PULMONARY THROMBOEMBOLISM

INTERNAL MEDICINE GRAND ROUNDS

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- If there is such a thing as truth
it is as intricate and hidden
as a crown of feathers.

Isaac Bashevis Singer

PULMONARY THROMBOEMBOLISM

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I. INCIDENCE, MORBIDITY AND MORTALITY

Pulmonary thromboembolism is not a disease. It is a complication of venous thrombosis that affects the medical practice of the majority of specialties. The incidence is high, and is associated with an impressive mortality if not clinically suspected, and with a significant mortality even if diagnosed and treated.

It was estimated in the late 60's that the incidence of PTE occurring in the United States was 650,000 per year, and that 15% of the deaths of hospitalized patients were caused by pulmonary thromboembolism (1,2). Recent autopsy studies report that this figure has dropped to 3.4-3.8% of in-hospital deaths, indicating that the incidence of fatal PE in this group of patients has declined significantly over twenty years (3-5). While this decline could be due to changing hospital populations, improved mechanisms for prevention of venous thrombosis is a likely contributing factor. However, only approximately 30% of significant emboli are clinically suspected antemortem, a figure that has remained unchanged since 1968 (6-8). In addition, once the diagnosis is made, the mortality of treated pulmonary thromboembolism remains as high as 7-8% (2,9).

This protocol reviews the risk factors for developing venous thrombosis, the clinical features and diagnosis of pulmonary thromboembolism, the pathophysiologic abnormalities, and the known as well as newer modalities of treatment.

II. SOURCES, ETIOLOGY AND HYPERCOAGULABLE STATES

Sources:

Any particle that moves through the venous system, if large enough, will become trapped in the pulmonary circulation, since nearly the entire cardiac output flows through the pulmonary arteries. Blood clots are the most common source of emboli to the lungs, although many other substances are known to produce emboli (10-13). It has been shown that most of significant pulmonary emboli arise from deep venous thrombosis (DVT) of the large vessels of the lower leg and pelvis (14,15). While almost half of the patients with DVT develop evidence of severe or fatal pulmonary embolism (14,16), there has been convincing evidence that asymptomatic blood clots that are restricted to the veins of the lower leg are not associated with significant pulmonary embolism (15,17). The key word is restricted, since fatal pulmonary emboli have been traced to origins from the popliteal and deep venous system of the calf (14,17,18). Thrombosis extending from the popliteal system and above have a greater likelihood of breaking loose and migrating to the pulmonary circulation. Thrombi identified by venography to have free ends extending into the lumen of a large vessel have been described to be highly associated with massive embolism (19). However, the actual size of an embolus is not always related to mortality. Factors such as underlying cardiac or pulmonary disease contribute equally since smaller emboli can produce greater physiologic disturbances in these patients (20). Significant emboli originating from the upper extremities or right ventricle of the heart are less common, and are usually associated with other medical conditions which predispose to DVT, such as trauma, presence of central venous catheters, or severe dilated cardiomyopathy (21,22).

It is interesting to note that two older autopsy studies identify a high proportion of patients (8-39%) as having PTE arising from the right heart (23,24). Havig, et al were unable to identify the right heart as a source in their study of 261 autopsies (14). It is uncertain whether the clots in the right heart in the older studies represent mobile thrombi that have more recently been identified by echocardiography. It is presumed that they are visualized in the right heart as they migrate to the pulmonary vasculature (25,26). This finding is important since these emboli often have a fatal outcome (26).

Etiology:

Immobilization promotes stasis and clot formation in the deep venous system, and was the most common underlying risk factor in the Urokinase Pulmonary Embolism Trial (27). Stasis from automobile or air travel has been associated with DVT and PTE (28), and the duration of bed rest up to 14 days was associated with a linear increase in incidence of DVT (14). Most medical conditions which promote stasis in the venous system have been associated with a higher incidence of DVT and PTE. In addition to stasis, release of activators of the clotting system due to endothelial damage is probably necessary.

Individuals at greater risk are older individuals (who are more likely to be immobilized or ill) and women who are obese (>20% ideal body weight) or are taking oral contraceptives (22,27). Other conditions that have been identified as predisposing to PTE include sickle cell disease, paroxysmal nocturnal hemoglobinuria, Bechet's syndrome, and pregnancy (29-34). Orthopedic surgery poses a special risk with 5% of those having elective hip replacement suffering major PTE and up to 2% die; major knee surgery has similar statistics (35). Fractured hip is associated with a much higher incidence (30%) of proximal DVT or PE (36,37).

Hypercoagulable states:

Hypercoagulable states have been identified that are associated with increased incidences of DVT and PTE. Perhaps the earliest form was described in 1865 by Trousseau who made the clinical association between thrombophlebitis and malignancy (38). This has been well substantiated since then and is associated with a variety of malignancies (38,39) [see table, from references 38,40].

FREQUENCY OF PE IN PATIENTS WITH CANCER

Pancreas	24-35%
Genitourinary (Other)	21%
Lung	20%
Colon	5-19%
Uterus, corpus, cervix	18%
Prostate	13-17%
Stomach	12-16%
Breast	15%
Other GI	10%
Lymphoma-leukemia	8-9%
CNS	8%
Unknown, primary, other malignancies	5-8%

Although there is a high association with mucin producing solid tumors, its pathophysiology is believed to be complex and varied, since the clotting system itself is a complex balance between thrombosis and thrombolysis (31). Although DVT and PTE are not in themselves hallmarks of underlying neoplasms, malignancies have been found in 25-35% of those patients with DVT and no other known risk factors (40,41). These were found by screening with routine examinations including serum CEA, LDH as well as chest radiographs and abdominal ultrasound or CT scan (41).

In recent years other forms of hypercoagulable states have been identified which are associated with DVT and PTE without other known risk factors. The best known of these are deficiencies of proteins which are involved in the fibrinolytic system or the inhibition of coagulation. These proteins include antithrombin III, protein C, protein S and plasminogen (42-46). Although not all with these deficiencies are at risk (47-48). In a recent study, the overall prevalence of congenital deficiencies in patients with unexplained venous thrombosis was 8.3 % which was higher than the control population without thrombosis, 2.2%. Thus, in those patients without known risk factors, over 90% cannot have their thrombosis explained by a currently identifiable congenital abnormality of the coagulation or fibrinolytic system. Furthermore, in that study neither a medical history of juvenile thrombosis, recurrent thrombosis, or a family history of thrombosis had a significant predictive value for detection of a deficiency, whereas the presence of all three had a predictive value of 30% (49).

Other, acquired alterations in the coagulation system are described that are associated with increased risk for DVT and PTE. The lupus anticoagulant (antiphospholipid antibody) is one such condition (50).

III. CLINICAL FEATURES

Signs and symptoms:

The Urokinase Pulmonary Embolism Trial established that there are no specific signs and symptoms of pulmonary embolism (27). The most common symptom found was chest pain (either pleuritic or nonpleuritic) which was present in 88% of 327 patients with documented pulmonary embolism by arteriography. Of almost equal frequency was dyspnea, present in 84% of the patients (27). Similarly, the most common sign was tachypnea (RR >16) [see table].

The UPET study, however, excluded 12% of the screened patients because of contraindications to thrombolytic therapy which may have introduced some bias. Important features are the relatively low incidence of hemoptysis, syncope, and clinical evidence of DVT (51). Similarly the physical findings of DVT have been found to be notoriously poor in establishing the presence of clot in the lower extremity (52,53). Fever is found in 50-60% of patients (54). Pleuritic chest pain alone is a poor predictor of PTE, since only 21% of 173 patients presenting to an emergency room with this complaint were subsequently diagnosed as having PTE (55). Thus, the physician must form a clinical opinion of the presence of PTE based on few clinical indicators and an index of suspicion based on known risk factors, or the absence of other clinical causes of the patients symptoms.

SYMPTOMS IN 327 PATIENTS WITH PTE
(from UPET study, references 27, 51)

Symptoms and signs	Percent
Chest pain	88
Pleuritic	74
Non-pleuritic	14
Hemoptysis	30
Dyspnea	84
Cough	53
Signs	
Respirations > 16	92
Pulse > 100	44
Cyanosis	19

Chest radiographs and ECG:

The initial evaluation of patients with suspected PTE or chest pain, dyspnea or tachypnea frequently includes chest radiography and ECG.

