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THE DIAGNOSTIC AND THERAPEUTIC APPROACH TO ACUTE VENOUS THROMBOEMBOLISM*

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Venous thromboembolism (VTE) encompasses a range of diseases which includes both deep venous thrombosis (DVT) and pulmonary embolism (PE). Pulmonary embolism most commonly results from thrombosis in the deep veins of the lower extremities, proximal to and including the popliteal veins. The non-specific nature of the clinical presentations of both DVT and PE may lead to substantial delays in diagnosis and initiation of therapy, in turn accounting for significant morbidity and mortality. More than half of the cases are never diagnosed and all too frequently PE is first determined at autopsy.[1,2] Awareness of the risk factors for DVT is a crucial first step in approaching the disease, both enhancing clinical suspicion and increasing the probability that appropriate prophylactic strategies will be utilised. A number of recent diagnostic and therapeutic developments have increased interest in this disease, and emphasis will be placed upon these. While prophylaxis is of paramount importance, it will not be included in this review.

THE DIAGNOSTIC APPROACH TO ACUTE DEEP VENOUS THROMBOSIS

Patients with acute lower extremity DVT often do not exhibit erythema, warmth, swelling, pain or tenderness, and the sensitivity and specificity of the clinical examination are too low to be relied upon.[3] When present, however, these findings merit further evaluation despite their lack of specificity. Distinguishing between acute and chronic DVT is even more difficult. This distinction 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 the postphlebitic syndrome. A discussion of the approach to acute DVT necessitates examination of the commonly used diagnostic techniques. In the setting of suspected acute DVT, objective diagnostic testing is essential.

Contrast venography

Contrast venography (CV) remains the gold standard test although it is invasive, requires the use of contrast media, and is rarely employed as the initial diagnostic test in patients with symptoms suggesting acute DVT. The proven utility of non-invasive technology, including impedance plethysmography (IPG) and compression ultrasound (US), have rendered CV much less popular. It is, however, nearly 100% sensitive and specific provided it is technically adequate and that strict diagnostic criteria are adhered to. Although adverse reactions such as pain, DVT, and reactions to intravenous contrast reactions including nephrotoxicity may occur, it is generally safe.[4] Relative contraindications to CV include acute renal failure, and chronic renal insufficiency

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with a creatinine of greater than 2-3 mg/dl. Idiosyncratic reactions may be minimised with antihistamines and corticosteroids.

Impedance plethysmography

Impedance plethysmography has been extensively investigated in prospective clinical trials, mainly in Canada and Europe.[5,6] 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 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 over the past several decades. It has been demonstrated that the sensitivity and specificity of IPG for detecting proximal DVT are both dependent on adhering to a validated protocol. Potential causes of false-positive results include increased intrathoracic pressure, increased intra-abdominal pressure and decreased venous return from the lower extremities, such as might occur due to obstruction of blood flow by tumour, or in patients with low cardiac output or severe peripheral vascular disease. Resolution rates for IPG-documented acute proximal DVT at 3, 6, 9 and 12 months have been found to be 67%, 85%, 92% and 95%.[7] Thus, IPG appears to be reliable in diagnosing recurrent DVT when interval IPG normalisation has been documented or if the previous episode is remote. 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.

Compression ultrasound with venous imaging

Compression ultrasound, with venous imaging (real-time B-mode imaging) is non-invasive, widely available and has proven to be accurate in 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 colour duplex instrumentation that display Doppler frequency shifts as colour superimposed on the grey scale image. Colour 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. Non-occlusive thrombi may be more easily documented with colour flow imaging, and calf vein evaluation, especially 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 colour Doppler, all rely upon 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. Among the useful features of US imaging is the ability to identify alternative pathology, such as Baker's cysts, haematomas, lymphadenopathy, femoral artery aneurysm, superficial thrombophlebitis, and abscesses.[8]

The sensitivity and specificity of compression US have both been above 90% in most studies of symptomatic patients and greater than 95% in several of them.[9-11] The duplex and colour-flow techniques have been evaluated in similar studies, and the results are similar to the above trials. When US is negative in the setting of suspected DVT, serial US has proven in symptomatic outpatients to be a sensitive means by which to detect proximal extension of calf DVT. Heijboer and colleagues[12] found that

when serial compression US remained negative (day one, two and seven), the incidence of VTE during the six-month follow-up period was only 1.5%.

