Thromboembolic disease: optimizing recognition

In one study of DVT patients, nearly 50% had two or more of the following: swelling above or below the knee, recent immobilization, history of cancer, and fever.

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Pulmonary embolism (PE) is a leading preventable cause of morbidity and mortality. Despite increased understanding of its pathogenesis, its incidence does not seem to have changed over the past 30 years.[1] It has been estimated that about 630,000 cases of PE occur in the United States annually[2] and that about 10% of patients with acute PE expire within an hour of onset.

Autopsy studies suggest that only one third of all cases of PE are diagnosed ante mortem.[3,4] Because PE can be clinically silent, prophylaxis is an important therapeutic approach, although it is not commonly implemented by physicians or surgeons.[5] All these data reflect the need for a more aggressive approach to diagnosing and treating this preventable disorder.

PATHOGENESIS

The Virchow triad—stasis, intimal injury, and hypercoagulability—has been recognized since the nineteenth century as a predisposing factor for the formation of thrombi. In a low-flow state (eg, bed rest), platelet aggregates form proximal to the venous valves of the leg and release potent mediators that initiate a cascade of events leading to thrombus formation. Depending on local fibrinolytic activity, the thrombus either resolves or propagates.

Conditions that promote hypercoagulable states (eg, antithrombin III, protein S, or protein C deficiency; factor V abnormality; estrogen therapy) tend to favor further growth. On the other hand, such factors as mobility and anticoagulation tilt the balance in favor of fibrinolysis and reduce the formation of new thrombi.

The current pathogenetic understanding is that the majority of PEs arise as a complication of deep-vein thrombosis (DVT) of the lower limbs, and, in fact, the source of PE has been traced to the deep venous system of the lower extremities in more than 90% of cases.[6,7] Thrombi formed in the calf veins generally remain in that region and rarely cause clinically significant PE. However, in the presence of extensive pulmonary vascular disease, emboli from calf-vein thrombi may attain considerable significance. In about 20% of patients with such

KEY PRACTICE POINTS

The acute onset of dyspnea is the most common symptom of pulmonary embolism.

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An estimated 19% of patients have had at least one prior clinically recognized episode of DVT or PE.

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Up to 20% of patients being treated for recurrent PE or DVT develop a new venous thromboembolism while undergoing treatment.

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Clinical manifestations of pulmonary embolism

At the extremes, PE may present silently in association with proximal-vein thrombosis without any symptoms referable to the chest, or it may present as a cardiac arrest. Between these extremes, three clinical syndromes have been described: (1) pleuritic pain or hemoptysis associated with pulmonary hemorrhage or infarction; (2) circulatory collapse associated with a massive embolus; and (3) isolated onset of dyspnea.