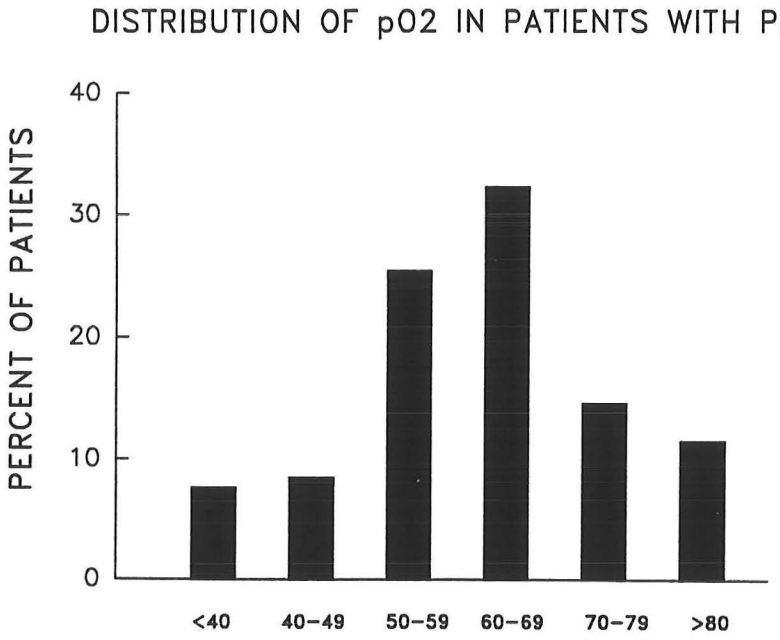
The most common radiographic manifestation of PTE is a clear chest x-ray. However, less than half of those with PTE may manifest some abnormality in the lung parenchyma, and almost one third will have evidence of pleural effusion (51,56). The parenchymal abnormalities are predominantly consolidation and atelectasis, which are likely secondary to smaller emboli producing infarction. Dilatation of the proximal pulmonary arteries with an abrupt taper or cut off of the distal vessel (Westermark's sign) is an infrequent finding, and when found is most likely associated with large PTE(57).

The characteristics of the pleural effusions are nonspecific, with approximately 60% being bloody, although transudates as well as exudates are found (56). Hence, thoracentesis may be withheld if the index of suspicion for acute PTE is sufficiently high that thrombolytic therapy is considered.

The ECG findings in acute PTE are equally nonspecific, with many abnormalities described in the UPET study. The classic finding of an S1Q3T3 was found in about 10% of cases and was also associated with massive PTE (58,59).

Arterial blood gases:

Several studies have described the presence of PTE without significant hypoxemia (51,60), and 12% of the patients from the UPET study had a pO_2 greater than 80 torr (see figure) (51).



However, one recent study demonstrated that while a "normal" pO_2 on room air may be a frequent finding in patients with PTE, a completely normal blood gas is not. Of those with documented PE 98% had increased $P(A\text{-}a)O_2$ and/or hypocapnea (60). Thus, ABG determinations that fall close to the normal range do not exclude PTE, and one must keep in mind the fact that patients with PTE often have underlying conditions which cause abnormal blood gases.

Laboratory tests:

Multiple attempts have been made to develop a laboratory test which is specific and sensitive for the diagnosis of DVT or PTE. These include tests for fibrin split products (FSP), plasma DNA, and urinary thromboxane B2 (61-66). However, all the assays are not sensitive or specific enough for widespread use. Underlying diseases that predispose to thrombosis and PTE frequently produce false positive results. Hence, it may be extremely difficult to find a factor in the urine or blood that is only released when the patient has a clinically significant thrombosis.

IV. MAKING THE DIAGNOSIS

Ventilation-perfusion scans:

The most widely used and sensitive test for PTE is perfusion lung scanning using technetium-99m-labeled macroaggregated albumin microspheres. After intravenous injection of the isotope, standard scanning of the lungs is performed in 6 views. The

macroaggregated spheres are large enough to occlude precapillary arterioles and produce accurate information about the blood flow through the pulmonary vascular bed. Any disturbance in blood flow will create an abnormal study. Thus, this technique is very sensitive, but not specific for PTE. It is considered a very safe procedure with an extremely rare complication (67-69). Specificity is improved by performing ventilation scans for comparison with the perfusion scan (16). Preserved ventilation in areas of perfusion defects are known as mismatched defects. Ventilation scans have typically been performed with radioactive xenon, although use of technetium aerosols have been reported as an acceptable alternative (70). On the other hand, the aerosol scans do no visualize wash-out which is helpful to know in patients with obstructive lung disease (53). The perfusion scan correlates well with the severity of embolization by angiography in acute PTE, but may underestimate it with chronic disease (71).

Earlier, non-prospective studies indicated that ventilation-perfusion scanning (V/Q) had predictive value when compared to pulmonary angiography (72). The perfusion defects were categorized by the size in relation to the anatomical blood flow patterns of the lung in terms of pulmonary segments or lobes. Scans were interpreted as high, low or intermediate probability. However, these studies have been criticized for being retrospective, not having uniform techniques, and not being blinded (72). High probability scans according to Hull, et.al. were defined as a perfusion scan with one or more segmental or larger defects with normal ventilation to that area. This finding was associated with a positive pulmonary angiogram in 86% of the patients (16). When venography was added, this increased to a positive diagnosis in 91% (16). However, reviewing the "older" literature reveals three studies that confirmed the results by angiography and used similar criteria for high probability and low probability scans as Hull (73-76). The results of these four studies are shown on the table.

NUMBER POSITIVE ANGIOGRAMS/NUMBER WITH V/Q SCAN INTERPRETATION

	Biello	Cheeley	McNeil	Hull	Total
Low Probability:					
Sub-segmental/non-segmental (single or multiple, V/Q match)	1/21 (5%)	0/19 (0%)	4/16 (34%)	4/15 (27%)	13%
High Probability:					
Segmental/lobar (V/Q mismatch)	25/26 (96%)	17/19 (89%)	32/32 (100%)	30/35 (86%)	93%

Hull reexamined his data using the criteria described by Biello and McNeil and determined that the sensitivity of their high probability criteria was only 56% (76). In other words, their criteria for high probability scans had a high specificity, but the sensitivity was not adequate (76).

The largest recent prospective study is the investigation of pulmonary embolism diagnosis (PIOPED) study, a multicenter prospective study of 933 patients. Criteria for high probability scans defined by the PIOPED study are shown below (77).

PIOPED CENTRAL SCAN INTERPRETATION CATEGORIES AND CRITERIA

High Probability

≥ 2 large segmental perfusion defects without corresponding ventilation or roentgenographic abnormalities or substantially larger than either matching ventilation or chest roentgenogram abnormalities

≥ 2 moderate segmental perfusion defects without matching ventilation or chest roentgenogram abnormalities and 1 large mismatched segmental defect

≥ 4 moderate segmental perfusion defects without ventilation or chest roentgenogram abnormalities

Low Probability

Nonsegmental perfusion defects

Single moderate mismatched segmental perfusion defect with normal chest roentgenogram

Any perfusion defect with a substantially larger chest roentgenogram abnormality

Large or moderate segmental perfusion defects involving no more than 4 segments in 1 lung and no more than 3 segments in 1 lung region with matching ventilation defects either equal to or larger in size and chest roentgenogram either normal or with abnormalities substantially smaller than perfusion defects

> 3 small segmental perfusion defects with a normal chest roentgenogram

The predictive value of a high probability scan in this study was 88% (102/124). However, only 41% of patients with documented PTE by angiography had high probability lung scans, the remainder were classified into less predictive categories (77). Thus, high probability scans are usually due to PTE, however, many if not most PTE are not associated with such scans.

On the other hand, **normal** lung scans in the absence of objective studies for DVT have been shown to have an exceedingly benign course. Thus, it can be considered safe to withhold anticoagulant therapy in this group of patients (78).

It is interesting to note that Hull et.al. found an incidence of DVT between 5 and 10% in patients with abnormal V/Q scans but with negative pulmonary angiography (16,79). Follow up of patients with non-high probability scans and negative studies for DVT also revealed a good prognosis without anticoagulation (79).

To summarize, ventilation-perfusion scans classified as high probability have a predictive value of at least 86%. However, any interpretation of lung scans **other than normal** can not be classified into any reliably predictive category. As suggested by Moser, for the diagnosis of PTE lung scans should be classified as normal, high probability or non-diagnostic (53). Clinicians should be wary of the interpretation of "low-probability" scans,

with the possible exception of those patients in whom the clinical suspicion of PTE is very low (73). It must be noted, however, that non-diagnostic lung scans may have value. The angiographer can use the information from the scans to determine the region of the lung to study first with selective angiography. This theoretically should increase the diagnostic yield and decrease the risk to the patient.

Pulmonary angiography:

The most direct method for demonstrating an embolism is via pulmonary angiography, which is still considered the standard for documenting PTE antemortem.

