American Thoracic Society
MEDICAL SECTION OF THE AMERICAN LUNG ASSOCIATION

The Diagnostic Approach to Acute Venous Thromboembolism

Clinical Practice Guideline

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INTRODUCTION

Venous thromboembolism (VTE) represents a spectrum of disease that includes both deep venous thrombosis (DVT) and pulmonary embolism (PE). Pulmonary embolism most commonly results from DVT occurring in the deep veins of the lower extremities, proximal to and including the popliteal veins. Both DVT and PE are frequently clinically unsuspected, leading to significant diagnostic and therapeutic delays and accounting for substantial morbidity and mortality. While there are as many as 260,000 patients in the United States in whom VTE is diagnosed and treated each year, more than half of the cases that actually occur are never diagnosed and as many as 600,000 cases may therefore occur (1). Because of the magnitude of the problem, and the variable diagnostic approaches that are feasible, this official statement outlining acceptable diagnostic approaches to VTE is presented. The treatment of acute VTE will not bc addressed.

To present a coherent position on the diagnostic approach to VTE, clinical trials evaluating the diagnostic approach to DVT and PE have been reviewed and are categorized as level 1 or level 2 (2). Level 1 studies are those that incorporate the following three criteria: (I) previous establishment of objective diagnostic criteria for normal and abnormal diagnostic studies, (2) independent comparison of the diagnostic result with contrast venography (CV) for DVT or with pulmonary angiography for PE, with readers blinded to the other test result, and (3) the prospective evaluation of patients who were enrolled consecutively. A clinical trial was accepted as enrolling consecutive patients only if this was explicitly stated or if the study stated that patients were excluded only if they refused consent or could not tolerate the diagnostic procedure. Other clinical trials were considered to be level 2. It should be emphasized that CV and pulmonary angiography have been established as gold standard diagnostic tests by default, so that when other modalities are evaluated, this a priori assumption exists (3). Relatively more data are presented for impedance plethysmography (IPG) and for ultrasound (US) imaging than for other diagnostic modalities because the data involving these technologies are more extensive and complex. More level I data exist for these techniques than for newer technology such as spiral computed tomography (CT) scanning or magnetic resonance imaging (MRI). For DVT and PE, background information is presented, followed by a discussion of the clinical diagnosis. Subsequently, each diagnostic technique is addressed. Final guidelines are ultimately presented for the diagnostic approach to both DVT and PE. The recommendations of the American Thoracic Society Clinical Practice Committee (4) were reviewed as this statement was developed and our goal was to adhere to these guidelines. The committee preparing this document was multidisciplinary, as recommended. Because different medical centers have different resources, clinical flexibility was built into the recommenda-

tions. The latter concept is of particular importance in the diagnostic approach to venous thromboembolism because although level 1 studies have been performed at some medical centers, validated protocols or the specific technology is not available everywhere and the resulting data may not be applicable at other centers.

THE DIAGNOSTIC APPROACH TO ACUTE DEEP VENOUS THROMBOSIS

Background

The clinical diagnosis of DVT of the lower extremities cannot bc established with certainty without objective testing. Contrast vcnography is invasive, requires contrast media, and is no longer appropriate as the initial diagnostic test for the evaluation of symptoms that suggest acute DVT. The proven utility of noninvasive technology, including IPG and compression US. as well as increasing experience with MRI, have rendered CV much less popular. Nonetheless, venography remains the gold standard test. The availability of and familiarity with certain technology may influence the diagnostic approach. The specific clinical scenario impacts on the diagnostic algorithm that is chosen. For example, while IPG and US are reliable for the diagnosis of symptomatic proximal DVT (involving the popliteal and/or more proximal veins), they are much less reliable for recognizing asymptomatic DVT. The sensitivity of certain diagnostic tests is influenced by thrombus location. Thrombi located between and including the popliteal and the iliac veins are the easiest to locate, and those above the iliac veins and in the calf veins are more elusive. The diagnosis of recurrent DVT remains a challenge. The D-dimer test has been evaluated in the setting of both acute DVT and acute PE and is discussed in the section, THE DIAGNOSTIC APPROACH TO ACUTE PULMONARY EMBOLISM, **below.** Currently available diagnostic modalities are reviewed. followed by recommendations for their USC. Diagnostic algorithms are then presented. The following clinical scenarios are considered in the context of each diagnostic test: (I) symptomatic proximal DVT, (2) asymptomatic proximal DVT, (3) calf DVT, (4) recurrent and chronic lower extremity DVT, and (5) upper extremity venous thrombosis.

Symptoms and Signs

Innumerable clinical investigations have established that DVT cannot be reliably diagnosed on the basis of the history and physical examination, even in high-risk patients (5). Patients with lower extremity DVT often do not exhibit erythema. warmth, pain, swelling. or tenderness. When five clinical studies were compared. for example, the sensitivity of calf pain for acute DVT varied from 66 to 91% and the specificity varied from 3 to 87% (6). In six studies that included evaluation for calf tenderness, the range for sensitivity was 56 to 82%, and the range for specificity was 26 to 74%. For Homans' sign, the sensitivity varied from 13 to 48%, and the specificity from 39 to 84% (6). **Swelling** of the calf or leg as a marker was also inconsistent. with the sensitivity ranging from 35 to 97% and the specificity from 8 to 88% (6). When present, however, these findings merit further evaluation despite their lack of specificity. *Thus, the clinical evaluation may imply the need for further evaluation but cannot, by itself; be relied on to confirm or exclude the diagnosis of DVT.* The presence of risk factors for DVT should always be rigorously scrutinized. The clinical examination and laboratory testing have been reviewed elsewhere (S-7). Our focus is on the diagnostic approach once DVT is clinically suspected but also includes the asymptomatic high-risk patient. Objective testing is also necessary to diagnose recurrent DVT.

Contrast Venography

While CV remains the gold standard technique for the diagnosis of symptomatic DVT, it is rarely performed because of the accuracy of noninvasive testing. Venography should be performed whenever noninvasive testing is nondiagnostic or impossible to perform. The technique of Rabinov and Paulin has been used consistently (8). Contrast venography has been considered nearly 100% sensitive and specific provided it is technically adequate and that strict diagnostic criteria are adhered to. Level 1 studies have not been performed because CV has been established, by default, as the gold standard test. Adequate CV requires complete visualization of the deep venous system, from the calf to the pelvic veins and inferior vena cava. The most reliable criterion for the diagnosis of acute DVT is a constant intralumenal filling defect evident in two or more views (8). An abrupt cutoff of a deep vein is another reliable criterion but requires cautious interpretation in patients with previous DVT. Other criteria such as nonvisualization of deep veins (may be clarified with injection of more contrast material), venous collaterals, or nonconstant intralumenal filling defects are less reliable and should not be used to confirm the diagnosis of acute DVT.

For symptomatic proximal DVT, CV is extremely sensitive and specific but noninvasive tests are more appropriate for first-line testing. Although CV is also sensitive for asymptomatic proximal DVT, it is generally not utilized as a screening test except in clinical trials. Venography appears to be the most sensitive test for calf DVT. The diagnosis of recurrent lower extremity venous thrombosis has proven challenging. It can be difficult to visualize a constant intralumenal defect with CV when veins have been thromboscd previously. Venography has been considered the gold standard technique for upper extremity thrombosis, but other modalities, such as US, are generally attempted first.

Disadvantages of CV include invasiveness. which may result in phlebitis or hypersensitivity reactions: however, it is generally safe and accurate. It may be painful, and poor venous access may make the test difficult or impossible to perform. Deep venous thrombosis may occasionally result from the procedure. Direct toxicity of the contrast agent may result in nausea and vomiting, flushing, nephrotoxicity, or cardiotoxicity. Nephrotoxicity is generally manifested by transient renal failure. Idiosyncratic reactions are not dose related and include urticaria, angioedema, bronchospasm. and cardiovascular collapse. Venography is more expensive than IPG or US but the cost varies among different institutions. Thus, CV has its limitations (3).

Relative contraindications to CV include acute renal failure, and chronic renal insufficiency with a creatinine level greater than 2 to 3 mg/dl. Idiosyncratic reactions may be minimized with antihistamines and corticosteroids. Arterial insufficiency is a relative contraindication in view of the possibility of extravasation of contrast with resultant cellulitis and the potential for tissue necrosis. Advantages and disadvantages of CV are outlined in Table 1.

Impedance Plethysmography

Background. Impedance plethysmography was developed in 1969 and has been extensively investigated in a number of prospective clinical trials, mainly from Canada and Europe (9-12). Compared with other diagnostic tests for DVT, it takes less technical training, is less expensive, and is portable. This technique detects increased venous outflow resistance in

TABLE 1

ADVANTAGES AND LIMITATIONS OF CONTRAST VENOCRAPHY FOR THE DIAGNOSIS OF ACUTE DEEP VENOUS THROMBOSIS

Advantages	Limitations
Sensitive*	Invasive
Specific'	Expensive
Generally available	Contraindications
Acute versus chronic DVT	Renal insufficiency
Less operator dependent than US	Severe contrast allergy
Most accurate test for calf DVT	Adverse effects (pain, DVT)
	Not portable

Definition of abbreviations: DVT deep venous thrombosis; US = ultrasound.
*This includes entire lower extremity as well as upper extremity deep venous thrombosis.

the deep veins of the proximal lower extremities. Impedance plethysmography has been compared with CV in consecutive symptomatic patients with suspected proximal DVT in a number of clinical investigations. Clinical trials have been conducted to establish the sensitivity of serial IPG and outcome in patients in whom the initial IPG was negative. Despite extensive outcome data, this diagnostic modality is less commonly used today, with US being more widely employed for evaluating suspected acute lower extremity DVT. An overview of the technique of IPG including its limitations, as well as results of clinical trials in both symptomatic and asymptomatic patients conducted, are presented.

Physiology and technique. Impedance plethysmography is a sensitive method for evaluating the rate of venous return from the lower extremity. The test relies on the principle that the volume of blood in the leg affects its ability to conduct an applied electrical current, which is inversely proportional to the impedance between two electrodes placed along the calf. To conduct the test, a small electrical current is passed between one set of electrodes, while the second measures changes in voltage. A cuff is inflated around the thigh to obstruct venous outflow but not arterial inflow. As blood accumulates in the leg below the cuff, impedance between the calf electrodes falls. When venous pressure builds to the point that it equals that of the cuff, venous outflow is reestablished, and the tracing plateaus. The sudden release of cuff pressure results in a sudden surge of blood flow proximally (the blood volume of the leg decreases), resulting in a rapid increase in impedance. If DVT is present in any major vein draining the lower extremity (from the popliteal to the iliac veins) the rate of venous emptying (and the increase in impedance) is significantly slower, and the tracing reveals a slower than normal return toward baseline. *This technique is insensitive to thromhi that do not decrease the rate of venous outflow, such as most calf thromhi and small, nonobstructing thromhi in the proximal veins.* Other causes of slow venous outflow, such as elevated central venous pressure, may yield bilateral false-positive results on IPG.

It has been demonstrated that the sensitivity and specificity of IPG for detecting proximal DVT are both dependent on adhering to the validated protocol (13). This includes careful leg positioning to avoid compression of the popliteal or femoral veins. The occlusive cuff is inflated to 45 cm of water for 45 s and is rapidly released. The impedance rise at the end of the occlusion is plotted against the fall as recorded 3 s after cuff release. If an equivocal or abnormal result is obtained, the procedure is repeated for 45 s of occlusion, then 120 s of occlusion, then 45 s and again 120 s. A result in the normal range terminates the sequence. A validated graph for plotting the results should be used. Results using computerized IPG devices have not been validated. It is important to emphasize that if different protocols are utilized, a degree of institution specificity will be imparted that may contribute to differences in results. The McMaster investigators, for example, have validated criteria for the technique based on their early results (13). Impedance plethysmography should be performed with standardized and commercially available equipment by trained technicians. Studies not utilizing such a protocol or those employing nonvalidated devices should not be used.

Limitations of impedance plethysmography. Certain limitations of IPG must be considered. The technique does not distinguish between venous obstruction due to DVT and that caused by nonthrombotic entities. Correct positioning of the legs is important to avoid obstructing venous outflow. Potential causes of false-positive results include increased intrathoracic pressure, increased intraabdominal pressure, and decreased venous return from the lower extremities, such as might occur owing to obstruction of blood flow by tumor. False-positive results can also result from poor arterial inflow such as low cardiac output states or severe peripheral vascular disease. These conditions are outlined in Table 2. Advantages and limitations of IPG are outlined in Table 3. Potential limitations of the sensitivity of serial IPG in symptomatic patients are discussed below.

TABLE 2

COMMON PHYSIOLOGICAL CAUSES OF FALSE-POSITIVE IMPEDANCE PLETHYSMOCRAPHY RESULTS

- Increased intraabdominal pressure
  - Massive obesity
  - Massive ascites
- Markedly increased central venous pressure
  - Vena caval obstruction
  - Cor pulmonale
  - Pericardial tamponade
  - Severe congestive heart failure
- Decreased arterial inflow to lower extremity
  - Severe peripheral arterial disease (atherosclerosis)
  - Cardiogenic shock
- Nonthrombotic venous outflow obstruction
  - Pregnancy
  - Abdominal masses
  - Pelvic masses'
  - Leg muscle tension*

* May result in unilateral venous outflow obstruction. Other factors listed are likely to cause venous outflow obstruction in both lower extremities symmetrically.

TABLE 3

ADVANTAGES AND LIMITATIONS OF IMPEDANCE PLETHYSMOCRAPHY FOR THE DIAGNOSIS OF ACUTE DEEP VENOUS THROMBOSIS

Advantages	Limitations
Noninvasive	Operator dependent
Safe	Asymptomatic proximal DVT
Inexpensive	Calf DVT
Portable	Nonobstructing thrombi
Symptomatic proximal DVT*	Potential false-positive tests+
Recurrent DVT‡	Not useful for upper extremity DVT
Numerous clinical trials to date	Casts/immobilization devices preclude use
No radiation	Note useful for alternative diagnoses

*Validated protocols must be adhered to for maximum sensitivity and specificity.
† See Table 2.
‡ The potential for normalization of the IPG after acute DVT increases with time. If possible, normalization should be documented in order to diagnose recurrent DVT definitively, particularly if the possible recurrence occurs within the first few months after the initial event.

