Diagnosis And Evaluation Of Thromboembolic Disorders

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Abstract: The most common types of thromboembolic disorders are lower extremity deep venous thrombosis and pulmonary embolism. Since the effectiveness of anticoagulation therapy for deep venous thrombosis and pulmonary embolism was established in 1960, knowledge of these disorders has increased rapidly. What has become clear is that the nonspecificity of symptoms and signs of these disorders has led to both overdiagnosis and undertreatment. This article presents a review of the natural history and clinical manifestations of deep venous thrombosis and pulmonary embolism and includes a discussion of their diagnostic evaluation. (J Am Bd Fam Pract 1989; 2:106-18.)

Natural History of Pulmonary Embolism

Along with pneumonia, pulmonary embolism is the most common acute pulmonary disorder in hospitalized patients.[1] It is the major contributing cause of death in 5 to 15 percent of adults dying in general hospitals.[2] More than 85 percent of pulmonary emboli are multiple and bilateral, with the majority occurring in the lower lobes, particularly the right lower lobe.[2] The frequency of pulmonary embolism is difficult to determine, but the most widely quoted numbers are provided by Dalen and Alpert,[3] who reported that of an estimated 630,000 patients with pulmonary embolism, approximately 10 percent died within the first hour. Of the 563,000 who survived more than 1 hour, the diagnosis was not made in 71 percent of cases. The cause of death in most untreated persons was recurrent pulmonary embolism. When the diagnosis was made and proper treatment instituted, survival increased from 70 to 92 percent.

Even patients with massive pulmonary embolism do well with treatment directed at preventing further pulmonary emboli. Eighty-four percent of patients in Dalen and Alpert's study with pulmonary emboli occluding more than 50 percent of the pulmonary circulation recovered.[3] This excellent prognosis is because pulmonary vascular obstruction begins to decrease almost immediately after pulmonary embolism occurs due to fragmentation of the clot upon impact and subsequent reshaping of it.[3,4] The major mechanisms that eventually lead to resolution of pulmonary vascular obstruction are fibrinolysis and organization.[1]

The rate of resolution of pulmonary vascular obstruction associated with pulmonary embolism has been assessed angiographically, hemodynamically, and by lung scan. Dalen, et al.[5] evaluated the angiographic and hemodynamic resolution of pulmonary emboli and found consistent correlation between the two. Although mild resolution is seen within days, the earliest complete resolution in their study was not seen until 14 days. Between 10 and 21 days, significant decreases in right cardiac pressures associated with clearcut angiographic improvement were seen. Though some patients may have complete resolution at this time, other clinicians have found patients to show pulmonary vascular obstruction for persistent periods.[6-10]

These data were consistent with the rate of resolution as assessed by serial lung scans in the Urokinase Pulmonary Embolism Trial.[11] By 14 days, 52 percent resolution had occurred. Seventy-three percent resolution was seen by 3 months, with minimal clearing thereafter. Tow and Wagner showed similar findings.[12]

The variability in rate of resolution is due to several factors. If a thrombus has become organized before release as an embolus, it will be less sensitive to fibrinolytic attack.[1,10,13] Individual differences in fibrinolytic activity also undoubtedly contribute.[1] However, the most likely cause of delayed resolution is recurrent pulmonary embolism that, if undetected, may lead to cor pulmonale.[3,13] Recurrent emboli in the presence of adequate anticoagulation are very uncommon.[3,13,14] Death following acute pulmonary embolism appropriately diagnosed and treated occurs in the

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following scenarios: First, patients with massive pulmonary embolism and cardiopulmonary shock may die within the first 24 hours despite appropriate intervention. Previously healthy patients who survive more than 24 hours have an excellent prognosis. Second are the patients who die after the first 24 hours. They usually succumb to recurrent pulmonary emboli or to underlying cardiopulmonary diseases or advanced malignancy. In these patients, the pulmonary emboli only contribute to death and are not the primary cause.[4]

Long-term prognosis of acute pulmonary embolism is largely determined by the pre-embolic cardiac status. In a 7-year, follow-up study by Paraskos, et al., 86 percent of patients without prior heart disease survived compared with only 19 percent of patients with underlying congestive heart failure.[15] Similar findings were shown by Hall, et al.[16] Neither study, nor the study by Dalen and Alpert,[3] showed cor pulmonale to be a prevalent long-term complication. Lastly, as noted by Hall, et al.[16] and conclusively shown by Gore, et al.,[17] patients with acute pulmonary embolism had an increased frequency of occult cancer.

Natural History of Deep Venous Thrombosis

More than 90 percent of pulmonary emboli arise from the deep venous system of the thigh and pelvis.[2,18] Exceptions to this are tumor emboli, amniotic fluid emboli, and thrombi that originate in the right side of the heart.[1] Unless related to indwelling catheters in the subclavian veins or the superior vena cava, thromboemboli generally do not arise in the upper extremity venous system, possibly because a greater inflammatory response produces more rapid organization of the thrombi.[19]

Thrombosis of the superficial veins of the leg is also not a significant embolic threat.[20] In addition, calf deep venous thrombi only rarely become emboli.[21,22] However, approximately 20 percent of calf deep venous thrombi propagate to the deep veins of the thigh, which do constitute an embolic risk.[22,23] Fifty percent of deep venous thrombi in the iliofemoral system will form emboli.[22,24] Once formed, deep venous thrombi require 7 to 10 days for fibrinolysis and organization.[1]