Since the mid 1960s pulmonary angiography has been the diagnostic standard against which other, less invasive measures are compared (80,81). The diagnosis is established only when an intravascular filling defect is seen within the lumen of a pulmonary artery, or an absolute cutoff is seen (82). Other, less specific, findings include focal areas of oligemia, "pruning" of the vascular tree and delayed venous visualization which can be seen with other pulmonary diseases and fail to establish the diagnosis (81,82). Nevertheless, the study is equivocal in 15% of the cases which may be improved by selective injection into the pulmonary artery (82). Although it is an invasive procedure, the complication rate is low (<5%) and the mortality is significantly less than 1% (82,83) Complications include cardiac perforation, arrhythmias, or cardiac arrest. Mortality is linked to elevated pulmonary artery pressures and is believed to be due to the increased pressure caused by the high osmotic load during injection (83,84). Using non-ionic contrast agents appears to be preferred, but is more expensive (85,86). It is generally recommended that the pulmonary artery pressures be measured at the time the angiogram is performed, and caution used when the right ventricular end diastolic pressure is greater than 20 mmHg, or the pulmonary artery systolic pressure is greater than 70 mmHg (84). Selective angiography can be utilized to minimize complications in those with significant pulmonary hypertension (87).

Recent studies have reported using intravenous digital subtraction angiography to detect pulmonary emboli (88,89). While initially promising, this technique requires special equipment and does not appear to be as accurate as direct pulmonary angiography (90,91). Thus, it has not evolved into widespread use.

The primary indications for pulmonary angiography are twofold (92):

1) An apparent discrepancy between the clinical suspicion of pulmonary embolism and the results of the V/Q scan and 2) invasive therapy such as embolectomy, caval interruption or use of thrombolytic therapy is considered.

The timing of the performance of the angiogram in relationship to the event has practical importance in establishing the diagnosis. Earlier studies with a canine model demonstrated that clot lysis was significant, if not complete, within 72 hours of the embolization (93). However, resolution rates of thromboembolism in humans is slower than those in canine models. Studies with repeated angiograms in humans demonstrated that intravascular filling defects following the acute event frequently persisted for 7 days, and about half had complete resolution by 14 days (94).

Other imaging modalities:

Other imaging modalities have been described for the detection of PTE; most have been investigational and have not been utilized in general clinical practice. Improved sensitivity of radionuclide perfusion scans is obtained with tomographic imaging using single-photon emission computed tomography (SPECT) (95). Although the sensitivity is good, the specificity has not been well established. Thus it is not likely to develop into a good screening tool. Reports of radiolabeled platelets used for scanning were published in the early 80s without much since then (96).

More recently is the development of the technique of fiberoptic angioscopy which is currently being used to differentiate acute from chronic emboli, or thromboemboli from other etiologies, such a tumors (97,98). There are anecdotal reports of large PTE detected by computed tomography (99). However, due to current difficulties with resolution, only large PTE in the main pulmonary arteries will be identified. However, CT scanning can also identify the wedge-shaped infarction due to smaller emboli (100), and since it is non-invasive, it may have a clinical role in those patients who have contraindications to pulmonary angiography.

MRI scans using the spin echo technique can also detect pulmonary embolism. Moving blood is not detected since it produces no signal, and no signal is produced in normally aerated lungs because of low tissue density (101). However, the vessel walls and emboli are of soft tissue density and are visualized. Studies have been performed experimentally in animals and anecdotal reports in humans (102). As the technology improves for MRI, this may progress to a superior noninvasive technique for the diagnosis of PTE.

V. DEEP VENOUS THROMBOSIS

Since treatment of both DVT and PTE is so similar, establishing the diagnosis of DVT in the face of suspected PTE is sufficient indication to initiate treatment. Between 50-70% of those with PTE also have demonstrable evidence of venous thrombosis, which is also to say that in those with known PTE a search for DVT will be negative 30%-50% of the time (16). Similarly, of those with DVT proven by venography, half will have asymptomatic PTE (52,103). It has been shown that the clinical diagnosis of DVT is not adequate, and there are few proven modalities for establishing or excluding the presence of DVT. In addition, since approximately 20% of calf vein thrombi propagate proximally, it is recommended that such patients be monitored serially and treated if evidence of propagation is found (52,104).

Venography:

Ascending contrast venography remains the" gold standard" for the diagnosis of thrombosis of the venous system (53,105), although it is an invasive study that is not without some risk and discomfort to the patient (106-108). The most notable is post-venographic thrombosis in 8% (108). Because of this, it does not lend itself well to repetitive studies, and is now reserved as the definitive study when other less invasive studies are equivocal or not available. Venography can identify those "floating" clots with

ends not attached to the caval wall and which are more likely to embolize (19). Finally, a negative venogram (in absence of PTE) has an excellent prognosis (109).

Impedance plethysmography (IPG):

Impedance plethysmography has been in use since the 1970s. There is ample evidence in the literature that when done correctly it is an excellent tool for diagnosing DVT. Several studies have demonstrated that impedance plethysmography will detect approximately 95% of all venous thrombi above the calves and less than seven days old (110-112). It will only detect 20% of calf vein thrombosis, however. In addition, there are conditions which can produce false positive results: congestive heart failure, marked local leg muscle tension, and severe peripheral vascular disease (111,112). Serial IPG, i.e. repeated several times for up to 14 days, is the current standard, as a single study produces a significant degree of false negative and false positive results (104).

Radioactive scanning:

Another proven modality for detection of DVT is scanning the leg with I^{125}-Fibrinogen. This technique detects over 90% of acute calf vein thrombi, but only between 60 and 80% of proximal vein thrombi. It is relatively insensitive to the upper thigh and pelvis (113). However, the combination of radiofibrinogen scanning with IPG can detect almost all DVT (109). Because it may take up to 72 hours for the scan to become positive, it has not become commonly used in community hospitals, but has been invaluable as a clinical research tool.

There are other imaging modalities using various new radiolabeled agents such as indium-labeled platelets, and RBCs labeled with technetium^{99m}, and tagged fibrin-specific monoclonal antibody, which generally remain investigational (96,114,115). Radionucleotide venography using the same preparation as that for lung scanning is used by some, but the results are not well substantiated, and it is not generally recommended (116).

Doppler and duplex scanning:

The pulsed doppler technique uses an ultrasound beam directed toward the vessel which is reflected by the flow of blood. If no blood is moving, no sound is recorded. This technique is very operator dependent and commonly uses subjective interpretation, so sensitivity and specificity have varied considerably. Recently a standardized objective method was described using a strip chart recording of flow and a device to record the mouth pressure generated during a Valsalva maneuver by the patient (117). This study reports a sensitivity of 91% and specificity of 99% with the improved results based on demonstrable absence of venous flow following the cessation of an adequate Valsalva maneuver (117). This study also reported missing thrombi restricted to the calf. However, since this is a noninvasive study which can be repeated serially, and many hospitals already have this equipment, this new data is encouraging.

Duplex scanning is similar to pulsed doppler scans with the addition of B-mode ultrasound to visualize the vessel. Its results are variable, and still not well established,

although its overall sensitivity and specificity are good and some advocate it to be superior to venography (118). There are three parameters that are examined with duplex scans. The first, visualization of the thrombus with ultrasound, is the least sensitive. The second, loss of compressibility of the vein has been reported as having both a high (118) and low (119) sensitivity and specificity. The third parameter is absence of flow, or better yet, absence of phasicity of flow with respiration or Valsalva (118). A recent review of studies comparing duplex scans with venography reports an overall sensitivity of 95% and specificity of 99% (120). Another prospective double-blinded study compared duplex scanning to venography and, found the sensitivity was best with absence of phasicity of flow with respiration (sensitivity and specificity of 92%) (119). Although there is some variability among reports, this seems to be a good non-invasive method to detect DVT. This technique is also limited when studying veins below the knee (121-123).

Other modalities:

MRI: MRI can be used to detect DVT. This may be particularly helpful in areas that are not well demonstrated with other modalities, such as the pelvis and upper extremities (124) Additional studies may reveal this to be a valuable technique.

VI. PATHOPHYSIOLOGY OF PULMONARY THROMBOEMBOLISM

Respiratory:

Immediately following occlusion of a pulmonary artery by embolism an increase in physiologic deadspace (VD/VT) occurs, and partial occlusion of a pulmonary artery results in areas that have high ventilation to perfusion ratios (125). Clinically, measurement of a VD/VT greater than 0.4 combined with normal spirometry has been reported as having a high sensitivity (91%) and specificity (94%) for PTE (126). It should be noted that the technique does not readily lend itself to general clinical application. In the spontaneously breathing human, elevation in arterial carbon dioxide levels due to increased dead space is not noted because hyperventilation also occurs and is a common physical sign (see above). A decreased pCO_2 is most common, although elevations in pCO_2 have been reported (127,128). The cause of hypercapnia is thought to be due to an inadequate increase in ventilation for the amount of deadspace involved, usually in patients on mechanical ventilators. In addition, an increase in the mixed venous pCO_2 due to a large right to left shunt has been proposed since all such patients had massive PTE (128). The mechanism of hyperventilation with PTE is still unclear but may be due to stimulation of irritant receptors in the lung (129).