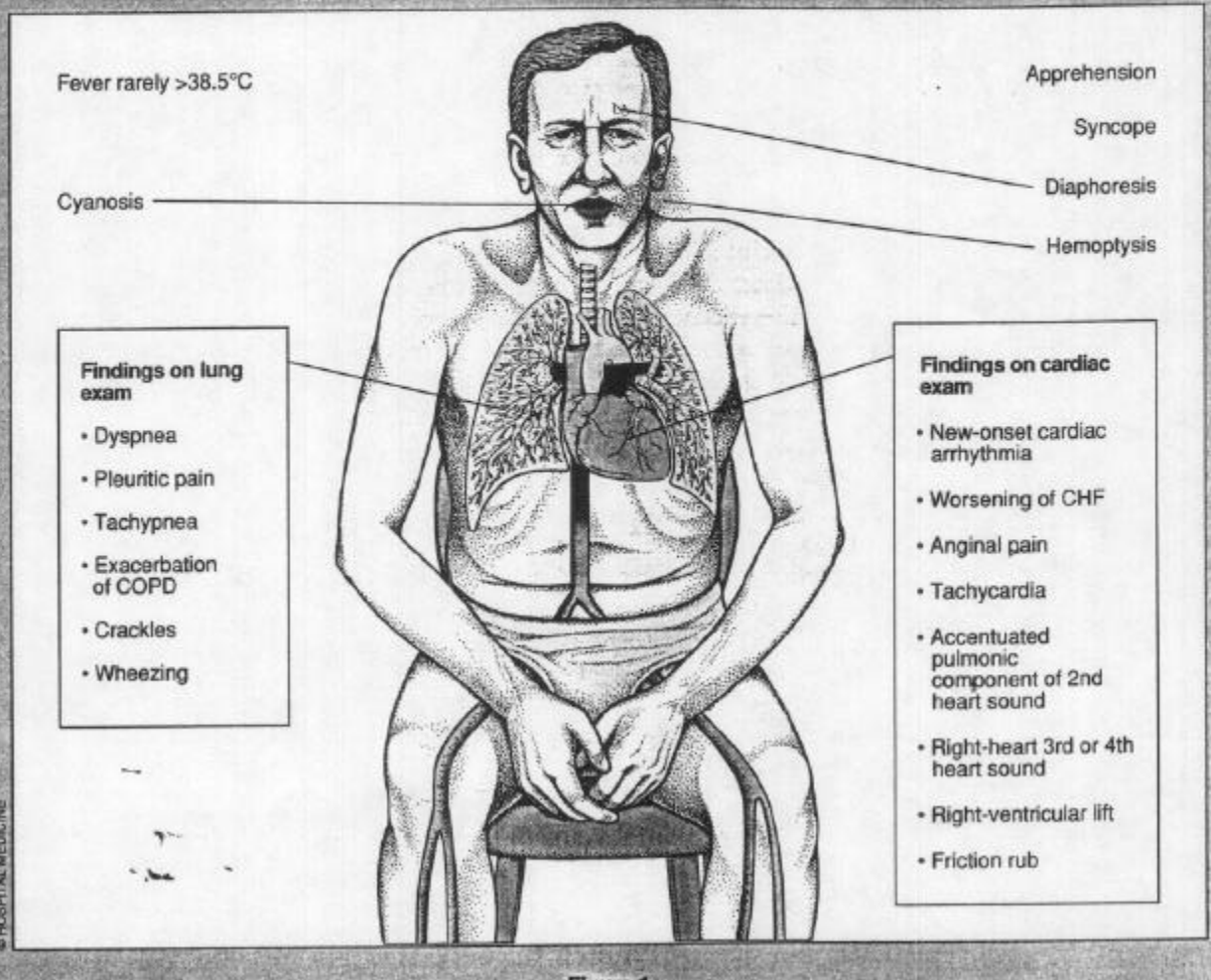

Figure 1

thrombi, the thrombi extend proximally to involve the popliteal veins and more proximal vessels. In this condition, the femoral and iliac veins may harbor a significant load of loose venous thrombi that are capable of breaking off at any time and lodging in the pulmonary arteries.

Evidence for this concept derives from studies using impedance plethysmography (IPG), which detects proximal-vein thrombosis but only 30% of calf-vein thromboses.[8] When anticoagulant therapy was withheld in patients with suspected DVT on the basis of negative serial IPG, the occurrence of PE during follow-up was extremely low.[9] In addition, about 50% of patients with proximal-vein thrombosis had ventilation-perfusion (V/Q) lung scans that were indicative of PE.[10,11] There was no adverse outcome associated with not treating calf-vein thrombosis with anticoagulants unless serial studies detected extension into the proximal veins.[9,12]

Some experts believe that calf-vein thrombosis without proximal ex-

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tension is of concern for two reasons: first, an increased risk of recurrence if anticoagulants are withheld, and second, the possible association of calf-vein thrombosis with symptomatic PE.[13,14] The clinical significance of these potential sequelae has yet to be determined.

Other venous sites are rarely implicated in acute PE. Among reported sites are the upper extremities, the right cardiac chambers, and the renal and (very rarely) hepatic veins. In most cases, a predisposing factor can be identified. Indwelling central venous catheters, temporary pacemakers, and right ventricular failure are the usual culprits.

