PULMONARY EMBOLISM

MEDICAL GRAND ROUNDS

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INTRODUCTION

The whole problem of pulmonary embolism has been put in proper perspective in a recent review (Dalen and Alpert, 1975). The incidence of pulmonary embolism is not known with certainty because of inaccuracies in clinical diagnoses and death certificates. From the best estimates available, the total incidence in the United States is approximately 630,000 per year, which makes symptomatic pulmonary embolism about half as common as acute myocardial infarction and three times as common as cerebral vascular accidents.

Pulmonary embolism is the sole cause of death in approximately 100,000 patients and is the major contributing cause in another 100,000 patients in the United States each year. With these estimates, pulmonary embolism is the third most frequent cause of death in the United States.

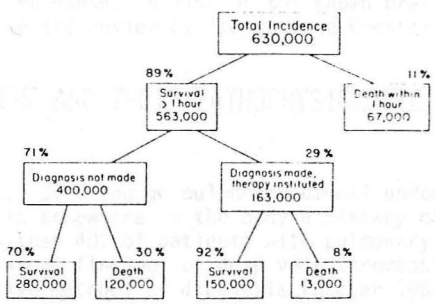


Fig. 1. Incidence of pulmonary embolism per year in the United States.

Eleven percent of these patients die within one hour before diagnosis can be made. Of those surviving greater than an hour, approximately 70% do not have the diagnosis made and in these, the mortality rate is approximately 30%. When the diagnosis is made, and therapy is instituted, the overall mortality rate is very low in the range of 8%. Even patients with massive pulmonary emboli, occluding more than 50% of the pulmonary circulation by angiography, have only a 9% incidence of death due to pulmonary embolism. If the massive pulmonary embolism is associated with systemic hypotension, the mortality rate is 32% (Alpert et al, 1976).

The late prognosis of patients treated for acute pulmonary embolism is very good. Sixty consecutive patients who were discharged after diagnosis and treatment of acute pulmonary embolism were followed for 1 to 7 years (Paraskos et al, 1973). Only 1 patient died of chronic cor pulmonale 15 months later. This patient had pulmonary artery pressure 115/40 with a mean of 60 mm Hg at the time of the original diagnosis, and was the only patient whose death was due to pulmonary embolism in the follow up period. Nearly every patient was treated either with inferior vena cava interruption or chronic anticoagulation with Warfarin. If patients have a chronic predisposition to venous thromboembolism and do not receive long term

anticoagulation, repeat cardiac catheterization frequently shows persistent moderate pulmonary hypertension (deSoyza and Murphy, 1972).

The major problem is not in improving treatment of patients in whom the diagnosis of pulmonary embolism is made. Our attention should be directed toward improving early detection with simple screening tests for both deep vein thrombophlebitis and pulmonary embolism, and in improving means of prophylaxis (Moser, 1976). Actually prophylaxis with low dose subcutaneous heparin is very effective (Kakkar et al, 1975). Therefore the major need is a simple, accurate, inexpensive screening test that could be applied to any patient with minimal symptoms or patients in high risk situations.

PREDISPOSING CAUSES:

It is relatively uncommon to have pulmonary embolism without a reasonable precipitating cause. A list of the known precipitating causes has been put together in the review by Tibbutt and Chesterman (1976). (See next page).

CLINICAL FINDINGS AND THEIR PATHOPHYSIOLOGIC BASIS.

SYMPTOMS.

Leg symptoms: Even though pulmonary emboli undoubtedly arise from deep vein thrombosis somewhere in the body a history of leg pain or swelling is present in less than 40% of patients with pulmonary emboli. This is partly because clinical findings of deep vein thrombosis correlate very poorly with objective methods of diagnosis (Haeger 1969, Kakkar, 1972). However, a large portion of medical patients with pulmonary emboli have no leg vein source when examined phlebographically (Bynum and Wilson, 1977).

Dyspnea: Wasted ventilation, increased respiratory rate and increased total ventilation are usually present and must undoubtedly be detected as inappropriate to the metabolic needs, thus producing a sensation of dyspnea (Stein and Levy, 1974). Robin (1960) proposed measurement of the arterial-alveolar CO_2 tension difference as a measure of dead space ventilation to judge the magnitude of pulmonary embolism. However, the test is of no use in differentiating patients with pulmonary emboli from patients with chronic obstructive lung disease (Nutter and Musumi, 1966). The arterial-alveolar CO_2 tension gradient also does not correlate well with the extent of pulmonary embolism evident on lung scans (Veerstraeaten et al, 1973) probably because of a number of compensatory mechanisms: (1) the low alveolar CO_2 tension in a region with the pulmonary artery occluded causes some bronchoconstruction and shift of ventilation away from that region (Severinghaus et al, 1961) (2) there is a tendency for atelectasis to occur in areas with pulmonary artery occlusion because of reduction of surfactant activity

TABLE 1

RISK FACTORS PREDISPOSING TO VENOUS THROMBOEMBOLISM

Increasing age [1, 2]	Trauma and burns [3]	Blood diseases
		Polycythaemia rubra vera [24]
Immobilisation [3]	Cancer [11, 17], especially:	Autoimmune haemolytic anemia [25]
	Lung	
Obesity [4, 5]	Gastro-intestinal (esp. pancreatic)	Sickle-cell disease [26]
		Paroxysmal nocturnal haemoglobinuria [27]
Varicose veins [6]	Genitourinary (esp. prostatic)	
		Multiple myeloma [28]
Heart disease [7] especially:		Primary amyloidosis [28]
Myocardial infarction [8, 9]	Oral contraceptives [18, 19]	Post splenectomy thrombocytosis [29]
Congestive cardiac failure [10]		
Artrial fibrillation [11]	Pregnancy [20]	
		Other medical conditions
Peri-operative [12, 13], especially:	Familial or constitutional factors	Ulcerative colitis [10]
Prostatic [14]	Previous thromboembolism [6]	Homocystinuria [31]
Biliary [15]	Blood group A [21]	Behcet's syndrome [32]
Gastric [15]	Antithrombin III deficiency [22]	Tetanus [33]
Lower limb [15]		'Strokes' [34]
Cardiac [15]	Plasminogen activator deficiency [23]	Acute paraplegia [35]
Porta-caval shunt [16]		Diabetes mellitus [36]
		Gout [36]
		Infection and malnutrition [37]

Key to authors

1 Coon and Coller (1959a)
2 Morrell and Dunnill (1968)
3 Sevitt and Gallagher (1961)
4 Turnbull (1960)
5 Hume et al. (1970)
6 Kakkar et al. (1970)
7 Morrell et al. (1963)
8 Murray et al. (1970)
9 Report of Medical Research Council (MRC) Working Party (1969)
10 Soloff and Rodman (1967a)
11 Coon and Coller (1959b)
12 Flanc et al. (1974)
13 Sigel et al. (1974)
14 Meyo et al. (1971)
15 Belding (1965)
16 Senior et al. (1966)
17 Lieberman et al. (1961)
18 MRC Subcommittee (1967)
19 Inman and Vessey (1968)
20 Walker et al. (1966)
21 Jick et al. (1969)
22 Egeberg (1965)
23 Nilsson and Isacson (1972)
24 Perkins et al. (1964)
25 Pirofsky (1969)
26 Edington and Gillies (1969)
27 Dacie (1967)
28 Catovsky et al. (1970)
29 Hirsh et al. (1966)
30 Duckert and Streuli (1966)
31 Carson et al. (1965)
32 Pitney (1972)
33 Symposium on Tetanus in Great Britain (1967)
34 Warlow et al. (1972)
35 Walsh and Tribe (1965)
36 Barker (1936)
37 Jones and Sabiston (1966)

(Finley et al, 1960) (3) in animals, within 8 days there is a marked increase in bronchial artery collaterals in an embolized area that could restore the CO_2 tension to normal (Parker and Smith, 1957).

In general the sensation of dyspnea in all pulmonary diseases correlates better with work of breathing than it does to arterial blood gas tensions. Comroe (1953) first proposed that some of the cardiopulmonary effects of pulmonary embolism might be due to serotonin. Thomas et al (1964 and 1966) found that release of autologous venous thrombi to the lungs of dogs resulted in bronchoconstriction with a rapid rise in total lung resistance and a fall in compliance. Heparin prevented the bronchoconstriction by inhibiting thrombin induced serotonin release from platelets adherent to the surface of the embolus. Other animal studies, though confirming a protective effect of heparin, could not attribute the effect to serotonin (Puckett et al, 1973). Man is less susceptible to the effects of serotonin than is the dog and man has a considerably lower serotonin content in his platelets. Although pulmonary emboli have been reported to masquerade as asthma and respond well to heparinization (Gurewich et al, 1963, Webster et al, 1966 and Olazabal, 1968), the diagnosis of pulmonary embolism may have been incorrect, for only a few of the patients had angiographic or autopsy proof of pulmonary embolism. Windebank et al, (1973) found wheezing in 11 of 250 patients studied consecutively for pulmonary embolism confirmed by pulmonary angiography. The majority of these patients either had an underlying allergic diathesis or had congestive heart failure. Pulmonary embolism masquerading as asthma if it ever occurs, must be extremely rare.

COUGH: Cough occurs in about 70% of patients and is usually nonproductive. It is probably related to stimulation of irritant receptors.