Limitations of compression US with venous imaging include certain patient characteristics which may limit venous compressibility. Obesity, oedema, leg tenderness as well as plaster casts or immobilisation devices limit access to the extremity. While there may be areas of focal incompressibility, these areas are usually bilaterally symmetric and colourflow imaging will generally reveal venous filling. Other possible causes of false-positive results include extrinsic venous compression by a pelvic mass or other perivascular pathology. False-negative studies may occur in cases of isolated calf DVT or in proximal DVT in asymptomatic patients even those of high-risk.[13] Ultrasound techniques are unreliable in detecting DVT in the iliac veins; CV and magnetic resonance imaging (MRI) are much more reliable in this setting.[14]

Magnetic resonance imaging (for the evaluation of deep venous thrombosis)

Magnetic resonance imaging has been used increasingly in the setting of acute DVT with advantage. Preliminary studies suggest excellent sensitivity and specificity not only for thigh DVT, but also for acute pelvic vein thrombosis.[14-19] Pelvic DVT may be difficult to evaluate by US and even by CV. Studies have validated the use of gradient echo 'white blood' MRI for the detection of DVT. These images may be supplemented by spin echo or fast spin echo blood images, although the latter are not recommended for primary diagnosis. Imaging should be performed in the axial plane and interpretations should be based upon review of source images rather than reprojections. During the procedure, the attending radiologist can scrutinise areas of suspected abnormalities using different techniques. Successful use reflects the involvement of an experienced radiologist.

The potential to distinguish acute from chronic DVT is a 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.[15] It has been suggested that inflammation surrounding a thrombosed vessel indicates acute DVT, while the absence of oedema suggests more chronic DVT.[16] These criteria require validation. Finally, preliminary studies in patients with pulmonary embolism suggest the MRI may be the first technique enabling both the lungs and the lower extremities to be evaluated for clot at the same time.[20-22]

Patients considered for MRI must be carefully screened for contraindications particularly with regard to the presence of metallic devices from injuries or surgery. Other possible contraindications include significant claustrophobia, the inability to co-operate, and massive obesity.

THE DIAGNOSTIC APPROACH TO ACUTE PULMONARY EMBOLISM

The clinical evaluation and initial laboratory studies

It is clear that PE cannot be unequivocally diagnosed solely on the basis of the history and physical examination, and this is underscored by the frequent failure to establish the diagnosis prior to autopsy.[1,2] The diagnosis should be considered whenever dyspnea is unexplained. Dyspnea, with or without associated anxiety, and pleuritic chest pain and haemoptysis are common in PE, but are non-specific, and one or more of these symptoms may be caused by, or occur concomitantly, with pneumonia, exacerbations of asthma or obstructive lung disease, congestive heart failure, or lung cancer. A search for PE may be appropriate despite possible alternative explanations if risk factors and the clinical setting are suggestive. Tachypnea and tachycardia are the most common

signs of PE but are non-specific. Light-headedness and syncope may be caused by PE but may also result from a variety of other disease states which cause hypoxaemia or hypotension. Pulmonary embolism should always be suspected when syncope or sudden hypotension develop, and these often indicate a substantial embolic burden. The findings on cardiac thrombus and pulmonary physical examinations are both non-specific for PE. Clinical suspicion becomes more powerful when considered in conjunction with VQ scanning.[23]

While electrocardiographic abnormalities may develop in the setting of acute PE, they are generally non-specific and include T-wave changes, ST segment abnormalities, and left or right axis deviation.[24] Patients with massive or submassive PE are more likely to manifest changes of acute cor pulmonale (S1 Q3 T3 pattern, right bundle branch block, P-wave pulmonale or right axis deviation).[24] The low frequency of specific ECG changes associated with PE was confirmed in the PIOPED study.[23]

Hypoxaemia is common in acute PE, but not universally present. Young patients without underlying lung disease may have a normal PaO_2. In a retrospective analysis of hospitalised patients with proven PE, the PaO_2 was greater than 80 mm Hg in 29% of patients less than 40 years old, compared with 3% in the older group.[25] The diagnosis of acute PE cannot be excluded by a normal PaO_2 and although the alveolar-arterial difference is usually elevated, it may rarely be normal in patients without pre-existing cardiopulmonary disease.