TABLE 4

SENSITIVITY AND SPECIFICITY OF IMPEDANCE PLETHYSMOGRAPHY FOR SUSPECTED SYMPTOMATIC PROXIMAL DEEP VENOUS THROMBOSIS*

Study	Ref. No.	Sensitivity (%)	Specificity (%)	Level of Evidence
Hull and coworkers (1976)	9	1241133 (93)	3861397 (97)	1
Richards and coworkers (1976)	10	30/37 (81)	78/90 (87)	2
Hull and coworkers (1977)	11	59/60 (98)	108/114 (95)	1
Hull and coworkers (1978)	12	155/169 (92)	305/317 (96)	1
Flanigan and coworkers (1978)	14	52/54 (96)	93/98 (95)	2
Hull and coworkers (1981)	16	74178 (95)	1571160 (98)	1
Peters and coworkers (1982)	17	36/39 (92)	1151124 (93)	2
Prandoni and coworkers (1991)	18	113/124 (91)	2821301 (94)	1
Ginsberg and coworkers (1994)	20	26/40 (65)	79185 (93)	2
Agnelli and coworkers (1990)	22	34135 (97)	46155 (84)	2
Heijboer and coworkers (1992)†	23	27/28 (96)	30136 (83)	1
Wells and coworkers (1995)†	24	76/99 (77)	330/354 (93)	1
Hamilton, Canada		46165 (71)	2771290 (95)	
Padua, Italy		30/34 (88)	53/64 (83)	

* All of these trials were prospective. Not all used contrast venography as the standard for comparison,

† These two studies prospectively compared impedance plethysmography and compression ultrasound in hospitalized patients and outpatients, respectively.

Early clinical trials: Establishing accuracy in symptomatic acute proximal DVT. Impedance plethysmography has the distinct advantage of outcome data that are available from large, prospective clinical investigations. Early studies (1976 to 1982) revealed sensitivities of 92 to 98% for symptomatic proximal DVT with confirmation using CV (9-12, 14–17), although one early study revealed a sensitivity of only 81 % (10). The poor sensitivity for calf DVT was soon established (sensitivity approximately 20%) (9-12, 16-20) although it appears that embolization from calf DVT is unlikely unless proximal extension occurs (21). Sensitivity and specificity values from clinical trials comparing IPG with CV in consecutive patients with symptomatic, suspected DVT and with independent interpretation of each study are included in Table 4 (9-12, 14, 16-18, 20). Subsequent developments included the use of a computerized IPG device (22) and clinical trials comparing IPG with US in outpatients and hospitalized patients (23, 24). These are discussed below. A major advance was the realization that serial IPG determinations over a IO- to 14-d period could detect extension of calf vein thrombi into the proximal veins, which necessitates treatment (25). While such extension may be the reason that IPG studies become positive during serial testing, it has also been suggested that some degree of undetectable extension into the proximal veins may have already occurred at the time of the initial test.

Management studies: Early success and later questions. Determining clinical outcome without anticoagulation in patients with negative serial IPG studies has been crucial in evaluating the validity of the technique. These management trials were conducted to prove that it was safe to withhold treatment in patients with suspected DVT if serial IPG studies remained negative during the 10- to 14-d study period. The importance of serial testing after an initially negative test is emphasized by five clinical trials revealing a conversion rate to positive of 1.4 to 19% (25-29) with the combined rate of conversion being 89 of 1,637 patients (5.4%) (Table 5). Although most such conversions occur during the first 3 d, some patients will take up to 2 wk to develop a positive test. The precise sensitivity of serial testing could not be determined because patients with persistently normal IPG studies did not undergo CV. However. in the five studies noted above, subsequent DVT or PE (no fatal PE) was documented in a maximum of only 2.5% of patients with normal serial IPG. Unfortunately, in another clinical trial, four patients died of PE after having normal serial IPG (30). In this trial, serial IPG testing was performed in 311 patients with clinically suspected DVT in whom initial IPG test-

TABLE 5

LEVEL 1 MANAGEMENT STUDIES WITH SERIAL IMPEDANCE PLETHYSMOCRAPHY IN PATIENTS WITH SUSPECTED DEEP VENOUS THROMBOSIS*

Study	Ref. No.	Conversion to Abnormal during Follow-up (%)	VTE in Patients with Normal Serial IPG (%)	PE Fatalities with Normal Serial IPG (%)
Hull and coworkers (1985)	25	191645 (2.9)	6/311 (1.9)	0
Huisman and coworkers (1986)	26	201309 (6.5)	2/289 (0.7)	0
Huisman and coworkers (1989)	27	30/161 (19)	1/131 (0.8)	0
Hull and coworkers (1990)†	28	21139 (1.4)	1/139 (0.7)	0
Heijboer and coworkers (1993)	29	181383 (4.7)	9/364 (2.5)	0
Total‡		8911,637 (5.4)	1911,234 (1.5)	O/l ,234 (0)

* The rate of conversion to abnormal during the serial studies and the rate of recurrent venous thromboembolism (VTE) are shown for each clinical trial.

† Pregnant patients.

‡ In an additional clinical trial (30) (not shown), IPG was performed with a computerized IPG technique (proven nonvalid). In this study, 10 of 311 (3.2%) patients developed VTE when serial IPG was normal and 4 died of Pt. Two of the deaths occurred during serial testing and one happened on the day after.

ing was normal. Four patients (1.3%) developed fatal PE despite the normal serial tests. Thcrc are several possible explanations for the poor outcome (31). These investigators used a protocol and a computerized device that differed from that validated by the McMaster group. It is conceivable that equipment or other technical factors may have played a role. Unvalidated protocols arc not acceptable and computerized IPG devices cannot be considered appropriate the present time. It is also possible that the four deaths were chance occurrences. The sensitivity of IPG in this study was 86%. Serial IPG studies have been compared with serial US in patients with suspected, symptomatic acute DVT and an initially negative study (*see* COMPRESSION ULTRASOUND WITH VENOUS IMAGING, *below*).

Additional concerns arose from the results of a retrospective clinical trial conducted by one of the McMaster groups (Hondcrson General Hospital), a group experienced with IPG. Anderson and associates (19) performed CV (or compression ultrasound in a minority of patients) in patients with abnormal IPG results, in those with normal IPG testing in whom DVT was highly suspected, and in those in whom serial IPG testing would be difficult. Impedance plethysmography was abnormal in only 37 of 56 patients with confirmed DVT (sensitivity, 66%). Of the 19 proximal DVT not detected by IPG. 12 (63%) were occlusive and 11 (58%) involved at least the poplitcal and superficial femoral veins. Thus, these investigators reported a lower sensitivity for IPG at their center than had been previously reported in symptomatic outpatients. Although consecutive patients had been enrolled, the study was retrospective. Further studies were indicated.

The same investigators, together with the group from Padua, Italy. then prospcctivcly compared IPG and US in 495 symptomatic outpatients with suspected DVT. using CV as the definitive answer (24). The prevalence of DVT was 130 of 495 (27%). Of these, 109 of 130 (84%) were proximal. Overall. the sensitivity of IPG was 77% and the specificity was 93%, compared with 90 and 98%, respectively, for US. There were significant differences in sensitivity and specificity between the two centers as a consequence of differences in size and location of thrombi. The majority of proximal thrombi not detected by IPG and US involved less than 5 cm of the distal half of the poplitcal vein and most of these thrombi occurred at one center (Hamilton). Exclusion of these thrombi from the analysis increased the sensitivity of US for proximal thrombi to X6 of X7 (99%) and improved the sensitivity of IPG to 72 of 79 (91%). The positive predictive value of US was strongly influenced by the number of abnormal venous segments. A higher prevalence of patients with less extensive, less occlusive thrombi at the Hamilton center appeared to be a factor in the difference in scnsitivitv.

Ginsberg and colleagues (20). another McMaster group (Chedoke-McMaster Hospital), also elected to reevaluate prospectively the sensitivity of IPG for proximal DVT as well as to relate the location and size of thrombi to the IPG result. Clinically suspected DVT in 132 consecutive patients was evaluated with IPG and 1 IX of these patients underwent CV. The other 14 patients underwent US and were felt to bc definitively diagnosed with proximal DVT. Of the 132 patients, 40 (30%) had proximal DVT. 7 (5%) had calf DVT, and 85 (64%) did not have DVT. The sensitivity of IPG for proximal DVT was 65% and the specificity was 93%. Of the proximal vein IPG detected 13 poplitcal thromb not involving the superficial femoral vein and 23 of (85%) the superficial femoral vein. patterns m ahave resulted i more vere and smaller, less occlusive thrombi re-i ferred (20). Potential explanations for the lower sensitivity sensitivities f r earlier studies such as repeated IPG testing p sion of patients with a known abnormal IPG in the study population (31). It has been suggested that modern CV techniques may detect early thrombi that would have been previously overlooked (32. 33). A shift in the referral pattern to patients with less extensive. less occlusive thrombi as well as heightened awareness of DVT and improved availability of testing facilities are explanations that have been given substantial credence (20, 24, 31, 32). Ginsberg and colleagues (20) recommended that, on the basis of their results, patients with a high clinical likelihood of DVT but a normal initial IPG should undergo US or CV instead of serial IPG. It has been argued that, on the basis of clinical outcome trials (34). the latter approach has not been proved necessary.

Impedance plethysmography in asymptomatic patients. The diagnostic accuracy of IPG in asymptomatic patients has been evaluated in a number of clinical trials, predominantly in patients undergoing total hip replacement or surgery for hip fracture (35–42). The sensitivity for proximal DVT has ranged from 12 to 64% and was less than 30% in three of these studies. In 106 asymptomatic patients undergoing IPG, US. and CV after total hip or total knee replacement, the sensitivity for IPG was 41.2% for proximal thrombi compared with 64.7% for US (42). Impedance plethysmography was also insensitive to calf vein thrombi in these patients. The low sensitivity of IPG in these asymptomatic patients may be attributed to the fact that the thrombi are often smaller and less likely to be occlusive (43). Agnelli and associates (22) utilized serial computerized IPG in 246 asymptomatic patients with a negative initial IPG undergoing elective total hip replacement or surgery for hip fracture. The sensitivity and specificity for DVT were 22 and 87% in the operated leg and 14 and 95% in the nonoperated Icg. respectively. The same investigators (41) subsequently determined that there was a significantly higher proportion of proximal DVT ($p = 0.001$), a significantly higher Marder score (index of throm bus size) ($p = 0.000$ I), and a significantly higher proportion of occlusive DVT ($p = 0.001$) in symptomatic patients than in asymptomatic patients. *Screening for D VT in asymptomatic high-risk patients has not proved useful* (*see* COMPRESSION ULTRASOUND WITH VENOUS IMAGING, below).

Recurrent and chronic deep venous thrombosis. The clinical diagnosis of recurrent DVT is nonspecific (44, 45). Impedance plethysmography may be especially useful to diagnose recurrence. since positive findings revert to normal as the DVT resolves and/or collateral circulation dcvclops. Resolution rates for IPG-documented acute proximal DVT at 3.6, 9, and 12 mo have been found to be 67, 85, 92, and 95%, respectively (46). Thus, IPG appears to be reliable in diagnosing recurrent DVT when the previous episode is more remote. *Impedance plethysmography is not useful for early recurrences unless IPG normalization has been documented.*

Compression Ultrasound with Venous Imaging

Background. Ultrasound has been studied extensively in the setting of suspected acute DVT as well as for screening asymptomatic patients deemed at high risk for acute DVT. Compression ultrasound with venous imaging (real-time B-mode imaging) is noninvasive, widely available. and has been proved accurate for diagnosing acute. symptomatic proximal DVT. In contrast to Doppler venous flow detection. which only offers information regarding blood flow, real-time sonography permits a two-dimensional cross-sectional representation of the lower extremity veins. The combination of these two techniques

is termed duplex ultrasound. Ultrasound technology has been advanced by the development of color duplex instrumentation that displays Doppler frequency shifts as color superimposed on a gray-scale image. Color duplex images display both mean blood flow velocity, expressed as a change in hue or saturation, and direction of blood flow as displayed as red or blue. Among the useful features of US imaging techniques are the ability to identify pathology other than DVT. Baker's cysts, superficial or intramuscular hematomas, lymphadenopathy, femoral artery aneurysm, superficial thrombophlebitis, and abscesses may be suggested or diagnosed (47). Advantages and disadvantages of US imaging are listed in Table 6.

Technique. Most medical centers utilize a combination of gray-scale, duplex, and color Doppler imaging. The technique requires a 3- to 7.5-MHz real-time transducer. The patient is positioned supine with the leg slightly externally rotated. The reverse Trendelenburg position may facilitate the examination by increasing venous distention. The compression technique is used, beginning at the inguinal ligament, and the common femoral vein and greater saphenous vein are evaluated. Radiologists frequently identify the vein below the bifurcation of the common femoral vein as the superficial femoral vein. This may be confusing because the superficial femoral vein is actually a component of the deep venous system. (The term "femoral vein" has replaced "superficial femoral vein," emphasizing its importance.) The deep femoral vein is evaluated at the bifurcation of the common femoral vein but cannot generally be visualized along its entire length. The prone or lateral position may aid in evaluating the calf and popliteal veins and the popliteal should be scanned at least to the level of the venous trifurcation, or 10 cm below the midpatellar point. Compression is applied with the transducer at short intervals over the entire length of the vessels. The pressure applied should be enough to indent the skin but not enough to compress arterial flow. This will allow complete compression of the normal opposing venous walls. Certain areas of incomplete compressibility (greater saphenous vein and common femoral vein juncture and superficial femoral vein at the adductor canal) may exist in the absence of DVT. Doppler studies can be used to confirm the presence of spontaneous venous flow. Respiratory phasicity and cessation of flow with the Valsalva maneuver offer indirect evidence of abdominal and pelvic venous patency. Color imaging appears to offer a superior evaluation of flow than can be achieved with duplex scanning. Nonocclusive thrombi may be more easily documented with color flow imaging, and calf vein evaluation and studies in obese patients are generally more easily achieved with this technique. Compression US with venous imaging (real-time B-mode imaging), duplex US, and color Doppler all rely on compression, at least to some degree, for the diagnosis of DVT. *While there are differences between the techniques, a clear advantage of one over another has not been demonstrated in prospective clinical trials as long as compression is used.* Color Doppler energy (power Doppler) has been utilized in the evaluation of thrombotic disorders. The color map in the power Doppler display shows the integrated power of the Doppler signal, which is related to the number of red blood cells producing the Doppler shift. Power Doppler imaging is more sensitive for the detection of low-amplitude. low-velocity flow than color Doppler and is relatively Doppler angle independent. However, power Doppler provides no velocity or directional information and is motion sensitive. This technique has proved valuable in other vascular US imaging applications and could prove useful for imaging patients with DVT to assess early recanalization or nonocclusive thrombus. However, no clinical trials have been performed to assess power Doppler in patients with DVT. Criteria for the diagnosis of acute DVT using US imaging are listed in Table 7.