Risk factors for thromboembolic disease can be either inherited or acquired.[25,26] Coon's review indicated that the greatest risk factor for deep venous thrombosis in any medically ill or surgical patient is a past history of deep venous thrombosis.[27] Between 30 and 40 percent of nonanticoagulated patients with acute myocardial infarction develop fibrinogen-detectable deep venous thrombi within 72 hours. The risk of pulmonary embolism in cancer patients depends on the underlying tumor. Pancreatic cancer has the highest risk (35 percent), followed by lung cancer (20 percent), genitourinary cancer (19 percent), colon cancer (19 percent), stomach cancer (16 percent), and breast cancer (15 percent). Leukemia, lymphoma, brain tumors, and head and neck cancers do not have an appreciable risk. Women taking oral contraceptive pills in the month before a surgical procedure have a four- to sixfold increased risk of a thromboembolic complication. This risk increases with increasing estrogen content and persists for up to 3 weeks following oral contraceptive pill discontinuation. Progesterones do not increase the risk of thromboembolism.[25] Other risk factors include type A blood group, pregnancy and puerperium, myeloproliferative disorders, inflammatory bowel disorders, homocystinuria, the Behcet syndrome, diabetes mellitus, chronic disseminated intravascular coagulation, systemic lupus erythematosis, and paroxysmal hemoglobinuria.[25]

As with pulmonary emboli, resolution rates for proximal deep venous thrombi have been evaluated. Serial impedance plethysmography measurements show a return to normal in approximately 30 percent of patients by 3 weeks, 50 percent by 6 weeks, and 60 percent at the end of 3 months of anticoagulation therapy.[28]

Clinical Manifestations of Pulmonary Embolism

Although most pulmonary emboli are clinically silent, the diagnosis should be considered in any patient at risk who experiences any acute nonspecific cardiopulmonary complaints.[2] The clinical diagnosis of pulmonary embolism is highly nonspecific because the signs and symptoms are not unique, and all may be caused by other cardiopulmonary disorders.

The classic triad of dyspnea, pleuritic chest pain, and hemoptysis is seen in only 22 percent of patients with pulmonary embolism.[29] Six percent of patients are totally without these symptoms.[29] Dyspnea is the most common symptom (Table 1),

Table 1. *Frequency of Symptoms in Pulmonary Embolism.*

Symptoms	McNeil Study[61]	Stein, et al. Study[29]	West Study[19]	Bell, et al. Study[30]
	Percent			
Dyspnea	58 at rest 61 mild to moderate exertion	84	88	84
Chest pain				
Pleuritic	54	74	72	74
Nonpleuritic	17	17	<5	14
Apprehension	—	63	55	59
Cough	—	50	54	53
Calf pain	—	39	—	—
Diaphoresis	—	36	—	27
Hemoptysis	18	28	34	30
Syncope	9	13	<5	13
Palpitations	—	10	—	—
Angina	—	1	—	—

and it often is of sudden onset and can be transient, resolving after a few minutes or hours.[1,18,19] Either dyspnea or tachypnea occurs in 96 percent of patients.[1] Dyspnea, tachypnea, or deep venous thrombosis is seen in 99 percent of patients.[1] In the Urokinase Pulmonary Embolism Trial (UPET), and the Urokinase Streptokinase Pulmonary Embolism Trial (USPET), only 6 percent were without a recognizable risk factor before the diagnosis of pulmonary embolism.[30] In a study of 215 patients with acute pulmonary embolism uncomplicated by preexisting cardiac or pulmonary disease, 76 percent had associated deep venous thrombosis, immobilization, surgery, stroke, or malignancy.[29]

Other clinical presentations that not infrequently turn out to be caused by pulmonary embolism are syncope, sudden deterioration in patients with congestive heart failure or chronic obstructive pulmonary disease, and sudden onset of atrial fibrillation.[18] Chest pain can be indistinguishable from myocardial infarction and described with the same gestures.[1,18,19] Recurrent bouts of hyperventilation in a patient with risk factors should arouse suspicion.[1,18]

Diagnosing pulmonary embolism when there is underlying chronic obstructive pulmonary disease is a particularly difficult clinical problem. The degree of risk is poorly defined[31,32] but has been reported to range from 9 percent[32] to 60 percent,[31] with cor pulmonale believed to be a major risk factor because of right cardiac mural thrombi.[33] Suspicion should be aroused when there is acute worsening of dyspnea, unresponsive to bronchodilators, associated with a decreased $Paco_2$ in a previously hypercarbic patient.[31,32,34] Other clues include hypoxia out of proportion to the level of mechanical deterioration and the finding of cor pulmonale in patients with a 1-second forced expiratory volume greater than 1.5 liters.[34] Ventilation-perfusion lung scans do not significantly aid in differentiating pulmonary embolism from worsening obstruction.[31]

The frequency of an increased respiratory rate is so marked that its absence makes the diagnosis of pulmonary embolism very unlikely.[30] As with dyspnea, tachypnea may be transient.[18] Tempera-

Table 2. *Frequency of Signs in Pulmonary Embolism.*

Signs	Stein, et al. Study[29]	West Study[19]	Bell, et al. Study[30]	Hull, et al. Study[60]
	Percent			
Tachypnea (respiratory rate >20/min)	85	88	92	70
Tachycardia (heart rate >100/min)	58	43	44	—
Increased pulmonic component of the second heart sound	57	54	53	—
Rales	56	54	58	—
Fever (temperature greater than 37.8°C)	50 (T≥37.5°C)	42	43	—
Deep venous thrombosis	41	34	32	—
Pleural rub	18	—	—	9
Cyanosis	18	—	19	6
Hepatomegaly	10	—	—	—
Hepatojugular reflux	5	—	—	—
Gallop	—	—	34	—
Jugular venous pulsations	—	—	—	12
Chest wall tenderness	—	—	—	10

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ture greater than 39 degrees centigrade due to pulmonary embolism may occur early, and low-grade fever may continue for 1 week or more (Table 2).[35] Because serum leukocytosis and polymorphonuclear, white-cell-predominant pleural effusions may occur with the fever,[36] acute bacterial pneumonia may be diagnosed erroneously.