CHEST PAIN: Pleuritic chest pain is more common with smaller pulmonary emboli. The visceral pleura has no pain fibers. In order to irritate the parietal pleura, there must be at least partial infarction, with involvement of the pleural surface. However, it is clear that pleuritic chest pain with pulmonary emboli can occur without an infiltrate being present on chest x-ray. More central anginal type chest pain occurs significantly more often with massive pulmonary emboli. (UPET, 1973; Sutton et al, 1969). A large pulmonary embolus obstructs considerably greater portion of the cross sectional area of the main pulmonary artery as it goes through the pulmonary valve than it does once it gets out into the main pulmonary arteries or fragments into smaller branches. The anginal pain is presumed to result from decreased coronary artery perfusion of the right ventricle, due to elevation of right ventricular pressures at a time that left sided pressures are transiently reduced.

HEMOPTYSIS: Hemoptysis is undoubtedly due to infarction of the lung and it is extremely rare to have more than blood streaking of the sputum without an infiltrate present on chest x-ray. Massive hemoptysis due to pulmonary emboli is extremely rare (Jay et al, 1976).

SYNCOPE:

Syncope occurred significantly more often in massive pulmonary emboli than sub-massive (UPET, 1973). Syncope, especially cough syncope, is a common feature of recurrent pulmonary embolism with severe pulmonary hypertension.

SIGNS:

TACHYPNEA: Rapid shallow breathing occurs in 75% of patients with pulmonary emboli. Experimental animal studies relate this to stimulation of J receptors that are dependent on a functioning vagus nerve (Widdicombe, 1973). Tachycardia occurs in only 67% of all pulmonary emboli, but is present in 97% of massive pulmonary emboli, (Sutton et al, 1969).

SIGNS RELATED TO PARTIAL OR COMPLETE PULMONARY INFARCTION: Pathologically, alveoli are filled with blood and edema fluid, initially (Castleman, 1965). If there is no necrosis of the alveolar walls,the area clears in a few days and is considered an incomplete infarction. The signs are essentially those of any area of consolidation, namely rales and tubular breath sounds. However, because of the very frequent association of an early pleural effusion, there may be more flatness than dullness to percussion and tactile fremitus may be decreased rather than increased. Pleural friction rub is seen in about 18% of patients with pulmonary emboli. A rub can occur without a radiographic density in the area on chest x-ray.

SIGNS RELATED TO PULMONARY HYPERTENSION: Increased pulmonic component of the second sound is common, but is also very common in other conditions confused with pulmonary embolism. A right ventricular heave is more suggestive but is very common in post-partal women without pulmonary emboli. Right sided S_3 or S_4 gallops are the more reliable signs but can be present with overwhelming hypoxemia from any cause. The cardiovascular response to pulmonary embolism is determined primarly by the magnitude of the embolic obstruction and the pre-existing cardiopulmonary disease (McIntyre and Sasahara, 1974). In patients with previously normal heart and lungs, pulmonary artery pressure correlated well with the percent vascular bed occluded. The pulmonary hypertension seen could be explained by the cardiac output and the available unobstructed pulmonary vascular bed without incriminating pulmonary vasoconstriction (Wilson et al, 1971). No patients with acute pulmonary emboli developed mean pulmonary arteries greater than 40 mm Hg (MyIntyre and Sasahara, 1974). The right ventricle is an ineffective pressure pump and at pressures higher than this in experimental animals tricuspid regurgitation develops (Knapp and Mullins, 1972). Pulmonary artery pressures were frequently out of proportion to the percent vascular bed occluded in patients with previous cardiovascular disease.

HYPOTENSION: If systemic hypotension is due primarily to pulmonary emboli, there is invariably elevation of right sided filling pressures (McIntyre and Sasahara, 1974). Therefore, it is very important in a hypotensive patient to obtain a central venous pressure or a pulmonary artery

pressure with a Swan Ganz catheter at the time that the patient is hypotensive.

Fever: Temperature greater than 102° F is extremely uncommon in pulmonary embolism. The only times I have seen temperature greater than this were in patients with good set-ups for septic pulmonary emboli and one patient who was mis-diagnosed for a long time and probably had superinfection of the infarct.

Cyanosis: Approximately 90% of patients with pulmonary emboli have lowering of the arterial-oxygen tension, but the hypoxemia is mild in most. Hypoxemia severe enough to produce cyanosis is usually not seen without massive pulmonary embolism. In series that include massive emboli with hypotension, there is a linear correlation between the pulmonary artery pressure and the arterial PO_2. However, in series that do not include massive pulmonary emboli with hypotension, there was no patient with a PO_2 less than 57. These 21 patients had no previous heart or lung disease (Wilson et al, 1971). In these patients, the amount of hypoxemia present could be explained by the degree of true shunting measured with 100% oxygen breathing studies. Patients without pulmonary infarction were able to take deep breaths greater than 80% of their predicted inspiratory capacity with assisted ventilation. The deep breaths thereby reduced their shunts to near normal. However, when patients resumed tidal volume breathing, their shunting promptly returned within 15 minutes, thus suggesting mechanical instability of the lungs. This was interpreted as a tendency to develop areas of microatelectasis surrounding the embolized areas and may be due to alteration in surfactant activity. Continued perfusion of these atelectic areas causes true intrapulmonic shunting. Saline extracts of human lungs with pulmonary infarction have decreased ability to reduce surface tension compared to normal lung extracts (Sutnick et al, 1967).

Studies in dogs indicated that true shunting measured with 100% oxygen breathing could not account for all of the hypoxemia following autologous emboli. Hypoventilation did not occur and diffusion impairment was minor. Therefore, it was concluded that ventilation/perfusion mismatching must be the primary cause of hypoxemia (Levy et al, 1969). In a subsequent study by the same group, venous admixture effect due to V/Q mismatching as well as increased total pulmonary resistance and decreased lung compliance could be prevented by prior heparinization (Levy and Simmons, 1975). Most of the patients studied by Wilson et al were on heparin at the time and this conceivably could have reversed bronchospasm and V/Q mismatching. However, the likely reason for the absence of V/Q mismatching in humans is that in humans much less serotonin may be released than in pulmonary embolism in dogs.

Although it is important to be aware of the signs and symptoms associated with pulmonary embolism, the clinical diagnosis of pulmonary embolism is extremely inaccurate (Hildner and Ormond, 1967, Modan et al, 1972). Therefore a compatible clinical picture should only suggest a need for more definite diagnostic measures.

LABORATORY AIDS

ROUTINE HEMATOLOGIC STUDIES

There are few conventional hematologic determinations that offer substantial diagnostic aid in pulmonary embolism. A moderate leukocytosis may occur and seldom helps distinguish thromboembolic disease from pulmonary infections. Platelet counts may be elevated as an "acute phase reactant" and should not be construed as necessarily indicative of an underlying thrombocytosis. In sickle cell anemia, characteristic blister cells have been reported on peripheral blood smears in the presence of pulmonary infarction. However, the reliability of this finding is unknown. (Barreras et al, 1968).

SERUM ENZYMES AND BILIRUBIN

In angiographically documented pulmonary embolism, LDH has been found elevated in 83% of one series (Szucks et al, 1971) and only 23% of another series (Light and Bell, 1974). LDH elevation was not dependent on radiographic evidence of pulmonary infarction (Szucks et al, 1971). An elevated LDH occurs in association with many other diseases that mimic pulmonary embolism, i.e., myocardial infarction, pneumonia and congestive heart failure. No combination of LDH, SGOT or bilirubin was frequent enough to be helpful (Szucks et al, 1971). When LDH isoenzymes were fractionated the mean LDH_3 level for patients with pulmonary emboli was significantly higher than the level of LDH_3 isoenzymes for patients with either congestive heart failure or pneumonia. However, there was considerable overlap in the isoenzyme patterns and they were of no use diagnostically in individual patients (Light and Bell, 1974).

NITRO BLUE TETRAZOLIUM TEST (NBT)

The NBT test nearly always has an elevated score in pneumonia and is rarely elevated in pulmonary embolism (Rowan et al, 1974; Hellum and Solberg, 1974).

ARTERIAL BLOOD GASES

Patients with acute pulmonary embolism nearly always have a respiratory alkalosis. CO_2 retention is extremely uncommon unless pulmonary embolism occurs in the setting of a comatose or a paralyzed patient on automatic ventilation. The arterial oxygen tension was reported to be 80 mm Hg or less in all patients with pulmonary embolism in whom it was measured by Szucks et al, (1971). However, others find a PO_2 of higher than 80 mm Hg on room air in approximately 10% of patients with pulmonary emboli (Wilson et al, 1971; UPET, 1973). From a practical point of view, when investigating young people with pleuritic chest pain, there is no significant difference in the arterial PO_2 in the patients in whom pulmonary embolism is proven as opposed to the PO_2 in those patients with other disorders (McNeil et al, 1975).

FIBRIN DEGRADATION PRODUCTS AND SOLUBLE FIBRIN COMPLEXES

In 1971 we reported our experience with 33 patients suspected of having pulmonary embolism who had diagnostic quality pulmonary angiograms (Wilson et al, 1971). When the angiograms were positive, 24 our of 25 patients had elevated fibrin split(degradation) products (FDP). When the angiogram was negative, only 2 out of 8 had elevated FDP. (Figure 2). Small pulmonary emboli had elevations of FDP equally high as larger emboli (Figure 3).