Arterial hypoxemia is a common finding in PTE as described above. One cause of the hypoxemia is the development of areas of true shunt or very low V/Q ratios caused by increased perfusion in the residual vascular bed, some regions of which are not well ventilated (127,130). In an experimental setting with dogs hypoxemia is due to ventilation-perfusion inequality, not true shunt (131). Pulmonary artery occlusion after 24 hours also causes decreased production of surfactant by the alveolar Type II cells resulting in atelectasis and edema (53). This also contributes to hypoxemia. In patients

with large enough PTE to increase the pulmonary artery pressure, shunting of blood may occur through a patent foramen ovale which is present in approximately 30% of the normal population (132). Finally, significant PTE can cause a reduction of the cardiac output due to acute right ventricular failure. The decrease in cardiac output causes a fall in the mixed venous oxygen level which magnifies the impact of the V/Q abnormalities (130). Wheezing is a prominent clinical finding in many patients with PTE and is likely due to serotonin release from platelets adherent to the emboli (133). Treatment with heparin has been credited with reversal of this phenomenon (125,134).

Pulmonary infarction is not common relative to the incidence of PTE. This is related to the fact that the lung receives oxygen from the airways, the pulmonary artery circulation, the bronchial artery circulation, and there is recent evidence that there is back perfusion from the pulmonary veins (135,136). Hence, infarction is less likely to occur in individuals with normal underlying lung.

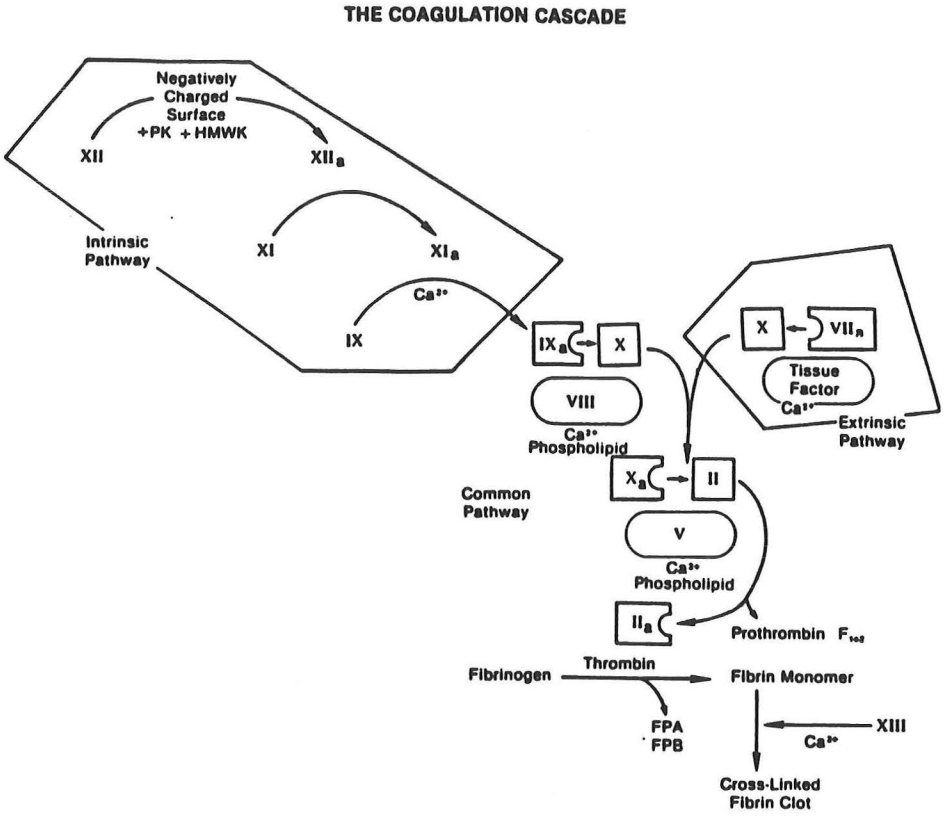
Hemodynamic effects:

Significant PTE result in a decrease in the cross sectional area of the pulmonary vascular bed. If the reduction is significant (greater than 50%), acute right ventricular overload occurs (137). In the presence of abnormal pulmonary vasculature from underlying cardiac or pulmonary diseases, significant loss of the vascular bed occurs with smaller embolic loads due to the loss of pulmonary vascular reserve (20,125). Experimentally, with massive PTE, there is a disassociation of the relationship between right sided and left sided hemodynamic pressures, and a maximum mean pulmonary arterial pressure is reached which is unaffected by rising left atrial pressures (138). This maximal PAP is similar to that found in acute PTE in humans (137). Hence marked pulmonary hypertension is unlikely in acute PTE but it may reach very high levels with underlying cardiopulmonary disease, or with chronic PTE (139,140). Interestingly, patients with symptomatic acute PTE rarely develop pulmonary artery hypertension (PAH) later on, as is found with occult disease (141). This may be related to further platelet deposition that is associated with microemboli (140,142). In animal models, other mechanisms have been identified that increase the pulmonary artery resistance. These are humoral factors such as serotonin or thromboxanes from platelets attached to the emboli (143,144). Serotonin antagonists and thromboxane inhibitors have been shown to produce a decrease in some of the hemodynamic abnormalities following embolism (145,146).

VII. THERAPY

Heparin:

The mainstay of therapy for DVT and PTE has long been the use of heparin. It is poorly absorbed from the GI tract and must be administered parenterally where it is bound to plasma proteins in addition to antithrombin III.



Mechanisms of action:

The antithrombin III-heparin complex inactivates many coagulation enzymes, including thrombin, and the activated factors X, XII, XI, and IX. Some circulating proteins also neutralize the anticoagulant effect of heparin which may contribute to heparin resistance in patients with inflammation and malignancies (147,148). Less heparin is required to neutralize small amounts of IIa and Xa which partially explains the rationale for low dose heparin as prophylaxis of DVT (149).

The effect of heparin varies widely among patients, and there is no easy mechanism to measure heparin levels in the serum. Hence anticoagulant effects are monitored by measuring the biologic effects on coagulation studies. Many studies have determined that efficacy is optimized if the activated partial-thromboplastin time (APTT) is kept within the range of 1.5 to 2.5 times control (150,151). It has also been shown that risk of bleeding increases as the dose is increased (148).

Administration and monitoring:

A loading dose (> 5,000 units iv) is recommended with PTE since heparin clearance is increased in this condition by un unknown mechanism (152). There is some evidence that heparin may counter the release of vasoactive amines from platelets, hence the rationale for large loading doses (> 10,000) recommended by some (53,135). Three recent prospective studies have been done which outline the duration of heparin administration as compared to episodes of major bleeding, recurrence rates of thromboembolism and fatal PTE (151,153,154). All three studies maintained the APTT within therapeutic range, and recurrence was determined by standard tests. Heparin was administered as a continuous infusion in these studies followed by oral anticoagulants. [see table] Other recent studies examined the route of administration of heparin intravenously vs. subcutaneously (155,156). The mean starting dose was the same in the two groups of patients, and the major bleeding episodes and recurrence rates were similar. The most important factor was monitoring of heparin effect with the APTT (157,158). In fact, one recent study suggested improved control of heparin therapy by using a standardized protocol (157).

Until recently heparin was given for a total of 7 to 10 days in treating DVT or PTE, to allow adequate time for the thrombus to become fixed to the vessel wall. However, there are two recent studies that indicate this time may be shortened to 5 days with oral anticoagulant therapy initiated at the same time as heparin [see table] (153,154).

RECURRENCES AND MAJOR BLEEDING WITH DIFFERENT DURATIONS OF HEPARIN INFUSION (147)

Study	Duration of Heparin Infusion Days	DVT or PE	Recurrence	Bleeding
Gallus (153)	4	PE or DVT	7/139 (5%)	3/139 (2.2%)
	9	PE or DVT	6/127 (4.7%)	2/127 (1.6%)
Hull (151)	10	DVT	3/58 (5.2%)	2/58 (3.4%)
Hull (154)	5	DVT	7/99 (7.1%)	7/99 (7.1%)
	10	DVT	7/100 (7.0%)	6/100 (6.0%)
Total			30/523 (5.7%)	20/533 (3.8%)

One should exercise caution when treating patients with massive PTE or large DVT with a short course since these patients were either excluded from these two studies or were not well represented by them (147).

