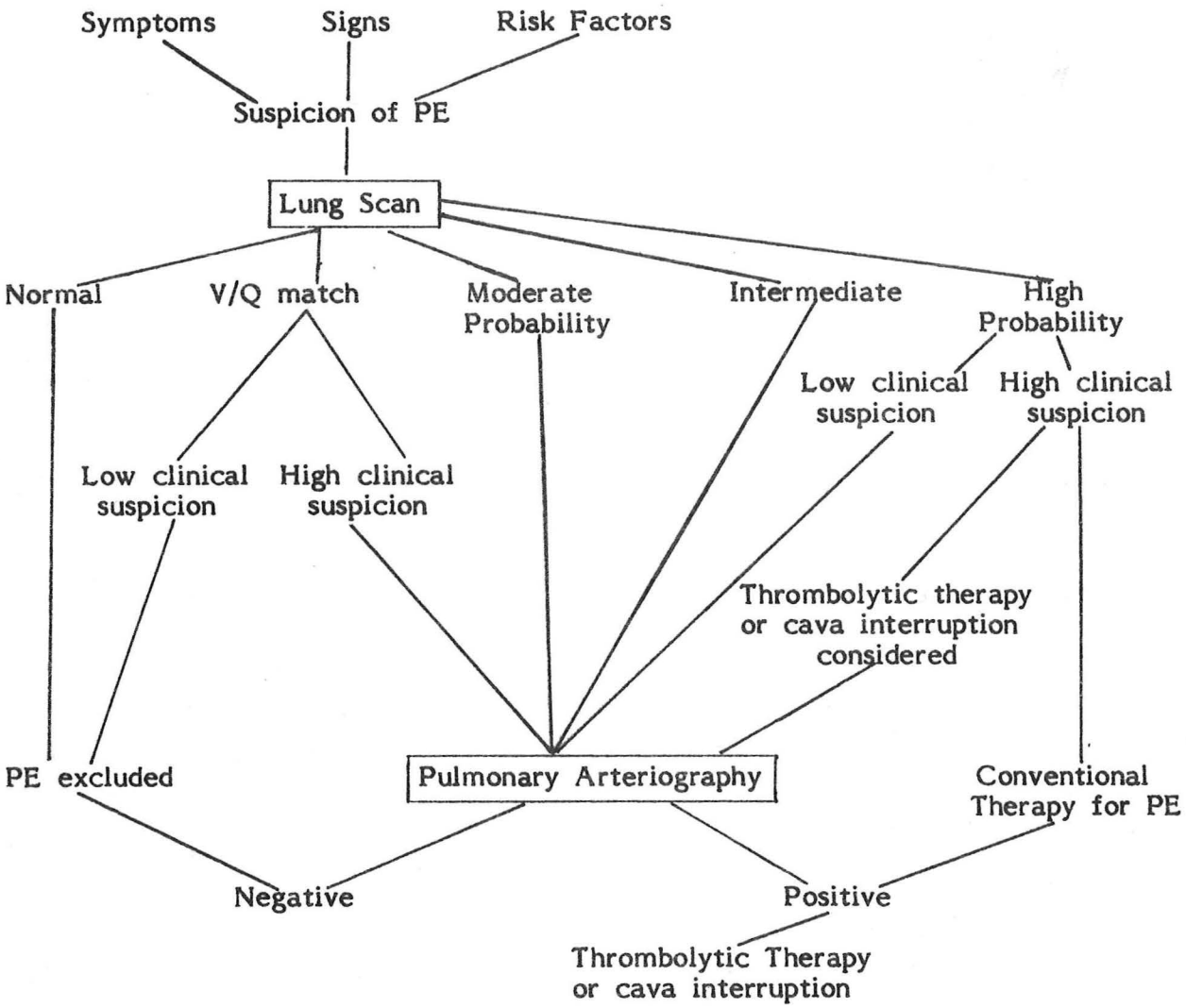
Rubin.

PULMONARY THROMBOEMBOLIC DISEASE



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I. Introduction

It has been conservatively estimated that 500,000 individuals in the United States suffer a pulmonary embolism (PE) each year, and between 10 and 20 percent of these patients will die as a result of this condition (1-4). Pulmonary embolism was the most common single cause of death in a survey performed at one large general hospital, accounting for one of every seven deaths (5); overall, it is the third most common cause of death in this country. The significance of this condition is further accentuated by the frequency with which pulmonary embolism escapes diagnosis: Autopsy studies have shown that, although significant emboli are demonstrated in 14 percent of autopsied patients, a definitive antemortem diagnosis is made in less than half of cases (6,7). Compounding the problem of underdiagnosis of PE - particularly in patients who are at risk - concern has been raised that there is a tendency to overdiagnose PE in individuals who are not particularly predisposed to its development (8), subjecting them to unnecessary and potentially dangerous diagnostic and therapeutic interventions.

The diagnosis of PE has traditionally depended upon a clinical suspicion followed by either noninvasive tests with variable specificity and sensitivity, or invasive and costly procedures. Accordingly, considerable controversy and, as a result, confusion, has been generated concerning the optimal approach to a patient suspected of having thromboembolic disease. This protocol reviews the clinical features and diagnostic approaches to PE, including an evaluation of newer modalities, and provides suggested guidelines for their use. Finally, the options and indications for the therapy and prophylaxis of venous thrombosis and PE will be reviewed.

II. Etiology

Venous thrombi are the most common source of PE, although thrombus originating from the right atrium (9-12) and non-thrombotic material including septic vegetations (13-15), tumor (16,17), amniotic fluid (18), air (19), fat (20), and mineral or vegetable material injected intravenously in conjunction with illicit drug use (21) may also embolize to the lung (22). The frequency with which venous thrombosis results in PE is not known, although autopsy studies suggest that over 60 percent of cases of deep venous thrombosis (DVT) have pathologic evidence of emboli (23). Gallus (24) reported that 4 of 9 patients with proximal DVT diagnosed by ^{125}I fibrinogen scanning had PE, whereas none of 92 patients with negative leg scans and none of 31 patients with calf vein thrombosis alone had PE. That distal, i.e. isolated calf vessel DVT is infrequently associated with PE has been confirmed by Moser and LeMoine (25): In their study, none of 21 patients with DVT limited to the calf veins had PE, while 8 of 15 with combined proximal (thigh) and distal (calf) thrombosis had PE (Table 1).

It has been estimated that 15-20 percent of emboli arise from thrombi in the pelvic veins or the prostatic plexus (26,27). Upper extremity venous thrombosis is uncommon and accounts for less than 1 percent of PE (28,29).

Table 1. Results of Ventilation and Perfusion Scans in 68 Patients†

Venogram	V/Q Scan*	
	Normal or Not Diagnostic	Mismatch
Negative	31 (8)	0
Distal only	21 (6)	0
Distal and proximal	7 (3)	8
Not done	1 (0)	0
Total	60 (17)	0

*Figures in parentheses indicate patients with abnormal scans classified as not diagnostic or embolism.
†From Moser and LeMoine: Ann Int Med 94: 439, 1981.

III. Predisposing Factors

A variety of factors predispose to the development of thrombosis and PE (Table 2):

Table 2. Frequency of Predisposing Factors by Massiveness of Pulmonary Embolism†

Predisposing Factor	Prevalence (%)		
	All patients (N=160)	Massive (N=90)	Submassive (N=70)
Concurrent venous disease	54	61	44
Immobilization (postoperative, fractures, other enforced bed rest)	59	63	54
Prior cardiopulmonary disease	35	33	37
Metabolic, endocrine, collagen, vascular, and misc. disorders	18	19	17
Malignant neoplasm	6	8	4
Oral contraceptive use (women only)	24	11	38

†From the Urokinase Pulmonary Embolism Trial. Circulation (Suppl) 47: II-1, 1973.

Approximately half of patients with PE have concurrent venous disease, although it may not be clinically obvious. Immobilization, either due to medical incapacitation, post-operative state, or fractures, predisposes to impaired venous blood flow and thrombosis (31).

Thromboembolism is most frequent in adults between the ages of 50 and 60 years (32,33) (Figure 1). This is probably more an indication of the frequency of other risk factors in this group rather than representing an independent factor.

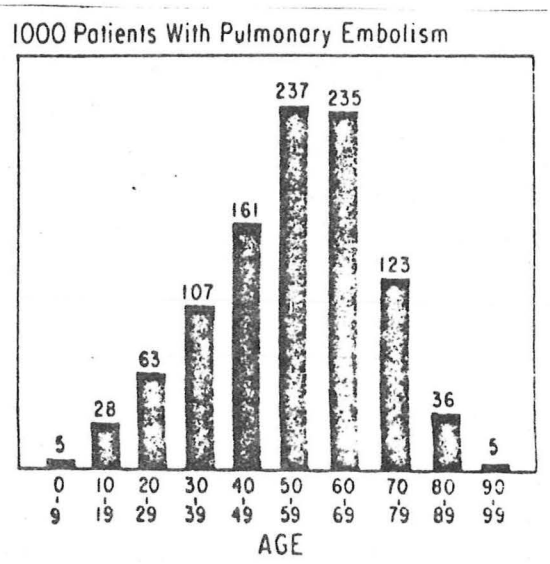


Figure 1. Age distribution in 1,000 patients with PE (from reference 32).

Although there does not appear to be a difference in frequency between the sexes (30), women taking oral contraceptives are at an increased risk for both DVT and PE (33).

Preexisting cardiac disease, particularly when atrial fibrillation or congestive heart failure are present, poses a major risk factor (30,34).

It has been estimated that 15 percent of patients with major trauma, particularly fractures and burns, experience PE during the course of their illness (34,35).

Obesity (>20 percent above ideal body weight) predisposes to PE, probably due to the frequency of coexistant cardiopulmonary disease and the sedentary lifestyles which are common in this population.

The association of recurrent, migratory thrombophlebitis and thromboembolism with malignancy was first reported by Trousseau (36). The incidence is greatest in the setting of adenocarcinoma (lung, gastrointestinal tract, pancreas, genitourinary tract) (37) and has prompted the hypothesis that mucin-secreting cells accelerate thrombus formation. Neoplastic cells produce histones, cathepsins and proteases which are capable of activating the coagulation cascade. Patients with malignancies have been reported to have shortened bleeding and clotting times and decreased prothrombin and partial thromboplastin times (36). A specific circulating thromboplastin has not, however, been identified.

The incidence of PE in pregnant women is several times greater than in non-pregnant females matched for age (38). The immediate post-partum period is the time of greatest risk (39,40).