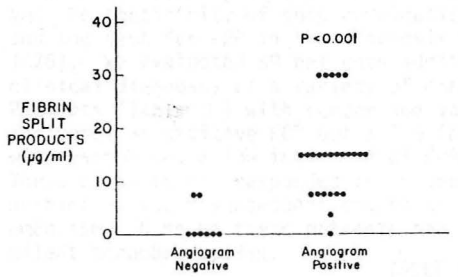


FIGURE 2 Fibrin split product concentrations in patients thought clinically to have pulmonary emboli.

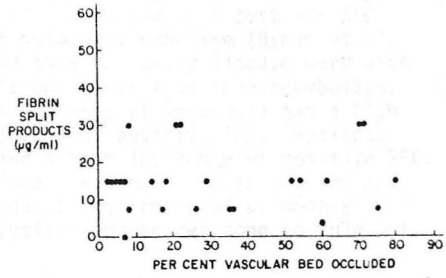


FIGURE 3 Fibrin split product concentrations related to extent of embolization estimated from pulmonary angiograms.

In Table 2 the reported experience with FDP in pulmonary embolism is tabulated. Most investigators find it very rare to have a negative FDP determination when pulmonary embolism can be documented by lung scan or pulmonary angiogram. A single exception to this is the report of Light and Bell in 1974. They found negative FDP in 28 out of 35 angiographically-documented cases of pulmonary embolism.

TABLE 2
FIBRIN DEGRADATION PRODUCTS (FDP) IN PULMONARY EMBOLISM

REFERENCE	DIAGNOSTIC METHOD	FDP + NO PUL EMB	FDP - PUL EMB PRESENT	TOTAL AGREEMENT TOTAL COMPARISONS
RUCKLEY ET AL BRIT MED J 1970	LUNG SCAN	6/6 (100%)	0/10 (0%)	10/16 (63%)
WILSON ET AL J CLIN INVEST 1971	PULMONARY ANGIOGRAM	2/8 (25%)	1/25 (4%)	30/33 (91%)
RICKMAN ET AL ANN INT MED 1973	PULMONARY ANGIOGRAM	3/22 (14%)	1/18 (6%)	36/40 (90%)
GUREWICH ET AL CHEST 1973	LUNG SCANS SOME ANGIOGRAMS	6/16 (37%)	1/14 (7%)	23/30 (78%)
LIGHT AND BELL ARCH INT MED 1974	PULMONARY ANGIOGRAM		25/35 (80%)	
BYNUM ET AL AM REV RESP DIS 1976	LUNG SCANS SOME ANGIOGRAMS	5/28 (18%)	5/29 (17%)	47/57 (82%)

I think that this was a methodological problem. They clotted plasma at 0°, a method known to minimize FDP levels in normals (Merskey et al, 1972). We clot whole blood at room temperature or 37° C. Because of this report we have looked at the problem again. We found negative FDP in only 5 of 29 (17%) cases of acute pulmonary embolism. Gurewich et al (1973) have reported that when fibrin split products are negative in pulmonary embolism that soluble fibrin complexes (SFC) detectable by his serial-dilution protamine sulfate (SDPS) test and related to minute thrombin generation are invariably present. Gurewich reported that he has found no instance of documented pulmonary embolism or symptomatic deep thrombophlebitis when both SFC and FDP were negative.

We have recently conducted a survey to evaluate both the sensitivity and the specificity of this combination of tests, the SDPS test for SFC and the test for FDP in the diagnosis of pulmonary embolism (Bynum et al, 1976). We evaluated 80 patients admitted to a pulmonary disease ward with clinical diagnoses of a variety of conditions other than thromboembolism. Patients (Table 3) with cancer and various types of pneumonia had a high incidence of positive FDP but a low incidence of positive SFC. Patients with asthma had a low incidence of FDP and a high incidence of positive SFC. These patients all responded to conventional treatment for asthma and had nothing in their subsequent course to suggest recurrence of pulmonary embolism. None of these patients had specific procedures done to rule out silent thromboembolism.

TABLE 3

FDP AND SFC IN NON THROMBOEMBOLIC PULMONARY DISEASE

DISEASE	NUMBER OF PATIENTS	FDP +	SFC +
CANCER	6	5 (83%)	0 (0%)
PNEUMONIAS	20	15 (75%)	1 (5%)
C.O.P.D.	13	7 (54%)	2 (15%)
TUBERCULOSIS	7	3 (43%)	1 (14%)
OTHER	21	8 (38%)	6 (29%)
ASTHMA	13	2 (15%)	6 (46%)

Table 4 shows our results in various populations. Positive FDP or SFC were found significantly more often in pulmonary embolism than in any of the other 3 populations. However, a positive test for either FDP or SFC alone was not specific for pulmonary embolism.

TABLE 4

POSITIVE RESULTS IN VARIOUS POPULATIONS

	NUMBER OF SUBJECTS	FSP ≥ 10μg/ml	SDPS TEST GRADE ≥ 10
NORMAL CONTROL	24	1 (4%)	4 (17%)
PULMONARY DISEASES OTHER THAN THROMBOEMBOLISM	80	40 (50%)	16 (20%)
ACUTE PULMONARY EMBOLISM	29	24 (83%)	21 (72%)
NEGATIVE PULMONARY ANGIOGRAM	28	5 (18%)	10 (36%)

In order to obtain better specificity, we looked at both tests together as suggested by Gurewich et al (1973)

TABLE 5
COMBINATION OF FDP AND SFC IN VARIOUS POPULATIONS

	N	BOTH POSITIVE	BOTH NEGATIVE
NORMAL CONTROLS	24	0%	79%
PULMONARY PATIENTS OTHER THAN PULMONARY EMBOLISM	80	4%	35%
ACUTE PULMONARY EMBOLISM	29	55%	3%
NEGATIVE PULMONARY ANGIOGRAM	28	7%	54%

It was rare to find both tests positive in conditions other than acute pulmonary embolism. Conversely if both tests were found negative, pulmonary embolism was very unlikely.

To assess further their diagnostic value, we measured FDP and SFC in patients at high risk for, but not suspected of having pulmonary embolism (PE); all had other potential reasons for positive tests. Categories were: (1) renal failure (RF), (2) postoperative pt (PO), (3) cardiorespiratory disease in intensive care units(ICU)(4)Pregnant & postpartum (OB), and (5) deep vein thrombosis (DVT).

Category	No.	FDP +	SFC +	Both +	Both -	FDP (mean±SEM)	SFC (mean±SEM)
1. R.F.	31	11(35%)	14(45%)	3(10%)	9(29%)		
2. P.O.	20	3(15%)	14(70%)	2(10%)	5(25%)		
3. I.C.U.	20	2(10%)	16(80%)	2(10%)	1(5%)	8.6±0.9	8.9±0.5
4. O.B.	28	2(7%)	20(71%)	2(7%)	8(29%)		
5. D.V.T.	16	4(25%)	13(81%)	4(25%)	2(13%)		
6. P.E.	39	26(67%)	36(92%)	24(62%)	1(3%)	23.9±6.4	11.5±0.5

FDP are positive more often in PE than all other categories combined ($P<0.001$) and mean values are higher in PE ($P<0.001$). The frequency of positive SFC is also greater in PE ($P<0.005$), and mean values are higher ($P<0.005$), than all others. Combined positivity of both tests occurred more often in PE than the rest ($p<0.02$) and was particularly useful in separating PE from RF, PO, ICU and OB, since both were positive in 10% or less in these categories. Both tests were negative more often in other categories than PE ($p<0.02$). These tests are helpful in diagnosing or excluding PE in high-risk patients. FDP are better than SFC as a single test, but a combination of both is most discriminating.

The low incidence of positive FDP in phlebographically diagnosed DVT confirms our original findings (Wilson et al, 1971) and those of others that FDP are more consistently elevated in pulmonary embolism than in DVT. (Ruckley et al, 1970). The more extensive the DVT the more likely FDP are to be elevated (Gurewich et al, 1973, Tibbutt et al, 1975). In DVT confined to

calf, FDP are rarely elevated (Gurewich et al, 1973, Gallus et al, 1973).

Use of FDP to screen for pulmonary embolism in high risk patients: Patients with total hip replacements have been followed post-op with daily measurement of FDP with conventional techniques and fragment E by radioimmunoassay. Six of the 33 patients developed pulmonary emboli. All six had elevated FDP on the day pulmonary embolism was diagnosed by lung scan, but FDP usually was not elevated prior to that day. Fragment E was also elevated in all six patients with pulmonary emboli and most patients had elevations at least five days before the embolus. Six of the 26 patients without pulmonary emboli had elevated fragment E, a false-positive rate of 23% (Cook et al, 1975). Similar studies need to be done with other new methods that are available for measuring by-products of thrombin such as the radioimmunoassay of fibrinopeptide A (Nossel et al, 1974) and by-products of plasmin such as radioimmunoassay of fragment D (Gordon et al, 1975).

ELECTROCARDIOGRAM

Two series with angiographically documented pulmonary embolism had normal ECG 70 to 75% of the time (Hildner and Ormond 1967, Sasahara et al, 1967). Fortunately ECG's are more helpful in massive pulmonary emboli where 20 of 35 had classic S_1 Q_3 T_3 pattern and 9 more had right bundle branch block with a total of 83% being abnormal (Sutton et al, 1969).