Clinical Manifestations of Deep Venous Thrombosis

With the exception of phlegmasia alba dolens and phlegmasia cerulea dolens, the signs and symptoms of deep venous thrombosis are nonspecific in the vast majority of patients.[27] More than 50 percent of patients with suspected deep venous thrombosis have the diagnosis excluded by objective testing.[37] Patients with relatively minor symptoms may have extensive deep venous thrombosis, whereas patients with marked symptoms may be entirely free of venous thrombosis, thus making clinical diagnosis unreliable.[37,38] Only 30 percent of patients with pulmonary embolism have symptomatic deep venous thrombosis.[20]

Venous thrombosis of the lower extremity produces only two phenomena that allow its detection: inflammation of the vessel wall and venous obstruction. Local redness, pain, and heat are not always extensive enough to be clinically detectable.[1] While venous obstruction predisposes to edema, incomplete obstruction, obstruction of a small drainage area, or obstruction of an area with collateral drainage will obscure this finding.[1] Because the signs and symptoms are so nonspecific, more than 50 percent of deep venous thrombi of the lower extremity are not clinically detectable.[1]

Haeger compared the results of venography with calf pain and tenderness, skin temperature changes, superficial venous dilation, Homan and Lowenberg signs, and unilateral ankle and calf edema.[39] Even when patients were subclassified into highly and moderately suspected groups, there were no significant differences between any sign or symptom among those with and without proved thrombosis. A similar study by McLachlin, et al. differed only in that unilateral ankle swelling was believed to be clinically significant, and a skin temperature change was associated with thrombosis.[40] However, ankle swelling was only significant for the left lower extremity.

Table 3 outlines the differential diagnosis.[37,38,41-45] Venous thrombosis is a recognized complication of leg trauma, but so is compartment syndrome, and both must be recognized on their own merits. Most cases of popliteal cyst have an associated history of knee arthritis, trauma, or operative repair. A ruptured popliteal cyst with associated calf pain, tenderness, and swelling is difficult to distinguish from an acute deep venous thrombosis. Milder forms of lymphedema may be pitting. Patients with varicose veins also frequently have pain, tenderness, and swelling in the calf after prolonged standing. Pain, tenderness, and swelling may occur in pregnancy or in oral contraceptive pill users secondary to venous dilation caused by estrogens. Unilateral leg swelling in pregnancy may also be caused by iliac vein compression from an enlarged uterus. Prolonged immobilization may lead to swelling because of altered sympathetic nervous system vascular tone, but immobilization also leads to venous stasis and a marked increased risk of thrombosis. In patients with an acute stroke, venous thrombi have been detected by fibrinogen scanning in 53 percent of paralyzed lower extremities but in only 7 percent of nonparalyzed legs.[46] Lastly, postphlebitic syndrome is a complication of earlier deep venous thrombosis and resulting venous valvular insufficiency. These patients may have repeated episodes of calf pain and swelling, and without objective testing, it is difficult to distinguish these episodes from complicating recurrent acute venous thrombosis.[38]

Table 3. *Differential Diagnosis of Clinically Suspected Deep Venous Thrombosis.*

1. Muscle strain or trauma	vasculitis, myositis, and
2. Compartment syndrome	panniculitis
3. Arterial insufficiency	8. Varicose veins
4. Ruptured popliteal cyst	9. Pregnancy and oral
5. Achilles tendinitis	contraceptive pill users
6. Knee or ankle arthritis	10. Neurogenic pain
7. Cellulitis, lymphangitis,	11. Postphlebitic syndrome

In summation, 50 percent or fewer clinically suspected cases of deep venous thrombosis are confirmed.[20,24] However, without objective testing, it is often impossible to rule out this diagnosis. Once the diagnosis of deep venous thrombosis has been excluded, it is then frequently possible to determine other causes of the symptoms.

Objective Testing for Pulmonary Embolism

Laboratory Data

Leukocytosis may occur with white-cell counts as high as 20,000 cells/mL.[1] There are, however, no routine blood tests that can establish the diagnosis of pulmonary embolism. The classic triad of elevated serum lactate dehydrogenase (LDH), elevated serum bilirubin, and normal aspartate transaminase is nonspecific and occurs infrequently in the presence of pulmonary embolism.[47] Creatine phosphokinase-MB titers and LDH_1/LDH_2 ratios, however, help to rule out acute myocardial infarction.[48]

Arterial blood gases drawn on room air, while helpful, are not diagnostic. While many cardiopulmonary conditions are associated with a decreased Pao_2, the Pao_2 is greater than 90 torr in 5 percent of otherwise normal patients with pulmonary embolism, and 10 to 15 percent have a Pao_2 greater than 80 torr. However, the Pao_2 is less than 80 torr if there is underlying cardiopulmonary disease.[2] Calculation of the alveolar-arterial gradient for oxygen is more sensitive, but even this is normal in rare cases.[19] Thus, low arterial Pao_2 is not specific, and a normal arterial Pao_2 does not automatically rule out pulmonary embolism.