Other conditions predisposing to PE include sickle cell disease (41,42), paroxysmal nocturnal hemoblobinuria (43), hereditary antithrombin III deficiency (44), homocystinuria (45), Behcet's syndrome (46), diabetes mellitus, and chronic respiratory disease (30).

IV. Clinical Features

A. Signs and Symptoms

The clinical signs and symptoms of patients presenting with PE are usually nonspecific (Table 3):

Table 3. Frequency of Symptoms and Physical Signs by Angiographic Massiveness of Pulmonary Embolism††

	Prevalence (%) Massiveness of pulmonary embolism		
	All patients (N=160)	Massive (N=90)	Submassive (N=70)
Symptoms			
Dyspnea	81	70	83
Pleuritic pain	72	62	84†
Apprehension	59	61	56
Cough	54	50	50
Hemoptysis	34	27	44
Sweats	26	27	24
Syncope	14	22*	4
Signs			
Rales	53	50	57
Elevated S_2P	53	60*	44
Thrombophlebitis	33	42	21
S_3, S_4 gallop	34	47*	17
Diaphoresis	34	41	24
Edema	23	24	21
Murmur	23	20	7
Cyanosis	18	28*	6

*Significant positive association with massive pulmonary embolism.
†Significant positive association with submassive pulmonary embolism.
††From the Urokinase Pulmonary Embolism Trial. Circulation (Suppl) 47: 11-1, 1973

Signs and symptoms which indicate an impaired right ventricular output, such as syncope, right-sided gallops and either central or peripheral cyanosis, are more commonly seen with massive embolism.

B. Chest Radiograph

The "classic" signs of PE on plain film can be divided into two categories - those associated with infarction and those which are not. However, the "classic" findings are unusual, and the most common finding is a normal film (Table 4). Indeed, the finding of marked dyspnea out of proportion to radiographic abnormalities should heighten one's suspicion for the presence of PE, particularly when it occurs in a patient with risk factors predisposing to its occurrence.

Table 4. Frequency of Preinfusion Chest Roentgenographic Abnormalities in 128 Patients †

Roentgenographic Finding	No.	%
Lung parenchyma	60	47
Consolidation	53	41
Atelectasis	26	20
Other	2	2
Pleural effusion	36	28
Diaphragmatic elevation	52	41
Pulmonary vessels	50*	39
Distention of proximal pulmonary arteries	30	23
Focal oligemia	19	15
Pulmonary arterial hypertension	4	3
Pulmonary venous hypertension	4	3
Other	3	2
Heart	24*	19
Right ventricular enlargement	7	5
Left ventricular enlargement	21	16
Right atrial enlargement	2	2
Left atrial enlargement	2	2

*Number of patients with at least one roentgenographic finding of that subgroup.
†From the Urokinase Pulmonary Embolism Trial. Circulation (Suppl) 47:II-1, 1973

C. Electrocardiogram

The "classic" pattern of $S_1Q_3T_3$ (Figure 2) described by McGinn and White (47) is seen only with massive PE, which occurs in approximately 10 percent of cases (48). Other ECG findings are usually nonspecific (Table 5).

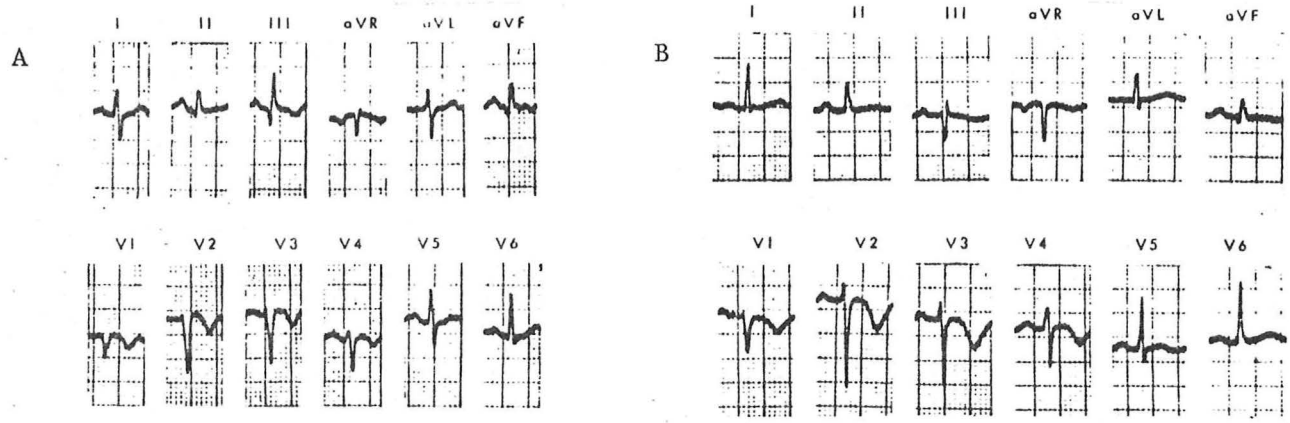


Figure 2. Electrocardiogram from a patient with massive PE. A, ECG on admission. Pulmonary artery pressure was 63/24 (mean 42 mmHg), cardiac index 0.9 L/min/m^2, lung scan showed 50 percent vascular occlusion. B, ECG one day later, PA pressure was 32/12 (mean 20 mmHg), cardiac index was 2.3 L/min/m^2.

Table 5. Frequency of Electrocardiographic Abnormalities in 132 Patients†

Abnormalities	No.	%
Rhythm disturbances	15*	11*
Premature atrial beats	5	3
Premature ventricular beats	23	9
Atrial fibrillation	4	3
Atrioventricular conduction disturbances		
First degree A-V block	6	5
P pulmonale	5	4
QRS abnormalities	86*	65*
Right-axis deviation	6	5
Left-axis deviation	16	12
Clockwise rotation (V_4)	37	28
Clockwise rotation (V_5)	10	8
Incomplete right bundle-branch block	7	5
Complete right bundle-branch block	15	11
Right ventricular hypertrophy	7	5
$S_1S_2S_3$	12	9
$S_1Q_3T_3$	14	11
Pseudo-infarction	14	11
Low voltage (frontal plane)	21	16
Left bundle-branch block	2	2
Left ventricular hypertrophy	3	2
Primary RST-segment and T-wave abnormalities	85*	64*
RST-segment depression (not reciprocal)	43	33
RST-segment elevation (not reciprocal)	14	11
T-wave inverstion	53	40
S_1T_3	25	19

* Number and percentage of patients with at least one abnormality in group.
† Circulation (Suppl) 47: II-1, 1973.

D. Arterial Blood Gases

The PaO_2 is often considered to be an important and useful discriminating laboratory test in pursuing a diagnosis of suspected PE. Although it is often stated that a PaO_2 greater than 85 torr makes PE unlikely, a normal PaO_2 does not exclude PE (Figure 3).

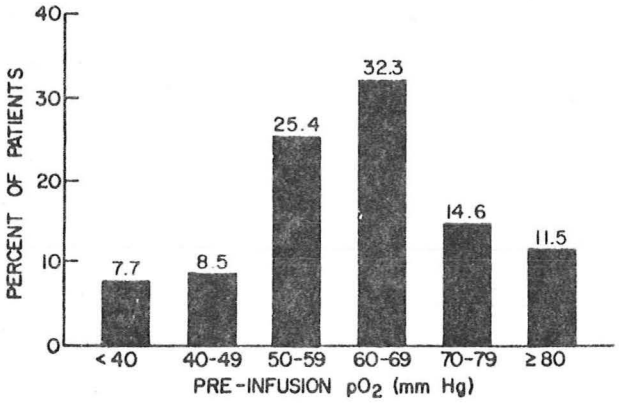


Figure 3. Distribution of PaO_2 values in patients with PE.

In the UPET study, 12 percent of patients with PE had a PaO_2 greater than 80 torr while breathing room air (30). In a study of 97 patients between the ages of 18 and 40 who underwent complete evaluation for pleuritic chest pain, the mean PaO_2 in those with PE was 81 torr, compared with a PaO_2 of 77 torr in those without PE (49). This included one patient with a PaO_2 of 108 torr (measured twice) who had multiple pulmonary emboli. Additionally, conditions which predispose to PE such as congestive heart failure and chronic respiratory disease also cause hypoxemia, and exacerbations of these conditions or acute illnesses complicating the chronic process, such as pneumonia, can clinically mimic PE and worsen hypoxemia. Thus, blood gas determinations may be necessary to determine the need for supplemental oxygen therapy or ventilatory support, but they lack the sensitivity or specificity necessary to rely on them as a diagnostic tool.

E. Other Laboratory Tests

Pleural effusions occur in approximately 30% of cases, but the chemical characteristics of the fluid are variable and there is no profile which is diagnostic of PE (50). Although thoracentesis may be indicated to exclude empyema in an occasional case, routine thoracentesis of a pleural effusion in a patient suspected of PE is not recommended because of the increased risk of bleeding with subsequent anticoagulation. Some authors consider a recent thoracentesis to be a relative contraindication to thrombolytic therapy (51,52).

An accurate, inexpensive screening blood test for DVT or PE would be very appealing, and a number of potential candidates have been proposed: The triad which Wacker et al (53) suggested to be diagnostic of PE consists of an elevated LDH and bilirubin with a normal SGOT, but it is present in only approximately 10 percent of patients (54). The mean LDH in the UPET study was normal (30).

Fibrin split products have been reported to be elevated in PE, but elevations are common in a variety of critical illnesses (55,56). The simultaneous elevation of split products and soluble fibrin complexes, although more specific for PE (Table 6), is found in only 50 percent of cases (57). Sipes (58) found plasma DNA was elevated in 19 of 23 patients with PE but in none of 49 patients with pneumonia, DVT or myocardial infarctions; however, subsequent studies have not confirmed either the sensitivity or specificity of this test (59).

Table 6. Combination of Fibrin Degradation Products and Soluble Fibrin Complexes in Various Populations †

Subjects	N	Both Positive (%)	Both Negative (%)
Normal control	24	0	79
Pulmonary diseases	80	4	35
Negative pulmonary angiogram	28	7	54
High risk for venous thromboembolism	100	9	23
Deep venous thrombosis	31	23	10
Acute pulmonary embolism	39	72	3

†From Bynum, LJ et al: Am Rev Respir Dis 114: 285, 1976.