CHEST ROENTGENOGRAM

Pathologically, pulmonary infarction implies alveolar wall necrosis. The classic description of a pulmonary infarct is an infiltrate in contact with a pleural surface with a convex margin pointing toward the heart. When such infarcts heal they leave linear shadows on the roentgenogram. Similar infiltrates that are transiently present for only a few days result from incomplete infarction with hemorrhage and edema in alveolar spaces but without alveolar wall destruction (Hampton and Castleman, 1940). Fleishner (1965) has emphasized the frequent finding of elevation of a hemidiaphragm, basal atelectasis, often plate-like atelectasis, pleural effusions, and occasionally areas of oligemia. Acute or chronic cor pulmonale may become evident by dilated hilar arteries, dilated pulmonary artery trunk, dilated azygos vein or superior vena cava, or dilatation of the right ventricle.

Only 10% of pulmonary emboli produce infarction in autopsy studies (Smith et al, 1965). However, most patients have multiple pulmonary emboli and therefore it is rare for patients to have a normal chest x-ray. A totally normal chest x-ray was found in only 7% of the series by Moses et al, (1974).

Cavity formation in pulmonary infarction is rare and is usually thought to be due to septic emboli. However, it has been described without evidence of sepsis (Greco and Ryan 1968; Sharp et al, 1971).

In an unpublished prospective study of 120 cases of pulmonary embolism (Bynum and Wilson, 1977) pleural effusion occurred in half the patients. Excluding patients with other possible causes for effusions, there were no patients with bilateral effusions and none exceeded one-third of a hemithorax.

Effusions were present on the day of admission and did not enlarge unless there was clinical and scan evidence of recurrence of pulmonary embolism at the time. Forty-nine percent of the effusions had an associated infiltrate and most of these took longer than 7 days to clear. Most effusions without infiltrates cleared within 7 days.

THORACENTESIS

There are no diagnostic pleural fluid findings in pulmonary embolism (Bynum and Wilson, 1976) Sixty-five percent of the effusions are grossly bloody and these are usually associated with infiltrates on the chest roentgenogram. Total white blood cell count varied from 22 to 57,000 cells per cubit ml. Standard criteria for an exudate (protein value greater than 3.0 grams per 100 ml, specific gravity greater than 1.016, and LDH value greater than 200 units) were found in about half the patients. The major value of thoracentesis is to exclude an empyema with its characteristic odor or a positive gram stain and to look for a grossly bloody pleural effusion. Other than trauma or malignant neoplasm, there are very few other causes of grossly bloody pleural effusion. Tuberculous effusions usually are not bloody.

PHLEBOGRAPHY

A number of different phlebographic techniques have been used in the past. The most complete filling of the venous tree is obtained by injecting contrast media through a vein on the dorsum of the foot with the patient upright without weight bearing (Rabinov and Paulin, 1972). However, a technique involving tourniquets with injection in the supine position may give better filling of the soleal veins (Nicolaides et al, 1971). Venograms are difficult to interpret especially in the calf veins. Non-filling of a vein is not acceptable as conclusive evidence of thrombosis nor are other ancillary findings such as flow patterns or abnormal collateral veins. The only reliable finding is a consistently demonstrable filling defect preferably surrounded by a layer of contrast media and seen in at least two projections in a well opacified vein (Williams, 1973). In the setting of a suspected pulmonary embolus with non-specific findings on lung scans, a positive phlebogram gives adequate confirmation of the diagnosis to warrant treatment. In surgical series, (Corrigan et al, 1975) negative phlebograms in the setting of suspected pulmonary emboli have been used as indications to withhold anticoagulation and none of the patients had recurrence of pulmonary embolism. However, in medical patients pulmonary embolism is frequently associated with negative phlebograms of the lower extremities (Bynum and Wilson, 1977).

LUNG SCANS

PERFUSION LUNG SCANS

Perfusion lung scans utilizing labeled macroaggregates of human serum albumin have been in use since the mid 1960's (Wagner et al, 1964) and are one of the most important advances in the diagnosis of pulmonary embolism. However, there are many technical and clinical pitfalls in interpreting lung scans (Moser and Miale, 1968). Anything that causes regional obstruction to ventilation or a density on a chest roentgenogram will cause a perfusion defect on a lung scan. It was soon realized that perfusion defects had a much higher probability of being due to pulmonary emboli if they corresponded to specific anatomic segments or lobes of the lungs (Poulose et al, 1970).

Characteristic patterns have been described for congestive heart failure:(a) irregular inhomogenous perfusion pattern corresponds to roentgenographic evidence of interstitial pulmonary edema (b) focal non-segmental perfusion defects superimposed upon the irregular pattern correspond to the alveolar pattern on concurrent chest roentgenograms (c) a reversal of the normal perfusion ratio between upper and lower lobes (d) cardiac enlargement and (e) changes due to pleural effusions. The perfusion defects due to pleural effusions characteristically are no larger than the density caused by the fluid on the chest roentgenograph. Focal perfusion defects due to alveolar infiltrates can precede or are followed by 24 hours the appearance or disappearance of the infiltrate (James et al, 1971, Gilday et al, 1972).

The most common pattern in emphysema is an irregular inhomogenous distribution of perfusion. Focal non-segmental defects are the next most common pattern. The focal non-segmental perfusion defects are usually better defined than those found in congestive heart failure. Asthma is associated with multiple focal defects that may be very sharp and easily confused with pulmonary emboli (Woolcock et al, 1966, Henderson et al, 1967).

A summary of the characteristic differences in lung scan patterns between pulmonary embolism, congestive heart failure and emphysema is shown in Table 6 (Gilday and James, 1972).

TABLE 6

LUNG SCAN PATTERN CORRELATION

Pattern	Pulmonary Embolism	Congestive Heart Failure	Emphysema
Focal Segmental/Lobar	+	−	−
Focal Nonsegmental	−	+	±
Irregular	−	+	±
Cardiomegaly	−	+	−
Reversal of Flow	−	+	±
"Fissure Sign"	+	+	±

+ High Probability; ± Occurs; − Low Probability.

Dogs receiving either 6 small emboli or three massive emboli have been studied with lung scans and angiograms (Moser et al, 1969). The lung scans missed 14% of small individual emboli and 23% of massive individual emboli. False positive interpretations occurred in 21% and 11% of the lobes of dogs with small emboli and large emboli, respectively. This incidence of false positive and false negative interpretations for individual lobes was no better or worse than for pulmonary angiography as indicated in Table 2. Studies have not been done to determine the smallest single pulmonary embolus that can be reliably detected.

TABLE 7

Correlation Between Anatomic Data and Angiographic-Scan Diagnoses of Lobar Involvement: Results are Composite of Interpretations by Two Observers.

	Diagnosis		
	Correct	Missed	False+
Small emboli			
Photoscan	19 (83%)	4	6
Angiogram	17 (74%)	6	8
Massive emboli			
Photoscan	29 (69%)	13	5
Angiogram	33 (79%)	9	7

Circulation, Volume XXXIX, May 1969

Gilday et al (1972) emphasized the fact that focal segmental or lobar perfusion defects had a high probability of being due to pulmonary emboli and that non segmental or diffuse perfusion defects had a low probability of being due to pulmonary emboli. The utility of this approach has been confirmed (Moses et al, 1974). It is useful to interpret lung scans in four categories: (1) high probability for pulmonary embolism (2) indeterminate for pulmonary embolism (3) low probability for pulmonary embolism and (4) normal.

HIGH PROBABILITY FOR PULMONARY EMBOLISM: Perfusion lung scan with multiple sharp perfusion defects segmental or lobar in the absence of radiographic densities (in some of the areas) and obstructive lung disease.

TABLE 8

		Pulmonary Angiograms		
AUTHOR	No.	Specific for PE per cent	Non-specific per cent	Normal per cent
Gilday et al, 1972	53	77	17	6
Moses et al, 1974	46	80	11	9

In general the larger the focal perfusion defect, the more likely

it is due to pulmonary emboli. However, extremely large defects such as involving a whole lung, prove to be due to pulmonary emboli by angiography in only about half the cases. (Gilday et al, 1972, McNeil, 1976).

Single perfusion defects were confirmed by angiography to be due to pulmonary emboli only half the time when lobar and never (9 patients) when segmental or smaller (McNeil, 1976).

INDETERMINATE FOR PULMONARY EMBOLISM: Perfusion defect only in an area of consolidation and/or pleural effusion on chest roentgenogram.

LOW PROBABILITY FOR PULMONARY EMBOLISM: Non segmental or equivocally segmental defects, often at the lung bases and frequently associated with obstructive lung disease or radiographic densities.

TABLE 9 Pulmonary Angiograms

Author	No.	Specific for PE per cent	Non-specific per cent	Normal per cent
Gilday et al, 1972	27	12	60	28
Moses et al, 1974	50	14	34	52

If a low probability scan was associated with a normal chest x-ray, pulmonary angiograms did not confirm pulmonary embolism on any of 18 patients (Moses et al, 1974).

Though most perfusion defects in COPD are non-segmental about 18 percent are focal segmental defects. These regions invariably have poor ventilation by ^{133}Xe scans in patients with negative pulmonary angiograms. The focal segmental perfusion defects occurred only in moderate to severe COPD (Alderson et al, 1976).