The majority of nonfatal PEs resolve without residual clinical abnormalities. However, in a small minority of cases (approximately 0.1%–0.5%[15]), they do not resolve. If residual pulmonary arterial obstruction is significant, the patient develops chronic thromboembolic pulmonary hypertension.

FACTORS PREDISPOSING TO DVT AND PE

The major risk factor for PE is recent immobilization. Data from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) reveal that more than 50% of patients had a history of immobilization within 3 months of suffering an acute PE.[16]

Previous DVT or PE is another important risk factor for venous thromboembolism, with an estimated 19% of treated patients having had at least one clinically recognized prior episode.[17] Further, 10% of patients who were receiving treatment for a first episode and up to 20% of those who were being treated for a recurrence developed a new venous thromboembolism while they were undergoing treatment.[18]

Pregnancy, particularly the postpartum period, has been associated with an incidence of venous thromboembolism up to 20 times higher than that in comparable nonpregnant women.[19] In fact, PE is a leading cause of maternal death following childbirth.

Pancreatic, gastrointestinal, lung, and gynecologic cancers have been associated with an increased state of coagulability. Whether the observed relationship between malignancy and venous thromboembolism has to do with procoagulant factors released by the tumor or with an associated comorbid state has yet to be fully elucidated. Other predisposing factors to increased coagulability include congestive heart failure, obesity, stroke, trauma, and hypercoagulable states.

Recently, resistance to activated protein C (APC), a key element in one anticoagulant pathway, has been implicated in the pathogenesis of familial venous thromboembolic disease.[20] APC achieves its anticoagulant effect by degrading activated factor VIII and factor Va. Factor V, although a procoagulant protein, has anticoagulant activity by acting as a cofactor for APC. A molecular defect in factor V decreases its anticoagulant activity without affecting its procoagulant activity, resulting in a hypercoagulable state. This genetic defect seems to be 5 to 10 times more common than antithrombin III, protein C, or protein S deficiency.

KEY PRACTICE POINTS

The proximal veins of the legs are the major source of pulmonary emboli.

■

A decreased PaO_2 with hypocapnia is highly suggestive of PE, but a normal PaO_2 or $A\text{-}aDO_2$ does not exclude it.

■

The chest x-ray shows elevation of the hemidiaphragm in 25% of PE patients; this is seen more often in those with massive embolization.

CLINICAL PRESENTATION OF DVT AND PE

DVT. The clinical diagnosis of DVT is notoriously unreliable, although there are some guidelines for the diagnosis of proximal-vein thrombosis. In one study, nearly half of patients were reported to have at least two of the five following hallmarks: swelling above the knee of the affected leg; swelling below the knee; recent immobilization; history of cancer; and fever.[21]

Other symptoms and signs of DVT are calf pain, a sense of "fullness" in the leg while standing or walking, increased skin temperature, erythema, and a palpable cord. Homan's sign, which involves tenderness on compression of the calf muscle or pain on dorsiflexion of the foot, is neither sensitive nor specific for DVT.