F. Radionuclide Studies

1. Lung Scan

The lung scan is the most widely used procedure in evaluating suspected PE. Since pulmonary blood flow will be diminished in areas supplied by occluded vessels, a radionuclide such as ^{99m}Tc-macroaggregated albumin (MAA) injected intravenously will be filtered by perfused pulmonary vessels which are greater than 10μ in diameter, giving an index of overall lung perfusion. Less than 0.2 percent of precapillary vessels are occluded for a period of 4 to 8 hours by this procedure. Although this procedure is generally tolerated by most patients, those with severe pulmonary hypertension or right-to-left shunts can experience worsening pulmonary hemodynamics or systemic embolization, respectively (60-63). In this setting, reducing the amount of injected MAA by 50 to 75 percent allows adequate vascular visualization with a reduced risk. Performing scanning over the brain or kidneys may confirm the presence of a right-to-left shunt.

Perfusion defects are not specific for PE. Any condition which interferes with the distribution of ventilation, such as pulmonary infiltrates due to infection or atelectasis, obstructive airways disease or congestive heart failure, will also interfere with pulmonary blood flow. The specificity can be increased by combining ventilation with perfusion scanning (64-67). Perfusion defects which are segmental or larger that ventilate normally (V/Q mismatch) reflect a high likelihood that PE is the etiology (Table 7). In contrast, areas that both ventilate and perfuse poorly or that retain activity during the washout phase are more consistent with parenchymal disease, although emboli cannot be excluded. A normal perfusion scan excludes PE, with the rare exception of a patient with massive, "saddle" embolism (68,69).

Table 7. Frequency of Venous Thromboembolism by Pulmonary Angiography, Venography, or Both, in Patients with Abnormal Perfusion †

Perfusion Abnormality	Ventilation Scan Result	Pulmonary Embolism by Angiography	Venous Thromboembolism by Angiography, Venography, or Both
		n(%)	
One or more segmental or greater defects	Mismatch 35	30 (86)	32 (19)
	Match 13	3 (23)*	6 (46)
One or more subsegmental defects	Mismatch 15	4 (27)	6 (40)
	Match 8	1 (13)	1 (13)
Indeterminate		2/12 (17)	7/12 (58)

*None of the four patients with a ventilation-perfusion match and pulmonary embolism shown by pulmonary angiography had chronic obstructive lung disease.
†From Hull, RD et al: Ann Intern Med 98: 891, 1983.

The radioactive gas most widely used for ventilation studies is ^{133}Xe. Ventilation scanning requires a closed system and a cooperative patient who can breath-hold for up to 30 seconds. Since up to 48 percent of studies would not require ventilation scanning to exclude PE, it is probably wise to reserve performing ventilation scanning until the perfusion study has been performed and reviewed (67).

There appears to be a reasonably good correlation between the degree of vascular obstruction determined by angiogram and that estimated by perfusion scan (30,70) (Figs. 4 and 5).

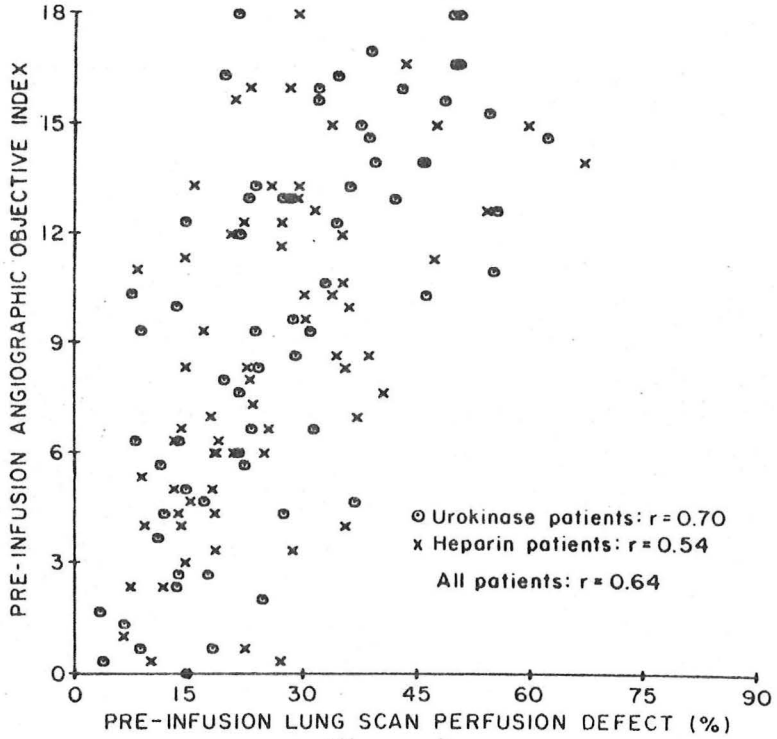


Figure 4.

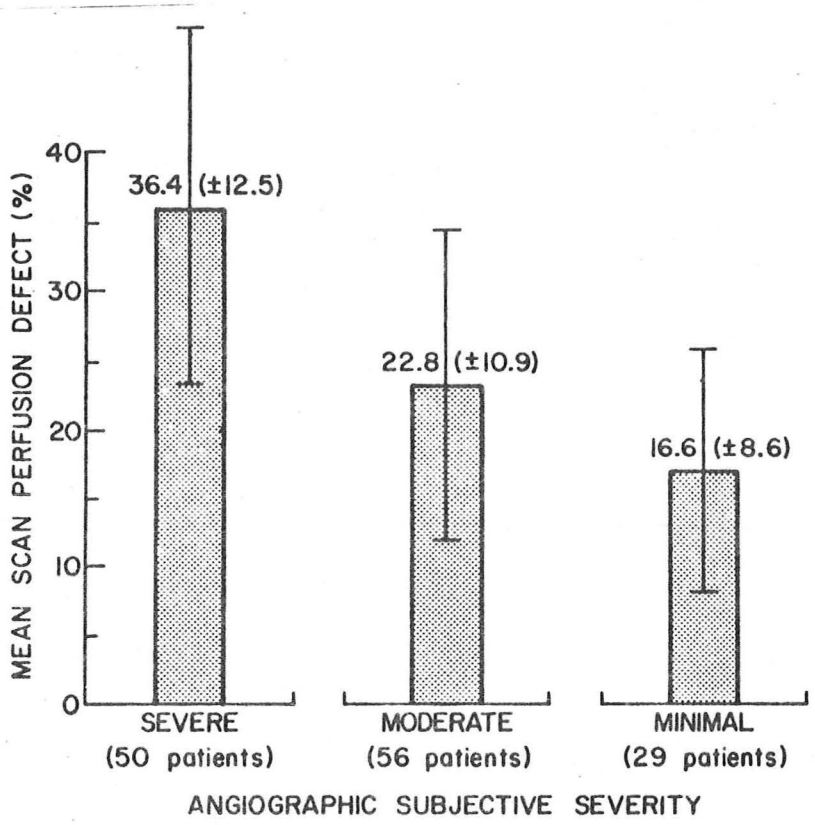


Figure 5.

G. Pulmonary Arteriography

Pulmonary arteriography is considered to be the most definitive diagnostic procedure in suspected PE (71), although up to 17 percent of studies may be indeterminate (72). The yield of a definitive diagnosis is enhanced by viewing in at least two projections and by performing selective vessel angiography (73). Bossart et al (74) demonstrated that 4 of 47 arteriograms which were reported as normal when a single projection was viewed were subsequently called positive for clot when a second projection was employed.

The arteriographic diagnosis of PE requires the visualization of clot in the pulmonary artery, either as an intravascular filling deffect or as an abrupt cutoff (75-77). Secondary signs, such as diminished perfusion, areas of oligemia, a prolonged arterial phase, delayed venous visualization and vascular tortuosity are not diagnostic for PE, and can be seen with parenchymal lung disease, mitral valve disease, left ventricular failure, primary and other forms of secondary pulmonary hypertension.

Despite its invasiveness, pulmonary arteriography can generally be performed safely. In several studies totalling nearly 2,000 patients undergoing arteriography the combined morbidity was less than 5 percent, and death occurred in five patients (0.26 percent) (78,79). Four of the five deaths occurred in patients with pulmonary hypertension and were probably related to the osmotic and pulmonary

vasoconstrictor effects of the contrast agent in the setting of a compromised right ventricle and pulmonary circulation (80-82). Mills et al (78) found that all 3 deaths during pulmonary arteriography in their study occurred in patients with overt right heart failure; They suggested a right ventricular end diastolic pressure (RVEDP) of 20 mmHg as the upper limit for using contrast material.

The risks of arteriography in the setting of pulmonary hypertension can be minimized by performing selective arteriography with hand injections rather than power injections into the main pulmonary arteries. There is preliminary evidence which suggests that iopamidol is better tolerated and safer than diatrizoate for pulmonary arteriography (83).

Less serious complications of pulmonary arteriography include hypotension, pyrogen reaction, bronchospasm, pulmonary edema, anaphylaxis, and arrhythmias. Cardiac or pulmonary artery perforation have also been reported.

Digital subtraction angiography (DSA) offers the theoretic advantage of visualizing the pulmonary circulation with the peripheral intravenous injection of contrast. Digital subtraction employs converting analog images to digital images, assigning discrete numbers of well-defined shades of gray, designated by successive integers. The image matrix is broken up into a defined number of squares, called pixels, and the analog information for each pixel is converted to the integer closest to the number defining the gray shade (84).

Because the transit time from an intravenous injection to the pulmonary arteries is relatively brief, the bolus of contrast remains fairly intact. However, motion artifact from both respiratory and cardiac activity have posed problems (85); These may be minimized by gating techniques. In 14 patients with suspected PE, 13 had "diagnostic quality" studies by DSA, and all 9 with positive studies by DSA had the diagnosis of PE confirmed by conventional arteriography (86). Pond (87) reported that 12 of 13 patients diagnosed as having PE by DSA were confirmed by conventional arteriography, and all 18 with negative DSA studies were negative by conventional arteriography as well.

A recent study by Kereiakes and his colleagues (88) suggests that computerized tomography may be useful for delineating proximal vessel thrombus in patients who are candidates for surgical embolectomy or thromboendarterectomy but in whom pulmonary arteriography is considered dangerous.

V. Deep Venous Thrombosis

A. Venography

Since PE frequently occurs in the setting of overt or occult deep venous thrombosis (DVT), diagnostic measures confirming the presence of DVT may be useful in the strategic approach to suspected PE. Contrast venography is the most accurate method of confirming DVT (89,90) although it is invasive and requires the use of contrast material. Complications include the postphlebographic syndrome consisting of pain, tenderness, swelling and erythema lasting up to 36 hours. The incidence has been reported to be as high as 25 percent of patients undergoing venography (91,92). Extravasation of contrast material can cause tissue necrosis (93). Pulmonary embolism is a rare complication of venography (94).