Most patients with PE have non-specific abnormalities in a chest radiograph. Common findings include atelectasis, pleural effusion, pulmonary infiltrates and elevation of a hemidiaphragm.[26] 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 hypoxaemia without evidence of bronchospasm or anatomic cardiac shunt is strongly suggestive of PE. Diagnosing other conditions such as pneumonia, pneumothorax or rib fracture which may cause symptoms similar to acute PE is important, but PE may co-exist with these and other cardiopulmonary disease.

The D-dimer test

The D-dimer is a specific degradation product released into the circulation when cross-linked fibrin thrombi undergo endogenous fibrinolysis. Numerous clinical trials have been undertaken to determine the utility of this test. Strategies have included the combination of ventilation-perfusion (VQ) scanning and D-dimer testing. Different assays have been evaluated using different cut-off values. 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 (< 500 ng/ml), measured by ELISA has a 95% negative predictive power. However, low D-dimer levels have been found in only about 25% of patients without PE.[27,28] A normal latex agglutination D-dimer does not appear to be reliable in excluding PE.[29,30] Management studies have been performed with therapeutic decisions based, in part, upon D-dimer results. Ginsberg and colleagues[31] 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 followed for three months: the negative predictive value proved to be 98.5% (95% confidence interval, 96.3-99.6), and 97.2% for the D-dimer test alone.

When the medical literature is systematically reviewed for publications that compare D-dimer results to 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.[32,33] At present, specific recommendations regarding the appropriate use of this test cannot be made. Future studies must be rigorous regarding the definitive presence or absence of DVT and PE, as well as addressing issues such as the extent of thrombosis, clinical setting and co-morbidity.

The ventilation-perfusion scan

The VQ scan remains the pivotal test at most institutions when acute PE is suspected. Unfortunately, this test is diagnostic in only a minority of cases: it is rarely interpreted as normal or highly probable. Most lung diseases affect pulmonary blood flow to some extent as well as affecting ventilation, thus decreasing the specificity of the VQ scan. Pulmonary embolism frequently occurs in the setting of concomitant lung disease such as chronic obstructive pulmonary disease (COPD) or pneumonia, further complicating evaluation.

The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) was a multicentre, collaborative effort designed to elucidate the sensitivity and specificity of the VQ scan in patients with suspected acute PE.[23] The importance of clinical suspicion combined with the VQ scan was a crucial aspect of the investigation. In this clinical trial, PE was proven or excluded by pulmonary arteriography or by autopsy. Criteria for the interpretation of VQ 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 proven PE in 96% of cases, but a low probability scan is also associated with PE in 40% of patients. The necessity of the ventilation scan has been debated.

The available data would suggest that if a ventilation scan cannot be performed, an isolated perfusion scan is useful if the interpretation is high probability, low probability, near normal or normal. A treatise on PE based upon the vast amount of data accrued upon the PIOPED has recently been published.[34]

Based on the PIOPED results, probability estimates for PE have been correlated with VQ scan results, and some of the original VQ scan diagnostic criteria have been revised. It has been suggested that these revived criteria be applied.[35]

The use of lower extremity studies when the ventilation-perfusion scan is nondiagnostic

In the setting of a nondiagnostic lung scan, evaluation of the lower extremities is an alternative means by which to establish the need for anticoagulation. Treatment can be initiated when a non-invasive study such as IPG or compression US is positive. The strategy after a negative study, however, depends upon the lung scan and upon the level of clinical suspicion. If the clinical suspicion for PE remains high, pulmonary angiography, or possibly serial non-invasive lower extremity studies would be appropriate. Serial leg studies have been shown to reduce the need for angiography and appear cost-effective.[36-38] Magnetic resonance imaging (MRI) may prove effective in this setting.