There has been controversy over the necessary extent of the US examination. When the (superficial) femoral vein is not evaluated, diagnostic efficacy may be reduced, perhaps to a clinically significant extent (48). In a study by Frederick and coworkers (48), six cases of isolated superficial femoral venous thrombosis were missed with an abbreviated protocol, amounting to 4.6% of the DVT diagnosed. It has been suggested by others that US evaluation from the inguinal ligament to the calf veins is not necessary. Pezzullo and colleagues (49), retrospectively evaluated 160 US examinations in 155 symptomatic patients and found 146 cases of proximal thrombosis. In 145 cases (99%), either the common femoral or popliteal vein was involved. In the other 14 of 160 cases (9%), isolated calf vein thrombosis was diagnosed. The limited examination decreased the examination time by 9.7 min, or 54%. More recent data have suggested an excellent outcome with US performed serially over 1 wk for suspected DVT. using a limited examination (also see SYMPTOMATIC ACUTE PROXIMAL **DEEP VENOUS THROMBOSIS, Mow).** In addition to controversy over the limited examination, the issue of unilateral versus bilateral studies in the setting of unilateral symptoms is debated (SO-52). The unilateral examination has been reported to decrease scanning time and cost, without a decrease in diagnostic yield (51). Naidich and associates (52) evaluated 245 patients with unilateral symptoms and determined that 180 had no DVT, 44 had ipsilateral DVT, 18 had bilateral DVT, and 3 had contralateral DVT. While it was argued that this supported the bilateral examination, the incidence of contralateral DVT

TABLE 6

ADVANTAGES AND LIMITATIONS OF COMPRESSION ULTRASOUND WITH VENOUS IMAGING FOR THE DIAGNOSIS OF ACUTE SYMPTOMATIC DEEP VENOUS THROMBOSIS

Advantages	Limitations
Noninvasive	Operator dependent
Safe	Less accurate for chronic DVT
Available	Symptomatic or asymptomatic calf DVT
Relatively inexpensive*	Less useful for pelvic DVT
Portable	Asymptomatic proximal DVT
Few contraindications	Massive obesity/severe edema
No radiation	Casts/immobilization devices
Symptomatic proximal DVT	
Upper extremity DVT	
May diagnose other pathology	
Numerous clinical trials to date	

* A bilateral study adds significantly to cost.

TABLE 7

CRITERIA FOR THE DIAGNOSIS OF ACUTE DEEP VENOUS THROMBOSIS USING COMPRESSION ULTRASOUND WITH VENOUS IMAGING

Primary Diagnostic Criterion	Secondary Diagnostic Criteria
Noncompressibility of a vein*	Echogenic thrombus within the vein lumen†
	Venous distention
	Complete absence of spectral or color Doppler signal from the vein lumen
	Loss of flow phasicity, response to Valsalva or augmentation

* This is the most reliable sign of acute DVT.

† Acute thrombus may be anechoic. Intralumenal echoes may represent a false-positive test.

TABLE 8

DIAGNOSTIC CRITERIA THAT AID IN DISTINGUISHING BETWEEN ACUTE AND CHRONIC DEEP VENOUS THROMBOSIS*

Characteristic	Acute	Chronic
Thrombus echogenicity	Hypoechoic	Echogenic
Vein lumen size+	Distended	Narrow, irregular
Compressibility	Spongy	Rigid, incompressible
Collateral veins	Absent	Present

* Serial studies reveal that approximately 50% of patients with an acute episode of DVT documented at ultrasound will have persistent sonographic changes such as incomplete compressibility at 6 to 12 mo follow-up (108, 109). Thus, caution is important in interpreting lack of, or partial, vein compressibility in a patient with previous DVT. A new area of noncompressibility is evidence of new thrombosis.

† Vein lumen size should be interpreted in the context of other findings (110).

was low (1%) and the presence of bilateral DVT has not been proved to have more impact on outcome than unilateral DVT.

Limitations of compression ultrasound with venous imaging. Venous compressibility may be limited by patient characteristics such as obesity. edema, and tenderness as well as by casts or immobilization devices that limit access to the extremity. While there may be areas of focal noncompressibility in these situations, these areas are generally bilaterally symmetric and color flow imaging will usually reveal venous filling. Other potential causes of false-positive results include extrinsic compression of a vein by a pelvic mass or other perivascular pathology (47) and thrombosis in the distal popliteal vein. False-negative studies may occur in the presence of calf DVT. with proximal DVT in asymptomatic (even high-risk) patients (53) or in the prcscncc of a thrombosed duplicated venous segment. Ultrasound techniques are unreliable in detecting DVT in the iliac veins; CV and MRI are much more reliable in this setting (54–56). Finally, because US may not return to normal after acute DVT has been diagnosed, it must be interpretcd with caution when attempting to diagnose recurrent DVT (Table 8). These limitations are discussed further in the following two sections.

Symptomatic acute proximal deep venous thrombosis. A number of clinical trials have suggested the accuracy of US in diagnosing suspected, acute DVT. A large retrospective outcome trial in which anticoagulation was withheld in the setting of negative US revealed only five episodes of VTE in 1,022 symptomatic patients (57). Two patients developed fatal PE more than 3 mo after the initial event. Prospective clinical trials in which consecutive patients have been evaluated and in which real-time B-mode compression US has been compared with CV in an independent, blinded manner have been useful in confirming the accuracy of the technique in patients with suspected acute DVT (42, 58–62). Other clinical trials utilizing the same technique have been conducted less rigorously, in that consecutive enrollment of patients is not documented (63-68). These level 1 and level 2 studies are shown in Table 9. The duplex and color-flow techniques have been evaluated in similar studies and the results arc similar to the above trials. Level 1 (69–72) and level 2 (73-76) studies for duplex US are shown in Table IO. with studies for color-flow Doppler in Table 11 (77-82). Studies in which independent, blinded readings of the diagnostic studies were not performed or not specified were not evaluated (83–85). When US is negative in patients with suspected DVT, serial US has proved to be a sensitive means by which to detect proximal extension of calf DVT in symptomatic outpatients. Heijboer and colleagues (2Y) found that when serial compression US remained negative (Days 1, 2, and 8), the incidence of VTE during the 6-mo follow-up period was only 1.5%, compared with 2.5% for serial IPG. These investigators examined only the common femoral and popliteal veins.

In a more recent clinical trial, Birdwell and associates (86) evaluated 405 consecutive outpatients with a suspected first episode of acute DVT. If the simple compression US (common femoral from inguinal line to bifurcation, and popliteal vein from proximal popliteal fossa to a point IO cm distal to the midpatella) was normal, anticoagulation was withheld regardless of symptoms and the test was repeated 5 to 7 d later. The initial US was normal in 342 patients and 7 of these patients developed an abnormal study during the serial follow-up. The initial US was abnormal in 63 patients. Over the 3-mo follow-up period, 2 of the 335 patients (0.6%) with normal serial US studies, from whom treatment had been withheld, de-

TABLE 9

ACCURACY OF REAL-TIME B-MODE (COMPRESSION) ULTRASOUND FOR SUSPECTED PROXIMAL DEEP VENOUS THROMBOSIS IN SYMPTOMATIC PATIENTS*

Study	Ref. No.	Number of Patients (Limbs)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
			Level 1 Studies			
Ginsberg and coworkers (1991)	42	65 (98)	35/38 (92)	57/60 (95)	35/38 (92)	57160 (95)
Lensing and coworkers (1989)'	58	209	66/66 (100)	1421143 (99)	66167 (99)	142/143 (99)
Cronan and coworkers (1987)	59	50	25/28 (89)	23123 (100)	25/25 (100)	23/23 (100)
Appelman and coworkers (1987)†	60	110	48152 (92)	58/60 (97)	48/50 (96)	58162 (97)
Monreal and coworkers (1989)†	61	69	40/42 (95)	18121 (86)	40141 (98)	18/24 (75)
Pedersen and coworkers (1991)‡	62	215 (218)	101/113 (89)	71173 (97)	1 ol /lo3 (98)	71 /83(86)
			Level 2 Studies*			
Fletcher and coworkers (1990)	63	44	14/14 (100)	29/30 (97)	14115 (93)	29/29 (100)
Chance and coworkers (1991)†	64	70	14/14 (100)	56160 (93)	14/1a (78)	56/56 (100)
Habscheid and coworkers (1990)	65	126 (174)	57/60 (97)	91/91 (100)	57157 (100)	91 /94 (92)
Gudmundsen and coworkers (1990)	66	150	60/60 (100)	87/90 (97)	60/63 (95)	87/87 (100)
Dauzat and coworkers (1986)	67	145	89/92 (97)	45/45 (100)	89/89 (100)	45/48 (94)
Aitken and coworkers (1987)	68	46	15/16 (94)	26/26 (100)	15/15 (100)	26/27 (96)

* All ultrasound studies included the common femoral, superficial femoral, and popliteal veins except where noted. All are prospective, using venography as the control with independent, blinded readings. Studies in which consecutive patient enrollment was not performed or not specified are noted. Most studies did not specify whether or not the patient population was inpatient or outpatient. Duplex ultrasonography and color-flow Doppler are presented on subsequent tables. Outcome studies are discussed in text

† Only the common femoral and popliteal veins were studied.

‡ Hospitalized patients.

§ All are designated as level 2 clinical trials because patients were not enrolled consecutively or this was not specified.

TABLE 10

ACCURACY OF DUPLEX ULTRASONOCRAPHY FOR PROXIMAL DEEP VENOUS THROMOSIS IN SYMPTOMATIC PATIENTS*

Study	Ref. No.	Number of Patients (Limbs)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
			Level 1 Studies			
O'Leary and coworkers (1988)	69	50	22/25 (88)	24125 (96)	22123 (96)	24/27 (89)
George and coworkers (1987)†	70	47 (52)	22/24 (92)	26126 (100)	22/22 (100)	26128 (93)
Mitchell and coworkers (1991)	71	65	23/24 (96)	28/35 (80)	23/29 (79)	28129 (97)
Quintavalla and coworkers (1992)	72	165	75/77 (97)	59160 (98)	75/76 (99)	59/61 (97)
			Level 2 Studies			
Vogel and coworkers (1987)‡	73	50	19/21 (92)	29/29 (100)	19/19 (100)	29/31 (94)
Mantoni and coworkers (1989)‡	74	90	34/35 (97)	48/50 (96)	34/36 (94)	48/49 (98)
Elias and coworkers (1987)§	75	430 (854)	2411241 (100)	5931606 (98)	2411254 (95)	5931606 (98)
Comerota and coworkers (1990)	76	65	37/37 (100)	24128 (86)	37/37 (100)	24125 (96)

* All studies are prospective, using venography as the control with Independent, blindedreadngs. Studies in which consecutive patients were not enrolled or in which blinded readings were not clearly stated are specified. All ultrasound studies included the common femoral, superficial femoral, and popliteal veins. The clinical trials listed include both inpatient and outpatientstudies. Outcome studies are discussed in text.

† Only the common femoral and popliteal veins were studied.

‡ Designated as level 2 because of lack of enrollment of consecutive patients or the fact that this was not specified.

§ Designated as level 2 because it is not clear that investigators were blinded to clinical and prior test information.

vcloped VTE while 4 of the 70 patients (5.4%) with either an initially abnormal or subsequently abnormal study (treated) developed recurrent VTE. None of the patients in the study died from acute PE.