Hull et al (67) provided a strategy for the approach to suspected PE based on their experience with 139 patients with abnormal lung scans: A ventilation-perfusion scan which shows either a V/Q match with segmental or subsegmental defects, or V/Q mismatch of subsegmental size should be followed by

venography for confirmation of the indication for anticoagulation, since these scan findings neither confirm nor exclude PE. They emphasized, however, that a normal venogram does not exclude thromboembolic disease, since it was seen in 30 percent of their patients with PE. Accordingly, a negative venogram should be followed by pulmonary angiography.

B. Doppler Ultrasound

Doppler ultrasound can diagnose venous outflow obstruction noninvasively when the normal phasic amplitude induced by respiration or the valsalva maneuver is not present (95) (figs. 6 and 7). Proximal (i.e. iliac, femoral, or popliteal) vein thrombosis can be detected in approximately 90 percent of cases, although non-occlusive thrombi may be missed (96). Additionally, the accuracy of the procedure is dependent upon technical expertise, and the results are not uniform.

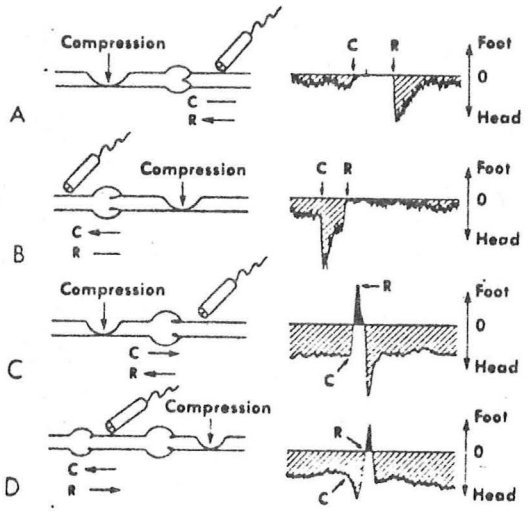


Figure 6. Venous flow responses to augmentation maneuvers. A and B show normal responses. C and D show responses typical of venous valvular incompetence. C denotes compression, R denotes release. (From reference 95).

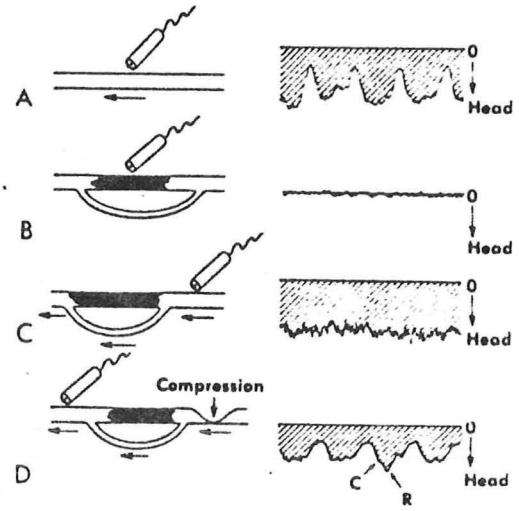


Figure 7. Venous flow patterns with obstructing thrombus. A, normal pattern; B, probe over obstruction; C, probe distal to obstruction; D, lack of augmentation with obstruction distal to probe. (From reference 95).

C. Impedance Plethysmography

Impedance plethysmography (IPG) measures limb blood flow by measuring changes in electrical resistance (Figure 8). The sensitivity of IPG is dependent on the location of the thrombus: Proximal DVT is associated with a specificity approaching 98 percent and a sensitivity of 95 percent (97-100) (Table 8). As with Doppler evaluation, non-occlusive thrombi may be missed (100).

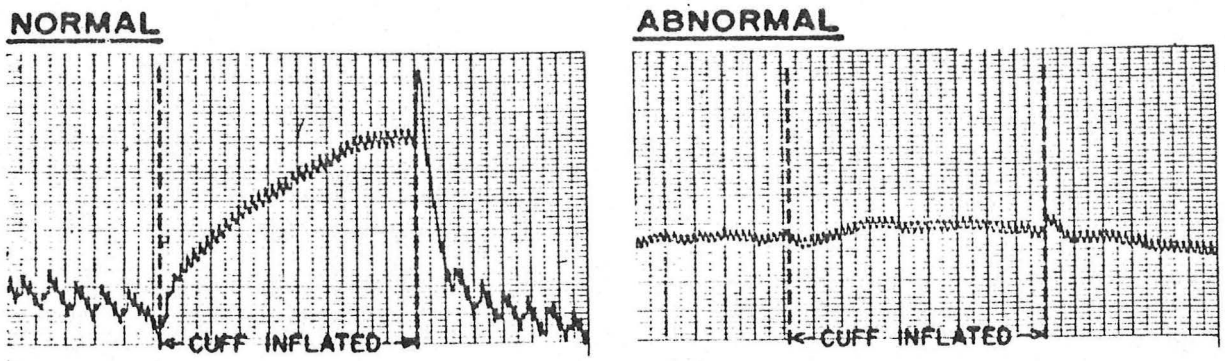


Figure 8. Impedance plethysmography in normal and DVT. (From reference 100).

Table 8. Accuracy of Impedance Plethysmography Versus Venography in Detecting Venous Thrombosis †

Study	Number of Venograms	Detection with Impedance Plethysmogram DVT (%)	Calf VT (%)	NL (%)
Hallbook and Ling	106	100	60	0
Cranley et al	302	----- 96 -----		2
Johnston et al	85	100	33	9
Wheeler et al	168	98	16	2
Hull et al	346	93	17	3
Mean		97	44	3

DVT = deep vein thrombosis; NL = normal; VT = vein thrombosis
†From Sasahara, AA et al: Am J Cardiol 43: 1214, 1979.

D. Radionuclide Studies

Isotopes can be used either to evaluate the patency of the venous system or to determine if active thrombus is being formed. To evaluate venous flow, ^{99m}Tc-MAA can be injected bipedally and the lower extremities scanned (101,102). Fibrinogen labelled with ^{125}I can be used to determine if fibrinogen is being actively incorporated by a forming thrombus: The radiolabelled fibrinogen will circulate in the intravascular space and its activity can be monitored with a scintillation counter (103). An increase in activity of 15 to 50 percent between points over 24 hours is indicative of a positive study (104) (Figure 9). The accuracy is reported to be greater than 90 percent, but false negatives may occur in high proximal vein thrombi (104). False positive studies occur with cellulitis, hematoma and prior contrast venography (105).

Indium-111-oxine tagged platelets have been demonstrated to selectively accumulate at sites of active thrombosis in both animals and humans (106,107). Fenech et al (108) reported a 95 percent sensitivity and 100 percent specificity for DVT using this technique. There are two major advantages of ^{111}In studies over ^{125}I-fibrinogen: a) heparin will interfere with ^{125}I fibrinogen incorporation in thrombus, whereas heparin therapy does not appear to affect ^{111}In studies,and b) Indium studies yield diagnostic information immediately, whereas ^{125}I fibrinogen studies require 24 hours. A disadvantage to this technique is that ^{111}In cannot gain access to a totally occluded vessel, potentially leading to a false negative study (107). Preliminary reports by Sostman et al (109) and Ezekowitz and his associates (110) have suggested that ^{111}In may be useful in the detection of PE as well as DVT. Although it is early in the application of radiolabelled platelet studies to the clinical setting, this technique offers promise as a tool to rapidly, reliably and noninvasively determine the presence of thrombosis and monitor its course.

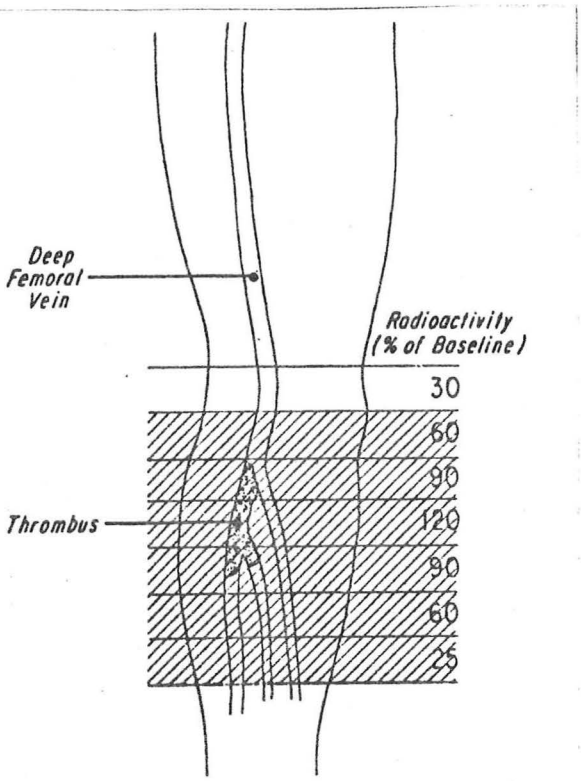


Figure 9. Radioactive fibrinogen scan showing thrombus in the posterial tibial vein. (From reference 32).

VI. Pathophysiologic Consequences of PE

The primary mechanical consequence of PE is a reduction in the cross-sectional surface area of the pulmonary vascular bed. In experimental conditions, a reduction in surface area of 50 to 60 percent or greater must be present before pulmonary arterial pressure rises; yet, pulmonary hypertension may complicate PE even when less than "massive" embolization has occurred. This suggests that vasoconstriction, in addition to mechanical obstruction, may be present and has prompted a search for a potential mediator.

Serotonin, a substance released by platelets and metabolized by the pulmonary endothelium, is a fairly potent pulmonary vasoconstrictor (111). Studies using cyproheptadine and Ketanserin, 5-hydroxytryptamine receptor antagonists, have shown an inhibition of the pulmonary pressor response and a decrease in intrapulmonary shunt after experimental embolus, suggesting a humoral role for 5HT (112) (Figs. 10 and 11).

Eicosanoids have also been suggested as possible mediators, since they possess both vascular smooth muscle stimulating effects and effects on platelet aggregation. Klotz et al (113) have shown that urinary excretion of thromboxane B_2 was increased in patients with either DVT or PE, and Utsonomiya and his associates (114) demonstrated that cyclooxygenase or thromboxane synthetase inhibition blunts the hypoxic response in experimental PE (Figure 12). However, the role which these or other circulating substances play in mediating the pathophysiologic consequences of clinical PE remains unknown.

