registry of 2454 patients with PE, 304 received thrombolysis, of whom 3.0% had intracranial bleeding.¹⁸ This contrast in bleeding rates points out how safety can vary markedly in the context of a controlled clinical trial compared with real-life clinical practice.

Hardly any data provide long-term follow-up of patients in clinical thrombolysis trials for PE. One small study demonstrated preservation of the normal hemodynamic response to exercise in patients who received lysis on average 7 years earlier, whereas those who had received heparin alone developed a pulmonary arterial hypertensive response.¹⁹

Embolectomy

For patients with contraindications to thrombolysis, catheter-based or surgical embolectomy should be considered if risk stratification indicates a high likelihood of an adverse outcome. Catheter-based approaches include clot fragmentation, rheolytic thrombectomy using a high-velocity saline solution jet to create a strong Venturi effect, and clot aspiration with a large syringe using a coronary guiding or Greenfield embolectomy catheter.²⁰

Open surgical embolectomy has recently undergone a renaissance. The operation had been disparaged because of historically poor survival. However, use of contemporary risk stratification provides early identification of patients who will deteriorate hemodynamically. They often have preserved systemic arterial pressure but profound right ventricular dysfunction. Successful outcome hinges on an interdisciplinary team dedicated to identify, screen, and operate on these patients. Round-the-clock availability is essential, because

these patients rarely present during the daytime on weekdays. Technical innovations include avoiding aortic cross-clamping, operating on a warm beating heart to prevent cold injury, and avoiding blind instrumentation of the pulmonary arteries. This approach to embolectomy resulted in an 89% survival rate in 29 operations performed in a 2-year time period at Brigham and Women's Hospital.²¹

Initiation and Monitoring Oral Anticoagulation

In the United States, warfarin is the only anti-vitamin K agent used for oral anticoagulation. It is administered after the initiation of unfractionated heparin or low-molecular-weight heparin, which are continued for 5 or more days until a stable dose of warfarin is achieved. For patients with PE, the dose of warfarin is titrated to a therapeutic international normalized ratio (INR), usually a target range of 2.0 to 3.0. Coordination of laboratory monitoring and dosing of warfarin for large numbers of patients is best accomplished with a multidisciplinary nurse-pharmacist-physician anticoagulation service.²² Some patients will be extremely sensitive to small doses of warfarin because of a genetic mutation that causes slow metabolism of the S-enantiomer of warfarin.²³ Excessively high INRs are classically managed by withholding warfarin and administering oral vitamin K.²⁴ For critically prolonged INRs, human recombinant factor VIIa concentrate can avert or reverse bleeding safely and rapidly.²⁵ Unfortunately, the INR is not ideal for monitoring anticoagulation intensity, because patients with similar INRs show wide individual variability in their tissue factor coagulation response.²⁶

Novel Anticoagulants

The next generation of anticoagulants to treat acute PE will provide simplified dosing with minimal laboratory monitoring. The anti-Xa agent fondaparinux is a synthetic pentasaccharide that, at a dose of 7.5 mg SC once daily, is at least as effective and safe as intravenous heparin.^{26a} Fondaparinux is already approved by the Food and Drug Administration at a dose of 2.5 mg daily for prophylaxis in patients undergoing total hip or knee replacement or hip fracture surgery.²⁷ Ximelagatran, an oral direct thrombin inhibitor administered in a fixed dose twice daily, is a promising alternative to warfarin in the treatment of venous thromboembolism²⁸ and in prophylaxis of patients undergoing total knee replacement.²⁹ Another approach that warrants investigation is combining optimal anticoagulant therapy with an antiplatelet regimen to provide additional antithrombotic protection. There is experimental and clinical evidence to suggest that antiplatelet agents can attenuate the pulmonary vasoconstriction, bronchospasm, and hypoxia associated with PE.³⁰

Optimal Duration and Intensity of Oral Anticoagulation

The rate of recurrent PE after discontinuing anticoagulation is twice as high in patients with idiopathic PE compared with PE ascribed to temporary risk factors such as surgery.³¹ Six months of anticoagulation for both idiopathic and nonidiopathic venous thromboembolism has been the standard duration of anticoagulation to minimize recurrences after discontinuation of therapy. This approach halved the rate of

recurrences, from 18% to 9.5%, during the 2 years after cessation of anticoagulation.³² However, when standard-intensity anticoagulation is continued indefinitely for patients at high risk of recurrent PE, such as those who have suffered a second episode of venous thromboembolism, major hemorrhaging may become problematic. In a Swedish trial, indefinite anticoagulation averted 0.43 episodes of recurrent thromboembolism per month per 100 patients at a cost of 0.20 major hemorrhages per month.³³