Similarly. Cogo and colleagues (87) evaluated the safety of withholding anticoagulation in patients with suspected DVT when compression US was initially negative and remained negative at repeat testing 1 wk later. A simplified compression US procedure limited to the common femoral vein in the groin and the popliteal vein down to the trifurcation of the calf veins was also performed in this study. Of the 1,702 patients included, US was abnormal in 400 patients initially and in 12 patients at 1 wk. Venous thromboembolic complications occurred in only one patient during the week of serial testing and in eight patients during the 6-mo follow-up period. It is important to note that although the extended popliteal examination did allow for the earlier identification of patients with proximal DVT. the procedure resulted in more false-positive results. The positive predictive value for the assessment of the common femoral vein and the popliteal vein in the popliteal fossa was 98.5%, but dccrcascd to 79% for the distal popliteal region. Thus. it appears safe to withhold anticoagulation in patients in whom one or two serial US (including distal popliteal scanning) arc negative over 5 to 7 d. The studies described above (86, 87) suggest that a single repeat study at 5 to 7 d is adequate if the initial study includes the femoral vein, the popliteal fossa, and scanning to 10 cm below the midpatella or to the trifurcation of the calf veins. *When patient follow-up cannot he guaranteed or in centers in which US has not proved sufficiently reliable, these serial US protocols should not be utilized.*

Asymptomatic acute proximal deep venous thrombosis. As is the case with IPG, real-time B-mode US, duplex US, and color-flow Doppler US have been used as surveillance techniques to evaluate asymptomatic patients at high risk for DVT. They have proved insufficiently sensitive in this setting. Without prophylaxis, the risk of DVT is approximately 50% after total hip replacement and as high as 65% after total knee replacement (89). Prospective clinical trials enrolling consecutive patients and using previously established objective criteria for CV and US with independent, blinded comparisons of the two techniques were assessed (level 1 trials) (43, 68, 90–98). Other studies were deemed level 2 (76, 99-102). Of the 11 level 1 studies, 5 used real-time B-mode US, 4 utilized duplex US, and 2 were color Doppler studies. When level1 studies were considered, US had a sensitivity of 62% (95 of 144 patients), a specificity of 97%, and a positive predictive value of 66% for detecting proximal DVT. For level 2 studies, the sensitivity was 95%, the specificity was 100%, and the positive

TABLE 11

ACCURACY OF COLOR-FLOW DOPPLER ULTRASONOGRAPHY FOR PROXIMAL DEEP VENOUS THROMBOSIS IN SYMPTOMATIC PATIENTS*

Study	Ref. No.	Number of Patients (Limbs)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
			Level 1 Studies			
Lewis and coworkers (1994)†	77	97	20121 (95)	75/76 (99)	20121 (95)	75/76 (99)
Rose and coworkers (1990)	78	69 (75)	25/26 (96)	49/49 (100)	25/25 (100)	49150 (98)
			Level 2 Studies‡			
Schindler and coworkers (1990)	79	97	54155 (98)	39/39 (100)	54/54 (100)	39140 (98)
Baxter and coworkers (1990)	80	40	11/12 (92)	26/26 (100)	11/11 (100)	26127 (96)
Baxter and coworkers (1992)§	81	40	15/15 (100)	20/20 (100)	15/15 (100)	20/20 (100)
Mattos and coworkers (1992)	82	75 (77)	32/32 (100)	44145 (98)	32/33 (97)	44/44 (100)

* All studies are prospectwe, using venography as the control with independent, blinded readings. Studies not enrolling consecutive patients are specified. All ultrasound studies included the common femoral, superficial femoral, and popliteal veins. The clinical trials listed include both inpatient and outpatient studies. Outcome studies are discussedin text.

† This study employed only color flow and did not utilize compression.

‡ Designated as level 2 because of lack of enrollment of consecutive patients or because this was not specified.

§ There were 50 patients initially enrolled but eight venographic and two ultrasound failures occurred.

predictive value was 100%. Asymptomatic patients undergoing orthopedic surgery have been scrutinized by metaanalysis and although duplex and color Doppler imaging may have theoretical advantages compared with B-mode imaging, this has not been clearly demonstrated (53). It is likely that the lower sensitivity of US in asymptomatic high-risk orthopedic patients occurs because thrombi in asymptomatic patients are smaller. fresh. and more easily compressible and nonocclusive. Outcome data evaluating US screening in these asymptomatic patients arc now available. In one double-blind, randomized, controlled trial involving 1,024 clcctivc total hip or knee arthroplasty patients receiving warfarin prophylaxis (and asymptomatic for DVT). screening US was performed at discharge (103). In patients in whom DVT was detected, warfarin was continued at a therapeutic dose, while in those with negative studies, it was discontinued. The total outcome event rate (venous thrombocmbolism plus bleeding) at 90 d was 1% for each group. In a large, prospective, Canadian clinical trial of 1,984 consecutive hip or knee arthroplasty patients receiving enoxaparin prophylaxis, predischarge compression US revealed only 3 patients (0.15%) with DVT (104). *These results suggest that a screening US at discharge in high-risk orthopedic putients receiving enoxaparin or warfarin prophylaxis is unnecessary.*

Acute calf deep venous thrombosis. When acute DVT is suspcctcd, one or both lower extremities are evaluated. A search specifically for isolated calf DVT is not generally undertaken since the proximal lower extremity is also evaluated in the setting of suspected calf DVT. However, it is useful to discuss the sensitivity and specificity of US for calf DVT since this entity is either treated or followed with serial noninvasive studies. Contrast venography has been considered the most accurate diagnostic test for acute calf DVT. As is the case with IPG, US cannot be relied on to exclude calf vein thrombosis. As noted above, serial US (or IPG) is appropriate in patients with symptoms of acute DVT and a negative initial study (86, 87), and some of these patients may have undetected calf DVT. which can be assessed (for possible extension) at follow-up. If, in a particular patient with suspected DVT, the initial US (or IPG) is negative and follow-up with serial studies cannot be guaranteed, then CV would be appropriate. Ultrasonography is specific for symptomatic acute calf vein DVT, and a positive test in this setting can usually be relied on. These recommendations are based on level 1 studies. Because the calf **veins are smaller** and characterized by slower flow, and because they arc more anatomically variable than the proximal lower extremity **veins,** US **assessment is** more difficult. Technically inadequate studies result more commonly than when the proximal veins are examined. In symptomatic patients with isolated calf DVT, the sensitivity of US has been shown to be 73% for compression US (65), 81% for duplex US (71). and 87% with color-flow Doppler (78). In each of these prospective studies, independent, blinded readings were performed for both US and CV. Except for the unclear question of consecutive enrollment in the compression US study (65). level 1 methodology was employed in these investigations. When the calf veins can be adequately visualized, the sensitivity and specificity are improved and range from 88 to 100% and from 83 to 100%, respectively (63, Xl, 10.5, 106). Because of the above-described technical considerations, however. the sensitivity is frequently much lower (67). The sensitivity of US for detecting isolated calf DVT in asymptomatic high-risk patients is even lower, ranging from 33 to 58% (91, 93, 97, 107). Clinical investigations evaluating US techniques for calf DVT are both level 1 and level 2. While many of the level 2 studies arc otherwise well dcsigncd, frequently it is not explicit that consecutive patients were enrolled.

Recurrent and chronic deep venous thrombosis. Distinguishing between acute and chronic DVT is crucial because after several weeks thrombi become adherent to the wall of the vein and are not likely to embolize. When patients present with recurrent symptoms, some will have recurrent DVT and others will have postphlebitic syndrome. Ultrasound techniques should not be considered reliable for recurrent DVT unless the test has been shown to normalize prior to the suspected recurrence. However, the rate of normalization of an abnormal US test after a first episode of acute DVT has been determined to be only 44 to 52% after 6 mo and 55% after 12 mo in two prospective follow-up clinical investigations (108, 109). Clot echogenicity does not accurately discriminate between acute and chronic DVT, but there does appear to be a positive correlation between venous distention and the age of the thrombus (109). However, a study of 975 legs of patients with suspected DVT evaluated vein diameter in normal veins and in those with acute and chronic thrombosis (1 IO). It was concluded that although veins involved by acute DVT tend to be larger than normal veins, and veins with chronic changes tend to be smaller than normal vessels, the mean differences are small. The differences appear to be most useful at the extremes of size. Thus, when evaluating a patient with suspected acute DVT, vein size should be interpreted in the context of other sonographic findings. Because previous DVT is a risk factor for recurrence, it may be appropriate to perform a follow-up US between 3 and 6 mo after anticoagulation is initiated, to serve as a baseline in the event that symptoms recur. There is, however, no uniformly accepted standard of care for repeating US after DVT is diagnosed.

Upper extremity deep venous thrombosis. Axillary–subclavian vein thrombosis commonly results from indwelling venous catheters but may be spontaneous, including the syndrome of "effort thrombosis." The diagnosis may be made by US, CV. or MRI. When US is utilized, criteria for the diagnosis are the same as in the lower extremities. Although compression techniques are employed, portions of the subclavian vein behind the clavicle cannot be compressed and greater reliance on Doppler evaluation is required. The internal jugular, subclavian, axillary, and brachial veins are generally evaluated. The superior vena cava and brachiocephalic vein are inaccessible or only partially accessible to US. While the sensitivity of US for symptomatic upper extremity thrombosis may range from 78 to 100% (111, 112), it has been shown to be as low as 31% in asymptomatic individuals after subclavian catheter removal (113). Most of the false-negative studies appeared to be due to short, nonocclusive thrombi. In a prospective study of 58 consecutive patients with suspected upper extremity DVT. central venous catheters, thrombophilic states, and previous leg DVT were significantly associated with upper extremity thrombosis (114). All patients were evaluated by objective testing for PE. Pulmonary embolism was detected in 36%. Thus. it appears that PE occurs in a substantial proportion of these patients.

Magnetic Resonance Imaging

Preliminary reports using MRI to detect DVT suggested that MRI was at least 90% sensitive and specific for acute symptomatic proximal DVT (115–1 18). A number of prospective clinical trials have evaluated MRI, using CV as the gold standard (Table 12), with several revealing sensitivity and/or specificity values as high as 100%. Less information is available for MRI as a screening modality in asymptomatic patients. It has been suggested that silent lower extremity DVT may be demonstrated with MRI (118). This is logical since MRI directly images thrombi, and can image nonocclusive clots. It does not rely on compression or other adjunctive techniques. However,

TABLE 12

SENSITIVITY AND SPECIFICITY OF MAGNETIC RESONANCE IMAGING FOR ACUTE DEEP VENOUS THROMBOSIS*

Study	Ref. No.	Number of Patients/Region Evaluated	Sensitivity (%)	Specificity (%)	Reference Test
Evans and coworkers (1993)†	54	61 total	38/40 (95)	131/135 (97)	Venography
		pelvic veins	9/9 (100)	52/55 (95)	Venography
		thigh veins	16/16 (100)	43/43 (100)	Venography
		calf veins	13/15 (87)	36/37 (97)	Venography
Holland and coworkers (1992)	117	40 pelvis/thigh	N/A (100)	N/A (90)	Venography
Spritzer and coworkers (1990)	115	54 pelvis/thigh/calf	28/28 (97)	22/24 (95)	Venography
Vukov and coworkers (1996)	119	10 calf	4/5 (80)	5/5 (100)	Venography
Erdman and coworkers (1990)	118	36 pelvis/thigh/upper extremity	27/30 (90)	6/6 (100)	Venography
Laissy and coworkers (1996)‡	55	21 pelvis/thigh	15/15 (100)	6/6 (100)	Venography
Dupas and coworkers (1995)§	56	25 pelvis	25/25 (100)	N/A (98)	Venography
Carpenter and coworkers (1993)‖	122	85 pelvis/thigh	27/27 (100)	71/74 (96)	Venography
Evans and coworkers (1996)	120	75 pelvis/thigh/calf	30/30 (100)¶	45/45 (100)	Serial US

Definition of abbreviations: N/A = not applicable; US = ultrasound

*All are level 2 studies.

†While this clinical trial met requirements for a level 1 study, the relatively small number of positive studies suggests that additional clinical trials are needed.

‡ Sensitivity and specificity for color Doppler US in these patients were 87 and 83%, respectively.

§ Included only patients with pelvic DVT proven by CV. Readers were aware that patients had DVT but were not informed of the specific location. Sensitivity and specificity values were based on venous segments. The specificity of 98% was based on two false-positive venous segments by MRI. The sensitivity and specificity for color Doppler US were 91 and 97%, respectively.

‖ In these 85 patients, 101 venous systems were evaluated. The sensitivity and specificity values were calculated for the 101 venous systems. The sensitivity and specificity for duplex US in the same patients were 100 and 96%, respectively.

¶ Of the 30 patients with acute DVT, 26 had femoropopliteal disease, 1 had isolated pelvic DVT, and 3 had isolated calf DVT.

in calf DVT, a change or lack of change on the images during compression from above and below may be useful (54). Magnetic resonance imaging appears less sensitive than CV for calf DVT (54. 119) but no level 1 studies with large numbers of calf DVT have been performed. Magnetic resonance imaging has also been compared with compression US for the evaluation of acute DVT (120).

There are a number of potential advantages of MRI (Table 13) and the technique is evolving. Preliminary studies suggest excellent sensitivity and specificity not only for thigh DVT, but also for acute pelvic vein thrombosis (54-56, 118, 121, 122). Pelvic DVT may be difficult to evaluate by US and even by CV. Although CV and IPG are accurate for iliac vein DVT, MRI may prove to be the superior test for noniliac pelvic vein thrombosis. Studies have validated the use of gradient echo "white blood" (blood imaged as a brighter intensity against a relatively darker background) MRI for the detection of DVT. Such images may be supplemented by spin echo or fast spin echo "black blood" images, but the latter are not recommended for primary diagnosis. Imaging should be performed in the axial plane and interpretations should be based on review of source images rather than reprojections. As the MRI study is performed, the attending radiologist can carefully scrutinize areas of suspected abnormality by using different techniques, and the success of the technology depends on the active involvement of an experienced radiologist. Distinguishing acute from chronic DVT is a potentially advantageous feature of MRI. Criteria that may suggest chronic DVT have also been used for CV and include irregular wall thickening in the presence of collateral veins, and a diminutive lumen (121). Erdman and colleagues (118) have suggested that inflammation surrounding a thrombosed vessel indicates acute DVT, while the absence of edema suggests more chronic DVT. Such criteria require validation.

TABLE 13

ADVANTAGES AND LIMITATIONS OF MAGNETIC RESONANCE IMAGING FOR THE DIAGNOSIS OF ACUTE DEEP VENOUS THROMBOSIS

Advantages	Limitations
Sensitive	Claustrophobia
Specific	cost
Safe	Not portable
Available	Calf DVT
Pelvic/IVC DVT	Metallic devices
Upper extremity DVT	Massive obesity
Bilateral examination	Reader expertise required
Alternative diagnoses	Only level 2 data available
No ionizing radiation	
Contrast unnecessary	
Repeat/detailed examination of questionable areas	
Potentially useful for acute versus chronic DVT	
Potentially useful for diagnosing pulmonary embolism	

Magnetic resonance imaging appears useful in evaluating upper extremity venous thrombosis (118, 123), although large comparative trials with CV have not been performed. The opportunity to diagnose nonthrombotic conditions by MRI is attractive. Diseases that have been diagnosed by MRI in patients with suspected DVT include cellulitis, edema, varices, hematomas, superficial phlebitis, joint effusions, myositis. and adenopathy (118). Other advantages of MRI include noninvasiveness, lack of operator dependence (although reader experience is necessary), and the ability to scan patients without intravenous access or contrast. Finally, preliminary (level 2) studies suggest that MRI is promising for the diagnosis of PE. so that it may be the first technique enabling both the lungs and the lower extremities to be evaluated for clot at the same time (124, 125).