PULMONARY ANGIOGRAPHY

Pulmonary angiography has been considered the discriminant diagnostic technique for PE.[39] The most common diagnostic algorithm for PE has consisted of VQ scanning followed by pulmonary angiography when the scan is nondiagnostic and the clinical suspicion high. The validity of this technique was established in the PIOPED.

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 be performed safely when the platelet count is at least 75,000/mm^3, and coagulation studies are normal or minimally abnormal. 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 the insertion of a temporary pacemaker during the procedure to protect against complete heart block. The electrocardiogram should be reviewed for potential arrhythmia.

Complications related to this procedure have been reported in several large clinical trials.[23] In the PIOPED, death occurred in 5 of 1,111 (0.5%) patients. Other severe complications in this trial included severe cardiopulmonary compromise requiring intubation or cardiopulmonary resuscitation in 4 (0.4%), renal failure requiring dialysis in 3 (0.3%), and groin haematomas requiring transfusion of two units of blood in 2 (0.2%). Death related to angiography has been documented in other clinical trials but occurs rarely. Bleeding may occur, particularly when thrombolytic therapy is administered, and a non-invasive diagnostic approach may reduce the frequency of this complication.[40] In general, when a definitive diagnosis is necessary, the benefit of the procedure outweighs the risk. The test requires experienced angiographers, physicians and support staff.

Spiral computed tomography (CT) scanning

Spiral (also termed helical) computed tomography (CT) scanning for diagnosing acute PE has recently been explored. This technique involves continuous movement of the patient through the CT scanner, and uses concurrent scanning by a constantly rotating gantry and detector system. Rapid scanning can be performed with continuous volume acquisitions obtained during a single breath. Retrospective reconstructions can be performed. A contrast bolus is required for imaging of the pulmonary vasculature. Limitations of spiral CT scanning include poor visualisation of the peripheral areas of the upper and lower lobes. Lymph nodes may cause false-positive results. Multiplanar reconstructions in coronal or oblique planes may aid in differentiating lymph nodes from emboli.

Sensitivity and specificity data from several large studies evaluating spiral CT scanning for acute PE are shown in Table 1.[20,41-44] 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 debated. In the PIOPED study, only 6% of patients had isolated subsegmental emboli.[23] Interestingly, two referee angiographers from the PIOPED agreed on the angiographic presence or absence of subsegmental emboli in only 66% of cases. Agreement was only 40% for a single subsegmental embolus.[23]

An advantage of spiral CT includes the ability to define non-vascular structures such as lymphadenopathy, lung tumours, emphysema, and other parenchymal abnormalities as well as pleural and pericardial disease. Smaller lymph nodes may result in false-positive studies, however. Additional, prospective, randomised, clinical trials comparing these techniques with the standard diagnostic approach to PE including outcome analyses will be useful. A large European trial is currently underway. Goodman and others,[41] have strongly endorsed the incorporation of CT scanning into diagnostic algorithms for PE. Contrast-enhanced electron beam CT also appears useful in

TABLE 1
Sensitivity and specificity of spiral CT for acute PE.*

Reference	Number of patients evaluated (number with proven PE)	Sensitivity (%)	Specificity (%)
Remy-Jardin(44)	42 (18)	100	96
Remy-Jardin(43)	72 (39)	91	78
van Rossum(42)	77 (39)	95	97
Sostman(20)	28 (21)§	73	97
Goodman(41)	20 (11)	86†	92†
		63‡	89‡

*All studies used pulmonary angiography as providing the definitive answer, except where noted.
†Main, lobar and segmental emboli.
‡All emboli including peripheral.
§ Of the 21 PE, 6 were proven by angiography and 15 by high probability VQ scan.

diagnosing acute PE, and shares many advantages and limitations with spiral CT.[45,46] The rapid (l00msec) scanning time makes breath holding unnecessary with electron beam CT and respiratory and cardiac motion artifact are minimised.