NORMAL PERFUSION LUNG SCAN: When we performed perfusion lung scans with ^{131}I-MAA using a rectilinear scanner and obtaining only 2 views, we saw 4 patients interpreted as having normal lung scans who had definite pulmonary emboli confirmed with pulmonary angiograms. However, if a good quality 4-view lung scan using a gamma camera and ^{99m}Tc labeled microsphere is normal pulmonary embolism is ruled out for all practical purposes.

TABLE 10 Pulmonary Angiogram

Author	No.	Specific for PE per cent	Non-specific per cent	Normal percent
Gilday et al, 1972	21	0	5	95
Moses et al, 1974	8	12	25	63

Lung scans are increasingly performed in outpatients complaining of pleuritic chest pain. In a retrospective analysis of 97 young patients (age 18-40) having perfusion lung scans, 95 percent of the pulmonary emboli could have been found if perfusion lung scans had been limited to patients who were post operative, had prior or current venous disease or had pleural effusions on chest x-ray. The final diagnosis in the 97 patients were:

Pleuritis or costochondritis	47%
Pulmonary embolism	21%
Pneumonia	18%
Miscellaneous diagnoses	8%

Of the 20 patients identified as having pulmonary embolism, 85% (17 patients) had lung scans highly probable for pulmonary embolism and 15% (3 patients) had indeterminate scans. At the same time 12 patients without pulmonary embolism had indeterminate scans. Thus, in this group of 97 patients, 15 required pulmonary angiography because of indeterminate scan. (McNeil et al, 1976).

VENTILATION SCANS

SINGLE BREATH OF ^{133}Xe WITH BREATH HOLDING AT TOTAL LUNG CAPACITY.

Patients with angiographically documented pulmonary embolism without infarction have normal ventilation in areas of decreased perfusion. Patients with emphysema have decreased ventilation in areas of perfusion defects when the perfusion scan is performed by IV injection of ^{133}Xe in saline with breath holding at TLC and the ventilation scan is performed by a single breath of ^{133}Xe gas in air (Medina, 1969). The injection and the single breath of ^{133}Xe have to be repeated for each view desired.

If the perfusion scans are first performed with ^{99m}Tc labeled microspheres, 4 views can be obtained and ^{133}Xe ventilation scans can then be performed in 1 or 2 views that show the perfusion defects best. Concern that scatter radiation from the 140 KeV gamma ray might interfere with a ventilation scan with a window set for the 81 KeV gamma ray of ^{133}Xe does not appear to be a significant problem (Jacobstein, 1974). Using ^{99m}Tc particle perfusion scans and then single breath ^{133}Xe ventilation scans in sequence, McNeil (1976) reports substantial improvement in the specificity of diagnosis of pulmonary embolism compared to perfusion scans alone in patients validated by pulmonary angiography. In patients with multiple defects on perfusion scan the probability that it was due to pulmonary emboli was enhanced if ventilation was normal in the area:

TABLE 11
VENTILATION SCANS IN PULMONARY EMBOLISM

Largest focal defect on Perfusion Scan	Probability of pulmonary embolus being found with pulmonary angiography	
	Perfusion scan alone	V/Q mismatch
Lobar	0.81	0.94
Segmental	.50	1.00
Subsegmental	.09	0.50

The main benefit of ^{133}Xe ventilation scans is in segmental size perfusion defects. With smaller perfusion defects, finding normal ventilation scans in the same regions is not specific enough to confirm the diagnosis of pulmonary emboli but makes pulmonary embolism considerably more likely. The only way to be sure in such instances is pulmonary angiography.

DYNAMIC VENTILATION SCANS - WASHOUT OF ^{133}Xe AFTER VENTILATORY EQUILIBRATION.

Some patients have too much pleuritic chest pain or are too dyspneic to cooperate with a breath-holding ventilation scan. Also, until recently, there was no study evaluating whether high V/Q regions reliably confirm pulmonary emboli in the presence of chronic obstructive ventilatory defects. The overall diagnostic accuracy in this situation is significantly improved by ventilation studies (Alderson et al, 1976). The ventilation studies were performed prior to the ^{99m}Tc particle perfusion study. Sequential scintiphotos of one view (probably posterior) were taken at 1 minute intervals during washout after closed circuit equilibration with a ^{133}Xe gas in air mixture. High V/Q regions were found in only 23 percent of the 136 angiographically documented emboli in 12 patients. However, at least one high V/Q region was present in 11 of the 12 patients with pulmonary emboli. Only 2 of the 28 patients with negative pulmonary angiograms had high V/Q regions. It appeared to be only because of the large number of pulmonary emboli (average of 11) in each patient that at least one resulted in a high V/Q region. Finding a high V/Q region in a patient with COPD suspected of having pulmonary emboli appears to be reasonable confirmation of the diagnosis. However, failing to find high V/Q regions may not reliably rule out pulmonary emboli when suspected.

PULMONARY ANGIOGRAPHY

HISTORY

Dr. J. R. Williams from Radiology and Dr. Curtis Wilcox in Pulmonary Medicine from this institution were the first to report the use of pulmonary angiography in diagnosing pulmonary emboli in 1963.

DIAGNOSTIC CRITERIA. Pulmonary angiography is generally considered to be the most definitive diagnostic technique available for pulmonary embolism. In an animal study of small and large pulmonary emboli confirmed by autopsy (Moser et al, 1969) filling defects were the most common and most reliable

defect found. Ninety-three percent of the filling defects found were confirmed at autopsy and were never false-positives in small emboli. The second most reliable angiographic abnormality was detection of an abrupt vessel cut-off, with 72% of these abnormalities being confirmed at autopsy. Decreased flow or tapering of vessels was less reliable and only 61% of these defects were confirmed at autopsy. (See Table 12).

TABLE 12

Incidence of Various Angiographic Abnormalities Detected and Correlation in Each Category with Postmortem Findings

		Diagnosis	
	No.	Correct	False+
Filling defects			
Small emboli	16	16 (100%)	0
Massive emboli	42	38 (90%)	4
	58	54	
Cutoffs			
Small emboli	9	6 (67%)	3
Massive emboli	16	12 (75%)	4
	25	18	
Decreased flow or tapering			
Small emboli	12	6 (50%)	6
Massive emboli	14	10 (71%)	4
	26	16	
Total	109	88 (81%)	

Using all of these diagnostic criteria, there was approximately a 20% instance of both false-positive and false-negative interpretations for involvement of individual lobes by pulmonary emboli. However, all dogs had multiple emboli and a false positive or a false negative diagnosis for an individual dog was not studied in this investigation. It is generally agreed upon to insist on filling defects or cut-offs for a definitive diagnosis of pulmonary embolism in humans (Stein et al, 1967, Dalen 1974). Many angiographers believe that pulmonary angiography is much better than lung scans. However, I agree with Moser that they are complementary. In his animal study using the combination of the two techniques lead to a higher incidence of correct diagnoses (90%) and either angiography (79%) or lung scanning (69%) alone in identifying lobes involved by pulmonary emboli.

INTERPRETATION OF ANGIOGRAPHIC FINDINGS: In a *normal* pulmonary angiogram, the left and right pulmonary arteries, the lobar arteries, and their first 3 subdivisions are well visualized by contrast media. There are no intra-

luminal filling defects or cut-offs. Each portion of the pulmonary circulation fills symmetrically and there are no areas of delayed filling or oligemia. (Dalen 1974).

An interpretation of *DEFINITE* pulmonary embolism is made when distinct filling defects or sharp arterial cut-offs are present.

EQUIVOCAL interpretation of the pulmonary angiogram is all that can be made if areas of oligemia or asymmetrical flow are the only abnormality. Oligemia can occur without pulmonary embolism and may be caused by any acute or chronic obstructive lung disease or by any of the conditions that cause a perfusion defect on lung scans. Asymmetrical filling, expecially delayed filling to both lower lobes, is common with left heart failure. (See Table 13)

TABLE 13

Relationship Between Pulmonary Capillary Wedge Pressure and Flow Pattern to Lower Lobes in Patients Without Pulmonary Embolism

Pulmonary Capillary Wedge Pressure (Mean, mm Hg)	No. of Studies	Patients with Bilateral Lower Lobe Delay (%)
<12	105	11
13-20	15	20
>20	27	48

Dalen: Cardiac Catheterization and Angiography 1974

Using these diagnostic categories, Alport and Dalen (1974) report only a 14% instance of equivocal diagnoses.

TABLE 14

RESULTS OF PULMONARY ANGIOGRAPHY IN 355 PATIENTS SUSPECTED OF ACUTE PULMONARY EMBOLISM 1964-73

Findings	Number	Percent
Definite	144	41
Equivocal	50	14
Negative	161	45
Total	355	100

Their institution has the policy of angiogramming nearly everyone with pulmonary embolism. However, we have the policy of accepting the diagnosis on the basis of a high probability scan, especially if confirmed by a normal ventilation scan in the same region. In our experience when pulmonary angiograms are done primarily to resolve the issue when there is a low probability lung scan, there is considerably higher incidence of equivocal angiograms (See Table 9 under Lung Scans). Thus, when angiograms are needed the most they do not settle the issue in 34% to 60% of the cases. Usually the clinician is not willing to withhold anticoagulation unless a definitely normal angiogram is obtained. When the conventional pulmonary angiogram is equivocal, selective injections of lungs, lobes or segments in various oblique positions (Bookstein, 1969) is helpful, but in our experience frequently does not resolve the issue. Pulmonary cineangiography focusing on an equivocal area can help (Meister et al, 1972).