Complications and contraindications:

The major complication of heparin therapy is bleeding. While some studies suggest there is a higher risk of hemorrhage with intermittent dosing of heparin, it was found that the studies using intermittent heparin had higher total doses (155). When the doses over

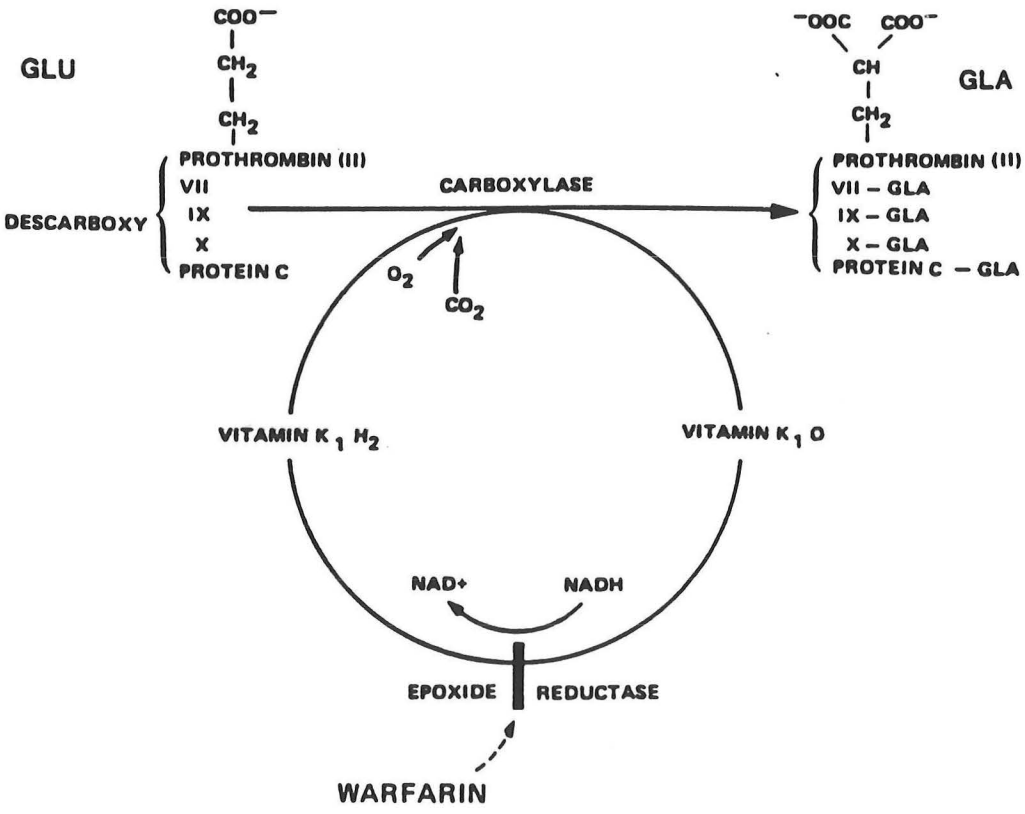
24 hours were the same, the bleeding complication rates were the same (156). In addition to simply overdosing heparin, factors which predispose patients to bleeding are a serious underlying illness, heavy alcohol consumption, and perhaps concomitant aspirin use (153).

Thrombocytopenia is well recognized as a complication of heparin therapy, but is usually asymptomatic (159,160). It tends to be more common with bovine lung than porcine intestine preparations (161-163). It is thought to be caused by an IgG-heparin complex, and usually begins between 6 and 12 days after heparin is started. It is completely reversible with platelet counts returning to normal after heparin is discontinued. Arterial thrombosis is a much less common complication resulting from platelet aggregation with an incidence less than 0.4%, but a significant fatality rate (164). Other less frequent side effects of heparin therapy include hypoaldosteronism (165), and osteoporosis (166) with chronic use.

Warfarin:

Mechanisms of action:

Warfarin acts by inhibiting vitamin K epoxide reductase (167), which results in depletion of vitamin KH2 and limits the addition of carboxyl groups to prothrombin, factor VII, factor IX, X and proteins C and S. Without adequate carboxylation, these proteins cannot undergo conformational changes required for them to bind to their cofactors, thus limiting their biological activity (168) [see figure].



Administration and monitoring:

Warfarin is bound to plasma proteins and has a half life of approximately 36-42 hours. There is a significant variation between the dosing and response of warfarin between patients, and variation can occur with the same subject treated over time (167). The variability may be due to differences in affinity of the receptor, availability of vitamin K (i.e. diet), and administration of other drugs. In addition, long term use is further complicated by patient non-compliance and physician complacency.

Warfarin does not exert its anticoagulant effect until the affected clotting factors are cleared from circulation. Factor VII does have a much shorter half life, 6-7 hours as compared to the other factors, which range from 72-96 hours. However, it is likely that the early anticoagulant effect from depletion of factor VII is counteracted by the thrombogenic effects from depletion of factor C which also has a short half life (169). Hence, in treatment of PTE, heparin therapy is initiated first, and continued for several days until adequate anticoagulation is achieved.

The test most commonly used to monitor therapy is the prothrombin time (PT), which is sensitive to decreased factors II, VII and X. The test is also sensitive to different sources of thromboplastin which is added to plasma to perform the study. In North America, the commercially available thromboplastin is not as sensitive as that available in Europe (170). Hence, for example, anticoagulation in the US is greater than that achieved in the United Kingdom for the same degree of prolongation of the PT. In 1983 the WHO recommended using an international standard for clinical use, the INR system, which uses a reference thromboplastin so that the PT results can be adjusted to the same standard from every country. However, this method has not yet achieved widespread use in the US or Canada, so one must be aware of these differences when interpreting the literature. This is well described in a recent review (167).

The dose of warfarin in the initial treatment of PTE, is usually 10 mg for the first two days followed by a reduction to about 5 mg per day. When adequate anticoagulation is achieved, (after a minimum of 5 days) heparin may be discontinued. The PT is monitored, and the dose adjusted to maintain it at 1.35 to 1.6 times control (or INR of 2.0 to 2.3). The PT is usually monitored daily initially, then twice a week for one to two months depending on the response. If adjustments of the dose are required, the frequency of monitoring should be increased accordingly. The likelihood of significant recurrence of DVT or PE has been demonstrated to be present for up to 4 to 6 months after diagnosis (171,172). However, in patients with massive PTE, or those with underlying conditions that are unlikely to improve, anticoagulation may be continued for much longer, or lifelong.

Warfarin has been well known to interact with many other drugs, some prolong the anticoagulant effect. These are summarized on the following table (167).

DRUGS THAT ALTER PROTHROMBIN TIME BY INTERACTING WITH WARFARIN

Prolongs PT	Reduces PT
Phenylbutazone	Cholestyramine
Metronidazole	Barbiturates
Sulfinpyrazone	Rifampin
Trimethoprim-sulfamethoxazole	Griseofulvin
Disulfiram	Carbamazepine
Amiodarone	Penicillins
Cephalosporins (2nd & 3rd generation)	
Clofibrate	**Inhibits Platelet Function**
Heparin	
Thyroxine	Aspirin
Cimetidine*	Other nonsteroidal anti-inflammatory drugs
Omeprazole*	Ticlopidine
Erythromycin	Moxalactam
Anabolic steroids	Carbenicillin

* Minimal effect

Complications and contraindications:

Like heparin, bleeding is the most frequent complication. Major bleeding appears to be increased in older patients (>65), those with a history of CVA or prior GI bleeding, and other serious coexisting conditions (173,174). The incidence of bleeding with Warfarin over three months therapy for DVT is reported as 17-22% (171). Another, less common complication is skin necrosis which occurs between the third to the eighth day of treatment. It is caused by extensive thrombosis of venules and capillaries within the subcutaneous fat. It has been reported to be associated with protein C and S deficiency, but can be found without these deficiencies (175).

Use of warfarin during pregnancy has been associated with fetal defects, and heparin is preferred if anticoagulation is needed during pregnancy (176).