Magnetic resonance imaging (for the evaluation of pulmonary embolism)

Details regarding MRI technique have been reviewed in the DVT section. Meaney and colleagues,[21] prospectively compared gadolinium-enhanced MR angiography with pulmonary angiography in 30 patients with suspected PE.[21] The patients were enrolled consecutively and the studies were interpreted independently in a blinded manner by three radiologists. The pulmonary angiogram was considered to provide the definitive answer. In the eight patients with emboli proven by pulmonary angiography, all five lobar, and 16 of 17 segmental emboli were identified by the MR technique. The sensitivities for MR angiography for each of the readers were 100%, 87% and 75%, with specificities of 95%, 100% and 95%. This technique may ultimately allow the simultaneous and accurate detection of both PE and DVT. Additional prospective investigations will determine the role of MRI in the evaluation of VTE.

Echocardiography

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 which may suggest acute PE.[47] Unfortunately, the finding of right ventricular dysfunction is non-specific and certain clinical conditions commonly confused with PE (such as acute COPD exacerbations) are also associated with abnormal right ventricular function. Large emboli may also be visualised within the main pulmonary artery with surface echocardiography, but this appears to be unusual.

Transoesophageal echocardiography has been utilised 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.[48] Intravascular ultrasound has been used to demonstrate PE but has not been widely applied.[49]

THERAPY FOR VENOUS THROMBOEMBOLISM

Anticoagulation

Anticoagulation reduces mortality in acute PE. When VTE is diagnosed or strongly suspected, heparin therapy should be instituted promptly unless contraindications exist

and the diagnosis should always be confirmed if anticoagulation is to be continued. Heparin prevents thrombus growth. Although it does not directly prevent the development of acute PE or dissolve thrombus, it allows the fibrinolytic system to act unopposed and more easily reduces the size of the thromboembolic burden. While thrombus growth can be prevented, early recurrence can develop even in the setting of therapeutic anticoagulation.

When continuous intravenous heparin is initiated, the activated partial thromboplastin time (APTT) should be followed at six-hour intervals until it is consistently in the therapeutic range of 1.5-2.0 times control values.[50] This range corresponds to a heparin level of 0.2-0.4 U/ml as measured by protamine sulfate titration. In general, heparin should be administered as an intravenous bolus of 5,000 units followed by a maintenance dose of at least 30,000-40,000 units per 24 hours by continuous infusion.[51] The lower dose is administered if the patient is considered at high risk for bleeding. This aggressive approach decreases the risk of subtherapeutic anticoagulation and although supratherapeutic levels are sometimes achieved initially, bleeding complications do not appear to be increased.[51]

More recent data continue to support aggressive heparin dosing. An alternative regimen consisting of a bolus of 80U/kg followed by 18U/kg/hr has been recommended.[52] Further adjusting of the heparin dose should also be bodyweight-based (Table 2). This weight-adjusted approach is recommended in the recent American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy.[53] Warfarin therapy may be initiated as soon as the APTT is therapeutic and heparin should be maintained until a therapeutic international normalised ratio (INR) of 2.0-3.0 has been overlapped with a therapeutic APTT for three consecutive days. While proximal lower extremity thrombus is more likely to result in PE, calf thrombi should either be watched for proximal extension over 10-14 days with non-invasive testing, or anticoagulation should be instituted.[54] Documented proximal DVT or PE should be treated for three months. Longer treatment is appropriate when significant risk factors persist. Both short and long-term anticoagulation guidelines are outlined in the ACCP Consensus Conference guidelines.[53]

TABLE 2
Body weight-based nomogram for heparin therapy in acute venous thromboembolism.*

Initial heparin dose: 80 U/kg bolus, then 18 U/kg/hr

Subsequent modifications:

APTT (sec)	APTT (times control)	Heparin dose adjustment
< 35	< 1.2	80 U/kg bolus, then increase by 4 U/kg/hr
35 to 45	1.2 to 1.5	40 U/kg bolus, then increase by 2 U/kg/hr
46 to 70	1.5 to 2.3	No change
71 to 90	2.3 to 3.0	Decrease infusion rate by 2 U/kg/hr
> 90	> 3.0	Hold infusion 1 h, then decrease rate by 3 U/kg/hr