Balloon occlusion selective pulmonary angiography: Because of an unacceptably high incidence of equivocal pulmonary angiograms when they are needed the most, we have investigated a technique involving hand injection of contrast media beyond a balloon tipped catheter occlusion of a vessel in question. (Wilson and Bynum 1976). This technique was shown to be safe in humans by Nordenstrom in 1954. We confirmed that the technique is safe in animal studies and then began using it in patients with an ordinary #7 Swan Ganz balloon-tipped catheter. Most of the equivocal areas on conventional angiograms are in the lower lobes and the balloon-tipped catheter can be manipulated into these regions with ease. With the balloon inflated and flow obstructed, meglumine diatrozoate (Renografin 76) is hand injected under fluoroscopic observation while a 105 mm photospot camera takes pictures anywhere from 1 to 4 frames per second. Small vessel detail in subsegmental and smaller vessels is greatly improved and filling defects in segmental size vessels become much more distinct. With this technique, we found that equivocal pulmonary angiograms had normal vessels in half the instances and had distinct filling defects in the other half. (See Table 15)

TABLE 15

RESULTS OF STANDARD AND BALLOON-OCCLUSION ANGIOGRAPHY IN 33 PATIENTS

Standard Angiogram	No.	Balloon-Occlusion Angiogram	No.
Normal, definite	3	Normal, definite	3
Emboli, definite	2	Emboli, definite	2
Normal, probable	10	Normal, definite	9
		Normal, probable	1
Emboli, probable	7	Emboli, definite	3
		Normal, definite	1
		Inconclusive*	1
		Not done†	2
Equivocal	8	Emboli, definite	4 (figure 4)
		Normal, definite	4
Not done**	3	Emboli, definite	1
		Normal but incomplete	2

*The probably abnormal vessel was not opacified owing to occlusion distal to its take-off. See text for details.

†The balloon-tipped catheter could not be advanced owing to venous spasm.

**The balloon occlusion study was done initially. Standard angiography was contraindicated owing to the poor condition of the patients.

Our criteria for normality in a conventional angiogram are more strict than those of most, and I think most angiographers would accept our category "probably normal" as being normal.

Diagnostic categories were defined as follows. (*1*) Normal, definite: Complete visualization of all branches, each showing total, regular opacification, with normal and uniform capillary filling throughout. (*2*) Emboli, definite: Presence of filling defects that are easily visualized and sharply outlined or cut-offs that are distinct and abrupt with concave margins, neither of which can be explained by uneven dilution ("streaming") of contrast material, branching or overlapping of vessels, or superimposition of adjacent densities. (*3*) Normal, probable: Opacification of all branches without filling defects or cut-offs, but with minor irregularities of vessel margins or incomplete visualization of one or more branches. (*4*) Emboli, probable: Major irregularities of opacification that resemble filling defects, but whose outlines cannot be completely defined, or cut-offs whose margin is indistinct, irregular, or convex. (*5*) Equivocal: Uneven vessel opacification without distinct defects or cut-offs, excessively rapid tapering or "pruning" of vessels, complete absence of one or more small branches without a definable cut-off, or localized decrease in capillary filling; in addition, any apparent filling defect that may be due to streaming, branching, or overlapping of other vessels.

Fig. 4 Equivocal angiogram found to be abnormal by balloon-occlusion study. A. Selective right pulmonary artery injection with standard techniques, showing poor filling of lower lobe branches owing to catheter recoil; this was the second attempt at selectively visualizing these vessels. B. Balloon-occlusion angiography showing definite cut-off in right lower lobe (arrow).

It is interesting that the balloon occlusion selective angiograms did not find pulmonary emboli in any of the patients with normal or probably normal angiograms. Also, the conventional angiograms that were considered to have "probable pulmonary emboli" were found to be normal in only one instance with the balloon occlusion technique. In other words, when an experienced angiographer interprets an angiogram as showing pulmonary emboli he is usually right, even when the filling defects and cut-offs aren't convincing to the novice. He is almost always right when he interprets pulmonary angiograms as normal, despite their having questionable filling defects when viewed by the novice. The major benefit of the balloon occlusion technique is that vessels that appear equivocal on routine angiography appear definitely normal or definitely abnormal with this technique. However, the actual accuracy of the balloon occlusion tehcnique needs to be proven with an independent method in animals and such a study is underway. Another advantage is that with much less experience when learning angiography, one can feel more confident about interpretations.

Risk of pulmonary angiography: In a large series of consecutive pulmonary angiograms (Dalen 1974) there was a 4% incidence of complications and a 0.4% mortality rate related to pulmonary angiography. The most serious complication was perforation of the right ventricle in three instances; the perforation sealed itself and was not fatal in any of these 3 cases. The two deaths included cardiogenic shock precipitated in a terminally

ill woman with primary pulmonary hypertension following contrast injection; the other death occurred shortly after angiography in a 77 year old woman with massive pulmonary embolism and severe right heart failure. In such circumstances it is now generally recommended to perform only selective lobar injections rather than main pulmonary artery injections. A number of large series of pulmonary angiograms have been reviewed (Stein et al, 1975) and report total complication ranging from 4 to 11 percent when such things as incision hematomas are included. Most of the series have no deaths related to pulmonary angiography.

For a patient who has had a previous allergic reaction to contrast media a pulmonary angiogram can be done without great risk if the patient is treated with a total of 150 mgms of Prednisone or an equivalent dose of a related steroid per day in divided doses starting 18 hours before the procedure is completed. (Zweiman et al, 1975). With such treatment only 3 of 37 persons with rash reactions during previous radiographic contrast material studies had adverse responses during a repeat contrast procedure. These were mild urticaria responses without any respiratory symptoms or hypotension. IV radiographic contrast studies were also repeated in 9 subjects who had had previous anaphylactoid responses with only one mild urticarial reaction occurring when covered by steroids. Another study has safely administered radiographic contrast media to patients with a history of a previous reaction by treating them with diphenylhydramine hydrochloride 50 mgm IV immediately before or orally 1 hour prior to the contrast media injection (Shatz et al, 1976).

Reliability of a normal pulmonary angiogram:

When clinical features suggest pulmonary embolism and the pulmonary angiogram is normal, clinicians frequently ask: "could the embolus have spontaneously lysed during the delay between the onset of symptoms and the angiogram?" Such rapid lysis is very unlikely. In the urokinase pulmonary embolism trial pulmonary angiograms and scans were repeated at 24 hours in 78 patients who were treated with heparin alone. With angiography the average decrease in previously documented embolic obstruction was about 20%. In another study (Dalen et al, 1969) angiograms were repeated 1 to 7 days after the initial study in 7 patients; 1 showed no angiographic change while the other 6 showed minimal resolution. Beyond 7 days complete resolution has been documented by several investigators (Fred et al, 1964, Dalen et al, 1969, Wilson et al, 1971). In 6 patients who died within 10 days of having had a negative pulmonary angiogram, none had evidence of pulmonary embolism at autopsy (Dalen, 1974). Sautter et al (1967) reported rapid lysis of a large pulmonary embolus in 1 lung within 30 hours. However, other emboli in the same patient in the opposite lung did not resolve within that period of time.

DIAGNOSTIC END POINTS:

Because of the inaccuracy of clinical diagnosis, the high rate of recurrence of untreated pulmonary embolic and frequent bleeding complications with anticoagulation, it is difficult to know where to stop in a diagnostic work up. A reasonable approach (that will undoubtedly have exceptions) when pulmonary embolism is suspected is as follows:

1. Pulmonary embolism is very unlikely, anticoagulation is withheld

or discontinued, and the diagnostic workup is stopped at any of the following steps:

a. Arterial oxygen tension is > 80 mm Hg and FDP/fdp is negative (< 10 µg/ml). With a very high index of suspicion the workup continues despite these results, especially in late recurrences of pulmonary embolism.

b. FDP and the SFC are both negative. (SDPS tests shows no fibrin strands or gels at the 24 hr reading).

c. A good quality 4-view ^{99m}Tc perfusion lung scan is normal.

d. The perfusion lung scan is "low probability" for pulmonary embolism and the chest roentgenogram is completely normal.

e. A ventilation scan with ^{133}Xe shows ventilation defects in the same regions as all defects on the perfusion scan.

f. Conventional pulmonary angiogram is normal or equivocal areas are normal with balloon occlusion selective angiograms.

2. *Pulmonary embolism diagnosis is accepted, and anticoagulation treatment is initiated or continued at any of the following steps:*

a. Compatible clinical findings with chest roentgenograms showing a wedge-shaped infiltrate (rounded medially) against a pleural surface ("Hampton's hump"), and a pleural effusion that is grossly bloody (not just serosanguineous).

b. Perfusion lung scan that is "high probability" for pulmonary embolism. "High probability" lung scans are not always confirmed by pulmonary angiography as resulting from pulmonary emboli, but this may be due to the fact that during spontaneous lysis of pulmonary emboli the angiographic defects disappear faster than lung scan perfusion defects. Large segmental perfusion defects can occur with chronic obstructive pulmonary disease severe enough to be symptomatic and clinically obvious. However, a perfusion defect in such circumstances should be considered low probability for pulmonary embolism even if it has sharp margins.

c. Perfusion lung scan that is "low probability" for pulmonary embolism but is associated with compatible chest roentgenographic abnormality and blood tests for FDP/fdp and SFC are both positive.

d. Perfusion lung scan defects associated with normal ^{133}Xe ventilation scan or with an objective test confirming deep venous thrombosis.

e. Pulmonary angiogram showing distinct filling defects or cut offs with the conventional technique or distinct filling defects with selective angiogram beyond a balloon occlusion.