The differential diagnosis of DVT includes superficial thrombophlebitis,

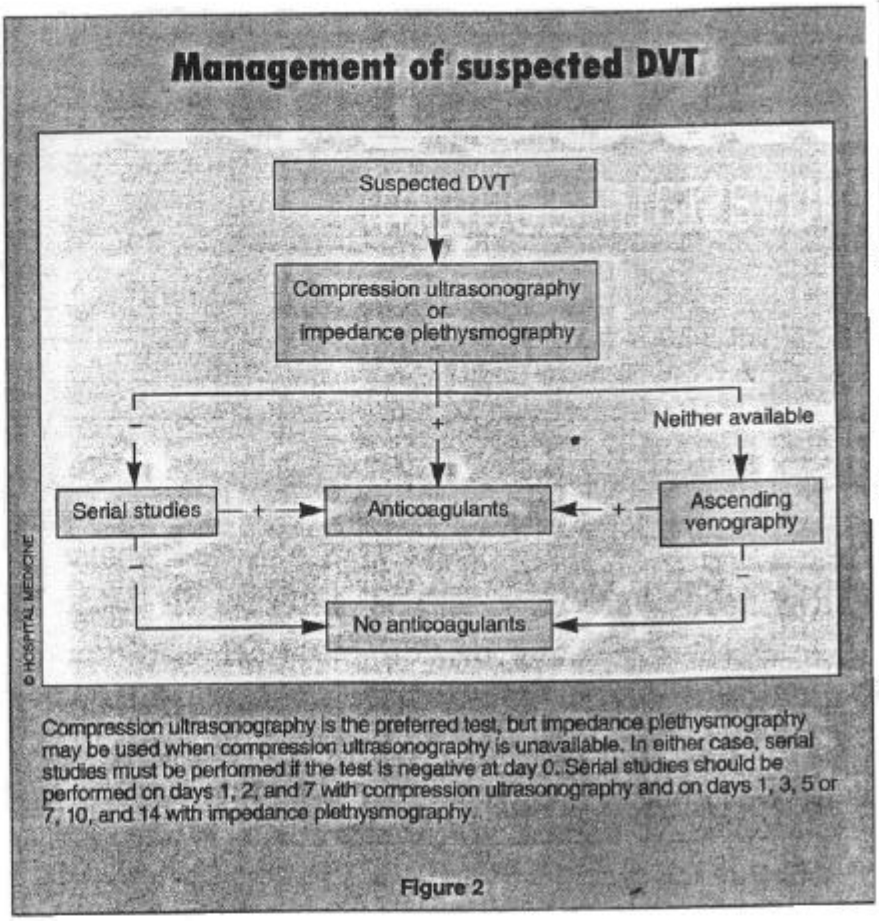
a torn calf muscle, hematoma, cellulitis, congestive cardiac failure, and Baker's cyst.

PE. In general, the clinical manifestations of PE correlate with the size of the embolus. A small PE may go undetected, whereas a massive PE can kill instantaneously. At the extremes, PE may present silently in association with proximal-vein thrombosis without any symptoms referable to the chest,[10,11] or it may present as a cardiac arrest (Figure 1). Between these extremes, three clinical syndromes have been described: (1) pleuritic pain or hemoptysis associated with pulmonary hemorrhage or infarction; (2) circulatory collapse associated with a massive embolism; and (3) isolated onset of dyspnea.[22]

Acute onset of dyspnea, pleuritic pain, and tachypnea are the primary symptoms of PE.[16] A new-onset cardiac arrhythmia, worsening congestive heart failure, or exacerbation of chronic obstructive pulmonary disease should raise the suspicion of possible acute PE. Syncope and anginal pain are a reflection of decreased cardiac output and right-ventricular ischemia, respectively, in the setting of massive PE.

Tachypnea and tachycardia are the most frequently reported signs of PE. Cardiac examination reveals an occasionally accentuated pulmonic component of the second heart sound, a right-heart third or fourth heart sound, and a right-ventricular lift, particularly with a large PE. Early examination of the lungs may yield normal results, but crackles may later be heard with the development of atelectasis. A friction rub and wheezing may be heard on some occasions. A pleural effusion of less than one third of a hemithorax may be present in some 50% of patients[16] and is usually detected radiographically. Fever, if present, rarely exceeds 38.5°C.

The differential diagnosis of acute PE includes the following: acute myocardial infarction (MI), aortic dissection, pneumothorax, pericarditis, and pneumonia.



Compression ultrasonography is the preferred test, but impedance plethysmography may be used when compression ultrasonography is unavailable. In either case, serial studies must be performed if the test is negative at day 0. Serial studies should be performed on days 1, 2, and 7 with compression ultrasonography and on days 1, 3, 5 or 7, 10, and 14 with impedance plethysmography.

Figure 2

MAKING THE DIAGNOSIS

The diagnostic reference test for DVT is contrast venography; for PE, it is pulmonary angiography. Prospective trials have shown that anticoagulants can safely be withheld in patients with suspected DVT and a negative venogram[23] and from patients with suspected PE and a negative pulmonary angiogram.[24]

DVT. Although they carry less risk and expense, noninvasive tests also have less diagnostic accuracy.