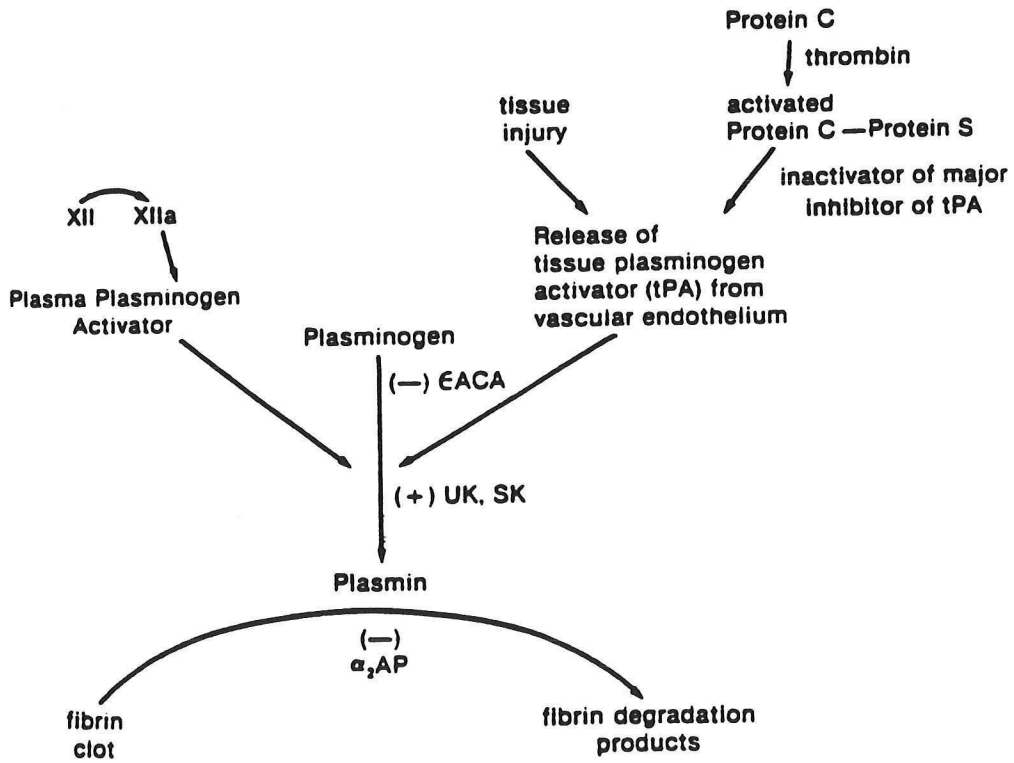
Chronic anticoagulant therapy:

Over the past decade it has been shown that chronic anticoagulation can be achieved with smaller doses of oral anticoagulation which produces less bleeding. Furthermore, heparin administered in a dose of 10,000 units twice a day, has been shown to be equally as effective when warfarin cannot be used (177,178). One must weigh the need for anticoagulation with the known side effects of either drug. Even lower doses of these drugs, or newer agents may prove effective in the future.

Thrombolytic therapy:

Anticoagulant therapy prevents formation of new clot while the endogenous fibrinolytic system slowly dissolves the existing thrombus. However, there are some instances when it is desirable to promote immediate lysis of the clot using an exogenous thrombolytic agent. Thrombolytic agents currently in use are: urokinase (UK), streptokinase (SK), and tissue plasminogen activator (rt-PA). All these agents produce lysis of blood clot. Urokinase and rt-PA activate plasminogen directly, while streptokinase forms a complex with plasminogen to form an activator that accelerates conversion of residual plasminogen to plasmin. Two other newer agents have been introduced and are derived from urokinase (recombinant single-chain urokinase plasminogen activator, rSCU-PA), and streptokinase (APSAC, an in vitro manufactured complex of human plasminogen and streptokinase). Both of these newer agents are supposed to have greater affinity for fibrin and greater potency than the parent drug, but of course, are more expensive (179). (179).

FIBRINOLYSIS



The earliest and largest trial comparing thrombolytic therapy with heparin for PTE was the UPET in 1973. That trial and two subsequent studies did not demonstrate significant improvement in mortality or longtime morbidity between those treated initially with thrombolytic therapy and heparin (180-182). However, there have been detailed physiologic studies that indicate better long term hemodynamics in those treated with fibrinolytic agents vs heparin (183-185). In fact, in the UPET study significant improvement was found at 24 hours in hemodynamically compromised patients treated with fibrinolytic agents vs heparin. This difference did not persist at one week (180). It has been stated that the overall numbers in these studies precluded identifying a significant difference in mortality unless the improvement is drastic (186). There are more studies examining the effects of thrombolysis vs heparin for treatment of DVT (187-190). The bottom line is that thrombolysis is useful for prevention of the postphlebitic syndrome, but with more bleeding complications. However, one long-term comparative study did not find a significant difference between heparin and UK (191).

Over the past decade, thrombolytic therapy has become one of the primary treatments for acute myocardial infarction, with massive promotions for the use of recombinant tissue plasminogen activator, rt-PA. In an attempt to improve the mortality rate of PTE, there has been a resurgence of clinical trials using rt-PA and comparing rt-PA to UK. Thus, in June, 1990, this agent was approved by the FDA for treatment of PTE. One of the first trials conducted found that of 45 patients randomized to receive either agent, clot lysis was better with rt-PA than with UK, and the bleeding complications were much greater with UK (192). However, this study was flawed by using a relatively rapid infusion of rt-PA (100 mg over 2 hrs) compared to a 24 hour infusion of UK. The PIOPED group also used rt-PA (40-80 mg given 1 mg/min) in 13 patients and were not impressed with the results (193). Current studies, however, tend to favor the shorter infusions of rt-PA as being more effective with less bleeding complications, although bleeding may still be significant (192,194,195) In an effort to find a superior method of delivery, Verstraete did not find any difference in clot lysis between intravenous or intrapulmonary infusion of rt-PA (196) Also, studies in dogs indicate the lytic effect of rt-PA is better than UK at a comparable dose, and this effect is improved by simultaneously improving cardiac output (197).

Complications and contraindications:

All fibrinolytic agents produce a generalized fibrinolytic state resulting in bleeding from any recent wound, including puncture sites. Thus, major bleeding is the most common complication and can be fatal. Studies on the use of rt-PA for myocardial infarction revealed that the incidence of fatal hemorrhagic stroke during infusions of 100 mg rt-PA ranged from 0.5 to 1% . In addition, the incidence of severe hemorrhage with SK infusions is higher for those patients 75 yrs or older (24% vs 11%) (198). The general contraindications for fibrinolytic therapy as outlined by the NIH are (199):

Absolute Contraindications

a) Active internal bleeding
b) Recent (within 2 months) cerebrovascular accident or other active intracranial process

Relative Major Contraindications

a) Recent (< 10 days) major surgery, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels
b) Recent serious gastrointestinal bleeding
c) Recent serious trauma
d) Severe arterial hypertension ($\geq$ 200 mmHg systolic or $\geq$ 110 mmHg diastolic)

Relative Minor Contraindications

a) Recent minor trauma, including cardiopulmonary resuscitation
b) High likelihood of a left heart thrombus, for example, mitral disease with atrial fibrillation
c) Bacterial endocarditis
d) Hemostatic defects including those associated with severe hepatic or renal disease
e) Pregnancy
f) Age over 75 years
g) Diabetic hemorrhagic retinopathy

Monitoring:

Fibrinolytic therapy may be monitored by examining decreases in the plasma fibrinogen concentration, since exogenous administration of thrombolytic agents affects all fibrinogen in addition to that within the targeted clot. In addition, the fibrin degradation products from clot lysis also prolong the thrombin time during thrombolytic therapy. Since heparin is also used following thrombolytic therapy, the thrombin time obtained with either ancrod or reptilase will be normal in the presence of heparin but will be increased by FDPs (179).

For long infusions (as with UK and SK), a thrombin time should be checked after 3-4 hours. It should be greater than 2X control value. Since streptokinase resistance may be found due to the presence of anti-streptococcal antibodies, failure of prolongation of the TT should result in discontinuation of therapy. For rt-PA, one should measure TT and/or PTT at conclusion of drug infusion, followed by initiation of heparin without a loading dose when the laboratory value has fallen to < 2X control. Heparin is started at the conclusion of UK and SK therapy in the same manner (179,200,201).

PHARMACOLOGIC CHARACTERISTICS OF THROMBOLYTIC AGENTS

	SK	APSAC	UK	rSCU-PA	rt-PA
Enzymology	Proenzyme	Proenzyme	Enzyme	Proenzyme	Enzyme
Administration	Continuous IV	Bolus	Continuous IV	Continuous IV	Continuous IV
Plasma Clearance (t 1/2), min	18-25	70-90 ·	13-20	5-8	2-6
Fibrin specificity	1+	1-2+	2-3+	2+	1-2+
Bleeding	4+	4+	4+	4+	4+
Allergic Side Effects	Yes	Yes	Rare	?	Rare
Cost	1+	3+	3-4+	?	4+

Conclusion:

Future trends in thrombolytic therapy with rt-PA may result in shorter infusions than currently used now (197). Nevertheless, there are not enough clinical studies available at this time to establish the superiority of one treatment over the other for all PTE. In addition, the increased bleeding complications from thrombolytic therapy must be considered. Until sufficient numbers of patients are studied, the indications for and dosing of thrombolytic therapy are not established. Thrombolytic therapy is usually reserved for patients with obstruction to a large segment of the pulmonary circulatory tree, or those with hemodynamic compromise, and should be considered for all such patients with no contraindication to fibrinolytic therapy (199). If angiography is available, it should be performed prior to initiating therapy. However, a high probability scan in the presence of a high clinical likelihood of PE has been considered acceptable by many experts (201).