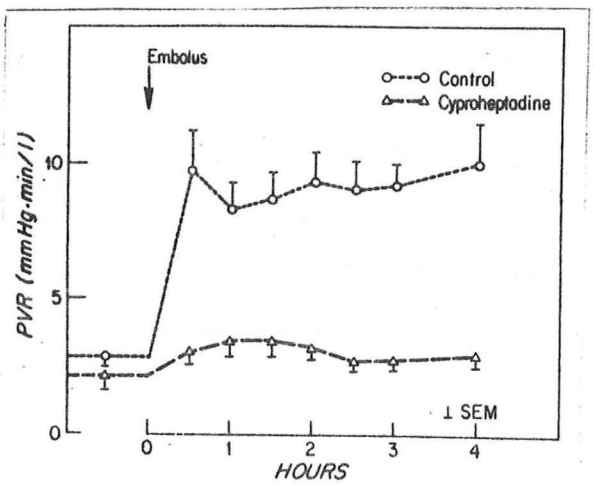


Figure 10. Effect of cyproheptadine on pulmonary pressor response to embolism. (From reference 112).

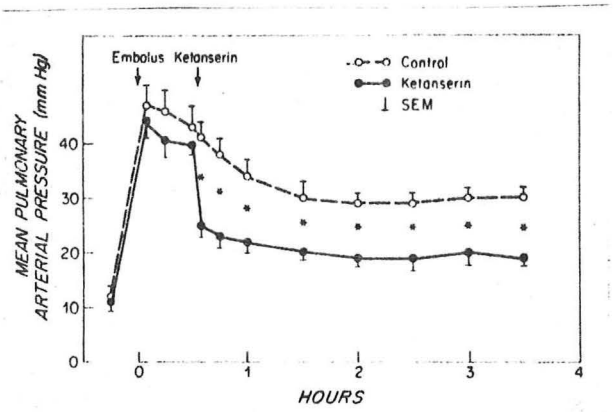


Figure 11. Effect of ketanserin on pressor response. (From reference 112).

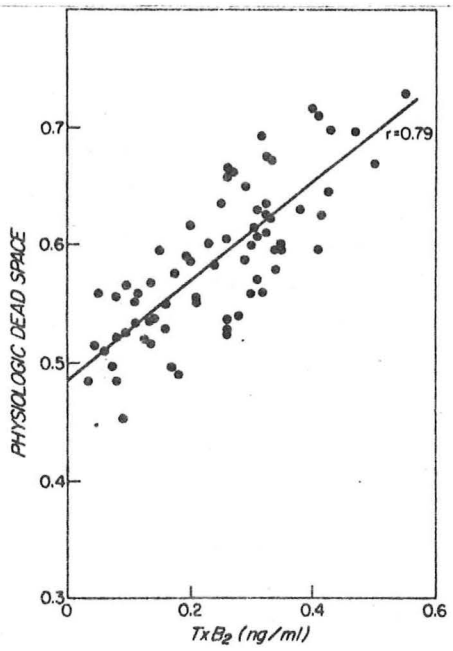


Figure 12. Relationship between serum TxB_2 levels and physiologic deadspace in experimental embolism. (From reference 114).

Pulmonary embolism is associated with abnormalities in both gas exchange and respiratory mechanics. Two mechanisms appear to be responsible for the hypoxemia (115): An increase in physiologic dead space, which is the result of lung units with high VA/Q ratios as a consequence of ventilation to poorly perfused areas; and an increase in shunt, resulting from atelectasis and/or edema (Figure 13). The atelectasis which occurs has been suggested to be the result of constriction of peripheral airways in response to the release of broncho-active substances (116-119) (Figure 14).

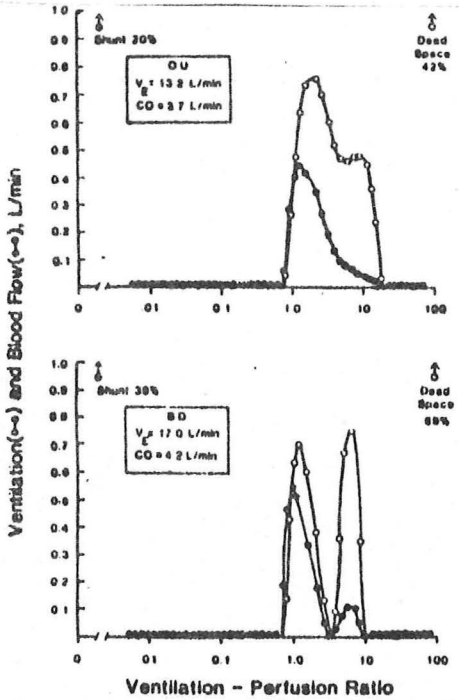


Figure 13. Gas exchange patterns in two patients with PE. (From reference 115).

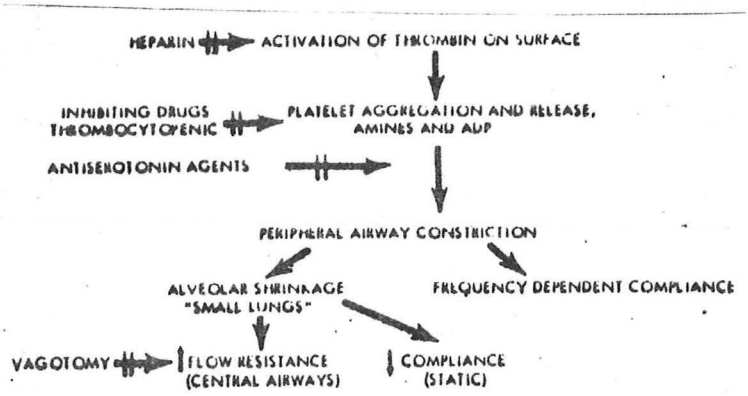


Figure 14. Scheme of factors involved in mechanical alterations contributing to altered gas exchange in pulmonary embolism. (From reference 116).

VII. Therapy

Two different medical approaches have been used to treat PE: Anticoagulation in order to prevent recurrence, and thrombolytic therapy with streptokinase or urokinase to dissolve existing clot.

A. Heparin

1. Mechanism of Action

Heparin has been considered the treatment of choice for DVT and PE for many years. It exerts its anticoagulant effects by binding to antithrombin: Heparin catalyzes the interaction of antithrombin III with the activated coagulation factors (XIIa, XIa, IXa, Xa, and IIa); the heparin:antithrombin III complex is a potent inhibitor of these activated clotting factors (120) (Figure 15).

It requires less heparin to prevent thrombosis by neutralizing small amounts of factors early in the cascade such as XIIa and XIa than it does to neutralize factors Xa and IIa, which are present in greater concentration once thrombosis has been initiated. This explains why low-dose heparin is effective in the prophylaxis, but not treatment of thrombosis.

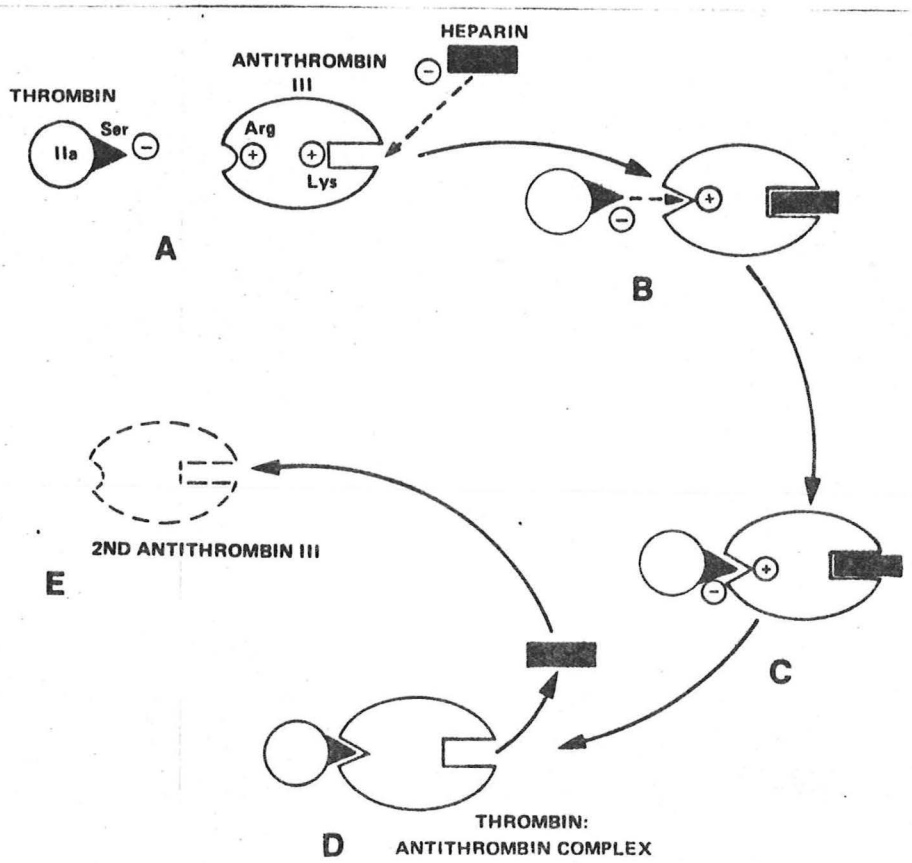


Figure 15. Mechanism of action of heparin.

2. Method of Administration and Monitoring

Heparin is administered intravenously for the management of PE: Large doses injected intermittently are associated with a higher incidence of hemorrhagic complications compared with a continuous infusion (121), probably because the half-life of heparin is increased at high doses (122).

Because of the greater amount of thrombin which must be neutralized, heparin clearance is increased in acute PE, necessitating higher doses earlier in the course of therapy (123-125). However, there is marked variability in the response to heparin, and monitoring the effects of therapy is necessary both to assure an effective anticoagulant effect and to avoid excessive anticoagulation with resultant bleeding.

A number of methods for monitoring heparin therapy have been proposed, including measurements of plasma heparin levels, inhibition of specific coagulation sites such as Factor IIa, inhibition of overall coagulation activity, and measurement of thrombin generation.

The activated partial thromboplastin time (aPTT) is the most widely used and most convenient monitoring test to perform. This test measures the in vitro activity of the intrinsic pathway by measuring the clotting time of plasma which is activated by a negatively charged agent such as Kaolin which is added with phospholipid and calcium. Maintaining the aPTT at 1 to 2 times control has been shown to be associated with fewer recurrences of thrombosis (120,126) (Figure 16). Heparin therapy is usually maintained for 7 to 10 days - the period during which activated platelets could retain Xa activity on their surface and would be protected from inactivation by heparin (127).