Compression ultrasonography has become the principal noninvasive test for the diagnosis of DVT and has superseded IPG in many institutions.[25] Although its accuracy in detecting calf-vein thrombosis in asymptomatic patients is poor, it is more accurate than venography for the detection of proximal-vein thrombosis in patients with suspected DVT.[26]

Compression ultrasonography is valuable in the management of patients with suspected DVT.[27] Withholding anticoagulants on the basis of negative serial compression ultrasonography over a 7-day period has been associated with a 1.5% incidence of venous thromboembolism over 6 months of follow-up.[27] This low incidence of DVT compares favorably with the 1.3% incidence seen

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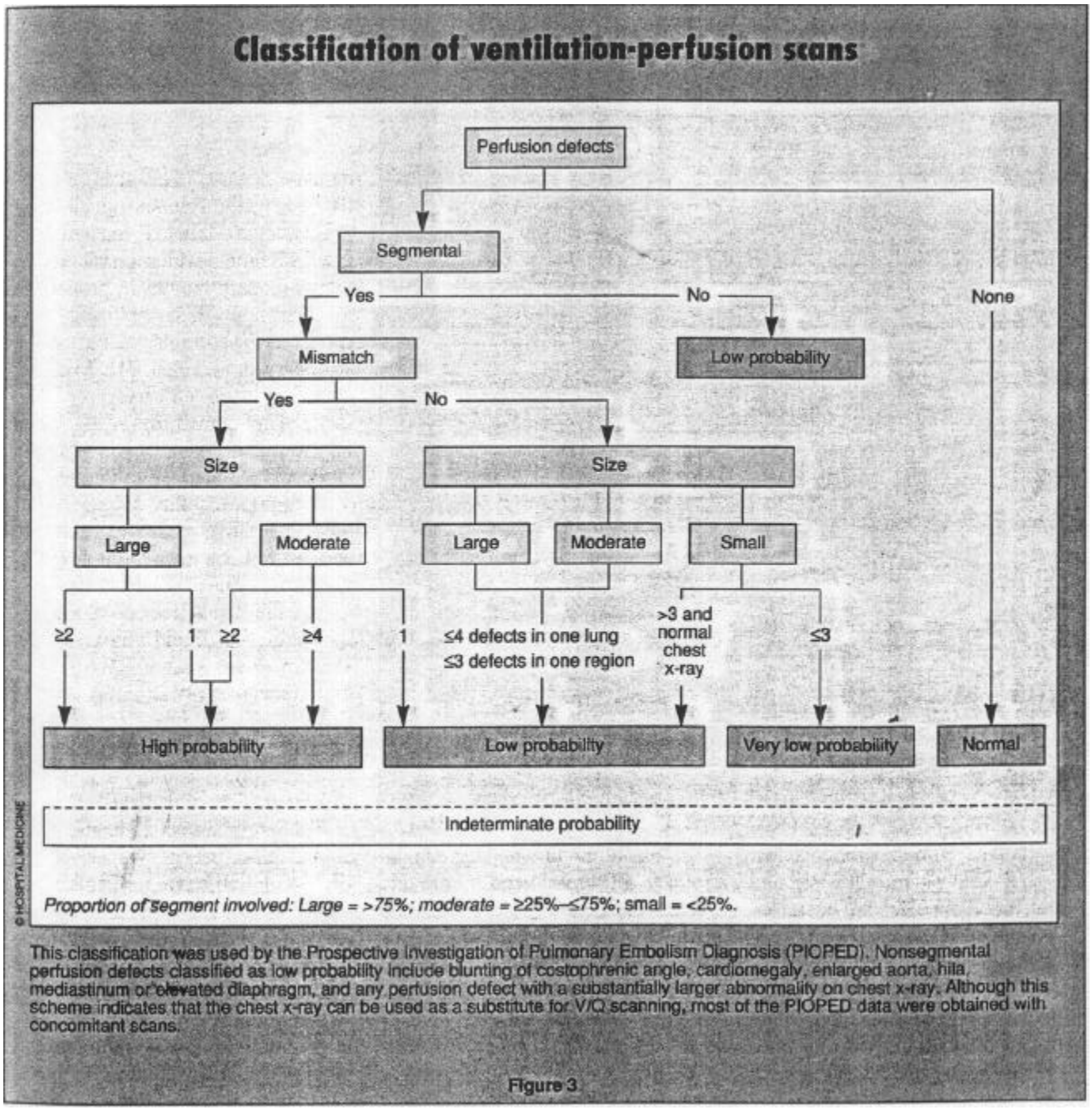