There are disadvantages of MRI. Patients must be carefully screened for contraindications to MRI, particularly with regard to metallic devices from injury or surgery. Other potential contraindications include significant claustrophobia, the inability to cooperate, and massive obesity. Although MRI is

available at all large hospitals, it may not be at smaller institutions, and reader expertise is crucial. It is relatively expensive, although cost-benefit analyses need to be performed. Multicenter. randomized clinical trials would be useful. An algorithm for the diagnostic approach to symptomatic, suspected acute DVT is presented in Figure 1.

THE DIAGNOSTIC APPROACH TO ACUTE PULMONARY EMBOLISM

Background

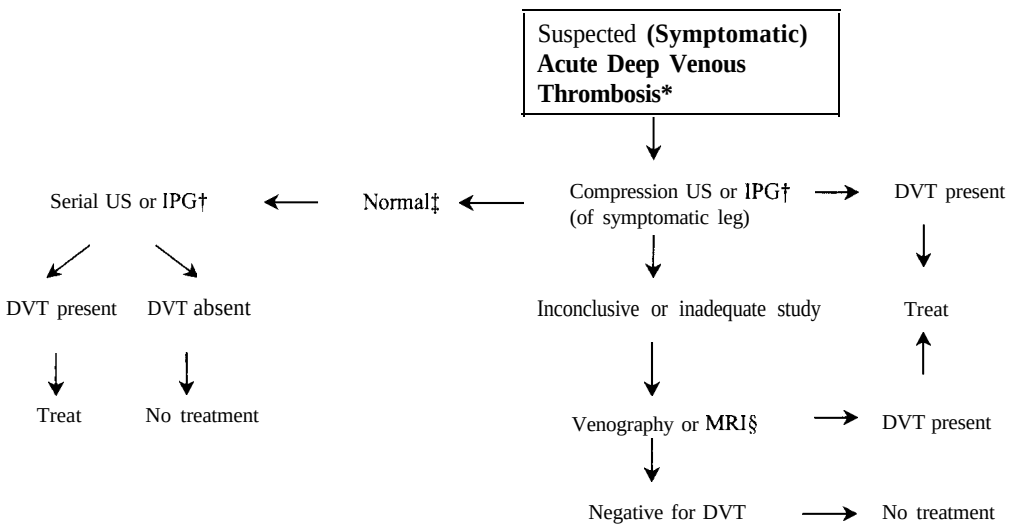
As with DVT, the diagnosis of PE cannot be established with certainty without objective testing. Suspicion of the diagnosis, based on the presence of risk factors and frequent, but nonspecific, clinical findings should lead to a thorough diagnostic evaluation that leads to either confirmation or exclusion of PE.

Symptoms and Signs

It is well established that PE cannot be unequivocally diagnosed solely from the history and physical examination and this is underscored by the frequent failure to make the diagnosis antemortem (126, 127). While certain symptoms are common, and may serve as important clues, the lack of specificity mandates additional testing when the clinical presentation is consistent with PE. Pulmonary embolism should be considered whenever unexplained dyspnea occurs. Dyspnea with or without associated anxiety, as well as pleuritic chest pain and hemoptysis, are common in PE, but are nonspecific, and one or more of these symptoms may develop with pneumothorax, pneumonia, pleuritis, exacerbations of chronic obstructive lung disease, congestive heart failure, or lung cancer. Tachypnea and tachycardia are the most common signs of PE but are nonspecific. Lightheadedness and syncope may be caused by PE but may also result from a number of other entities that result in hypoxemia or hypotension. Pulmonary embolism should always be suspected in the setting of syncope or sudden hypotension and these often indicate a large clot burden. The cardiac and pulmonary physical examinations are both nonspecific for PE. The index of clinical suspicion does, however, become a more useful parameter when considered in conjunction with ventilation-perfusion ($\dot{V}/\dot{Q}$) scanning (128). Diagnostic efforts directed at possible PE may be appropriate despite alternative explanations if risk factors and the clinical setting are suggestive. Dyspnea, tachypnea, clear lung fields, and hypoxemia may be attributed to a flare of chronic obstructive disease or asthma when underlying PE may in fact, be present.

Electrocardiography

While electrocardiographic abnormalities may develop in the setting of acute PE, they are generally nonspecific and include T-wave changes, ST segment abnormalities, and left or right axis deviation. In the Urokinase Pulmonary Embolism Trial (UPET) electrocardiographic abnormalities were demonstrated in 87% of patients with proven PE and who were without underlying cardiopulmonary disease (129). These findings were not specific for PE, however. In this large clinical trial, 26% of patients with massive or submassive PE and 32% of those with massive PE had manifestations of acute cor pulmonale (S1 Q3 T3 pattern, right bundle branch block, P-wave pulmonale, or right axis deviation). The low frequency of specific electrocardiogram (ECG) changes associated with PE



* First episode of suspected (symptomatic) acute lower extremity DVT

† Duplex or color-flow US may be utilized, although there is no proven superiority over compression US alone. Scenarios associated with false-positive IPG studies must be realized.

‡ Because the sensitivity of US or IPG for calf DVT is lower than for proximal DVT, three studies over 7 to 14 d (IPG) or one to two studies over 5 to 7 d (US) are needed to detect proximal extension (see text). Outcome study results from large clinical trials may not necessarily be applicable at all medical facilities. If a patient cannot return for a repeat study, if iliac thrombosis is suspected, or if an urgent diagnosis is deemed necessary, a more rapid evaluation using venography (or MRI) should be undertaken.

§ Although MRI appears accurate for lower extremity DVT (level 2 studies), it is more expensive than US or IPG and is generally not indicated as the initial diagnostic test.

Figure I. Diagnostic algorithm for patients with symptoms suggesting acute deep venous thrombosis. The recommended diagnostic approach allows for some flexibility depending upon the resources at a particular institution.

was confirmed in the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study (128).

Arterial Blood Gas Analysis

Hypoxemia is common in acute PE, but is not universally present. Young patients without underlying lung disease may have a normal Pa_{O_2}. In a retrospective analysis of hospitalized patients with proven PE, the Pa_{O_2} was greater than 80 mm Hg in 29% of patients less than 40 yr old, compared with 3% in the older group (130). The alveolar-arterial oxygen tension difference was abnormal in all patients, however. A subset of patients participating in the PIOPED study and suspected of PE with no history or evidence of preexisting cardiac or pulmonary disease was evaluated, and the Pa_{O_2} and alveolar–arterial difference values were compared (131). Patients with and without PE could not be distinguished on the basis of either of these values. The alveolar-arterial difference was elevated by more than 20 mm Hg in 76 of 88 (86%) patients with PE, however. The diagnosis of acute PE cannot be excluded on the basis of a normal Pa_{O_2} and although the alveolar-arterial difference is usually elevated, it may be normal in patients without preexisting cardiopulmonary disease.

Chest Radiography

The majority of patients with PE have an abnormal but nonspecific chest radiograph. Common radiographic findings include atelectasis, pleural effusion, pulmonary infiltrates, and elevation of a hemidiaphragm (131). Classic suggestions of pulmonary infarction such as Hampton's hump or decreased vascularity (Westermark's sign) are suggestive but infrequent. A normal chest radiograph in the setting of severe dyspnea and hypoxemia without evidence of bronchospasm or anatomic cardiac shunt is strongly suggestive of PE. The presence of a pleural effusion increases the likelihood of PE in young patients who present with acute pleuritic chest pain (132) In general. however, the chest radiograph cannot be used to prove or exclude PE conclusively. Diagnosing other processes such as pneumonia, pneumothorax, or rib fracture, which may cause symptoms similar to acute PE, is important, but PE may coexist with other cardiopulmonary processes.

D-Dimer

Noninvasive blood tests have been evaluated in hopes of identifying a specific marker of VTE. D-dimer is a specific degradation product released into the circulation when cross-linked fibrin undergoes endogenous fibrinolysis (133). A number of clinical trials have been undertaken to determine the utility of this test. Strategies have included the combination of V/Q scanning and D-dimer testing. Different assays have been evaluated with different cutoff values utilized. Generally, either an enzyme-linked immunosorbent assay (ELISA) or a latex agglutination test has been performed. In patients with suspected PE, a low plasma D-dimer concentration (< 500 ng/ml), measured by ELISA, has a 95% negative predictive power. However, low D-dimcr levels have been found in only about 25% of patients without PE (134, 135). A latex agglutination test indicating a normal D-dimer level does not appear to be reliable in excluding PE (136, 137).

When the medical literature is systematically reviewed for publications that compare D-dimer results with the results of other diagnostic tests for venous thromboembolism, there appears to be substantial variability in assay performance, heterogeneity among the patient population, and inconsistent use of definitive diagnostic criteria for venous thromboembolism (138, 139). Becker and colleagues (138) performed a thorough review of the available literature and evaluated publications that compared D-dimer results with those of objective diagnostic tests for DVT or PE. Each study was evaluated independently by three reviewers. Articles meeting appropriate standards were designated level 1. The following conclusions were reached: (I) results of clinical studies utilizing one manufacturer D-dimer assay cannot be extrapolated to another; (2) no one test has been established as the best. The ELISAs are sensitive but cannot be performed rapidly. The latex tests, while rapid, have not been proved to be sufficiently sensitive. There are insufficient data available regarding the newer immunofiltration techniques: (3) future studies should be more rigorous regarding the definitive presence or absence of DVT and PE, and should as well address issues such as the extent of thrombosis, clinical setting, and comorbidity; and (4) additional outcome studies are needed.

Since the publication of above-described review, both DVT and PE management studies have been performed with therapeutic decisions based, in part, on D-dimer results. Ginsberg and colleagues (140) evaluated the results of a bedside whole blood agglutination D-dimer assay together with IPG in patients with suspected DVT. When both studies were negative, anticoagulation was withheld and the patients were monitored for 3 mo. In this group of patients, the negative predictive value was 98.5% (95% confidence interval, 96.339Y.6). For the D-dimer test alone, the negative predictive value was 07.2%. Perrier and colleagues (141) evaluated 308 consecutive patients presenting to the emergency room with suspected PE. Each patient was managed according to a diagnostic protocol including an assessment of clinical probability, V/Q scan, ELISA plasma D-dimer, and lower extremity US. Of the 308 patients, 106 (34%) had diagnostic $\dot{V}/\dot{Q}$ scans (high probability in 63 and normal in 43). The noninvasive evaluation was diagnostic in 125 patients (62%). In 4X patients, PE was ruled out by a nondiagnostic lung scan together with low clinical probability. In 53 cases, it was ruled out by a quantitative D-dimer of less than $500\ \mu g/L$. Only 77 of the 202 patients with nondiagnostic $\dot{V}/\dot{Q}$ scans required pulmonary angiography. At 6-mo follow-up, only 2 of the 199 patients in whom the diagnostic protocol had ruled out PE had a VTE event. Using the same cutoff value for the quantitative D-dimcr test, these investigators subsequently reported that of 198 patients with suspected PE and a D-dimer level, $< 500\ \mu g/L$, 196 were free of PE, 1 had PE, and one was lost to follow-up (142). Thus, the negative predictive value of the D-dimer test was approximately 196 of 198 (99%). These data, although from one group of investigators, are encouraging. Rapid "bedside assays" are becoming increasingly available and additional outcome studies will further define their role. However, the D-dimer test cannot be recommended as a standard part of the PE or DVT diagnostic algorithm at the present time.

The Ventilation-Perfusion Scan

The ventilation-perfusion (V/Q) scan has long been considered the pivotal diagnostic test in acute PE. Unfortunately, the $\dot{V}/\dot{Q}$ scan is diagnostic in a minority of cases; that is, it is rarely interpreted as normal or high probability. Most lung diseases affect pulmonary blood flow to some extent as well as ventilation, decreasing the specificity of the $\dot{V}/\dot{Q}$ scan (143–149). Pulmonary embolism frequently occurs in the setting of concomitant lung disease such as chronic obstructive pulmonary disease (COPD) or pneumonia, further complicating the diagnostic evaluation (127, 150,151).

The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) was a multicentcr, collaborative effort designed to determine the sensitivity and specificity of the $\dot{V}/\dot{Q}$

scan in patients with suspected acute PE (128). The importance of clinical suspicion (made without knowledge of the scan results) combined with the V̇/Q̇ scan was a crucial aspect of the investigation. In this clinical trial, PE was proven or excluded by pulmonary angiography or by autopsy. In patients in whom the pulmonary angiogram was nondiagnostic, PE was excluded by the absence of an adverse event over the course of 1 yr, without therapy. Criteria for the interpretation of V̇/Q̇ scans from the PIOPED subsequently became widely adopted. The most important information derived from the study was the concept that PE is often present in patients with nondiagnostic lung scans when associated with a high clinical suspicion of PE. In this setting, a high-probability lung scan is associated with proved PE in 96% of cases, but a low-probability scan is also associated with PE in 40% of patients. When a high-probability V̇/Q̇ scan is associated with a low or uncertain clinical suspicion for PE likelihood, the likelihood of PE is only 56 and XX%, respectively (Table 14). A treatise on PE based on the vast amount of data accrued by the PIOPED has been published (152).