Because of the high risk of recurrent venous thromboembolism after cessation of oral anticoagulation, a series of trials examined prolonged anticoagulation regimens in patients with idiopathic PE and DVT. A Canadian study demonstrated that a strategy of prescribing 2 years of warfarin anticoagulation is more effective than 3 months of therapy.³⁴ An Italian trial showed that the clinical benefit associated with extending the duration of anticoagulation to 1 year is not maintained after the warfarin is discontinued.³⁵

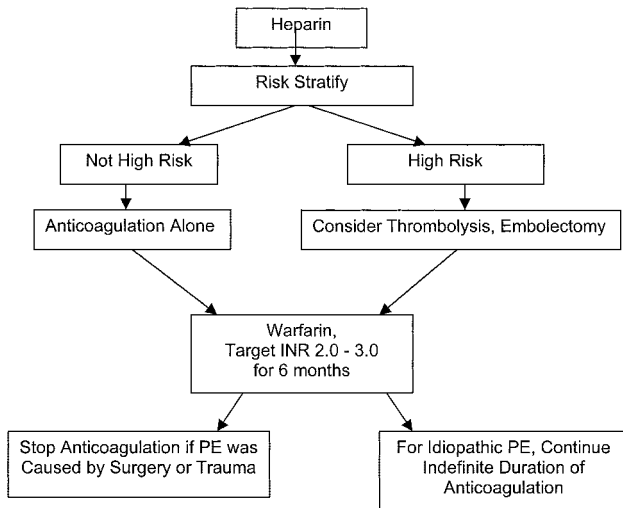
A subsequent Canadian trial found that prolonged-duration conventional-intensity warfarin, with a target INR of 2.0 to 3.0, is more effective and no less safe than low-intensity warfarin, with a target INR of 1.5 to 1.9.³⁶ An international trial, Thrombin Inhibitor in Venous Thromboembolism (THRIVE) III, randomized 1233 patients with idiopathic venous thromboembolism who had received 6 months of standard warfarin therapy to an oral direct thrombin inhibitor (ximelagatran 24 mg twice daily) versus placebo for 18 months.^{36a} The ximelagatran group exhibited an 84% decrease in recurrent events compared with placebo, from 12% to 2%, with no increase in major bleeding.

The PREVENT Trial tested low-intensity warfarin, target INR of 1.5 to 2.0, against placebo in 508 patients with idiopathic PE or DVT who had previously completed an average of 6 months of standard anticoagulation.³⁷ Patients assigned to low-intensity warfarin required routine blood testing only once every 2 months. Warfarin reduced by two thirds the frequency of recurrent events. All subgroups benefited, including patients with factor V Leiden or the prothrombin gene mutation.

Based on presently available evidence, we recommend a fixed course of 6 months of anticoagulation for patients with PE attributable to surgery or trauma. Most other patients should receive indefinite-duration therapy (Figure).

Prevention

Prevention is critical in reducing the death rate, morbidity, and cost of PE. Mechanical measures include graduated compression stockings, intermittent pneumatic compression devices, and placement of a temporary or permanent inferior vena caval filter. Intermittent pneumatic compression stimulates endogenous fibrinolytic activity in addition to direct physical stimulation of increased venous blood flow.³⁸ Pharmacological options include unfractionated heparin, low-molecular-weight heparin, warfarin, and fondaparinux.²⁷ For patients at high risk, a combination of mechanical and pharmacological measures can be used, such as graduated compression stockings plus intermittent pneumatic compression boots plus low-molecular-weight heparin.



Therapeutic strategy for pulmonary embolism.

Perioperative prophylaxis is widely accepted by general, subspecialty, and orthopedic surgeons. However, because of abbreviated hospitalizations, most postoperative PEs occur after hospital discharge. After surgery for abdominal and pelvic cancer, 4 weeks of enoxaparin prophylaxis was safe and reduced by more than half the frequency of venous thromboembolism compared with enoxaparin prophylaxis for 1 week.³⁹ A meta-analysis of randomized trials indicated that among patients undergoing total hip or knee replacement, extended-duration prophylaxis for 30 to 42 days reduced the frequency of symptomatic venous thromboembolism by approximately two thirds without an increase in major bleeding complications. There was a greater reduction in venous thromboembolism among those undergoing hip replacement compared with knee replacement.⁴⁰

In contrast to surgical patients, hospitalized medical patients often do not receive effective, evidence-based prophylaxis.⁴¹ Two large placebo-controlled trials have demonstrated the efficacy of fixed, low-dose, low-molecular-weight heparin for reducing the DVT rate among hospitalized patients with medical illness. A double-blind study of 1102 patients showed that enoxaparin 40 mg once daily reduced the frequency of DVT by two thirds without an increase in major bleeding.⁴² Another trial with similar design studied more than 3000 patients with medical illness and found that a fixed dose of dalteparin 5000 units daily halved the DVT rate compared with placebo.