This classification was used by the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). Nonsegmental perfusion defects classified as low probability include blunting of costophrenic angle, cardiomegaly, enlarged aorta, hila, mediastinum or elevated diaphragm, and any perfusion defect with a substantially larger abnormality on chest x-ray. Although this scheme indicates that the chest x-ray can be used as a substitute for V/Q scanning, most of the PIOPED data were obtained with concomitant scans.

Figure 3

when a similar management plan was followed on the basis of negative contrast venography.[23]

Other methods of diagnosing DVT, such as radioactive fibrinogen uptake scanning, are not available in most centers. Nuclear magnetic resonance imaging is expensive, and nuclear venograms are insufficiently sensitive and specific for this diagnosis.

An algorithm for the management of patients with suspected DVT is given in Figure 2.

PE. Laboratory tests are nondiagnostic in most cases of PE, but they can be useful in ruling out conditions that mimic PE clinically. The white blood cell count is usually normal or slightly elevated in PE. A decrease in the partial pressure of arterial oxygen (PaO_2) along with hypocapnia is highly suggestive of PE, but a normal PaO_2 or alveolar-arterial difference for O_2 ($A\text{-}aDO_2$) does not exclude it.

The chest x-ray may be completely normal in acute PE. Elevation of the hemidiaphragm is observed in approximately 25% of patients with PE and is seen more frequently in those

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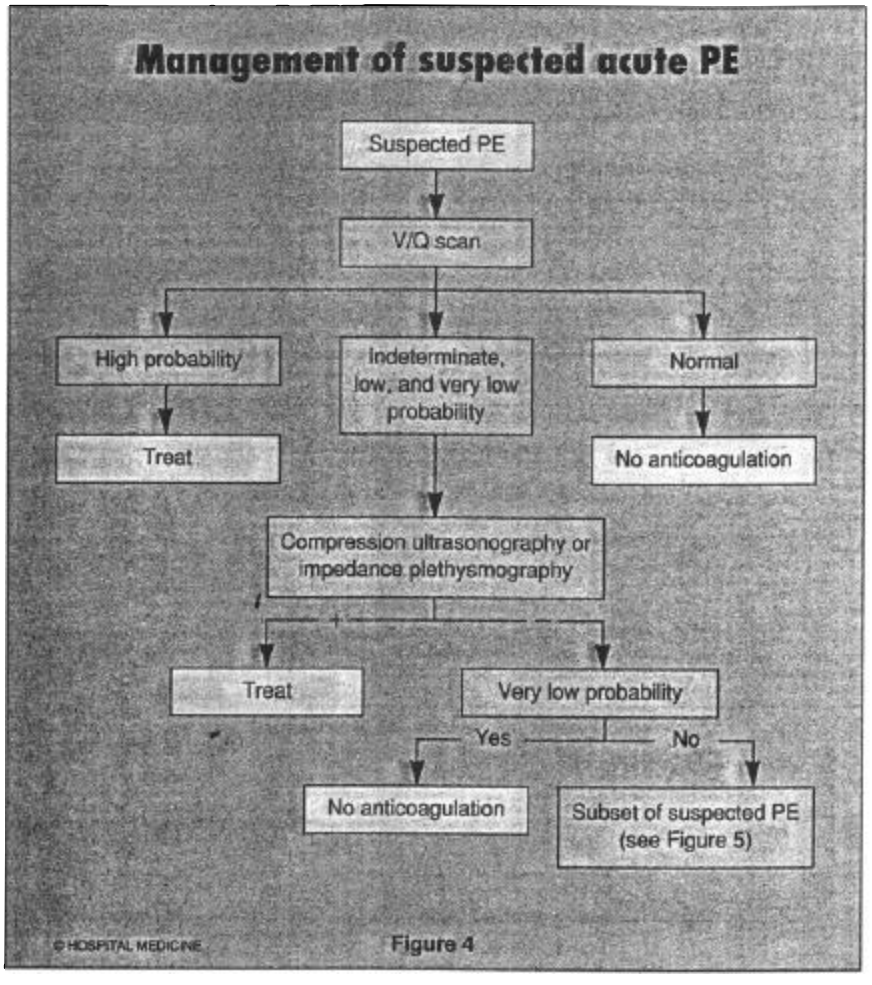