Chest Radiography

Although often initially believed to be negative, retrospectively, up to 90 percent of patients with proved pulmonary embolism have an abnormal though nonspecific chest radiograph at some time in their treatment.[49] The chest radiograph is necessary for the proper evaluation of ventilation-perfusion lung scans, but its chief diagnostic value is in ruling out other disease. Radiographic findings associated with acute pulmonary embolism include infiltrate (50 percent), diaphragmatic elevation (40 percent), pleural effusion (33 percent), atelectasis (27 percent), and focal oligemia (2 percent). Focal oligemia, known as the Westermark sign, is strongly suggestive of pulmonary embolism. Another uncommon but highly suggestive sign of pulmonary embolism is the Hampton hump, a classically wedge-shaped, often rounded, pleural-based infiltrate, which is most often seen in the lower lobes in pulmonary infarction.[49]

Pleural Fluid Analysis

The analysis of pleural effusion in the presence of pulmonary embolism is extremely valuable. Characteristics include: bloody appearance (65 percent); protein in exudative range (65 percent); polymorphonuclear, white-cell predominance (61 percent); specific gravity in exudative range (56 percent); LDH in exudative range (42 percent); and the combination of bloody appearance, polymorphonuclear predominant, and exudative characteristics (27 percent).[36] Only a small percentage of cases show the combination of findings considered characteristic of this disorder, namely, serosanguineous fluid with a polymorphonuclear, white-cell predominance.[50] The presence of clear fluid in no way excludes the diagnosis. More than one-third of patients in Bynum and Wilson's study had lymphocyte counts exceeding 70 percent of the total pleural white-cell count.[36] However, in the absence of trauma or cancer, a bloody, exudative effusion is highly suggestive of pulmonary embolism.[36]

Electrocardiogram

The electrocardiogram is abnormal in up to 85 percent of patients with acute pulmonary embolism, but the changes are often transient and very nonspecific.[2] The electrocardiogram can be useful in differentiating acute pulmonary embolism from acute myocardial infarction. Unfortunately, the electrocardiogram in the setting of pulmonary embolism may simulate an inferior wall infarction with Q waves and T wave inversions in leads II, III, and aVF or an anteroseptal infarction characterized by QS or QR waves in V1 and T wave inversion in the right precordial leads.[51] Table 4 lists the frequency of electrocardiographic abnormalities noted in patients without prior cardiopulmonary disease. Of note is the absence of atrial flutter or fibrillation that appears to occur predominantly in those patients with pulmonary embolism who have preexisting cardiac disease.[51]

Radionuclide Lung Scanning

The means for assessing the pulmonary vasculature by injection of isotope-labeled albumin aggregates were developed in the early 1960s. There have been isolated case reports of patients with "normal" perfusion scans found to have pulmonary emboli by angiography[52,53]; however, a completely normal perfusion scan taken from six projections virtually excludes the diagnosis of pulmonary embolism.[1,2,18,19,54-56] The specificity unfortunately is poor. Multiple cardiopulmonary

Table 4. *Electrocardiographic Manifestations of Pulmonary Embolism in Patients without Prior Cardiopulmonary Disease (Stein, Dalen, McIntyre, et al. Study[51]).*

Findings	Percent of Patients
T wave inversion	42
S-T segment depression	26
S-T segment elevation	16
Normal electrocardiogram	13
S1/Q3/T3 pattern	12
Pseudoinfarction	11
Complete right bundle branch block	9
Right axis deviation	7
Left axis deviation	7
Clockwise rotation	7
S1/S2/S3 pattern	7
Incomplete right bundle branch block	6
Right ventricular hypertrophy	6
Low voltage	6
P pulmonale	6
Premature ventricular contractions	3
Premature atrial contractions	2
First-degree heart block	1

disorders are able to alter regional pulmonary blood flow including emphysema, tuberculosis, asthma, pneumonia, atelectasis, pulmonary vasculitis, and congestive heart failure.[1,2,18,19,52,55] False-positive perfusion scans are common. In the USPET study, 83 percent of patients with a positive perfusion scan had a normal pulmonary angiogram.[30] In a study of perfusion scans in 61 clinically asymptomatic, apparently normal volunteers, 5 percent showed major perfusion abnormalities that were indistinguishable from pulmonary embolism.[57]

Attempts have been made to improve the specificity of perfusion scans by classifying the defects according to size and number (Table 5).[52,54,56,58,60,61,64,70] Another way to increase the predictability of perfusion scans is to compare them with chest radiographs. Most patients with proved pulmonary embolism have abnormal though nonspecific chest radiographs.[49,52,55,59] However, a normal chest radiograph in the presence of severe dyspnea without clinical signs of bronchospasm is strongly suggestive of pulmonary embolism.[2,55] Indeterminate scans (scans with matched perfusion defects and chest radiograph abnormalities) have a reported likelihood of pulmonary embolism ranging from 17 percent[60] to 47 percent.[61] Biello, et al.[62] found that 7 percent of patients with perfusion defects smaller than corresponding chest radiograph abnormalities, 27 percent of patients with perfusion defects equal in size to chest radiograph abnormalities, and 89 percent of patients with perfusion defects larger than corresponding chest radiograph abnormalities had pulmonary emboli at angiography.