All hospitals should develop and enforce protocols that ensure routine prophylaxis of patients at moderate and high risk of venous thromboembolism. Implementation of clinical guidelines can be facilitated with computer-based order entry systems. This approach has been proven to motivate physicians to order prophylaxis on an orthopedic surgical unit.⁴³ Enforcing the use of evidence-based prophylactic regimens during hospitalization and extending these protocols at the time of discharge to skilled nursing facilities, rehabilitation hospitals, and home will enhance patient safety.

Summary

Acute PE is increasingly appreciated as a major cardiopulmonary illness and public health issue. As the public becomes

familiar with signs and symptoms of PE and DVT, more patients will be transported to emergency departments for urgent evaluation and treatment. Great progress has been made in the rapid detection and exclusion of PE, especially with the advent of D-dimer testing and chest CT scans. Rapid risk stratification facilitates selection of patients who warrant aggressive intervention with thrombolysis or embolectomy. For patients with idiopathic venous thromboembolism, there seems to be a lifelong tendency for recurrent thrombosis unless anticoagulation is continued.

New frontiers in molecular genetics will provide a better appreciation of the interaction between inherited and environmental risk factors for PE. Novel mutations for thrombophilia will emerge in patients who presently have normal laboratory evaluations. Point of care blood testing will provide accurate screening of patients with suspected PE to triage those most appropriate for noninvasive imaging. When PE is confirmed, cardiac biomarkers will assist in rapid risk stratification so that the intensity of treatment matches the predicted risk profile of the patient. The definition of idiopathic PE will undergo refinement, and indefinite duration anticoagulation will become commonplace. Novel anticoagulant regimens will be safer and more convenient. Efforts to prevent PE will be pervasive, and computerized order entry and surveillance will ensure that hospitalized patients received appropriate prophylaxis.

References

1. Wicki J, Perrier A, Perneger TV, et al. Predicting adverse outcome in patients with acute pulmonary embolism: a risk score. *Thromb Haemost.* 2000;84:548-552.
2. Grifoni S, Olivetto I, Cecchini P, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. *Circulation.* 2000;101:2817-2822.
3. Konstantinides S, Geibel A, Olschewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. *Circulation.* 2002;106:1263-1268.
4. Kucher N, Printzen G, Doernhoefer T, et al. Low pro-brain natriuretic peptide levels predict benign clinical outcome in acute pulmonary embolism. *Circulation.* 2003;107:1576-1578.
5. ten Wolde M, Tulevski II, Mulder JW, et al. Brain natriuretic peptide as a predictor of adverse outcome in patients with pulmonary embolism. *Circulation.* 2003;107:2082-2084.
6. Kucher N, Printzen G, Goldhaber SZ. Prognostic role of BNP in acute pulmonary embolism. *Circulation.* 2003;107:2545-2547.
7. Raschke RA, Gollighere B, Peirce JC. The effectiveness of implementing the weight-based heparin nomogram as a practice guideline. *Arch Intern Med.* 1996;156:1645-1649.
8. Gould MK, Dembitzer AD, Doyle RL, et al. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials. *Ann Intern Med.* 1999;130:800-809.
9. Breddin HK, Hach-Wunderle V, Nakov R, et al. Effects of a low-molecular-weight heparin on thrombus regression and recurrent thromboembolism in patients with deep-vein thrombosis. *N Engl J Med.* 2001;344:626-631.
10. Beckman JA, Dunn K, Sasahara AA, et al. Enoxaparin monotherapy without oral anticoagulation to treat acute symptomatic pulmonary embolism. *Thromb Haemost.* 2003;89:953-958.
11. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med.* 2003;349:146-153.