Figure 4

with massive embolization. Atelectasis, unilateral pleural effusion, and pleural-based opacities are occasionally identified. Decreased peripheral pulmonary vascularity with abnormal radiolucency in some areas, known as the Westermark sign, often with prominence of the proximal pulmonary artery segment, is helpful but not specific.[16]

In most patients with PE, the electrocardiogram shows sinus tachycardia or nonspecific ST-segment or T-wave abnormalities. Supraventricular tacharrhythmias (atrial fibrillation or flutter) can be an early manifestation of acute PE. A right-axis deviation, incomplete right bundle-branch block, or $S_1Q_3T_3$ pattern is seen predominantly in patients with massive PE.

Levels of D-dimers, degradation products of crosslinked fibrin, are usually elevated in DVT, PE, and acute MI, although their diagnostic role is controversial and their value may be greater in excluding than confirming the diagnosis of PE. D-Dimer levels are measured by ELISA (enzyme-linked immunosorbent assay), which has a high specificity and low sensitivity, although further studies are needed to define the role of this measurement. However, it has been suggested that PE can be eliminated in patients with plasma levels of D-dimers below 500 µg/L.[28]

V/Q scanning is currently the principal noninvasive test for the diagnosis of PE and should be considered in all patients with suspected PE, even those with preexisting cardiopulmonary disease. The scan is performed by intravenous injection of ^{99m}Technetium-labeled macroaggregated albumin, which distributes in the pulmonary arteries in proportion to blood flow. If the perfusion scan results are abnormal, a ventilation scan is recommended. The PIOPED classification of V/Q scans[29] is summarized in Figure 3, and an algorithm for the management of patients with suspected PE is given in Figure 4.

A high-probability V/Q scan has an 87% positive predictive value that a PE will be found on pulmonary angiography. Thus, a high-probability V/Q scan is useful for confirming the diagnosis of PE, and a normal scan virtually rules out the diagnosis. Unfortunately, only a minority of patients have a high-probability or near-normal V/Q scan. Nonetheless, a low-probability scan has a 14% positive predictive value for PE.[24]

The V/Q scan is nondiagnostic in about 75% of patients with suspected PE. Some will have positive venous studies for proximal-vein thrombosis, for which the treatment is the same as for PE; therefore, no further investigation is necessary. Patients whose initial venous studies are negative should undergo pulmonary angiography. However, this approach can create a considerable financial burden for many institutions.

Pulmonary angiography carries a relatively low risk when performed by an experienced operator.[25] Two angiographic findings are highly suggestive of PE: abrupt vascular cutoff and intraluminal filling defect. Other abnormalities have been described but are less reliable, particularly in patients with less extensive PE.