Ventilation lung scanning was introduced in the late 1960s in an effort to increase the diagnostic specificity of perfusion lung scanning. Ventilation scanning is based on the assumption that vascular obstruction will cause a perfusion defect without interrupting ventilation (ventilation/perfusion mismatch), whereas most other disease processes causing perfusion defects will produce ventilation defects in the same area (ventilation/perfusion match). Unfortunately, with the exception of multiple segmental-lobar defects, the addition of ventilation scanning does not add significantly enough information to allow changes in management (Table 5).[53,60,63,64]

Because of poor spatial resolution, ventilation scans can be normal despite parenchymal abnormalities sufficient to produce perfusion defects.[53] Ventilation scanning is helpful in patients with large perfusion defects if a mismatched defect is found. However, large perfusion defects with matched ventilation defects may not be sufficient to add or withhold treatment. With small perfusion defects, a mismatch indicates neither a high nor a low likelihood of pulmonary embolism.[60,64] Common conditions in which

Table 5. *Lung Scan Patterns.*

	Percent
Prevalence of indeterminate scans	14–25
Lung scan patterns with pulmonary embolism documented by angiography	
Single defect	
Perfusion scan alone	10–22
Ventilation/perfusion match	0–10
Ventilation/perfusion mismatch	10–33
Multiple subsegmental defects	
Perfusion scan alone	7–38
Ventilation/perfusion match	0–25
Ventilation/perfusion mismatch	0–66
Multiple segmental-lobar defects	
Perfusion scan alone	63–76
Ventilation/perfusion match	20–36
Ventilation/perfusion mismatch	86–100

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ventilation/perfusion mismatches may be seen other than acute pulmonary embolism include previous pulmonary embolism, pneumonia, bronchogenic cancer, previous radiation therapy, and emphysema.[65] In addition, according to West,[19] submassive pulmonary embolism commonly has ventilation defects associated with perfusion defects.

Bell and Simon,[66] in a national cooperative study, reported an observer variance in interpretation of perfusion scan data of 67 percent versus less than 6 percent disagreement in interpretation of pulmonary angiograms. Variance was noted to be greater for submassive than for massive emboli, and some scans interpreted as "low probability" were shown to have positive angiograms. The study concluded that, in addition to poor specificity, observer variance can make scan reports suspect.

As with any laboratory test, the predictive value of the results varies with the prevalence of disease in the given population. Application of this concept to lung scanning was introduced by McNeil, et al.[61] Patients were clinically rated as having either low, average, or high risk of pulmonary embolism. Probabilities of pulmonary embolism were then calculated for various scan patterns by comparing them with angiograms and the data then categorized based on prior rating of clinical risk. Patients with the most specific scan pattern had probabilities of pulmonary embolism of 54 percent, 80 percent, and 96 percent, respectively. Thus, patients with the most specific scan pattern but with low clinical risk were found to have angiographic evidence of pulmonary embolism in only 54 percent of cases. Clinical rating was subjectively determined. Other studies also have supported the use of clinical impression in assessing the likelihood of pulmonary embolism.[60,64] A large factor responsible for the differences among studies comparing ventilation/perfusion scanning with angiography may lie in the selected populations. The major factor in more accurate diagnosis of pulmonary embolism may not be better scintigraphic data but better probability estimates of disease.[56] The main difficulty in determining the posttest probability of pulmonary embolism from a given lung scan pattern is that the results depend on the pretest probability, which is related to risk factors and clinical presentation.[59]

Thus, lung scanning cannot be considered to have diagnostic significance independent of the clinical situation. A normal six-view perfusion scan is adequate to rule out pulmonary embolism; however, an abnormal scan must be interpreted in light of the clinical presentation. If a patient is in a high-risk group and has suggestive clinical manifestations, then one or more segmental or larger mismatched defects with a normal chest radiograph could be considered adequate for a presumptive diagnosis of pulmonary embolism.[19] If the clinical presentation is less straightforward, the abnormal lung scan can neither establish nor exclude the diagnosis of pulmonary embolism, and the workup should then proceed to the definitive test, pulmonary angiography.[19]

Pulmonary Angiography

Pulmonary angiography was developed in the early 1960s and is the gold standard for the diagnosis of pulmonary embolism. Angiographic findings that are considered positive are an abrupt cutoff of a major vessel due to total obstruction by an impacted clot and a filling defect caused by a clot incompletely obstructing a pulmonary artery.[1,2,18,19] Other findings such as delayed filling of a lung zone, delayed venous emptying, absence of small branches, abnormal vessel tapering, and dilation of the right ventricle and the great veins are not as specific.[1] If neither a cutoff nor a filling defect is visible on a good-quality angiogram, it can be assumed that no significant embolus is present.[18] The associated mortality from angiography is less than 0.5 percent, and the morbidity is 4.0 percent.[2,19] A review of 1350 pulmonary angiograms over an 11-year period showed only three deaths. All deaths were in patients with cor pulmonale and right ventricular pressures greater than 20 mmHg.[67]

The primary issue, however, is the relative risk of angiography versus the risk of treating patients without pulmonary embolism as though that disorder were present. Heparin is responsible for the majority of drug-related deaths in relatively healthy patients.[68] As for Coumadin™, it is one of eight drugs most responsible for hospital admissions.[66] Morbidity and mortality of heparin therapy and subsequent Coumadin™ therapy run 25–30 percent and 1.0–2.4 percent, respectively.[19,54] Part of the process for deciding whether to anticoagulate involves the patient's history. Thromboembolic risk factors, clinical presentation, and individual risks of anticoagulation or pulmonary angiography must be weighed. Overall, the risk of complications from empiric treat-

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ment with anticoagulant drugs probably outweighs the risk of complications from pulmonary angiography.[2,19,53-55,63]