*From American College of Chest Physicians Guidelines[53] and Raschke *et al.*[52]

A number of prospective, randomised, clinical bids have demonstrated the efficacy and safety of LMWH (low molecular weight heparin) in the treatment of established acute proximal DVT using recurrent symptomatic VTE as the primary outcome measure, and several meta-analyses have been conducted.[55-59] These agents can be administered

once or twice per day subcutaneously even at therapeutic doses and do not require monitoring of the APTT (activated partial thromboplastin time). Factor X levels may prove useful but are not likely to be frequently required. In two large randomised (Canadian and European) trials, therapy with LMWH was safely initiated at home or continued at home after a brief hospitalisation.[55,56] A more recent study has suggested the efficacy of LMWH in the setting of acute PE.[60] Unfractionated and LMWH are compared in Table 3. Advantages of the LMWH preparations are shown in Table 4.

TABLE 3
A comparison of low-molecular-weight heparin with unfractionated heparin.

Characteristic	UFH*	LMWH†
Mean molecular weight	12,000-15,000	4,000-6,000
Protein binding	substantial	minimal
Platelet inhibition	substantial	minimal
Anti-Xa activity	substantial	substantial
Anti-IIa activity	substantial	minimal
Vascular permeability	moderate	none
Microvascular permeability	substantial	minimal

* Unfractionated heparin
† Low-molecular-weight heparin

TABLE 4
Potential advantages of low-molecular-weight heparins over unfractionated heparin.

- Similar or superior efficacy
- Similar or superior safety
- Superior bioavailability
- Once or twice daily dosing
- No laboratory monitoring*
- Less phlebotomy
- Subcutaneous administration*
- Earlier ambulation
- Home therapy in certain patient subsets

*For both prophylaxis and treatment.

Complications of anticoagulation

Complications of heparin treatment include bleeding and heparin-induced thrombocytopenia (HIT). The rates of major bleeding in recent trials using heparin by continuous infusion or high-dose subcutaneous injection are less than 5%. Heparin-induced thrombocytopenia (defined as a platelet count less than 150,000 mm^3) typically develops five or more days after the initiation of heparin therapy, occurring in 5% to 10% of patients.[61] Low-molecular-weight heparins and heparinoids may be considered in this setting since the formation of heparin-dependent IgG antibodies and the risk of HIT appears to be lower with these substances. In a large clinical trial, heparin-induced thrombocytopenia occurred in nine of 332 patients receiving standard unfractionated heparin compared with none of 333 patients receiving enoxaparin.[62] Eight of the nine patients receiving standard heparin developed one or more thrombotic events. However, it is important for clinicians to realise that HIT can occur with the use of either form of heparin. Platelet aggregation studies should be performed to determine that a

LMWH preparation may be used safely in the setting of HIT caused by unfractionated heparin. The heparinoid compounds appear to exhibit even less cross-reactivity with the heparin-induced antibody than the LMWH compounds.[63]

Vena cava interruption

If anticoagulation cannot be administered or continued, inferior vena cava (IVC) filter placement can be undertaken to prevent lower extremity thrombi from embolising; the primary indications include contraindications to anticoagulation, recurrent PE while on adequate therapy and significant bleeding complications during anticoagulation.[64] Filters are sometimes placed in the setting of massive PE when it is believed that any further emboli might be lethal.[64] A number of filter designs exist; they are effective and complications are unusual. Potential mechanisms of IVC filter failure include filter migration, improper filter positioning, and formation of thrombosis proximal to the filter with subsequent embolisation. Rare complications include clinically significant perforation of the IVC, cephalad migration, and displacement of the filter during insertion. Occasionally, IVC obstruction due to thrombosis at the filter site may occur. Deaths due to filter placement are exceedingly uncommon. In general, anticoagulation is continued when a filter is placed if and when it is deemed safe.