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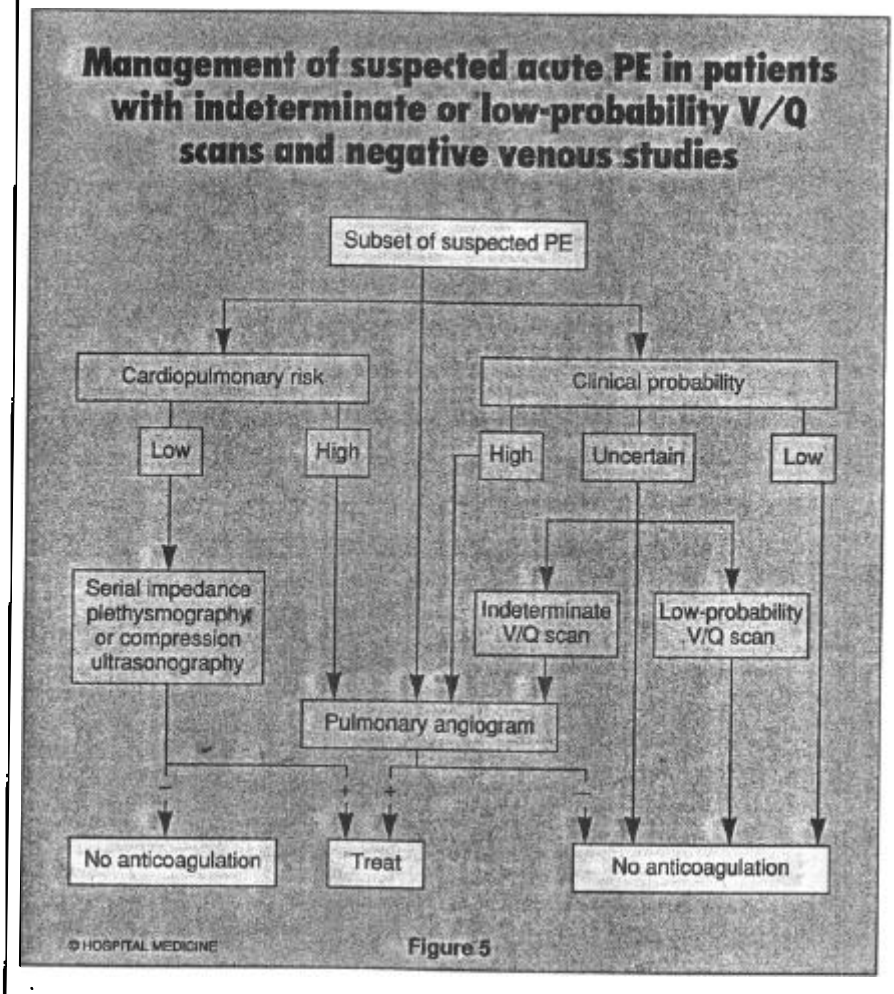

Figure 5

Potential complications of pulmonary angiography include bleeding, renal failure, allergic reaction to the contrast agent, pulmonary artery rupture, and cardiopulmonary arrest. Critically ill patients are the most susceptible to these complications. Those with renal disease, right-ventricular failure, or bleeding diathesis are also prone to complications.

Various approaches to limiting the need for pulmonary angiography have been proposed (Figure 5). In one study, patients with suspected PE and no severe cardiopulmonary disease who had nondiagnostic (indeterminate or low-probability) V/Q scans were not given anticoagulation unless the initial IPG (on day zero) was positive or subsequent studies became positive. Serial studies were performed on the first, third, and fifth or seventh, tenth, and fourteenth day after presentation.[30] Following this approach, the rate of venous thromboembolism in 414 patients was 3%, similar to the rate (1%) in the 315 patients with normal V/Q scans.

Other investigators have proposed a strategic approach that combines V/Q scanning with clinical assessment and noninvasive tests for proximal-vein thrombosis.[31] Ensuring the accuracy and precision of clinical assessments is a difficult problem, one that has been addressed by several investigators.[32,33] For example, it has been suggested that an indeterminate-probability V/Q scan be considered confirmatory of PE unless the patient has no history of immobilization in the preceding 3 months, is <59 years old, and has pulmonary edema and a left pleural effusion on chest x-ray.[33] In patients with low-probability V/Q scans, PE may be considered unlikely unless there is a history of immobilization and no pulmonary edema on chest x-ray.[33]

These approaches are based on retrospective data and have not been validated by prospective trials. Nevertheless, they may be of value in patients at high cardiopulmonary risk when pulmonary angiography is unavailable and the patient cannot be transferred to another facility. □

Next month, the authors discuss therapy and prophylaxis.

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