Indications for pulmonary angiography when there is suspected pulmonary embolism include: (1) clinical story overwhelming with a negative perfusion scan; (2) indeterminate or low-probability lung scan; (3) suspected pulmonary embolism in the presence of pulmonary parenchymal lung disease or congestive failure; (4) positive lung scan in a previously healthy young patient with an unlikely clinical history; (5) high risk for anticoagulation—peptic ulcer disease, bleeding diathesis, recent aspirin use; (6) when patients may be subjected to high-risk treatment such as thrombolytic agents, inferior vena cava interruption, or surgical embolectomy.[1,2,53,55,57]

There have been isolated reports of falsely negative pulmonary angiograms,[70] especially with emboli in the peripheral pulmonary circulation.[34,71] A recent study found that 4 out of 40 patients with negative conventional angiograms had pulmonary emboli detected by balloon-occlusion cineangiography.[71] However, in a frequently quoted study performed with selective pulmonary angiography with superselective magnification views of abnormalities seen on perfusion lung scanning, none of 167 untreated patients with negative selective angiograms observed over a 6-month period died of thromboembolic disease.[72] The implications of the study are that emboli too small to be seen are too small to be significant. The conclusions of this study have recently been challenged based on statistical grounds.[59,63] In a clinical trial by Hull, et al., all patients with negative results by both venography and pulmonary angiography had anticoagulant therapy withheld irrespective of clinical findings and findings on ventilation/perfusion lung scanning.[64] One patient died unexpectedly of a pulmonary embolism 2 weeks after entry into the study. At the time of entry, the results of the patient's lung scan indicated a segmental mismatch; the angiogram was normal. Venography at the time showed deep venous thrombosis confined to the calf. The patient was not anticoagulated. The embolus may have come from a location other than the deep veins of the lower extremity, or the pulmonary embolus may have derived from the deep veins of the legs with most of the embolus breaking away from the thrombus before the time of venography and then reforming. As mentioned,[24,37] 5 to 20 percent of patients with calf-vein thrombi have thrombus propagation to the deep veins in the thigh of which an estimated 50 percent will form emboli.[22,24] Hull's study also showed that the frequency of negative venograms associated with angiographically documented pulmonary emboli is 30 percent.[64] Overall, however, it is widely agreed that hemodynamically significant but angiographically negative pulmonary emboli are rare.[53,54,72] Although false-negative pulmonary angiograms may occur, the risk of anticoagulation probably outweighs the risk of falsely negative angiograms, especially if associated venograms or impedance plethysmograms are also negative.

Objective Testing for Deep Venous Thrombosis

Ascending Venography

Venography is the reference standard for the diagnosis of deep venous thrombosis.[2,18,20,37] The principal criterion for the diagnosis is the presence of an intraluminal filling defect that is constant in all films and seen in a number of projections.[20,37] Other venographic abnormalities such as nonfilling of a segment of the deep venous system or nonfilling of the entire deep venous system above the knee may be caused by technical artifact.[37] Complications include deep venous thrombosis caused by contrast-induced damage to the endothelium in a small percentage of patients with initially negative venograms,[20] superficial thrombophlebitis, hypersensitivity reactions, and local skin and tissue necrosis secondary to extravasation of dye at the site of injection.[20,37] Lastly, visualization of the external and common iliac veins is inadequate in up to 18 percent of patients[21] who occasionally require more invasive femoral or iliac venography for adequate visualization.[38]

Impedance Plethysmography (IPG)

IPG is a noninvasive technique that detects volume changes in the leg.[20] If venous outflow is obstructed by the presence of venous thrombosis, changes in calf-volume caused by a pneumatic thigh cuff will be altered and detected by circumferential calf electrodes.[20] The cumulative results of multiple studies show a sensitivity of 95 percent and a specificity of 96 percent for detection of proximal lower extremity thrombosis.[37] However, detection of calf-vein thrombosis ranges from only 16 to 60 percent[73] because many do not obstruct the main outflow tract.[20] The test does

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not distinguish between thrombotic and nonthrombotic obstruction to venous outflow and thus can cause false-positive results in settings such as an incorrectly positioned leg, a tense patient with contracting leg muscles, venous compression by an extravascular mass, venous outflow obstruction caused by increased central venous pressure, and decreased filling because of decreased blood pressure or peripheral vascular resistance.[37]

In addition to an inability to detect most calf-vein thrombi, IPG may also miss nonocclusive proximal vein thrombi and occlusive proximal vein thrombi associated with well-developed collateral vessels.[38] As mentioned, calf-vein thrombi are not a significant embolic risk,[21,22] but they may propagate to the deep veins of the thigh.[23] A recent study, however, has reported the safety of withholding anticoagulation therapy in patients with repeatedly negative IPG evaluations and shown such follow-up to be as sensitive as combined IPG and ^{125}I fibrinogen scanning (see below).[74]

Thus, for patients with clinically suspected deep venous thrombosis, a positive IPG in the absence of clinical conditions known to produce false-positive results can be used to make therapeutic decisions. A normal IPG essentially excludes the diagnosis of occlusive proximal deep venous thrombosis but does not exclude the diagnosis of calf deep venous thrombosis or a nonocclusive proximal deep venous thrombosis.