12. Lewis BE, Wallis DE, Berkowitz SD, et al, for the ARG-911 Study Investigators. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. *Circulation*. 2001;103:1838–1843.
13. Greinacher A, Janssens U, Berg G, et al. Lepirudin (recombinant hirudin) for parenteral anticoagulation in patients with heparin-induced thrombocytopenia. Heparin-Associated Thrombocytopenia Study (HAT) investigators. *Circulation*. 1999;100:587–593.
14. 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: Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. *N Engl J Med*. 1998;338:409–415.
15. White RH, Zhou H, Kim J, et al. A population-based study of the effectiveness of inferior vena cava filter use among patients with venous thromboembolism. *Arch Intern Med*. 2000;160:2033–2041.
16. Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. *Lancet*. 1993;341:507–511.
17. Konstantinides S, Geibel A, Heusel G, et al. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med*. 2002;347:1143–1150.
18. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet*. 1999;353:1386–1389.
19. Sharma GVRK, Folland ED, McIntyre KM, et al. Long-term benefit of thrombolytic therapy in patients with pulmonary embolism. *Vasc Med*. 2000;5:92–95.
20. Goldhaber SZ. Integration of catheter thrombectomy into our armamentarium to treat acute pulmonary embolism. *Chest*. 1998;114:1237–1238.
21. Aklog L, Williams CS, Byrne JG, et al. Acute pulmonary embolectomy: a contemporary approach. *Circulation*. 2002;105:1416–1419.
22. Grasso-Correnti N, Goldszer RC, Goldhaber SZ. The critical pathways of an anticoagulation service. *Crit Pathways Cardiol*. 2003;2:41–45.
23. Higashi MK, Veenstra DL, Kondo LM, et al. Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. *JAMA*. 2002;287:1690–1698.
24. Weibert RT, Le DT, Kayser SR, et al. Correction of excessive anticoagulation with low-dose oral vitamin K1. *Ann Intern Med*. 1997;126:959–962.
25. Deveras RA, Kessler CM. Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. *Ann Intern Med*. 2002;137:884–888.
26. Brummel KE, Paradis SG, Branda RF, et al. Oral anticoagulation thresholds. *Circulation*. 2001;104:2311–2317.
- 26a. The Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med*. 2003;349:1695–1702.
27. Bounameaux H, Perneger T. Fondaparinux: a new synthetic pentasaccharide for thrombosis prevention. *Lancet*. 2002;359:1710–1711.
28. Eriksson H, Wahlander K, Gustafsson D, et al, for the THRIVE Investigators. A randomized, controlled, dose-guiding study of the oral direct thrombin inhibitor ximelagatran compared with standard therapy for the treatment of acute deep vein thrombosis: THRIVE I. *J Thromb Haemost*. 2003;1:41–47.
29. Francis CW, Davidson BL, Berkowitz SD, et al. Ximelagatran versus warfarin for the prevention of venous thromboembolism after total knee arthroplasty: a randomized, double-blind trial. *Ann Intern Med*. 2002;137:648–655.
30. Sobieszczyk P, Fishbein MC, Goldhaber SZ. Acute pulmonary embolism: don't ignore the platelet. *Circulation*. 2002;106:1748–1749.
31. Pinede L, Ninet J, Duhaut P, et al. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. *Circulation*. 2001;103:2453–2460.
32. Schulman S, Rhedin AS, Lindmarker P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism: Duration of Anticoagulation Trial Study Group. *N Engl J Med*. 1995;332:1661–1665.
33. Schulman S, Granqvist S, Holmstrom M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism: Duration of Anticoagulation Trial Study Group. *N Engl J Med*. 1997;336:393–398.
34. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med*. 1999;340:901–907.
35. Agnelli G, Prandoni P, Becattini C, et al, for the Warfarin Optimal Duration Italian Trial Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med*. 2003;139:19–25.
36. Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med*. 2003;349:631–639.
- 36a. Schulman S, Wahlander K, Lundström T, et al. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *N Engl J Med*. 2003;349:1713–1721.
37. Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med*. 2003;348:1425–1434.
38. Comerota AJ, Chouhan V, Harada RN, et al. The fibrinolytic effects of intermittent pneumatic compression: mechanism of enhanced fibrinolysis. *Ann Surg*. 1997;226:306–313.
39. Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med*. 2002;346:975–980.
40. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet*. 2001;358:9–15.
41. Goldhaber SZ, Dunn K, MacDougall RC. New onset of venous thromboembolism among hospitalized patients at Brigham and Women's Hospital is caused more often by prophylaxis failure than by withholding treatment. *Chest*. 2000;118:1680–1684.
42. 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: Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med*. 1999;341:793–800.
43. Durieux P, Nizard R, Ravaud P, et al. A clinical decision support system for prevention of venous thromboembolism: effect on physician behavior. *JAMA*. 2000;283:2816–2821.

KEY WORDS: thrombosis ■ embolism ■ pulmonary heart disease ■ thrombosis ■ thrombolysis