The effect of prior cardiopulmonary disease. As the extent of cardiopulmonary disease increases, it becomes increasingly likely that the lung scan will be nondiagnostic. On the basis of the original PIOPED criteria, patients with normal chest radiographs had intermediate-probability V̇/Q̇ scans in only 13% of cases, while low- and near normal/normal-probability scans occurred in 35 and 45% of these patients, respectively (128). Intermediate-probability scans were seen in 33% of patients with no prior cardiopulmonary disease and in 43% of those with any form of cardiopulmonary disease. With even more complex underlying disease, i.e., COPD, 60% of patients had intermediate-probability scans. Fewer patients with COPD had high-probability scans or nearly normal scans than did patients without cardiopulmonary disease. However, among each of the above-described patient groups, including those with COPD, the positive predictive value of high, intermediate, low, and nearly normal scans was similar (151,153)

The perfusion scan alone. The value of the perfusion scan without a ventilation scan has been examined (128, 154). A randomly selected subset of patients from the PIOPED with suspected acute PE had perfusion scans interpreted in a blinded manner, independent of, as well as in combination with, the ventilation scan. Pulmonary embolism was proved by pulmonary angiography in 29 of these 98 patients, and excluded by angiography in 33 patients or by outcome analysis in 5 patients. Neither outcome analysis nor angiography could be performed in the remaining 31 patients. In the 67 patients in whom the presence or absence of PE was certain, the positive predictive value of a high-probability perfusion scan (93%) did not differ from the V̇/Q̇ scan group (94%). Similarly. an intermediate-probability perfusion scan was no less predictive of PE than an intermediate probability V̇/Q̇ scan, and a low probability perfusion scan was no less predictive than a low-probability V̇/Q̇ scan. There were not enough near normal/normal perfusion scans to make a useful comparison with V̇/Q̇ scans. The available data would suggest that if a ventilation scan cannot be performed, an isolated perfusion scan is useful if the scan is high probability, low probability, near normal, or normal (154). Unfortunately, there has been controversy over whether a ventilation scan should ever be performed after a perfusion scan. Certain individuals believe that a ^{133}Xe ventilation scan can be effectively performed after a perfusion scan (155). Others suggest that the scattered radiation from the previously administered ^{99m}Tc perfusion particles substantially decreases the accuracy of the washout phase of the ventilation scan, particularly if ^{99m}Tc is used for the ventilation scan (156). Because ^{127}Xe has a higher inherent photon energy than ^{99m}Tc, ^{127}Xe ventilation studies can be performed after the perfusion scan. However, ^{127}Xe is expensive and not readily available. Details regarding appropriate techniques for V̇/Q̇ scanning are available elsewhere (157).

In the PISA-PED study, only perfusion scans were utilized (158) and one or more segmental perfusion defects were considered diagnostic of PE. This is important because a single perfusion defect has not been found to be a consistent predictor of PE. A positive perfusion scan had a positive predictive value of 95% and a negative scan had a negative predictive value of 81%. Only 21% of patients had clinical and perfusion scan results that were contradictory. These results appear superior to the PIOPED results, but the study populations differed. In the PISA-PED, 24% of patients had normal perfusion scans compared with 2% in the PIOPED. The interpretive criteria differed as well. On the basis of the PIOPED results, probability estimates for PE have been correlated with V̇/Q̇ scan results and some of the original V̇/Q̇ scan diagnostic criteria have been revised. It has been suggested that these revised criteria be applied (159). It is important to emphasize that probability estimates based on different interpretive schemes have varied considerably (152).

The nondiagnostic ventilation–perfusion scan: Use of lower extremity studies. When the lung scan is nondiagnostic, evaluation of the lower extremities is an alternative means by which to establish the need for anticoagulation. This approach is only appropriate, however, if the patient is considered stable with adequate cardiopulmonary reserve, i.e., absence of hypotension or severe hypoxemia. There have been no universally accepted definitions of adequate reserve, however. Treatment can be initiated when a noninvasive study such as IPG or compression US is positive. The strategy after a negative study, however, depends on the lung scan and upon the level of clinical suspicion (160). When the scan is in the nearly normal or low-probability category, the leg study is negative. and the level of clinical suspicion is low, no further testing is necessary, but this situation does not generally even merit performing the lower extremity study to begin with. With a low-probability scan together with a negative IPG (or US) study, and an uncertain or high clinical suspicion for PE, the clinical likelihood of PE has been estimated to be approximately Y and 25%. respectively (161). While no treatment and treatment have been recommended in the two latter situations, respectively (160), the approach to such patients should probably be individualized. In patients with intermediate-probability scans, further diagnostic testing would be recommended when the

TABLE 14

CLINICAL ASSESSMENT AND VENTILATION-PERFUSION SCAN PROBABILITY IN PIOPED*

	Clinical Probability		
V̇/Q̇ scan (Probability)	Highly Likely (80–100%)	Uncertain (20–79%)	Unlikely (0–19%)
High	28/29† (96%)	70/80 (88%)	5/9 (56%)
Intermediate	27/41 (66%)	66/236 (28%)	11/68 (16%)
Low	6/15 (40%)	30/191 (16%)	4/90 (4%)
Near normal/normal	0/5 (0%)	4162 (6%)	1161 (2%)
Total	61/90 (68%)	1701569 (30%)	211228 (9%)

Definition of abbreviations: PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis.

* Modified from Reference 128.

† Number of patients with proven PE per number of patients with the specific scan result.

lower extremity study is negative. The "further evaluation" would traditionally involve pulmonary angiography, particularly in an unstable patient. In a stable patient, serial noninvasive lower extremity studies would also be appropriate.

Serial noninvasive lower extremity studies offer the opportunity to scrutinize the patient with a nondiagnostic lung scan more closely. Hull and colleagues (162) prospectively evaluated 1,564 consecutive patients with suspected PE and adequate cardiopulmonary reserve who underwent V/Q scanning and serial IPG. Adequate reserve was defined as the absence of the following: pulmonary edema, right ventricular failure, hypotension (systolic blood pressure <90 mm Hg), syncope. acute tachyarrhythmias, forced expiratory volume <1.0 L, vital capacity <1.5 L, $Po_2<$ SO mm Hg or $Pco_2>45$ mm Hg. Of the 627 patients with nondiagnostic lung scans and negative serial IPG in whom treatment was withheld, only 12 (1.9%) had VTE on long-term follow-up. Of interest, 4 of the 586 (0.7%) untreated patients with normal lung scans, and 8 of the 145 (5.5%) patients with high-probability scans (who received treatment), developed VTE subsequently. This plan has been shown to reduce the need for angiography and appears cost effective (163,164). Thus, it appears appropriate to incorporate such an approach at centers where these validated protocols are utilized **and** where follow-up is guaranteed. On the basis of available data in which the sensitivity of MRI in clinical studies of suspected lower extremity DVT has been examined, this technique may prove effective in the setting of a nondiagnostic V/Q scan (level 2 studies) (I 18, 120-122).

Pulmonary Angiography

Pulmonary angiography has been considered the gold standard diagnostic technique for PE. The historic development of this technique has been described (165, 166). The most common diagnostic algorithm for PE has consisted of V/Q scanning followed by pulmonary angiography when the scan is nondiagnostic and the clinical suspicion high. The validity of this approach was established in the PIOPED (167). All patients were monitored for 1 yr after the pulmonary angiogram was performed to determine the incidence of PE, complications of anticoagulation, or death. Patients were scrutinized in detail for the possibility of PE. and a negative angiogram reading could potentially bc reversed by the outcome classification committee. Among 1,111 patients in whom pulmonary angiography was performed, 383 (35%) had positive angiograms, and 681(61%) had negative studies. Angiography was nondiagnostic in 35 patients (3%) and was not completed in 12 individuals (1%), generally because of associated complications. It is important to emphasize that these PIOPED readings were consensus readings with the potential for more detailed scrutiny than in the usual clinical setting. The interobserver agreement in the PIOPED was, nonetheless, not perfect. Both angiography readers agreed that PE was present or both agreed that it could not be diagnosed with certainty in 92% of cases. Both agreed that PE was absent or both agreed that it could not be excluded with certainty in 82% of cases. Interobserver agreement was 98% for lobar PE, YO% for segmental PE. and only 66% for subsegmental emboli (167). The incidence of nondiagnostic angiograms in the PIOPED is, however, similar to that determined in other large studies (168). Nonethclcss, the sensitivity, specificity and complication rate of this technique in the community hospital setting are not entirely clear (169).

Pulmonary angiography for the purpose of diagnosing acute PE is unnecessary when the perfusion scan is normal. Relative contraindications to the procedure include significant bleeding risk and renal insufficiency. The procedure can generally safely be performed when the platelet count is at least 75,000/mm^3 and if coagulation studies are normal or minimally abnormal (170). In patients with renal insufficiency, adequate hydration must be maintained before, during, and after the angiogram. Diseases such as diabetes or multiple myeloma may increase the frequency of acute renal insufficiency after angiography. The presence of a left bundle branch block is an indication for a temporary pacemaker during the procedure to protect against complete heart block. The electrocardiogram should be reviewed for any potential arrhythmias. Pulmonary angiography should be performed by an experienced angiographer. The most frequent site of access is the femoral vein, preferably on the right. The basilic vein or the right internal jugular may also be used. A number of different catheters have been utilized for the procedure. with a Grollman or pigtail catheter being commonly used (170). Biplane angiography allows for two views with each contrast injection. Subselective (lobar or segmental) injections are often useful, with or without magnification. Balloon occlusion angiography may also be useful (171). The technique of selective pulmonary angiography and details regarding interpretation have been reviewed and are not discussed in detail here (166, 170). Pulmonary embolism is definitively diagnosed angiographically by the presence of an intralumenal filling defect in two views and the demonstration of an occluded pulmonary artery with or without a trailing edge. Secondary criteria are nonspecific and include reduced perfusion and flow, abnormal pulmonary parenchymal stain, tortuous peripheral vessels, and delayed venous return (170).

Complications related to pulmonary angiography have been reported in several large clinical trials (128, 167, 168, 172). In the PIOPED, death occurred in the setting of pulmonary angiography in 5 of 1,111 patients (0.5%) (167). Other severe complications in this trial included severe cardiopulmonary compromise requiring intubation or cardiopulmonary resuscitation in four patients (0.4%) renal failure requiring dialysis in three (0.3%), or groin hematomas requiring transfusion of two units of blood in two (0.2%). Less severe complications included an elevation in the serum creatinine without the need for dialysis. This occurred in IO patients (0.9%). Major complications of angiography were reported in 43 of 1,350 patients (3%) patients by Mills and colleagues (172). Death occurred in three patients (0.2%), each with pulmonary hypertension and cor pulmonale. Other major complications included cardiac perforation in 14 (I%), major arrhythmias in 11(1%), cardiac arrest with successful resuscitation in 6 patients (0.4%). and significant contrast reaction in 4 patients (0.3%). Death related to angiography has been documented in other clinical trials but appears rare. Dalen and associates (168) reported significant complications in 13 of 367 patients (4%) undergoing angiography because of suspected PE, including one death (0.3%). Hull and associates (173) reported no deaths among 104 patients. Bleeding in patients undergoing angiography may occur, particularly when thrombolytic therapy is administered, and a noninvasive diagnostic approach may reduce the frequency of this complication (174, 175). Except for renal insufficiency, complications related to age do not appear more common when angiography is performed (167. 176). In general, when a definitive diagnosis is necessary, the benefit of the procedure outweighs the risk.

Major complications due to pulmonary angiography appear to have been reported to bc more common in patients referred for the procedure from medical intensive care units. Of the 1,111 patients described from the PIOPED study, 5 of I22 (4%) developed major complications compared with Y of 989 (1%) who were not as critically ill (167). It is interesting that in

the preceding study, the frequency of complications due to pulmonary angiography was not shown to be related to the presence or absence of PE or to the level of pulmonary artery pressure (177). An exhaustive review of literature regarding the complications of pulmonary angiography has been published (177). While pulmonary angiography has been considered the most accurate diagnostic procedure for PE, this technique is occasionally nondiagnostic. It is invasive, expensive, and requires experienced physicians and support staff.

Spiral (Helical) Computed Tomography

The utility of spiral CT scanning for diagnosing both acute and chronic PE has been explored, accompanied by a number of reviews and commentaries (178. 179). This technique involves continuous movement of the patient through the CT scanner and allows concurrent scanning by a constantly rotating gantry and detector system. This technique enables rapid scanning with continuous volume acquisitions obtained during a single breath. Retrospective reconstructions can be performed. As with pulmonary angiography, a contrast bolus is required for imaging of the pulmonary vasculature. Limitations of spiral CT scanning include poor visualization of the peripheral areas of the upper and lower lobes. Horizontally oriented vessels in the right middle lobe and lingula may also be inadequately scanned owing to volume averaging. Lymph nodes may result in false-positive studies. Multiplanar reconstructions in coronal or oblique planes may aid in differentiating lymph nodes from emboli.

Sensitivity and specificity data from several studies evaluating spiral CT scanning for acute PE are shown in Table 15 (180-186). In several level 2 studies, spiral CT has been associated with greater than 95% sensitivity and specificity (180, 182). This technique has been utilized when previous studies have not been diagnostic. Ferretti and associates (187) used spiral CT in patients with suspected PE only after the $\dot{V}/\dot{Q}$ scan was found to be intermediate probability and duplex US was determined to be normal. If the CT did not show PE, the patient was not anticoagulated. At 3-mo follow-up, 6 of 112 patients (5.4%) with normal findings at spiral CT had experienced PE (i.e., 6 apparent false-negative CT scans). In spite of a sensitivity of greater than 90% in several studies, one study of 47 patients with suspected PE suggests a cautious approach to the use of spiral CT (186). The spiral CT scans were interpreted by two chest radiologists at the institution where the studies were performed (first by individual and then by consensus reading). All of the scans were then reviewed in the same manner by two radiologists from the second medical center. Using pulmonary angiography as the true result, the sensitivities for the readers from the first and second institution, respectively, were only 60 and 53%; the specificities were 81 and 97%, the positive predictive values were 60 and 89%, and the negative predictive values were 81 and 82%. It is important to note that interpretation at the CT workstation. rather than reading cut film, may enhance accuracy.