3. *Pulmonary angiography is essential in the following situations:*

a. Perfusion lung scan shows a defect only in the regions of an infiltrate and/or pleural effusion demonstrated by chest roentgenography.

b. Pulmonary embolism is thought to be the cause of or to occur in the presence of asthma. Asthma itself causes very impressive sharp perfusion defects on lung scans. A normal ventilation scan in the region of a large perfusion defect would probably be specific for pulmonary emboli, but no studies have been done to validate this.

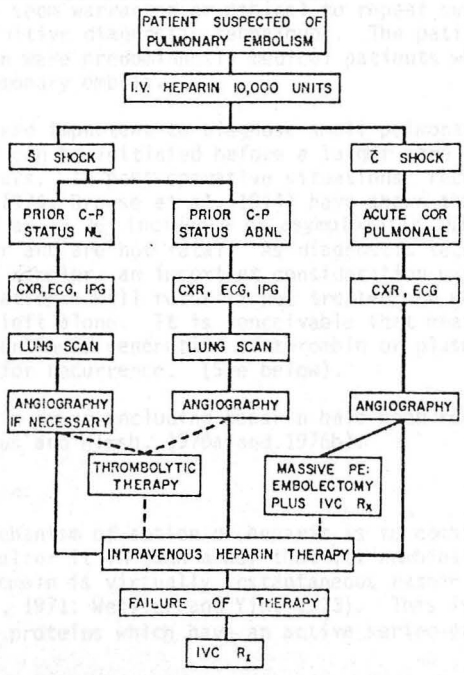
c. The combination of other diagnostic tests has not given a high confidence level for the diagnosis of pulmonary embolism, particularly if the patient seems at high risk of bleeding or if a vena cava interruption procedure is being considered.

d. If right heart catheterization will answer other important diagnostic considerations such as the degree of pulmonary hypertension, the presence of restrictive cardiomyopathy or constrictive pericarditis, the presence of significant pericardial effusion, or left heart failure as the cause for pulmonary hypertension.

e. Pulmonary embolism of sufficient magnitude to consider pulmonary embolectomy.

Our diagnostic approach is similar to that outlined by Sharma, Sasahara and McIntyre in Disease-a-Month, April, 1976, except that we find FDP and SFC to be useful and do not always insist on pulmonary angiography when previous cardiopulmonary disease is present.

Fig. 5 —An approach to diagnosis and therapy. C-P status = cardiopulmonary status; CXR = chest x-ray; IVC Rx = inferior vena caval interruption; NL = normal; ABNL = abnormal; IPG = impedance phlebography. Dashed lines indicate alternative methods of Rx.



TREATMENT

HEPARIN IN ACUTE PULMONARY EMBOLISM

History:

Heparin was discovered in Howell's laboratory by McLean in 1916. A preliminary study of its use and effectiveness in pulmonary embolism in humans was reported by Murray and Best in 1938. In 1942 Bauer reported dramatic reduction in morbidity and progression of phlebographically diagnosed deep vein thrombophlebitis confined to the calf when compared to historical controls also confined initially to the calf before heparin was available. Reports of untreated pulmonary embolism in the 1940's were associated with mortality in untreated cases ranging from 30% to 87% (Tibbutt and Chesterman, 1976). Barrett and Jordan (1960) performed the only controlled study of heparin in pulmonary embolism recorded in the literature. Patients with the clinical diagnosis of pulmonary embolism were randomly assigned to no treatment versus heparin, 10,000 units IV every 6 hours for 6 doses with an oral anticoagulant, nicoumalone, started on the first day of therapy. By the time 19 patients were entered into the control group there had been 10 recurrences and half of these were fatal. All of the five patients were confirmed to have recurrent pulmonary emboli at autopsy. On ethical grounds the authors felt that the randomized study had to be stopped. They continued to collect a total of 54 patients treated with heparin and phenendione, and there was only one non-fatal recurrence of pulmonary embolism. This study has the major objection that all diagnoses were on clinical grounds which is notoriously unreliable. However, all of the 5 deaths were confirmed by autopsy to be due to recurrent pulmonary emboli. Because of this it does not seem warranted or ethical to repeat such a study in the days of more definitive diagnostic techniques. The patients studied by Barrett and Jordan were predominantly medical patients who had very symptomatic major pulmonary emboli.

It is considered important to diagnose small pulmonary emboli early so that treatment can be initiated before a larger more symptomatic or fatal embolus occurs. In post operative situations, recent studies (Lahnborg et al, 1974; Browse et al, 1974) have shown that routine lung scans demonstrate an 18-36% incidence of asymptomatic pulmonary emboli which do not recur and are not fatal. As diagnostic techniques become more accurate and simpler, an important consideration may be methods to determine which patients will recur if not treated and which patients would do well if left alone. It is conceivable that measurement of by-products of the continued generation of thrombin or plasmin could identify patients at risk for recurrence. (See below).

Antithrombotic drugs including heparin have been recently reviewed extensively (Gallus and Hirsh, 1976a and 1976b).

Mechanism of Action:

The major mechanism of action of heparin is to combine with antithrombin III and alter it in such a way that its combination with and inactivation of thrombin is virtually instantaneous rather than a slow reaction (Yin et al, 1971; Wessler and Yin, 1973). This is also true of other coagulation proteins which have an active serine protease such

as factor XII, XI, IX and X (Rosenberg, 1973, Deykin, 1977). The antiplatelet action of heparin is controversial. There are animal studies suggesting that heparin has some fibrinolytic action (Silver and Hall, 1966; Gurewich and Thomas, 1970), however, this is probably mainly an effect of the prevention of accretion of new fibrin on existing pulmonary emboli while normal spontaneous fibrinolytic mechanisms cause lysis of the embolus (Cade, et al, J Clin Invest, 1975).

Kinetics:

The half life of heparin injected as a bolus of 70 units per kilogram in patients with venous thromboembolism averages 63 minutes when plasma heparin activities were used for the calculation, and 84 minutes when activated partial thromboplastin time (APTT) was used. Patients with pulmonary embolism had significantly shorter half lives in the range of 38 minutes with both methods (Hirsch et al, 1976).

Anticoagulant versus antithrombotic effect.

Animal studies: Lee White clotting times need to be prolonged twice normal to prevent experimental thrombosis by serum injection and stasis (Wessler and Morris, 1955) as well as by electrical current induction of a thrombus (Carey and Williams, 1960). The activated partial thromboplastin time (APTT) needed to be prolonged one and a half times normal to prevent thrombus formation by the serum infusion and stasis technique in rabbits (Zucker et al, 1969).

In the only experimental animal study comparing continuous with bolus intravenous heparin the continuous heparin was more effective in preventing ^{125}I fibrinogen incorporation into a propagating thrombus. However, this required doses 2 or 3 times the equivalent doses given to humans. The same total dose was relatively ineffective by intermittent injection every 4 hours, but there was no residual heparin effect on blood samples taken 3 hours after an injection. In normal rabbits, an APTT of approximately 50 seconds associated with a plasma heparin activity of approximately 0.2 units per ml was required to prevent fibrinogen incorporation into the clot. An APTT of 50 sec was one and one-half times the normal control. It was interesting that when rabbits were transfused with cryoprecipitate to raise their concentration of factor VIII and fibrinogen the in vitro dose response curve of the APTT prolongation in response to plasma heparin activity was markedly flattened (less increase in APTT for the same increase in heparin concentrations). In these animals incorporation of ^{125}I fibrinogen into the clot was still accomplished at a mean plasma heparin activity of 0.2 units per ml, but this was associated with a mean APTT of only 30 seconds. However, a 30 second APTT was still one and a half times the control APTT's of 20 in those animals transfused with cryoprecipitate. It is known that APTT's are shortened significantly in patients who develop asymptomatic post operative thrombophlebitis detected by ^{125}I fibrinogen technique. If this animal study can be extrapolated to man it would suggest that prolonging an APTT one and one-half times the patients base line control rather than one and one-half times

an average normal control would be sufficient to prevent further propagation of thrombi. There are no human studies that address this issue.

Human studies: Basu et al (1972) reported a prospective study of the value of monitoring continuous intravenous heparin with an APTT. The goal was an APTT between 60 and 100 seconds with a method with a linear in vitro dose response curve to heparin. With this approach there was only an 8% bleeding complication rate. In 162 patients with venous thromboembolism, only 5 had a recurrence. Patients with recurrence generally had an APTT less than 50 seconds for several days before their recurrence and their APTT's were significantly lower than the group of patients who had no recurrence. The major problem with this study is that all of the diagnoses including recurrences were on clinical grounds. In the urokinase pulmonary embolism trial the majority of patients who had recurrence either had a LWCT below 20 minutes during heparin therapy or had a prothrombin time of 18 seconds or less during oral anticoagulation (12 of 34 patients, 35%). With longer LWCT or prothrombin times the recurrence rate was 16% (20 of 123 patients).

Which Coagulation Test to Use.