Thrombolytic therapy

The most common use of these agents is in patients with haemodynamic instability (hypotension) or severely compromised oxygenation.[65] Stable patients with a significant embolic load are individualised, often receiving treatment in the absence of absolute or relative contraindication. For example, strong arguments for thrombolytic therapy can be made when the perfusion defect by lung scan or pulmonary arteriogram is extensive, even without clear hemodynamic instability. Another setting in which thrombolytic therapy may be considered is when extensive DVT accompanies a submassive PE. There are no clinical studies suggesting a reduction in mortality in the latter circumstance, and perhaps future clinical trials will clarify these guidelines. Thrombolytic regimens approved by the United States Food and Drug Administration for the treatment of acute PE are presented in Table 5. Coagulation assays are unnecessary during thrombolysis since the approved regimens are administered as fixed doses. It is recommended that heparin be withheld until the thrombolytic infusion is completed.

The method of delivery of thrombolytic agents has also been investigated. While a number of investigators have employed standard or low-dose intrapulmonary arterial

TABLE 5
Thrombolytic therapy for acute pulmonary embolism: regimens approved for use in the United States.

Streptokinase: 250,000 U IV (loading dose over 30 min); then 100,000 U/hr for 24 hr*
Urokinase: 2000 U/lb IV (loading dose over 10 min); then 2,000 U/lb/hr for 12 to 24 hr
Tissue-type plasminogen activator: 100 mg IV over 2 hr

*Streptokinase administered over 24 to 72 hr at this loading dose and rate has also been approved for use in patients with extensive DVT.

thrombolytic infusions, in order to deliver a high concentration of drug in close proximity to the clot,[67,68] intravenous therapy appears adequate in most cases.[62] More direct techniques, such as catheter-directed administration of intra-embolic thrombolytic therapy have also been utilised,[69] although large clinical trials have not been performed.

Haemorrhage is the primary adverse effect associated with thrombolytic therapy and generally occurs at sites of invasive procedures such as pulmonary arteriography or arterial line placement.[70] Thus, when thrombolytic therapy is administered, invasive procedures should be minimised. The most devastating complication associated with this form of treatment is the development of intracranial haemorrhage. Clinical trials have suggested that this occurs in significantly less than 1% of patients.

Pulmonary embolectomy

Pulmonary embolectomy may be performed in the setting of acute massive PE. While many patients die from PE before surgical embolectomy would be feasible, some deteriorate hours after the initial episode suggesting that surgery may occasionally be worthwhile. In one series of 71 embolectomies performed under cardiopulmonary bypass, hospital mortality was 29%.[71] The mortality in those patients who had not sustained a cardiac arrest preoperatively was only 11%, however. Transvenous embolectomy via a suction-catheter device has been used but has not received widespread acceptance.[72]

Haemodynamic management of massive PE

Massive PE should always be suspected as the cause of sudden hypotension, extreme hypoxemia, electromechanical dissociation or sudden cardiac arrest. If the patient is stable enough, VQ scanning should be performed. Although PE should be proven prior to the initiation of thrombolytic therapy, echocardiography may support the diagnosis of massive PE and may also suggest the need for these agents.[73] Once massive PE associated with hypotension and/or severe hypoxemia is suspected, supportive treatment is immediately initiated. Intravenous saline should be infused rapidly, but cautiously, since right ventricular function is often markedly compromised. Dopamine or norepinephrine appear to be the favoured choices of vasoactive therapy in massive PE and should be administered if the blood pressure is not rapidly restored.[73] Oxygen is administered and thrombolytic therapy is considered as described above. Intubation and institution of mechanical ventilation are instituted as needed to support respiratory failure.

CONCLUSIONS

Venous thromboembolism remains a substantial cause of morbidity and mortality, largely because of its non-specific and variable clinical presentations. Awareness of clinical risk factors and a low threshold for proceeding with the diagnostic evaluation are crucial. Objective testing for both DVT and PE are mandatory. New diagnostic modalities such as MRI and spiral CT are being investigated. Novel therapeutic agents such as the LMWH compounds are beginning to change the way therapy is approached. The International Co-operative Pulmonary Embolism Registry represents the largest prospective PE registry ever undertaken and enrolment is now complete.[74] Such collaborative efforts will enhance international communication and in turn increase the number and quality of international randomised clinical trials, helping to unify the approach to VTE. The future appears promising.

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