Spiral CT has the greatest sensitivity for emboli in the main, lobar, or segmental pulmonary arteries. The importance of subsegmental emboli as well as the accuracy of pulmonary angiography for emboli this size have been questioned. Oser and colleagues (188), determined retrospectively that of 76 consecutive pulmonary angiograms, 23 (30%) revealed only subsegmental emboli. Nineteen angiograms (25%) revealed only a single PE. Thirteen of the 19 single emboli were subsegmental only. In the PIOPED study, however, only 6% of patients had isolated subsegmental emboli (128). The latter prospective evaluation is likely more representative. Interestingly, however, two referee angiographers from the PIOPED agreed on the presence or absence of subsegmental emboli in only 66% of cases. Agreement was only 40% for a single subsegmental embolus (128). Using selective pulmonary arteriography, Quinn and colleagues (189) emphasized excellent agreement on main, lobar, and segmental emboli, but only 13% agreement on subsegmental emboli. Variations in technique and advances in technology may already be impacting on the utility of spiral CT. Remy-Jardin and associates (190) used spiral CT with thinner sections and revealed that the mean number of analyzable segmental arteries per patient increased from 85% (for 3-mm-thick sections) to 93% (for 2-mm sections) (190). These investigators also evaluated multiplanar two-dimensional (2D) reformations in 35 patients with suspected PE (191). Overlapped transverse sections as well as 2D reformatted images of obliquely oriented pulmonary arteries were analyzed. Among the 20 patients with unequivocal central PE on tranverse images, 2D reformations enabled a more precise analysis of the extent of PE in 13 cases. In nine patients with an uncertain diagnosis of PE on transverse sections, the 2D reformations allowed PE to be excluded in all

TABLE 15

SENSITIVITY AND SPECIFICITY OF SPIRAL COMPUTED TOMOGRAPHY SCANNING FOR ACUTE PULMONARY EMBOLISM*

Study	Ref. No.	Number of Patients Evaluated (Number with Proven PE)	Sensitivity (%)	Specificity (%)	Level of Evidence
Remy-Jardin and coworkers (1992)	180	42 (18)	100	96	2
Remy-Jardin and coworkers (1996)	181	72 (39)	91	78	2
van Rossum and coworkers (1996)	182	77 (39)	9s	97	2
Sostman and coworkers (1996)	183	28 (21)†	73	97	2
Goodman and coworkers (1995)	184	20 (11)	86‡	92‡	2
			63§	89§	
Mayo and coworkers (1997)	185	139 (46)'	87	95	2
Drucker and coworkers (1998)	186	47 (15)	60'	81'	2
			53	97	

* All studies used pulmonary angiography to provide the definitive answer, except where noted.
† Of the 21 PE, 6 were proven by angiography and 15 by high-probability $\dot{V}/\dot{Q}$ scan.
‡ Main, lobar, and segmental emboli.
§ All emboli including peripheral.
‖ Of the 46 PE, 12 were proven by angiography, 29 by high-probability $\dot{V}/\dot{Q}$ scan together with spiral CT, 3 by virtue of a positive Doppler US study, and 2 by clinical follow-up.
¶ The two sensitivity and specificity values represent readings at two different institutions.

cases (191). Thus, advances in technology are likely to enhance the usefulness of spiral CT for diagnosing PE.

An advantage of spiral CT includes the ability to define nonvascular structures such as lymphadenopathy, lung tumors. emphysema, and other parenchymal abnormalities as well as pleural and pericardial disease. Smaller lymph nodes may result in false-positive studies, as suggested, however. Goodman and others (192,193) have strongly endorsed the incorporation of spiral CT scanning into diagnostic algorithms for PE. Others have suggested that this technique is more suitable as a confirmatory technique than as a screening study and that further studies are needed (186). Additional prospective clinical trials comparing these techniques with the standard diagnostic approach to PE are forthcoming. The results of a large, prospective, multicenter clinical trial conducted by the European Society of Thoracic Radiology evaluating spiral CT with angiographic correlation are currently being analyzed. A second multicenter clinical trial is in the planning stages in the United States and will include centers that participated in the PIOPED. The advantages and limitations of spiral CT are included in Table 16.

Contrast-enhanced electron beam CT also appears useful in diagnosing acute PE, sharing many advantages and limitations with spiral CT (194,195). The rapid (100-ms) scanning time makes breath holding unnecessary with electron beam CT, and respiratory and cardiac motion artifacts are minimized. In one comparison with pulmonary angiography. only 8 of 720 vascular zones (1.1%) were considered inadequately visualized with electron beam CT. The entire examination took approximately IO to 15 min in each case. As with helical CT. three-dimensional reconstruction techniques can be applied to the opacified pulmonary vasculature to better define vessels lying within the plane that has been sectioned. Smaller clinical trials. descriptive studies. and case reports suggest that CT scanning will become more widely applied as additional data become available (196–202).

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is also being utilized to evaluate clinically suspected PE (124,125,183, 203-206). In a comparison of noncontrast-enhanced MRI with spiral CT. the average sensitivity of CT for five observers was 75%; for MRI it was 46%. The average specificity of CT was89%, compared with 00% for MRI (183). However, when the two most experienced readers were tested, the sensitivity and specificity for MRI were 73 and 97%. respectively. Thus, reader expertise does not lead to perfect sensitivity and specificity. Mcaney and colleagues (124) performed a prospective analysis of gadolinium-enhanced MR angiography and pulmonary angiography in 30 patients with suspected PE. The patients were enrolled consecutively and the studies were interpreted independently in a blinded manner by three radiologists. Criteria for the diagnosis of PE for both tests were the presence of an intravascular filling defect or occlusion of avessel with a "trailing embolus" sign. The pulmonary angiogram result was considered the definitive answer. In the 8 patients with proven emboli by pulmonary angiography. all 5 lobar and I6 of 17 segmental emboli were identified by the MR technique. The sensitivities for MR angiography for each of the readers were100,87, and 75%, with specificities of 95, 100, and 95%. The authors emphasize that the technique is rapid. accurate, avoids nephrotoxic iodinated contrast. and is better accepted by patients than pulmonary angiography. While larger studies arc needed, the methodology applied in this clinical trial otherwise met level 1 criteria. There are moredata available for diagnosing PE by spiral CT than by MRI at the present time, but MRI has several attractive advantages. including excellent sensitivity and specificity for the diagnosis of DVT together with the potential for performing perfusion imaging. This technique may ultimately allow the simultaneous and accurate detection of both PE and DVT. Additional prospective investigations will determine the role of this modality in the evaluation of VTE (*see* THE DIAGNOSTIC APPROACH IO ACUTE DEEP VENOUS THROMBOSIS, *above*, for specific imaging technique).

TABLE 16

ADVANTAGES AND LIMITATIONS OF SPIRAL COMPUTED TOMOGRAPHY SCANNING FOR THE DIAGNOSIS OF PULMONARY EMBOLISM

Advantages*	Limitations
Specificity+	
Availability	Expense'
Safety	Not portable
Relative rapidity of procedure	Need contrast bolus comparable to angiogram
Diagnosis of other disease entities	Poor visualization of certain regions§
Retrospective reconstructions	Contraindications
Advancing technology	Renal insufficiency
	Contrast allergy
	Level 2 data only, with variable results
	Reader expertise required

* In clinical trials to date, high sensitivity and specificity have been limited to emboli in the main,lobar, and segmental vessels.

† High specificity requires reader expertise. Level 1 data are not available.

‡ A number of issues impact on cost effectiveness, including the need for subsequent studies after a nondiagnostic initial study (e.g., V/Q scan) and the potential cost savings in patients with alternative diagnoses detected at CT scan.

§ The sensitivity is inadequate for subsegmental emboli. The ability to diagnose subsegmental emboli is also limited with pulmonary arteriography. Horizontal vessels in the right middle lobe and lingula, and the peripheral lung, may be poorly visualized. Lymph nodes may result in false-positive studies.

Echocardiography

Right ventricular failure is the ultimate cause of death in patients who succumb to acute PE. Dysfunction of the right ventricle frequently accompaniesmassive PE. and this finding has been shown to correlate not only with larger emboli hut also with recurrence of PE (175, 207. 208). Studies of patients with documented PE have revealed that more than 80% of patients have imaging or Doppler abnormalities of right ventricular size or function that may suggestacute PE (209, 210). Unfortunately, the finding of right ventricular dysfunction is nonspecific and certain clinical conditions commonly confused with PE (such as acute COPD exacerbations) arc also associated with abnormal right ventricular function. Visualization of large emboli within the main pulmonary artery has been reported with surface echocardiography. but this appears to be unusual (21 1). While most cchocardiographic studies have focused on global measures of right ventricular dysfunction. such as qualitative hypokinesia or chamber dilation, there is some evidence that regional right ventricular dysfunction (akinesia of the mid-free wall with apical sparing) may bemore common in acute PE. McConnell and colleagues (212) evaluated this concept in 85 hospitalized patients with right ventricular dysfunction from a variety of causes, including 13 patients with acute PE. This pattern of dysfunction was shown to have 77% sensitivity and 94% specificity for the diagnosis of acute PE. In this study, nine patients with primary pulmonary hypertension demonstrated more global right ventricular dysfunction. Additional data are needed.

Transesophageal echocardiography has been utilized to document emboli in the main or right pulmonary artery. and in some cases the left pulmonary artery. In nearly all cases.

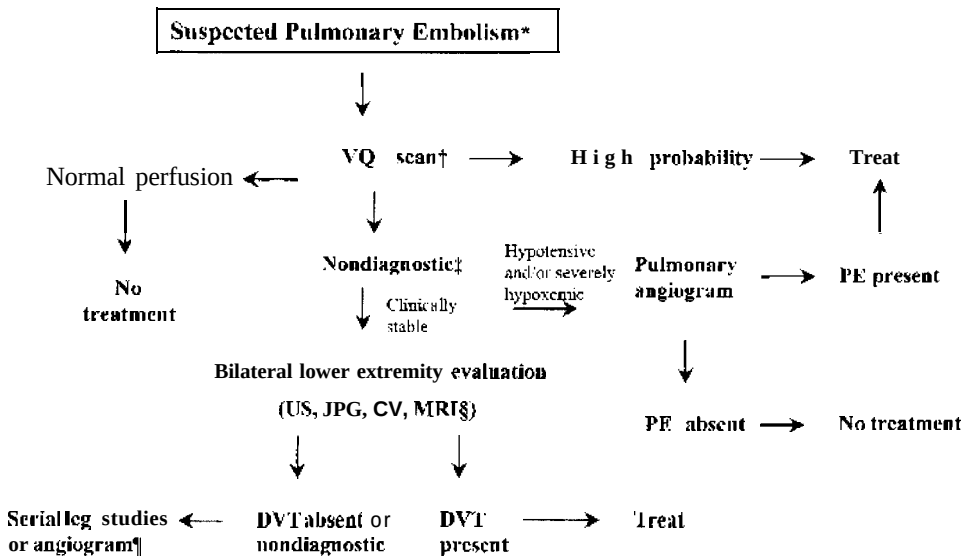
only massive emboli have been imaged (213-215). The use of contrast may enhance the visualization of the left pulmonary artery (216). Intravascular ultrasound has been shown to reveal PE in both an experimental model and in patients with PE but has not been widely applied (217.218). With the development of more maneuverable catheters, this technique may prove more useful.

At the present time, the role of surface echocardiography for the diagnosis of acute PE remains undefined. Until level 1 data become available, echocardiography cannot be considered a primary diagnostic test for the investigation of clinically suspected acute PE. However, clinicians should recognize that that this technique may yield important diagnostic information when it is performed to evaluate symptoms or signs of acute cardiopulmonary disease, such as sudden hypotension. In particular, surface or transesophageal echocardiography techniques arc diagnostic when they identify thromboemboli in the right heart or central pulmonary arteries. Regional dysfunction, as described above (212), would appear to hold promise for enhancing the specificity of echocardiography for acute PE, but level 1 studies should be performed. Limitations of echocardiography include massive obesity and severe hyperinflation due to COPD. A detailed review of the use of various echocardiographic techniques for acute PE has been published (219). The integration of echocardiography into the diagnostic evaluation needs further clarification and the utility of the technique may change with further advances in technology (220). An algorithm for the approach to suspected acute PE is presented in Figure 2.

THE DIAGNOSTIC APPROACH TO ACUTE VENOUS THROMBOEMBOLISM: FINAL SUMMARY AND RECOMMENDATIONS

I. *Symptomatic acute lower extremity DVT. (See* Figure 1 for algorithm.) Contrast venography remains the gold standard test for acute lower extremity DVT. However, with confirmation of the accuracy of noninvasive testing, CV is rarely utilized as the initial test. The initial diagnostic modality for suspected, symptomatic acute proximal DVT should be compression (or duplex) ultrasound, or IPG (by validated protocol); this decision is institution dependent. Validated protocols should be adhered to for each diagnostic test.

Positive IPG studies can be relied on as long as the clinical



* The history, physical exam, ancillary testing and recognition of risk factors leading to suspicion of pulmonary embolism (PE) are discussed in the text. When PE is suspected and the risk of bleeding deemed low, it is appropriate to begin anticoagulation while diagnostic testing is underway.

† A perfusion scan alone may suffice. Diagnostic alternatives to the ventilation-perfusion (VQ) scan, include spiral computed tomography (CT) and magnetic resonance imaging (MRI). These are being used increasingly, and also require institutional and reader expertise and further validation in well designed trials.

‡ Patients with low probability VQ scans and low clinical suspicion are unlikely to have PE. Others require further evaluation. There are several options when the VQ scan (or spiral CT or lung MRI) is nondiagnostic. Pulmonary angiography is the appropriate approach if the patient is unstable. Otherwise, leg studies can be performed. If spiral CT or lung MRI is performed, a negative result should be interpreted together with the level of clinical suspicion. Although these techniques appear to be sensitive, additional studies (pulmonary angiography or leg studies) should be performed as deemed appropriate.

§ A positive test is useful. The sensitivity for compression ultrasound (US) and impedance plethysmography (IPC) is low in asymptomatic patients, and negative or nondiagnostic studies require additional data. MRI appears sensitive in this setting, but no level 1 data exists. The role of D-dimer testing in clinical algorithms is not clearly established, but recent data from a few centers suggest that the sensitivity of certain assays may help exclude VTE whien combined with other diagnostic test restuls (see text). General recommendations that can be extrapolated to all centers cannot be made at present.

¶ Negative serial IPG in this setting has been associated with excellent outcome without anticoagulation at certain centers.

figure 2. Diagnostic algorithm for patients with symptoms suggesting acute pulmonary embolism. As with the approach to acute deep venous thrombosis, the recommended diagnostic approach allows for some flexibility depending upon the resources at a particular institution.

conditions associated with a high false-positive rate are realized. This recommendation is based on level 1 studies. If the test is initially negative, the diagnostic approach should be individualized. Outcome studies suggest a low risk without anticoagulation, provided serial IPG studies over a 7- to 14-d period remain negative. The decision to do further testing, rather than serial IPG, depends on the clinical setting, diagnostic testing resources, and the experience at the particular institution.