Surgical Intervention:

Embolectomy:

Even when massive PTE or hemodynamic compromise is present, surgical embolectomy is rarely indicated. With the use of cardiopulmonary bypass, the mortality of this procedure in patients with acute PTE who have survived the first two hours is in the range of 23-25% (202). It should be emphasized that these figures are from institutions where these procedures are performed frequently. On the other hand, this procedure is used with relative success as treatment for pulmonary hypertension secondary to chronic PTE (203-205). In a recent study the perioperative mortality was 12.6%, with 31.5% of the patients requiring mechanical ventilators for more than 5 days (203). Pulmonary edema and pulmonary hemorrhage were significant complications, and have been described by many (206,207). Failure to decrease the pulmonary vascular resistance intraoperatively by more than 50% was a predictor of hospital mortality, as was the duration of cardiopulmonary bypass. Nevertheless, of the survivors, there appears to be a significant improvement in functional status (203).

Vena Caval Interruption:

In some instances it is necessary to physically prevent migration of additional clot from the lower extremities to the pulmonary circulation. This is usually accomplished by inserting a mechanical filter transvenously into the inferior vena cava. Indications for insertion of these devices are listed below:

1) DVT or PTE with Contraindication to anticoagulation
2) Failure of adequate anticoagulation
3) Prophylaxis against any further PTE, usually in presence of massive PTE, or chronic PTE with evidence of pulmonary hypertension (208)

Currently there are several different devices available, and some of the older devices have either changed or have been removed from the market (e.g.Mobin-Uddin Umbrella). The five devices available in 1991 are shown in the following table:

Filter type	Max IVC Diam Recommended (mm)	Tilting Significant	IVC Patency (%)	Incidence Recurrent PE (%)	MRI Interference?
Greenfield stainless steel	28	Yes	95-97	5	Yes
Greenfield titanium	28	Yes	?	?	No
Bird's nest	40	No	80-97	3	Yes
Vena-tech	28	Yes	93	2	Yes
Simon nitinol	28	No	92	1	No

[from reference 209]

When selecting which filter to use, one must consider the following: filtering efficiency of both large and small clots, impedance of blood flow, low morbidity (penetration of vena caval wall, migration of filter, morbidity associated with device placement), and interference with MRI, i.e. ferromagnetic properties. None of the above filters meet all the requirements (209).

Other complications include migration of filters, perforation of vena cava into other structures such as aorta, ureter,etc., rarely embolization of the filter itself, and clot formation on the proximal surface of some filters have been described (208,210-212). Experience with a new removable filter has been reported (213). This filter is designed to temporarily prevent recurrent PTE while thrombolytic therapy is initiated, thus it is associated with bleeding complications.

Severe coagulopathy that would result in significant bleeding from puncture site, and a patient who would not cooperate with the procedure or post procedure protocol.

It is recommended that a venacavogram be done before the placement of transvenous filters in order to identify the precise extent of the clot in relation to the renal veins, establish the diameter or the IVC and to identify any significant collateral circulation (209). If it is necessary to place a filter above the renal veins, use of the 24-Fr Greenfield filter is recommended due to its documented high patency rate, while the Birds nest filter currently is recommended as the filter most suited for general use (209,214).

VIII. PREVENTION

The best means of decreasing mortality from PTE is to prevent their occurrence in the first place. This seems obvious, but is of major importance since 70-80% of those who die of PTE do so within the first few hours, often before diagnosis and therapy can be initiated (1,2). There is compelling evidence that the overall incidence of DVT and PTE in hospitalized patients is decreasing (3-5). It is believed that this is due to improved techniques for prevention of clot formation in those patients who are identified as high risk. The principle involved is the reversal of conditions that promote clot formation in the first place: stasis, the clotting mechanism, and damage to the vessel intima. The majority of studies on prevention are conducted with surgical patients since these are an easily

matched population of patients. Furthermore, the incidence of DVT detected by leg scanning in orthopedic patients is probably the highest, see Table (35).

INCIDENCE OF THROMBOEMBOLIC COMPLICATIONS IN ORTHOPEDIC SURGERY

	Deep vein thrombosis (%)	Pulmonary embolism (%)	Fatal Pulmonary embolism (%)
Trauma	?20	?10	?1
Hip fracture	11-74	4	4-10
Total hip replacement	40-58	5-10	2-5
Total knee replacement	50-70	5-10	1-5

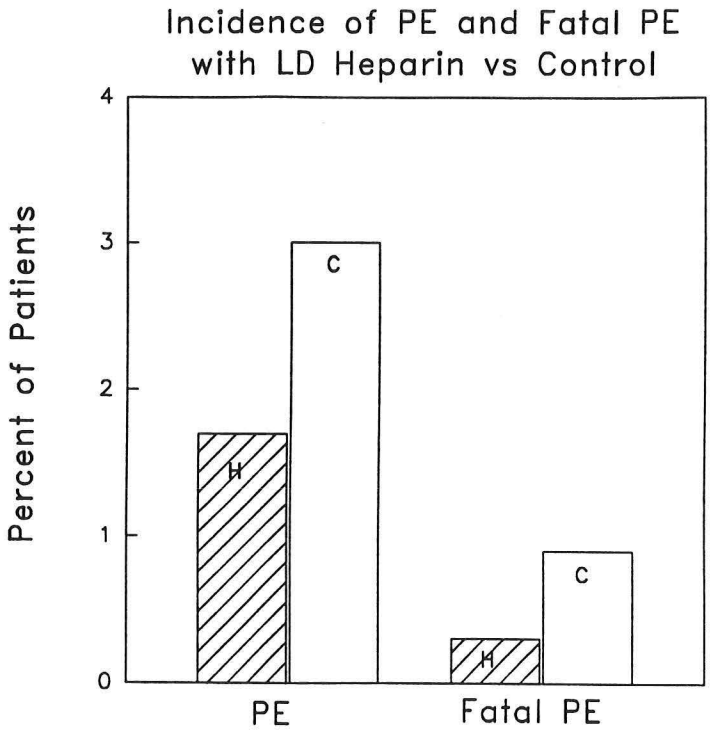
Increasing blood flow:

Over the past decade patients undergoing surgery are encouraged if not pushed to early ambulation and discharge from the hospital. This has certainly contributed to the decrease in mortality since the incidence of clot formation increases with the duration of bed rest. While patients are hospitalized, other attempts have been made to increase blood flow through the venous system of the legs. Elastic compression stockings have been shown to reduce the incidence of DVT as determined by I^{125} radiofibrinogen scans from 32% to 11.5% overall in general surgical patients (215). However, only those stockings that provided graduated compression which varied over the ankle, calf, knee, lower and upper thighs, were effective (215). On the other hand, these stockings must be individually fit which may discourage routine use. In order to provide pulsatile flow through the leg, intermittent pneumatic compression devices were developed (IPC). These devices consist of boots that fit around the calves or entire legs. Through use of air compartments, the devices are rhythmically inflated and deflated, which causes blood to be pumped through the lower leg. Interestingly, IPC has been demonstrated to increase fibrinolysis in surgical patients, and prostacyclin produced by endothelial cells was found to be 16 times greater in those exposed to pulsatile flow (216,217), which suggests that IPC prevents clot formation through additional mechanisms. Use of these devices in high risk orthopedic patients reduces the incidence of DVT to 22% from 47% (218). Devices which fit up to the thigh giving full-leg sequential compression have been reported to increase flow better than those providing knee-length uniform compression (219). The combination of graduated compression stockings with IPC also has been shown to give additive effects (220). It seems logical to use either graduated compression stockings or knee-length sequential compressive devices in all patients at risk, since they are relatively easy to use, with no complications of bleeding.

Heparin:

A recent extensive review of multiple comparable trials demonstrated that in surgical patients at risk for PTE (general surgical,urological, and orthopedic) use of "low-dose" heparin produces a significant reduction, of approximately 68%, in the incidence

of DVT as detected by radiofibrinogen scans, or venography (221). Collins, et al point out that although several orthopedic trials with low dose heparin do not show a reduction in incidence of DVT, this was likely due to the small numbers used in any one study since the combined results from multiple studies demonstrated the beneficial effects of low dose heparin, see figure (221). This review also concluded that the incidence of fatal PTE was reduced by approximately 47%, and established that heparin administered subcutaneously as 5,000 units either every 8 or 12 hours produced equal effects. "Excessive bleeding" was noted to be increased in the groups receiving heparin by about 66%, with an increase of 227% in urologic patients (221). However, the overall mortality, including that from hemorrhage, was still less in the heparin treated patients. Many surgical studies include wound bleeding as significant bleeding which was reported to be as high as 27% (222).



In addition to low-dose heparin, the addition of dihydroergotamine, which is added to increase the vascular tone of peripheral veins and enhance blood flow, has been reported to increase the effectiveness (223,224). Also use of adjusted dose heparin to prolong the APTT may add further to the prophylaxis of DVT with less bleeding complications (35) In order to reduce the increased risk of bleeding in surgical patients receiving prophylactic anticoagulation, trials have been conducted with low molecular weight heparin. The results of recent studies seem to indicate that this agent produces a similar or better reduction in incidence of DVT while having a slightly lower incidence of important hemorrhage (225-227).