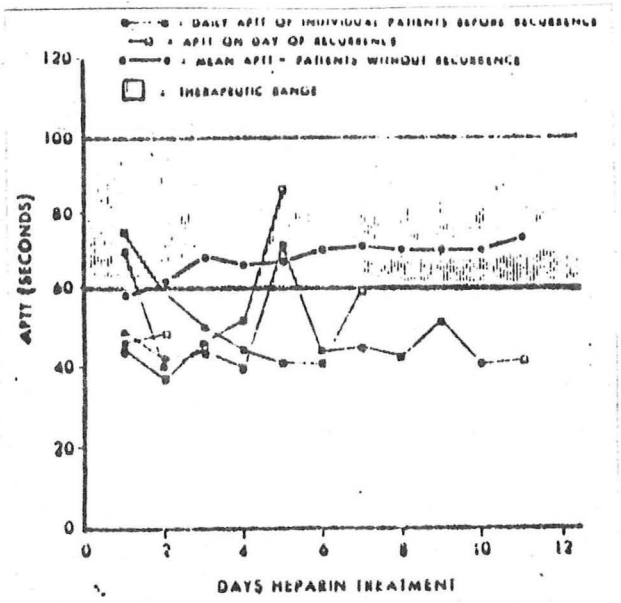


Figure 16. aPTT of 5 patients with recurrence and mean APTT of 157 patients without recurrence. (From reference 126).

There does not appear to be a difference in activity between bovine lung or porcine intestinal mucosal heparin, although bovine lung heparin has been associated with a higher incidence of heparin-induced thrombocytopenia (128-130). There is no evidence that calcium heparin is superior to sodium heparin.

3. Side Effects

a. Hemorrhage

The most serious side effect of heparin is bleeding, and it is the leading cause of drug-related deaths in hospitalized patients (131). The frequency of major bleeding is between 5-10 percent of patients receiving full-dose heparin (30,132,133); low-dose subcutaneous heparin infrequently causes major hemorrhagic complications. The factors that contribute to bleeding complications are listed in Table 9.

Table 9. Factors Associated with Increased Risk of Bleeding During Therapy with Heparin

Dose of heparin (ref. 134)
Excessive anticoagulation (aPTT 3 times control) (ref. 121)
Method of administration - Intermittent vs. continuous infusion (ref. 121)
Specific risk factors - coagulopathy, thrombocytopenia, age, bleeding tendency (malignancy, GI bleeding, alcholism, uremia)
Drugs - aspirin, nonsteroidal anti-inflammatory agents

b. Heparin-Associated Thrombocytopenia

In approximately 5 percent of patients, heparin can produce significant thrombocytopenia (130, 134-137). Thrombocytopenia can occur at any day of treatment but usually occurs 6 to 12 days into a course of therapy (130). Both intravenous and subcutaneous administration have been implicated. The mechanism remains unknown, although there are a number of observations which suggest an immune mechanism: Platelet-associated IgG is elevated in most cases (137,138), and heparin-dependent binding of complement to platelets has also been reported (137). Arterial thrombosis can complicate heparin-induced thrombocytopenia, and results in death in nearly 30 percent of afflicted patients (130,134-141). Nevertheless, most patients with heparin-associated thrombocytopenia do not experience morbididity from this complication. It has been recommended that oral anticoagulation should be begun simultaneously with heparin and that heparin be discontinued when an adequate level of anticoagulation with oral agents is achieved in order to minimize the risks of heparin (130); however, it is not yet known whether this approach is associated with a comparable reduction in the incidence of thrombotic recurrence as compared with a 7 to 10 day course of heparin therapy.

c. Osteopenia

Patients who receive low-dose heparin for six months or longer are at risk for the development of osteopenia and spontaneous bone fractures (142). The value of supplemental vitamin D or calcium in preventing this complication has not been proven.

d. Hypoaldosteronism

Heparin depresses aldosterone within 4 to 8 days of beginning therapy and can result in a reduction in serum sodium in normals (143,144). In patients with renal insufficiency significant hyperkalemia may result (145).

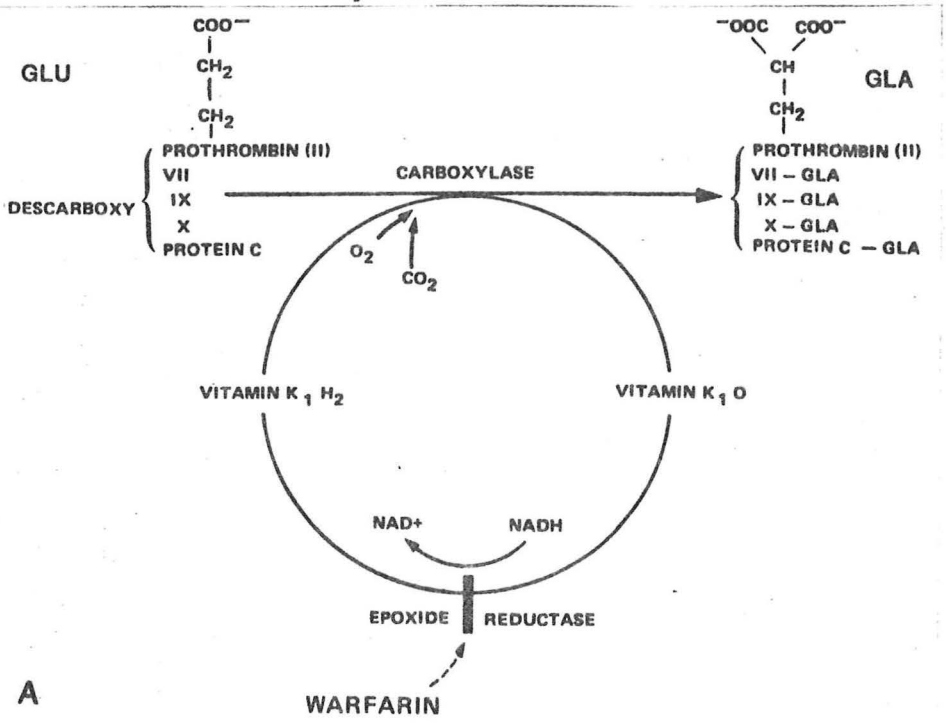
B. Oral Anticoagulants

1. Warfarin

a. Mechanism of Action and Therapeutic Use

Warfarin sodium (Coumadin ^{R}) is named after the Wisconsin Alumni Research Foundation, of the University of Wisconsin, where the original development of this drug occurred. Warfarin competitively inhibits Vitamin K epoxide reductase, thereby inhibiting the addition of carboxyl groups onto glutamic residues of factors II, VII, IX, and X and Protein C, a step which is required for their biologic activity (146) (Figure 17).

The pharmacologic activity of warfarin is dependent on the depletion of existing active Vitamin K-dependent factors, of which Factor VII has the shortest half-life (4-6 hours) and Factor II the longest (>100 hours). Because of the long half-life of the drug (approximately 36 hours), changes in the prothrombin time (PT) will not be reflected for 3 to 4 days after the dose of warfarin has been adjusted.



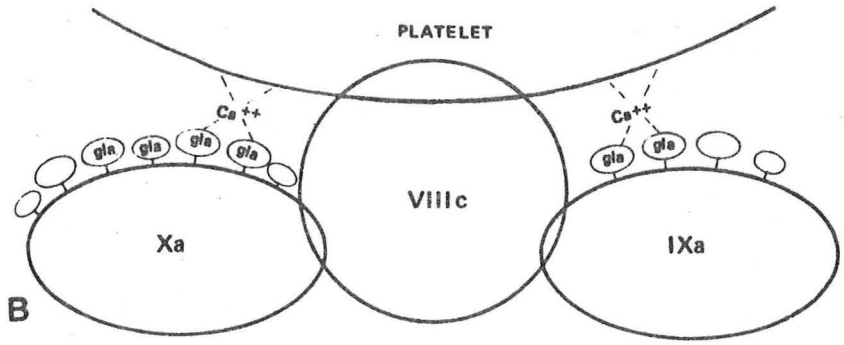


Figure 17. Mechanism of action of warfarin.

Ninety percent of warfarin is bound to albumin. A number of drugs can alter bioavailability of warfarin either by displacing it off albumin or altering hepatic metabolism (Table 10).

The prothrombin time (PT) is monitored during warfarin therapy, and maintaining it at 1½ to 2½ times control is associated with a low risk (< 2 percent) of recurrence of thrombosis. In the United States, rabbit brain thromboplastin reagent (Simplastin) is generally used and is less sensitive to small changes in the Vitamin K-dependent factors than the human brain thromboplastin (BCT, British Comparative Thromboplastin) used in the U.K. Accordingly, a ratio of 1.5 measured with Simplastin is comparable to a ratio of 2.5 using BCT; it is therefore worthwhile knowing which method is used, particularly if several laboratories are utilized to monitor a patient's PT.

Table 10. Factors Affecting Prothrombin Time with Warfarin Therapy

Increased Prothrombin Time		Decreased Prothrombin Time	
Drugs	Conditions	Drugs	Conditions
Heparin	Liver Disease	Diuretics	Uremia
Aspirin	Hypermetabolic state	Barbituates	Hereditary resistance
Phenylbutazone		Cholestyramine	
Clofibrate		Rifampin	
Sulfonamides			
Metronidazole			

Since the incidence of recurrent thrombosis becomes insignificant after four months, therapy is generally discontinued at this point (146-148). Patients who have had a "massive" embolism or those with recurrent PE should probably be treated for life.

2. Complications

The major complication with warfarin is bleeding and it occurs in approximately 20 percent of patients, of which one-quarter are major (149,150). The bleeding complications are correlated both with the degree of anticoagulation and with the presence of coexisting medical conditions.

Major bleeding should prompt maneuvers which return the PT to normal. Fresh frozen plasma can be given every 6 to 8 hours, and vitamin K can be given parenterally, although the latter will take up to 12 hours to reverse the warfarin effect.

Warfarin-induced skin necrosis is more common in women and usually occurs within 10 days of beginning treatment. It is manifested by painful erythematous lesions on the trunk and extremities which progress to infarction or hemorrhagic bullae. Its development constitutes an absolute contraindication to continuing warfarin therapy (148). The mechanism responsible is unknown.