Compression US has proved highly sensitive and specific in symptomatic patients with acute proximal DVT, and is an appropriate initial diagnostic test. This recommendation is based on level 1 studies. Compression US with venous imaging (real-time B-mode imaging), duplex US, and color Doppler all rely on vein noncompressibility as the primary criterion for the diagnosis of DVT. A clear advantage of one US technique over another has not been demonstrated in prospective clinical trials as long as compression is used. Each of the US modalities is highly operator dependent. Level 1 data exist supporting the use of serial US testing (repeat US in 5 to 7 d) in patients with suspected, symptomatic acute DVT and an initially negative US. Although it has been suggested that IPG might be less sensitive than US for thromhi that barely extend into the popliteal vein, significant differences in outcome have not been demonstrated when serial testing is used. Serial IPG and US are sensitive methods by which to detect proximal extension of calf DVT in symptomatic outpatients, and this approach is supported by level1 data. This method of follow-up is more practical at some institutions than others.

When the US examination is abbreviated, such as omitting evaluation of the superficial femoral vein (now termed femoral), diagnostic efficacy may be reduced, and the need to evaluate from inguinal ligament to calf veins has been controversial. While certain studies have suggested that as many as 5% of DVT might be missed with an abbreviated procedure, outcome studies utilizing this approach have been conducted. Data suggest that a simplified compression US procedure limited to the common femoral vein in the groin and the popliteal vein down to the trifurcation of the calf veins (or approximately 10 cm below the midpatella) can be performed in suspected DVT and, if normal, a second study can be repeated 1 wk later. Two negative studies 5 to 7 d apart are associated with an acceptably low rate of venous thromboembolic complications when anticoagulation is withheld. If acute DVT is detected, evaluating the opposite leg is unlikely to impact immediately on therapy.

If the diagnosis remains in question after US or IPG is performed, or if the results conflict with strong clinical suspicion, CV or MRI is appropriate. While the use of MRI in the setting of a nondiagnostic US examination appears promising, level 1 evidence is not available. Gradient echo "white blood" MRI has been validated for the detection of DVT. Such images may be supplemented by spin echo or fast spin echo "black blood" images, but the latter are not recommended for primary diagnosis. Interpretation should be based on review of source images rather than reprojections. While MRI is not the initial diagnostic technique for symptomatic DVT, in certain settings, such as massive edema, plaster Icg casts, or inadequate visualization of the pelvic veins, it appears to be an appropriate option. This technique is the first to enable both the lungs and the lower extremities to be evaluated for clot at the same time, although large level 1 trials have not been performed. An additional advantage of both MRI and US is the potential to diagnose extravascular disease. Contraindications to MRI include significant claustrophobia, the inability to cooperate, massive obesity, and the presence of certain metallic devices. These should be carefully reviewed before proceeding with the technique. Some institutions utilize MRI extensively while others use it very little. The success of the technology depends on the involvement of an experienced radiologist.

Various D-dimer assays have been evaluated in the setting of acute DVT and PE (see PE recommendations). While quantitative D-dimer data have suggested excellent sensitivity from several groups of investigators, and outcome data are emerging, general recommendations cannot be made for the use of this assay at present.

For acute calf DVT, CV has been considered the most accurate diagnostic test. Neither IPG nor US can be relied on to exclude calf vein thrombosis for which treatment is controversial. *However, serial IPG or US is a sensitive means by which to detect extension of calf DVT into the popliteal veins which clearly requires therapy.* If, in a particular patient with suspected DVT, follow-up cannot be guaranteed, then CV would be appropriate. Ultrasonography is specific for symptomatic acute calf vein DVT, and a positive test in this setting can be relied on. These recommendations are based on level 1 studies. Magnetic resonance imaging appears to be sensitive and specific for symptomatic acute calf DVT. The use of MRI in this setting is based on level 2 data, and additional data should be acquired.

The diagnosis of pelvic vein thrombosis is complex. Contrast venography, MRI, and IPG are sensitive for iliac vein thrombosis. For non-iliac vein pelvic thrombosis, MRI may be superior (level 2 studies).

Ultrasound is less reliable for pelvic vein DVT.

2. *Asymptomatic acute lower extremity DVT.* A search for lower extremity DVT is sometimes undertaken in high-risk patients without suggestive symptoms, such as those individuals who have undergone total hip or total knee replacement. However, in the latter population of (appropriately anticoagulated) patients, performing screening US at hospital discharge does not appear justified. Although US appears specific in asymptomatic patients, the predictive value of a positive test is too low to be relied on. The sensitivity of US is too low for the technique to be considered reliable as a screening test, even in high-risk patients (e.g., after total hip or knee replacement). Magnetic resonance imaging appears to be capable of diagnosing silent DVT. Small. nonocclusive thrombi have been demonstrated by MRI. *Outcome data to date indicate that there is no proven utility in screening asymptomatic patients.*

3. Recurrent and chronic lower extremity DVT. Diagnosing recurrent lower extremity venous thrombosis has proved challenging. No single test is ideal. Even CV does not always provide definitive information. It can be difficult to visualize a new intralumenal defect with CV when veins have been thrombosed previously. Over time, the rate of normalization of IPG increases, and is as high as 95% at 12 mo. In centers where this test is utilized, it is appropriate to repeat it to establish normalization. In patients with previous DVT in whom resolution has been documented, IPG can be used to diagnose even an early recurrence. This is supported by level1 data. In contrast, US is less likely to normalize, and recurrence cannot be reliably proved unless the test has been shown to revert to normal prior to the recurrence, or unless the noncompressible segment is in a new location. While it might appear prudent to repeat the US examination in 3 to 6 mo to determine whether it has returned to normal, there arc no level 1-based data to support the latter concept. In some instances, CV and MRI may distinguish acute from chronic DVT. The criteria used for this distinction require validation, and are based on level 2 data. More experience is required before firm recommendations can be made. Magnetic resonance imaging would appear

to hold the most promise in distinguishing acute from chronic DVT, even without a baseline study.

4. ***Acute upper extremity DVT.*** The presence of risk factors such as the presence of intravascular catheters should raise the index of suspicion for acute upper extremity thrombosis and CV is accurate for thrombosis in this region. However, US appears to be the appropriate initial study, based on acceptable specificity and noninvasiveness (level 2 data). The sensitivity of US for upper extremity thrombosis may be significantly reduced in the asymptomatic patient, however. Impedance plethysmography is not utilized for upper extremity DVT. Magnetic resonance imaging appears to be an appropriate diagnostic modality for suspected upper extremity DVT, if US is nondiagnostic or inadequate, based on level 2 studies. As with the lower extremity evaluation, MRI and US offer the possibility of diagnosing extravascular disease.

THE DIAGNOSTIC APPROACH TO ACUTE PULMONARY EMBOLISM: FINAL SUMMARY AND RECOMMENDATIONS

I. ***The standard approach to patients with suspected acute PE. (See*** Figure 2 for algorithm.) The history, physical examination, chest radiograph, electrocardiogram, and arterial blood gas analysis are often useful in suggesting the presence or absence of PE. This information may aid in the assessment of patients with nondiagnostic lung scans. ***Clinical information by itself; however, is inadequate to confirm or exclude the diagnosis of PE.*** Ventilation-perfusion scanning is an appropriate initial diagnostic test in this setting. When technically adequate, a normal lung perfusion scan reliably excludes acute PE. In suspected acute PE, a high-probability $\dot{V}/\dot{Q}$ scan is considered diagnostic, unless the level of clinical suspicion is deemed low. A high-probability scan is much less useful in the setting of a previously high-probability scan, unless interval scans have been performed. Unfortunately, the $\dot{V}/\dot{Q}$ scan is most often nondiagnostic. In such cases, when PE is suspected, additional testing is indicated. Pulmonary angiography is an appropriate subsequent diagnostic modality. This approach is supported by level 1 data. Pulmonary angiography remains the gold standard test for acute PE, and positive and negative tests can generally be relied on. Nondiagnostic pulmonary angiography can occur. Because of the invasiveness, expense, and potential inconvenience of angiography, several other possible diagnostic algorithms can be considered (see below).

Stable patients with suspected acute PE, nondiagnostic lung scans, and adequate cardiopulmonary reserve (absence of hypotension or severe hypoxemia) may undergo noninvasive lower extremity testing to rule in DVT. This approach has been best studied with serial IPG. A single US or IPG, when positive, presents the opportunity to treat without further testing. These recommendations are supported by level 1 data. However, a precise definition of "cardiopulmonary reserve" has not been agreed on. Magnetic resonance imaging of the lower extremities may also be useful after a nondiagnostic lung scan (level 2). If the lower extremity test is negative, pulmonary angiography is an appropriate option. The option of serial noninvasive lower extremity testing in the setting of suspected PE should be performed only in centers where follow-up is guaranteed and validated protocols are utilized.

2. Use ***of the spiral CT scan or MRI for the initial approach to suspected PE or in the setting of a nondiagnostic V/Q scan.*** Another potential approach to suspected acute PE involves the use of either spiral CT or MRI. However, no level 1 studies have been completed to support the use or nonuse of either technique for suspected PE. Although the sensitivity and specificity of these techniques may vary with reader experience, spiral CT has been shown, in some studies, to be quite specific for acute PE. Pulmonary emboli in the main, lobar, or segmental vessels can be diagnosed with a moderate to high degree of sensitivity with spiral CT. The spiral CT data available meet level 2 criteria; thus, more clinical studies are needed. Level 2 studies suggest the potential use of MRI for diagnosing PE. These techniques also offer more opportunity to make alternative diagnoses than does the V/Q scan or pulmonary angiogram. Reader and institution experience should be taken into consideration when utilizing spiral CT or MRI for the diagnosis of acute PE. Precise recommendations for the use of these techniques await the completion of large, multicenter clinical trials. It would appear likely that their use will increase as the technology continues to advance.

3. Use ***of the perfusion scan without the ventilation scan.*** If a ventilation scan cannot be performed, an isolated perfusion scan is useful if the scan is high probability, very low probability, or normal. This approach is supported by level 1 data. A subsequent ventilation scan is potentially useful if the perfusion scan is intermediate probability. The value of ^{99m}Tc or ^{133}Xe for ventilation imaging after perfusion scintigraphy is controversial, although computer subtraction techniques may be useful. Ventilation imaging with ^{81m}Kr or ^{127}Xe is accepted in this setting, but these agents are expensive and their availability is limited.

4. Use ***of the D-dimer assay to investigate suspected PE.*** An elevated concentration of plasma D-dimer, by itself, is too nonspecific to be diagnostic of DVT or PE. Different assays cannot be clinically applied interchangeably and although rapid results cannot always be obtained, rapid "bedside" assays are now available. D-dimer testing offers no additional information in patients with diagnostic lung or leg studies but may ultimately prove useful when the latter are nondiagnostic. In several studies, a quantitative D-dimer (performed by ELISA) of less than 500 $\mu g/L$ has been shown to effectively exclude PE. Level 1 data (including management data) is emerging for the use of the D-dimer assay in acute DVT and PE at certain centers but the wide variability among the assays and in their testing characteristics continues to limit the general application of the test.

5. Use ***of echocardiography in the approach to suspected acute PE.*** At the present time, the role of surface echocardiography for the diagnosis of acute PE remains undefined. In many institutions, surface echocardiography can be rapidly obtained. A clinical presentation suggestive of acute PE together with unexplained right ventricular hypokinesis and/or dilation by surface echocardiography may be strongly suggestive of, but not diagnostic of, acute PE. Such findings are more commonly associated with clinically massive PE. Thrombus directly visualized in the right atrium or ventricle is compelling evidence for PE. Clots may occasionally be imaged in the proximal pulmonary arteries. Transesophageal echocardiography and intravascular ultrasound have been utilized for the diagnosis of PE, but these are most useful for massive PE and except in unusual circumstances do not, at present, have a role in the diagnostic approach to acute PE. All clinical trials evaluating right ventricular function as an indication of the presence of acute PE are level 2 studies. The integration of echocardiography into the diagnostic evaluation needs further clarification and the utility of the technique may change with further advances in technology.

THE FUTURE

Future investigations involving VTE will be productive with regard to characterization of genetic risk factors, diagnosis,

therapy, and prevention. Data currently being analyzed include that from the International Cooperative Pulmonary Embolism Registry (ICOPER), a prospective, multicenter, international, extensive collection of data from approximately 2,500 patients with pulmonary embolism (221, 222). Analysis of such data will assist in the delineation of appropriate issues to study in prospective randomized trials as well as serving as an opportunity to unite investigators from different countries in the approach to VTE. Certain areas in the diagnostic realm clearly merit continued investigation, which will require an ongoing analysis of the capabilities of the technology involved. Further discovery and characterization of thrombophilic states such as activated protein C resistance and the prothrombin 20210A gene defect will necessitate alterations in the design of clinical trials and may affect our approach to DVT surveillance. Nuclear imaging technology may improve, and MRI and CT technology will continue to evolve. The European Society of Thoracic Radiology prospective spiral CT investigation and others will add to our knowledge base. The use of MRI, with its potential ability to distinguish acute from chronic thrombosis, may not only lead to more appropriate initial therapeutic stratification but may aid in the determination of the duration of and aggressiveness of therapy. CT scanning will become faster and undoubtedly more accurate. The latter techniques will likely replace angiography and venography altogether. Hematologic studies, such as of the D-dimer, while not currently playing a significant role in the diagnosis and treatment of VTE at most centers may evolve into more universally applicable techniques, particularly when used together with other diagnostic modalities. Outcome studies will become increasingly important as the sensitivity and specificity of diagnostic tests as well as therapeutic modalities continue to improve. Technological advances, however, could consume increased health care dollars which may not necessarily be available. Both the tertiary care/academic medical center and the community hospital need to be considered with these efforts. Accordingly, cost-benefit analyses are essential.

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