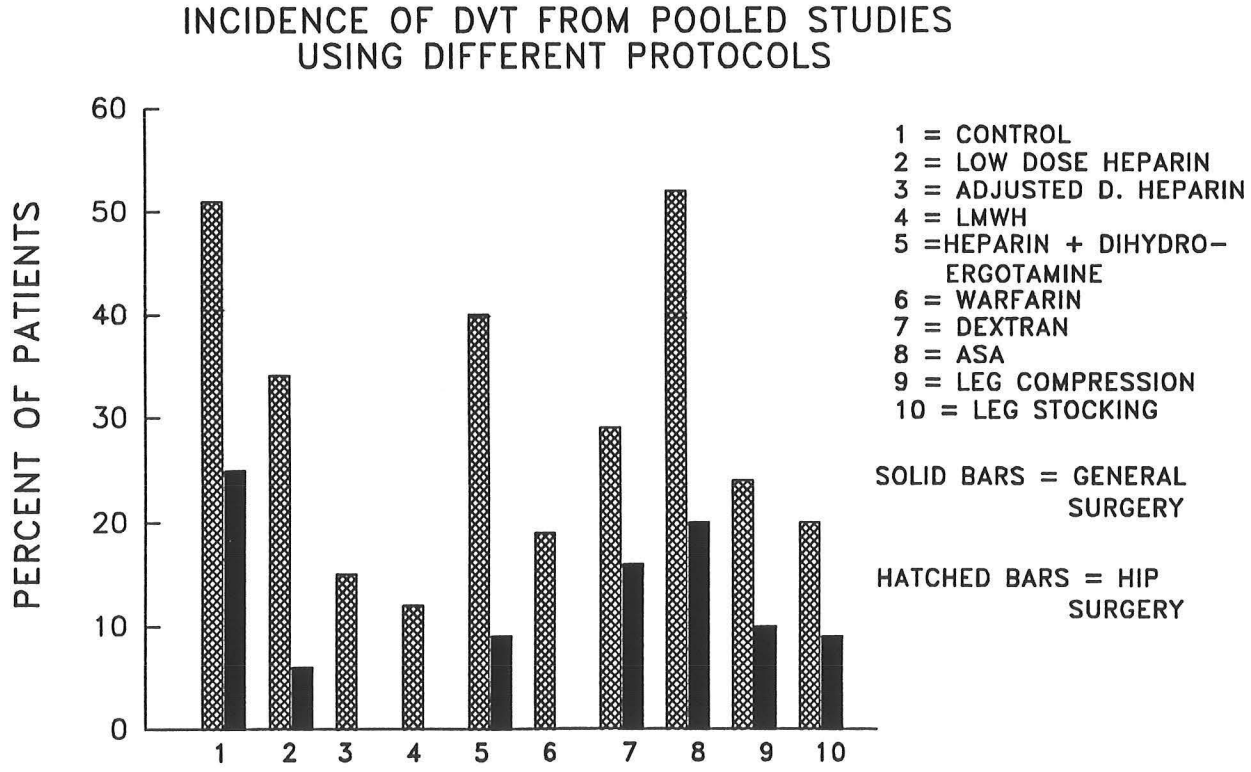
Warfarin:

Warfarin therapy has also been used to prevent DVT in surgical patients, particularly those with hip surgery. Very low doses such as 1 or 2 mg are given preop, followed by an increase postop to therapeutic levels (228). While data indicates warfarin is associated with a reduction in rates of DVT of about 48%, this is also associated with an equal increase in significant bleeding (35). In patients who cannot tolerate any risk of increased bleeding, i.e. neurosurgical patients, pneumatic compression devices with graduated compression stockings appears to be the best option (229).

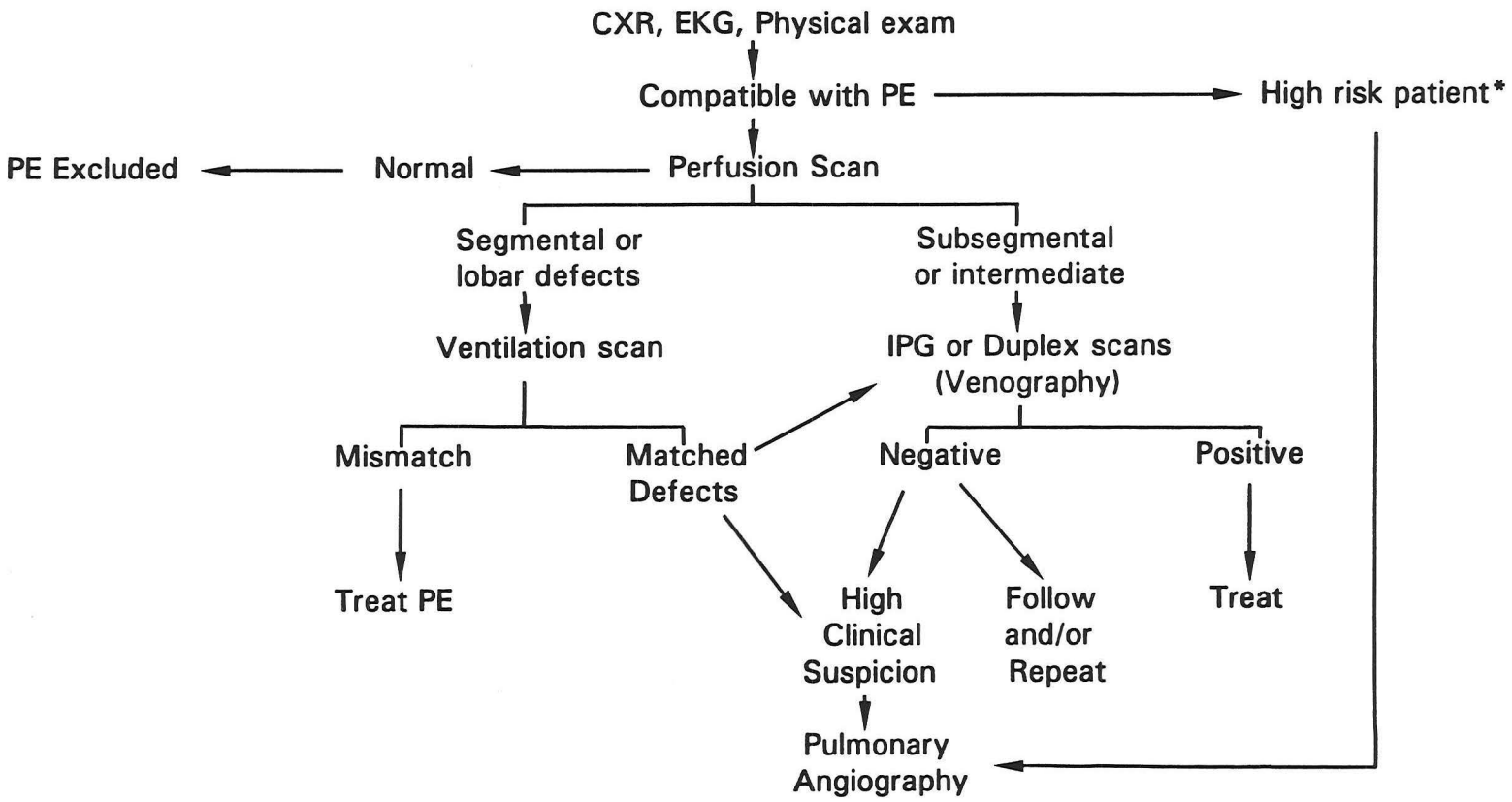
Other:

It has been demonstrated that trauma or surgery is associated with a decrease in antithrombin III, and this may contribute to the predisposition of these patients to DVT. Administering antithrombin III with low dose heparin has been shown to improve the effectiveness of DVT prophylaxis in patients receiving total hip or knee replacement (230). There are other protocols used for prophylaxis, such as low molecular weight dextran (231), and antiplatelet drugs (232) which have been advocated. The choice of the regimen for prophylaxis varies with the patient population treated. However, it is important that those known to be high risk be given prophylaxis. It has even been advocated that those at very high risk, but who have contraindications to every form of prophylactic treatment, such as severe trauma patients, have vena caval filters placed (53). In contrast, an excellent review using meta-analysis describes the effectiveness of different prevention modalities in general surgical patients. Orthopedic cases were excluded (233).

The following is a summary of many different protocols used as prophylaxis for DVT in patients undergoing either general (233) or hip (35) surgery.



A PRACTICAL DIAGNOSTIC ALGORITHM



*Massive PE suspected, significant cardiopulmonary disease
Thrombolytic or IVC filter considered

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