C. Adjusted Dose Heparin versus Warfarin for Chronic Therapy

Hull and his colleagues (151) have recently reported that heparin administered subcutaneously in doses adjusted to prolong the aPTT to 1½ times control was as effective as warfarin in terms of recurrence rates and was associated with a complication rate of 2 percent, versus 18 percent with coumadin. The average dose of heparin in this study was 10,000 units twice daily. This regimen may be particularly useful in patients who have experienced or are at risk of developing hemorrhagic complications with warfarin.

D. Thrombolytic Therapy

1. Pharmacology

Thrombolytic therapy with streptokinase (SK) or urokinase (UK) activates plasminogen, which results in lysis of clot. Urokinase directly activates plasminogen, while streptokinase forms a SK:plasminogen complex which stimulates the conversion of plasminogen to plasmin (152-154). Although approximately 5 percent of patients, particularly those who have received streptokinase previously or who have had a recent streptococcal infection, will experience an allergic reaction or resistance to SK (155), the expense of UK (10 times greater than SK) has made SK the thrombolytic agent of choice.

The Urokinase Pulmonary Embolism Trial (UPET) compared the effects of heparin with thrombolytic therapy in PE (30): Although perfusion was improved sooner with UK, there were no differences in perfusion assessed by scintigraphy between the groups at one year (Figure 18).

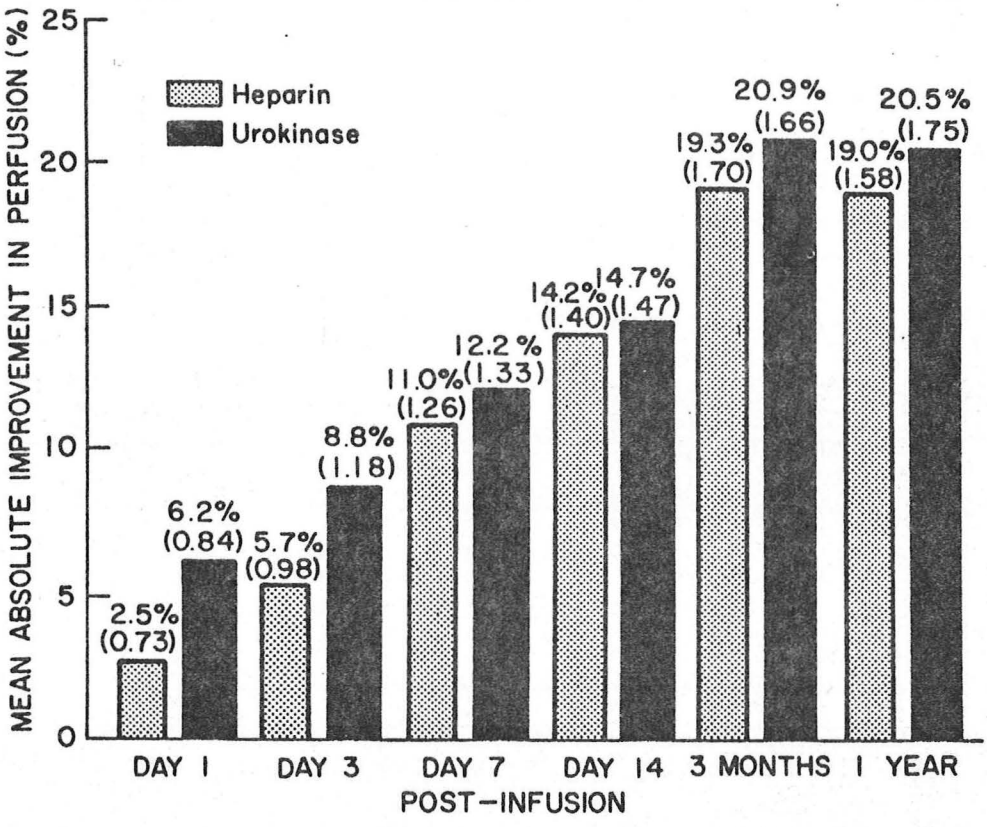


Figure 18. Comparison of improvement in perfusion in lung scan defects with heparin and urokinase.

Additionally, there were no differences in overall mortality (Table 11) or incidence of recurrence (Table 12).

Table 11. Mortality within 2 weeks of entering UPET†

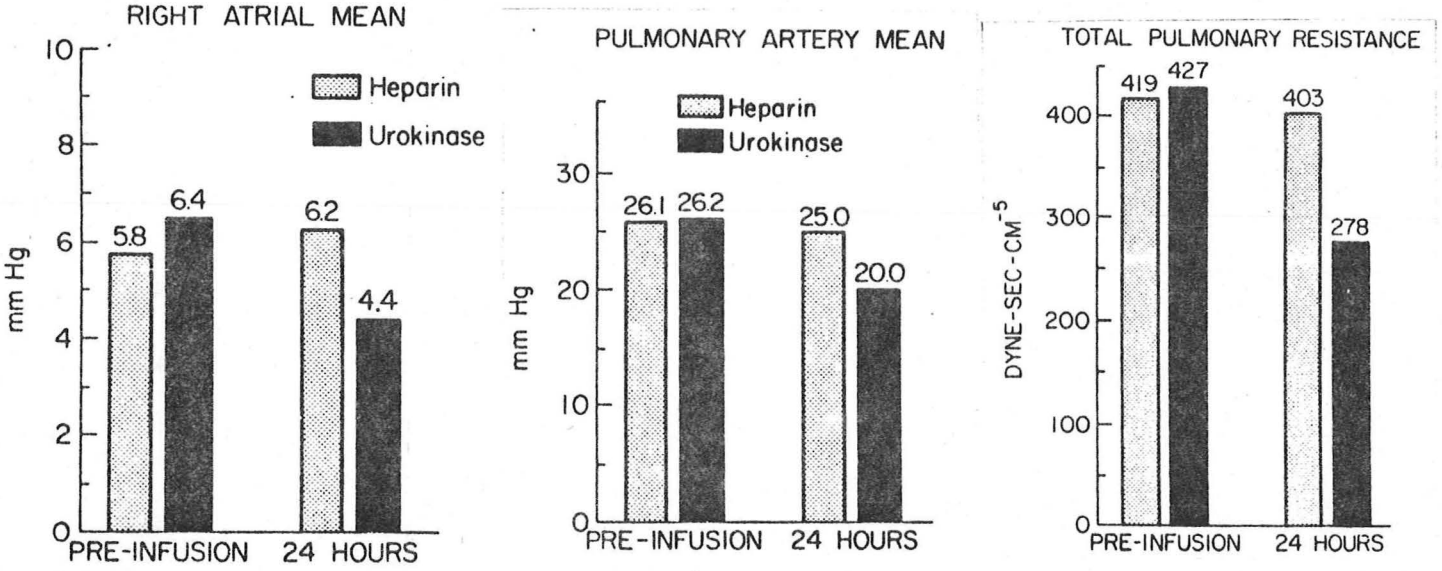
	Heparin patients (N=78)			Urokinase patients (N=82)		
	No.		%	No.		%
	No. dead	No. in class	% of class	No. dead	No. in class	% of class
Deaths within 14 days	7		9.0	6		7.3
Within 48 hours	2		2.6	3		3.6
48 hours to 14 days	5		6.4	3		3.6
Death by patient class*						
I-S	3	34	8.3	0	33	0.0
I-M	3	39	7.7	2	40	5.0
II-S	1	1	100.0	2	2	100.0
II-M	0	4	0.0	2	7	38.6

*I=shock absent; II=shock present; S=submassive pulmonary embolism; M=massive pulmonary embolism.
†From Urokinase Pulmonary Embolism Trial. Circulation (Suppl) 47: II-1, 1973.

Table 12. Incidence of Recurrent Embolism in UPET

	Heparin patients (N=78)	Urokinase patients (N=82)
Recurrent embolism		
Total	18	14
Clinical evidence*	6	4
Scan evidence	5	5
Both scan & clinical evidence	7	5
Inferior vena caval interruption	9	3
Pulmonary embolectomy	0	0
Myocardial infarction	1	0
Stroke	1	1

There were, however, significant improvements in hemodynamic parameters in the UK-treated, but not the heparin-treated, group (Figs. 19-21).



Figures 19-21. Comparison of the hemodynamic effects of heparin and urokinase in the UPET. (From reference 30).

These findings, coupled with the observations of Schwarz et al (156) that hemodynamics and exercise are normalized when SK is used to treat massive PE and those of Sharma and associates (157) that SK improves lung capillary perfusion and diffusion at one year while heparin does not, suggests that thrombolytic therapy should be considered the treatment of choice for PE when hemodynamic compromise is present (158).

Because SK and UK indiscriminantly lyse clot, bleeding complications with thrombolytic therapy are common. Forty-five percent of patients receiving UK and 27 percent receiving heparin in UPET had bleeding (Table 13). This incidence is higher than with subsequent experience with SK, owing probably to the frequency which invasive procedures were performed in the UPET. More careful attention to contraindications and avoiding unnecessary procedures should reduce the incidence of complications to the 7 to 10 percent range. The risk of bleeding does not correlate with any specific laboratory abnormality.

Table 13. Hemorrhagic complications in the UPET

	Urokinase (82 patients)		Heparin (78 patients)	
	No.	%	No.	%
Bleeding (totals)	37	45	21	27
Moderate	15	18	10	13
Severe	22	27	11	14
Recurrent pulmonary embolism	14	17	18	23
Inferior vena caval interruption	3	4	9	12
Deaths (totals)	6	7	7	9
Within 24 hours	1	1	2	3
24 hours to day 14	5	6	5	6

2. Monitoring Therapy

Almost all patients will develop a lytic state after a 250,000 unit bolus of SK followed by an infusion of 100,000 units/hour. Once verification of a lytic state has been accomplished, usually by demonstrating that the thrombin time is at least twice control after 2-4 hours, no further adjustment in dose is necessary. Therapy is continued for 24 hours for PE (up to 72 hours for DVT), and heparin therapy is then instituted (152-155).

3. Contraindications

The contraindications to thrombolytic therapy are listed in Table 14. Bleeding can generally be managed with local, conservative measures, but life-threatening hemorrhage may require fresh frozen plasma or whole blood to replete factors V, VII and fibrinogen. On rare occasion, epsilon-aminocaproic acid (EACA), 5 grams IV over 30 minutes, followed by 1 Gram/hr is necessary to rapidly reverse the lytic state.

4. Tissue Plasminogen Activator

Tissue plasminogen activating factor (tPA) may allow a more preferential lysis of clot without depleting fibrinogen, and theoretically could be useful in treating PE with fewer adverse effects. When fibrin is formed, small amounts of plasminogen become bound to it, and tPA is adsorbed on the fibrin surface and activates plasminogen. The plasmin remains bound to the fibrin clot and degrades it. The small amount of plasmin released into the circulation is rapidly neutralized by circulating antiplasmin (159). This approach holds promise for both coronary thrombosis as well as PE.