Doppler Ultrasonography

Doppler ultrasonography is an alternate noninvasive test for proximal deep venous thrombosis that detects changes in venous blood flow velocity.[25] In skilled hands it is almost as sensitive to proximal vein thrombosis as IPG but is also insensitive to calf-vein thrombosis.[20] Interpretation of Doppler ultrasonography, however, is subjective in contrast to IPG, which gives objective results.[37] Advantages of Doppler ultrasonography over IPG include greater specificity in patients with increased central venous pressure or arterial insufficiency and usefulness with patients in traction or in plaster leg casts.[20]

^{125}I Fibrinogen Leg Scanning

^{125}I fibrinogen leg scanning is based upon the incorporation of circulating labeled fibrinogen into a forming thrombus. Scanning after a single injection is possible for up to 7 days.[38] In patients with acute deep venous thrombosis, the leg scan usually becomes positive within 24 hours. Occasionally, it may take 48 to 72 hours for enough labeled fibrinogen to accumulate in the thrombus to be detected.[20]

Venous thrombosis is suspected if there is an increase in the radioactive reading of more than 20 percent at any point compared with the readings over adjacent points on the same limb, with the same point on the previous day, or with the readings over the corresponding point on the opposite leg.[38] Venous thrombosis is diagnosed if the scan remains abnormal at repeated examination and the abnormality persists for more than 24 hours.[38]

Fibrinogen leg scanning detects more than 90 percent of acute calf deep venous thrombi but only between 60 to 80 percent of proximal deep venous thrombi.[38] An abnormal fibrinogen scan associated with a normal venogram may occur because of inflammation, hematoma, uptake in a surgical wound, or nonvisualization of the thrombus by the venogram.[38] False-negative scans occur when a thrombus forms after most of the labeled fibrinogen has been cleared from the circulation, when the thrombus is too small to detect, and when the thrombus is proximally located.[26]

Because of the lack of sensitivity of proximal deep venous thrombi, leg scanning should never be used alone with suspected venous thrombosis.[37] A prospective study of 322 patients with symptoms suggestive of deep venous thrombosis compared venography with combined IPG-fibrinogen scanning.[21] Of the 322 patients, 163 went untreated because of negative results by both IPG and leg scanning. Of the 163 untreated patients, 7 percent had calf-vein thrombi shown by venography. During a 3-month follow-up period, none of the 163 patients went on to develop signs of thrombus extension or pulmonary embolism. Together, they have a sensitivity and specificity of 94 percent and 91 percent, respectively.[75]

Workup of Suspected Thromboembolism

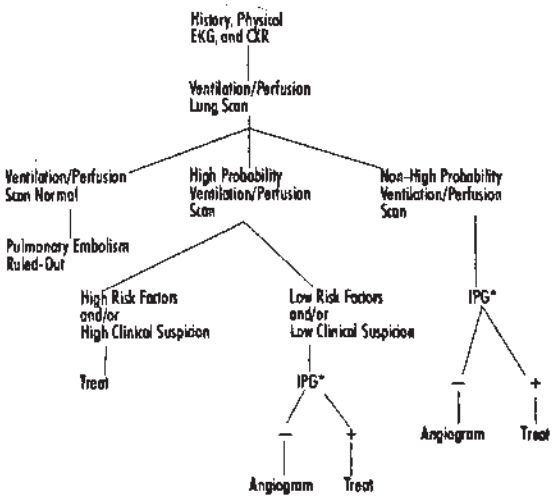
Approach to the Diagnosis of Deep Venous Thrombosis

Hull, et al.[74] compared combined IPG and serial ^{125}I fibrinogen leg scanning with serial IPG alone

for the diagnosis of deep venous thrombosis. IPG performed on the day of referral and, if negative, repeated the following day, again on days 5–7, and on day 10 is as effective as the combination of IPG and leg scanning in the diagnosis of clinically suspected deep venous thrombosis. Furthermore, the study showed it safe to withhold anticoagulation therapy from patients who remain negative by serial IPG measurements. If the IPG becomes positive during this time, a diagnosis of deep venous thrombosis is made and treatment instituted. A positive IPG in the presence of conditions known to produce false-positive results should be confirmed by venography. Ascending venography can also be used as a first-line diagnostic test but, as mentioned, occasionally has difficulty visualizing the external and common iliac veins[21] and may have complications due to the contrast material.[20]

Approach to the Diagnosis of Pulmonary Embolism

The possibility of pulmonary embolism should be considered in any person at risk who experiences any acute cardiopulmonary distress. In the UPET/USPET studies, only 6 percent of patients without recognizable underlying risk factors had pulmonary emboli.[30] The importance of clinical presentation is emphasized in that only 4 percent without either dyspnea or tachypnea had pulmonary emboli.[29] Both electrocardiogram and chest radiograph are helpful in ruling out other diseases. Lung scanning should be used if by the end of this preliminary workup some other illness has not been diagnosed as the cause of the symptoms (Figure 1). A completely normal six-view perfusion scan essentially excludes the diagnosis of pulmonary embolism.[1,2,18,19,54-56] The significance of a positive lung scan varies according to the pattern of defects (Table 5), the risk factors and presentation of the patient,[61] and interpreter variance.[66] A high-probability lung scan in a person with major risk factors, or strong clinical suspicion, should be treated.[63] A high-probability lung scan in a person with minimal risk factors, or low likelihood based on clinical presentation, deserves consideration for further workup.[57,60,61]



*IPG. In the absence of conditions likely to produce false positive tests.

Figure 1. Approach to the Diagnosis of Suspected Pulmonary Embolism.