Table 14. Contraindications to Thrombolytic Therapy

I. Absolute contraindications
  A. Risk of CNS hemorrhage
    1. History of cerebrovascular accident
    2. Intracranial neoplasm
    3. Cranial surgery or head trauma within 10-14 days
  B. Risk of massive hemorrhage
    1. Major thoracic or abdominal surgery
    2. Cardiopulmonary resuscitation
    3. Biopsy in a location inaccessible to external compression
    4. Parturition

Within 10 days

II. Relative contraindications
  1. Coagulation defects (thrombocytopenia, coagulation factor deficiency)
  2. Uncontrolled severe hypertension
  3. Recent invasive procedures (lumbar puncture, thoracentesis, paracentesis, organ biopsy, or puncture of noncompressible blood vessel)
  4. Other system diseases, including visceral carcinoma, endocarditis, and active tuberculosis

E. Surgical Management of PE

Surgical therapy of PE can be divided into procedures which are designed to remove emboli from the lungs and those which prevent recurrence by interrupting the vena cava.

1. Embolectomy

Pulmonary embolectomy for acute, massive PE is rarely indicated. It should be reserved for patients with a documented massive PE who are in refractory shock and in an institution where the expertise exists in performing this procedure. In a collected series of 137 patients undergoing acute pulmonary embolectomy, overall mortality was 70 percent. The most frequent complication is reperfusion pulmonary edema and hemorrhage (160).

The experience with embolectomy for chronic, recurrent emboli is more encouraging. Of 85 patients reported in the literature who have undergone embolectomy, death as a result of the procedure occurred in 22 percent (161). Survivors have manifested improvement in hemodynamics, gas exchange, and activity tolerance. Reperfusion hemorrhage remains the most significant problem (161,162). Bronchial arteriography has been reported to be useful in determining the patency of pulmonary arteries distal to occluding lesions by retrograde filling through collateral vessels (162). Moser and his associates (163) recently reported their experience with thromboendarterectomy in 15 patients with unresolved, chronic thrombotic major pulmonary artery occlusion: Thirteen survived surgery and had hemodynamic and functional improvement. This technique offers promise for the rare case of chronic cor pulmonale resulting from recurrent emboli.

2. Inferior Vena Cava Interruption

Although most patients with PE can be successfully managed with anticoagulants, on rare occasion interruption of the inferior vena cava is necessary to prevent recurrence. The generally accepted indications for vena cava interruption are listed in Table 15.

Table 15. Indications for Inferior Vena Cava Interruption

1. Prophylaxis against recurrence (after acute massive PE or chronic recurrent small vessel emboli)
2. Contraindication to anticoagulation
3. Complication with anticoagulation
4. Recurrence of PE despite adequate anticoagulation

From Goldhaber SZ: Am J Med 76: 512, 1984.

A variety of surgical approaches and devices have been used (Figure 22).

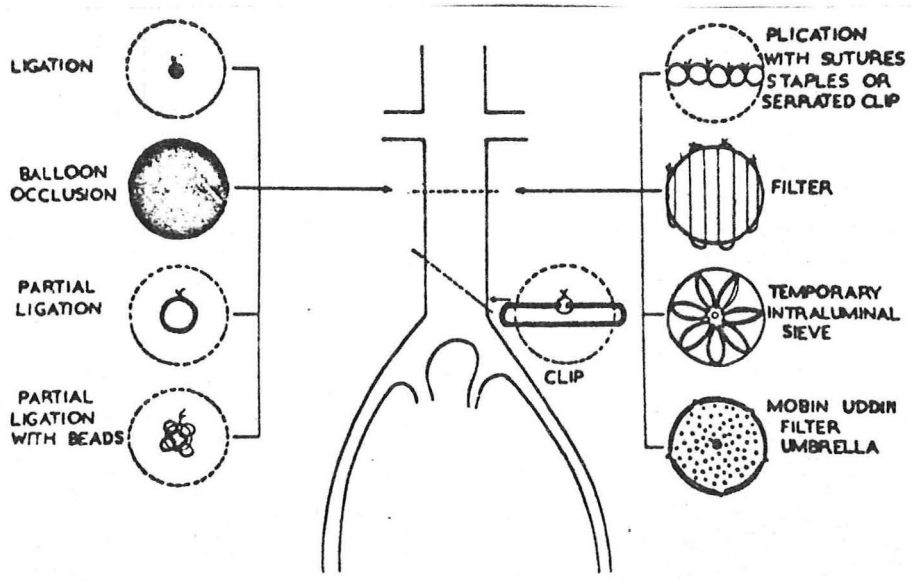


Figure 22. Methods and devices used for inferior vena cava interruption.

Early surgical approaches included plication and external clipping, but these approaches necessitated general anesthesia and a laparotomy in unstable patients, and were associated with a significant incidence of recurrent embolism through collateral channels. Additionally, there was a high incidence of leg edema, ulcers, stasis dermatitis or venous claudication (166-170).

The development of the Mobin-Uddin umbrella in 1970 represented a significant advance in that it could be inserted percutaneously via the internal jugular vein (171). However, filter migration, erosion of the vena cava, and recurrent embolism from clot adherent to the proximal part of the umbrella have been serious complications reported with its use (172,173).

The Kimray Greenfield filter may also be inserted percutaneously via the internal jugular or femoral vein. It has a high patency rate and is easier to insert than the Mobin-Uddin umbrella (174-177). Complications appear to be less frequent than with other procedures (Table 16).

Table 16. Experience with the Kimray Greenfield Filter

Filters inserted: 41 in 37 patients Follow-up time (average) 17 months	
Mortality: 6 died of cardiac, neoplastic, neurologic causes - rate	16.2%
Morbidity:	
Recurrent embolism: 1	2.7%
Edema: 1 severe	2.7%
2 mild	5.4%
Phlebitis: 2 late	5.4%
Hemorrhage: 1 late	2.7%
Migration: 0	0%
Patency: Venocavograms at 0.5-3 years in 14 pts., 13 patent	92.8%

Hunter (178) recently reported his experience with a catheter-delivered detachable balloon which is secured by hyperinflation in the distensible inferior vena cava: No recurrence of emboli or balloon migration were reported in 135 patients. Approximately 30 percent had mild lower extremity edema. These data suggest that this device may be an alternative to filters where expertise in its insertion is available.

VIII. Prophylaxis of DVT and PE

The identification of clinical risk factors for the development of DVT and PE has enabled investigators to attempt to reduce their occurrence by means of a variety of chemical and mechanical prophylactic measures.

A. Heparin

Sharnoff (179) first confirmed that low-dose heparin reduces the incidence of DVT postoperatively. At least 27 controlled trials have confirmed these findings - A mean reduction in the incidence of DVT from 25 percent in the control group to 7 percent with heparin (180-182). Several studies have also demonstrated that

heparin reduces the incidence of major PE from approximately 6 percent to 0.6 percent (180). The incidence of bleeding complications varies from 0 to 27 percent (182), but bleeding is usually mild and not life threatening. The usual dose is 5,000 units subcutaneously every 8 to 12 hours, with therapy begun two hours postoperatively in surgical patients.

Several high-risk groups are not protected by low-dose heparin: Patients undergoing total hip replacement or major urologic surgery do not appear to benefit from the above-stated regimen (180,181-184). Leyuraz et al have (185) recently demonstrated that, in patients undergoing total hip replacement, an increased dose of subcutaneous heparing (averaging 18,900 units per day), adjusted according to the aPTT, resulted in fewer thromboembolic episodes and no greater incidence of hemorrhagic complications than patients receiving fixed-dose "mini-heparin": Proximal thrombi developed in 5 percent of patients receiving adjusted dose heparin versus 32 percent in the group receiving low-dose therapy.

Kakkar and his associates (186) recently reported that low-dose heparin with dihydroergotamine was more effective than heparin alone. Dihydroergotamine is said to constrict the peripheral veins and enhance venous return. Ergotism has been reported, but is rare. Although this compound is now commercially available, further studies confirming this initial report will be necessary before its widespread use can be recommended.

Not only is prophylactic heparin effective and generally safe, it is relatively inexpensive as well: The routine use of low-dose heparin in patients over the age of 40 undergoing general surgery or patients with other predisposing conditions costs approximately $870.00 per life saved by avoidance of PE (187).

B. Warfarin

Postoperative anticoagulation with warfarin is the best technique for the patients at greatest risk, but the incidence of major bleeding complications is high (188).

C. Antiplatelet Drugs

1. Dextran

Dextran, either as Dextran 70 (Macrodex) or Dextran 40 (Rheomacrodex) is an effective antithrombotic agent (189). Dextran decreases platelet adhesiveness through changes in the platelet membrane (190,191). Additionally, Dextran 70 renders fibrin polymers more susceptible to plasma degradation (191). In addition to the expense, dextran's expansion of intravascular volume contributing to volume overload is a drawback to its use in high risk patients.

2. Aspirin

Low doses of aspirin inhibit platelet cyclooxygenase, resulting in a reduction in thromboxane A_2, the major platelet derived product of arachidonic acid and an inducer of platelet aggregation. Vascular endothelium production of Prostaglandin I_2 (prostacyclin) - its major product of arachidonic synthesis and a potent inhibitor of platelet aggregation, is not significantly inhibited (192,193).

The British Medical Research Council (194) did not find low-dose aspirin to be beneficial in patients undergoing general surgery. In orthopedic patients the results

have been conflicting. Several reports have suggested that aspirin is effective when combined with dipyridamole (195-198).

D. External Pneumatic Compression (EPC)

Fourteen trials, numbering over 1,600 patients, have shown EPC to be effective and comparable to low-dose heparin: The average reduction in incidence of post-operative DVT was from 22.9 percent to 6.7 percent (180,199-202). This mode has been reported to be effective even in patients who do not benefit from heparin (hip surgery, suprapubic prostatectomy, cystectomy) (180).

In addition to the mechanical effect of augmenting venous flow, EPC induces local and systemic fibrinolysis (202,203).

IX. Conclusion

Pulmonary embolism remains a serious condition which has generated controversy regarding both the optimal diagnostic and therapeutic approaches. The development of newer modalities will eventually yield more efficient and safe approaches to both diagnosis and therapy: However, at the present time there is no definitive approach that can be recommended, and management must be individualized based on the patient's clinical status and the experience and expertise available at a particular institution.

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