For those with a high-probability lung scan with minimal risk factors or low-clinical likelihood or a low-probability lung scan, IPG can be used to assist in further evaluation. Patients who have a clinically suspected pulmonary embolism with lung scan patterns regarded as low probability have been shown to have a significant frequency of deep venous thrombosis.[57,64] As mentioned, 50 percent of deep venous thrombi in the iliofemoral system will become emboli.[22,24] Thus, in the absence of conditions that could cause a false-positive IPG, a patient with a positive IPG with the above lung scans should be treated.[63] Generally, there is high correlation between IPG and venography for proximal lower extremity deep venous thrombosis.[37,74] A positive IPG in a setting known to cause false-positive results should be followed up with a venogram.[37] However, approximately 30 percent of patients with angiographically documented pulmonary emboli have negative venograms.[57] Thus, a negative IPG when there is a high-probability lung scan with minimal risk factors or low clinical likelihood, or when there is a low-probability lung scan, should be followed by an angiogram because thromboembolism cannot be excluded.[63]

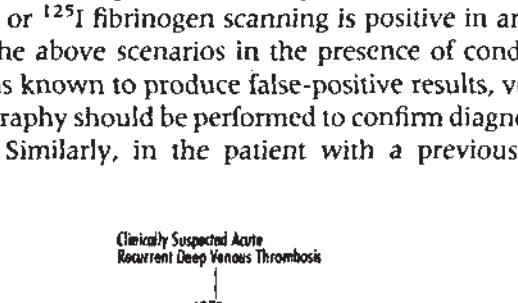
Finally, in those with documented and treated pulmonary emboli, a perfusion lung scan should be done at about 3 months postdischarge from the hospital. This will serve as a baseline, because rarely is there significant further resolution of perfusion defects after this time.[11]

Approach to the Diagnosis of Acute Recurrent Deep Venous Thrombosis

Diagnosis of recurrent deep venous thrombosis is particularly difficult. Not only is the clinical diag-

nosis nonspecific, but each of the objective diagnostic tests becomes limited. The diagnostic hallmark of venography, a constant intraluminal filling defect, may be masked because of obliteration and recanalization.[14] Persistent venous outflow obstruction may be the residual of a previous deep venous thrombosis, thus predisposing to false-positive IPG results.[14] Conversely, false-negative results may be obtained because of the development of large collateral channels.[14] ^{125}I fibrinogen scanning is insensitive to proximal deep venous thrombosis.[14]

Recurrent deep venous thrombi rarely develop during adequate anticoagulation.[3,13,14] Thus, obtaining a baseline IPG at the time of discontinuation of at least 3 months of anticoagulation will serve as a useful reference for evaluating future symptoms.[38] Having a normal baseline IPG at the time of suspected reoccurrence simplifies the diagnostic evaluation. As outlined by Hull, et al.,[37] if the IPG is now positive in the absence of conditions known to produce false-positive results, anticoagulation therapy should be started (Figures 2, 3). If the IPG is negative, ^{125}I fibrinogen leg scanning is performed daily for 72 hours together with IPG. If both tests remain negative, the diagnosis of recurrent deep venous thrombosis is excluded. If either becomes positive in the absence of conditions known to produce false-positive results, anticoagulation therapy is begun. If either IPG or ^{125}I fibrinogen scanning is positive in any of the above scenarios in the presence of conditions known to produce false-positive results, venography should be performed to confirm diagnosis. Similarly, in the patient with a previously



*In the absence of conditions likely to produce false positive results.
**See Figure 3.
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Figure 2. Approach to the Diagnosis of Suspected Acute Recurrent Deep Venous Thrombosis.

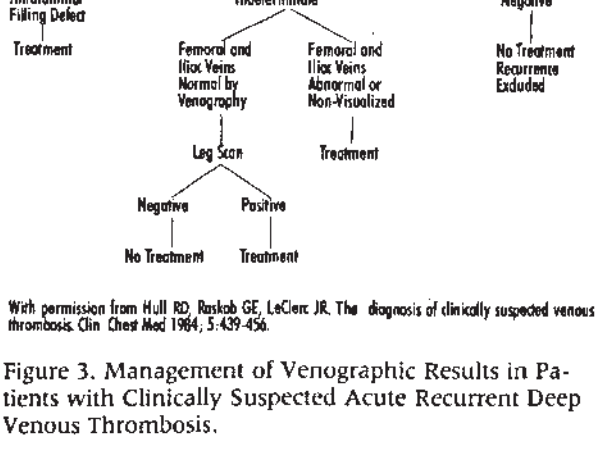

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Figure 3. Management of Venographic Results in Patients with Clinically Suspected Acute Recurrent Deep Venous Thrombosis.

abnormal or unknown IPG result who on referral now has a positive result, venography should be performed because the abnormal IPG does not distinguish between acute recurrent deep venous thrombosis and chronic venous outflow obstruction. In this situation, decision to treat should be based on a positive or negative venogram. If the resulting venogram is indeterminate, but the femoral and iliac veins are normal, ^{125}I fibrinogen leg scanning should be used to make the treatment decision. If the venogram is indeterminate, but the femoral and iliac veins are abnormal or poorly visualized, anticoagulation should be started.

Summary

The evaluation of suspected thromboembolic disorders is difficult because the signs and symptoms of deep venous thrombosis and pulmonary embolism are nonspecific, and a wide variety of disorders may present with similar symptoms. However, clinical suspicion may be modified by the presence or absence of risk factors for thromboembolism, presence or absence of tachycardia and tachypnea, findings on chest radiograph and electrocardiogram, and examination of the lower extremities. If at this point a thromboembolic disorder cannot be ruled out, noninvasive objective testing should be used, but with full recognition of the limitations of each modality. If a diagnosis is still in doubt, angiography and venography should be performed as needed.

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