The time honored Lee White clotting time (LWCT) is a very poorly reproducible test with an ill defined end point. It has been used to monitor continuous heparin effectively (O'Sullivan et al, 1968). Only 4 of 100 patients had significant bleeding and 3 of these had Lee White clotting times greater than 60 minutes. In the urokinase pulmonary embolism trial during the first 24 hours when all patients received continuous heparin infusion, 9 of the 10 bleeds were associated with Lee White clotting times greater than 60 minutes.

The APTT correlates well with Lee White clotting time with some reagents (Hirsh et al 1970; Hirsh and Gallus, 1973). However, many commercial agents varied considerably in their sensitivity to heparin *in vitro*. (Soloway et al, 1973, Shapiro et al, 1977).

A clinical laboratory should perform an *in vitro* study to insure that their reagent has a linear dose response curve for the APTT time plotted against increasing doses of heparin (Genton, 1974). Even after taking these precautions our thromboembolism research lab has found that the APTT does not correlate as well with LWCT in patients with venous thromboembolism being treated with heparin as does another simple test, the whole blood activated partial thromboplastin time (WBAPTT).

We performed the WBAPTT in a manner similar to that suggested by Baden et al (1972). One tenth of a ml of APTT reagent (General Diagnostics) is placed in a test tube. Two tenths of a ml of freshly drawn whole blood in a plastic syringe is added to the APTT reagent. The tube is tilted every 15 seconds until a firm clot forms. The test is reproducible and has a very sharp end point. Normal values in our lab are 2.8 ± .4 minutes.

Comparing all three tests in all of our patients some of whom receive bolus and some of whom receive continuous heparin, both the APTT and the WBAPTT discriminate patients who bleed better than the Lee White clotting time does.

TABLE 16

COAGULATION TEST LIMITS WITH BEST DISCRIMINATION
FOR BLEEDING WITH INTRAVENOUS HEPARIN
(BOLUS AND CONTINUOUS)

BLEEDING COMPLICATION	NUMBER OF PATIENTS	FREQUENCY WITH WHICH INDIVIDUAL TESTS > LIMIT		
		LWCT OF 30 MIN	APTT OF 60 SEC	WBAPTT OF 5.6 MIN
NONE	55	40%	22%	19%
MINOR	16	54%	31%	42%
MAJOR	11	57%	70%	50%

Bleeding Complications.

Bolus intravenous heparin: Bolus heparin in large arbitrary doses has been used effectively. Bauer (1964) reported his experience with nearly 1,000 patients treated for thrombophlebitis or pulmonary embolism with boluses of 15,000 units IV every 4 hours for the first 24 hours, then diminishing 2 to 4 times per day, spaced so that the patients did not get injections during the night. He had an acceptable recurrence rate of 5% and a remarkably low rate of bleeding complications of 1.5% minor bleeds and no major bleeds. In another study with similar arbitrary total dose spaced at 6 hour intervals after the first 24 hours, there was a 15% instance of bleeding (6% major bleeding) (Kernohan and Todd, 1966). We have treated 9 patients with randomization to the Bauer regimen with 5 bleeding complications (1 major bleed) and no recurrences.

When moderate doses in the range of 100 units per kilogram are given IV bolus every 4 hours around the clock, either as an arbitrary dose or controlled with APTT's, there has been a high instance of bleeding complications. Two recent reports have found this method to have significantly higher bleeding complication rates than continuous heparin (Salzman et al, 1975; Glazier and Crowell, 1976). However, there are objections to both of these papers. Objective diagnostic criteria such as high probability lung scans, pulmonary arteriograms, or phlebography were not used in the original diagnoses. In Glazier's paper all of the recurrences were on the basis of clinical criteria without objective tests. In both studies high risk patients were not identified and randomized separately from low risk patients. In unpublished observations we have found significantly major bleeding rates (requiring discontinuation of heparin) in high risk patients as opposed to low risk patients regardless of the method of administration.

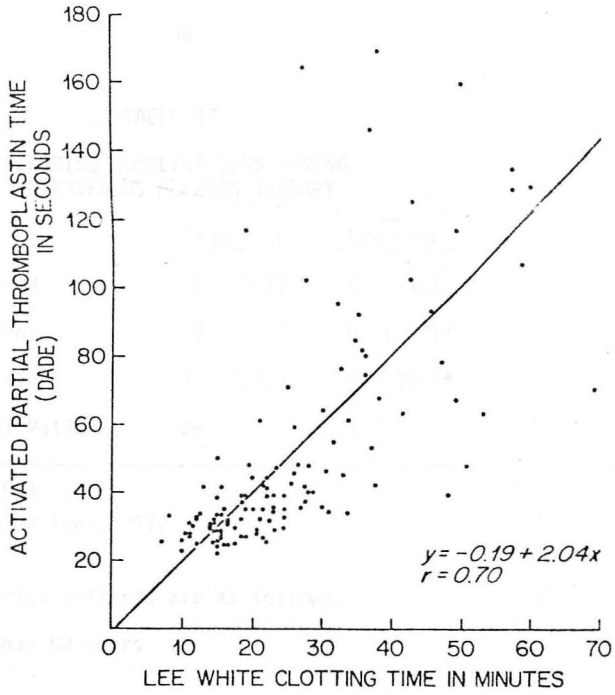


Figure 6

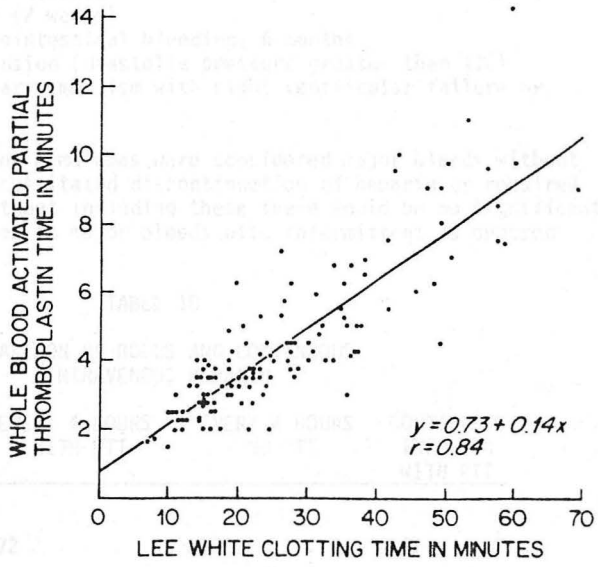


Figure 7

It is apparent that the WBAPTT correlates better with Lee White clotting times than does the APTT performed on plasma which has been collected in citrated vacutainer tubes. Others have apparently had the same problem and Hirsh has recently (1976) identified the problem as being due to a chemical leaking out of the blue rubber stopper of the vacutainer tube. This material inactivates heparin. The Becton-Dickinson Co. is aware of this problem and is in the process of correcting it.

TABLE 17

BLEEDING COMPLICATIONS DURING
INTRAVENOUS HEPARIN THERAPY

	High Risk	Low Risk
Minor Bleed	8 (27%)	5 (15%)
Major Bleed	9 (30%)	0 (0%)*
Fatal Bleed	17 (57%)	5 (15%)*
Number of Patients	29	35

* $P < .001$

Bynum and Wilson, 1977

Our criteria for high risk patients are as follows:

1) age greater than 60 years
2) coagulopathy
3) uremia
4) alcoholic liver disease
5) recent surgery (2 weeks)
6) previous gastrointestinal bleeding, 6 months
7) severe hypertension (diastolic pressure greater than 110)
8) massive pulmonary embolism with right ventricular failure or hypotension

In Salzman's paper wound hematomas were considered major bleeds without stating whether they necessitated discontinuation of heparin or required blood transfusions. Without including these there would be no significant or impressive differences in major bleeds with intermittent as opposed to continuous heparin.

TABLE 18

COMPARISON OF BOLUS AND CONTINUOUS
INTRAVENOUS HEPARIN

HEPARIN REGIMEN	EVERY 4 HOURS WITH PTT	EVERY 4 HOURS NO PTT	CONTINUOUS INFUSION WITH PTT
NUMBER OF PATIENTS	72	68	69
MAJOR BLEEDING	6 (8%)	7 (10%)	1 (1%)
RECURRENCES	1	1	1
DAILY HEPARIN	31,700	35,600	24,500

Salzman et al, 1975

In Glazier's paper there was an unusually high instance of bleeding complications with intermittent heparin of 81%. They had an unusual therapeutic goal for the APTT of 40 to 60 seconds and did not state what reagent was used for the APTT. They may have been attempting to monitor heparin with a reagent that was very insensitive to heparin. We have 31 patients randomized to receive bolus heparin IV every 4 hours in the dosage range close to 100 units per kg of body weight. There has been a 32% incidence of bleeding (4 minor [13%] and 6 major [19%]) with 4 recurrences.

We are investigating the efficacy of an arbitrary dose of 60 units per kg of ideal body weight IV every 4 hours around the clock. Deykin apparently treats many patients in a similar manner (Deykin, 1976). He recommends that if bolus intravenous heparin is used that it be used in a dose of approximately 5,000 units IV every 4 hours adjusting the dose up or down by a thousand units for extremes of body weight. We have treated 5 patients randomized into this group with 1 minor bleed and no recurrence.

Continuous intravenous heparin:

We have treated 7 patients randomized to receive an arbitrary dose of approximately 1,000 units of heparin per hour for an average size person. There has been one minor bleed, no major bleed and no recurrences. In 27 patients randomized to have their dose of heparin regulated by the APTT or LWCT there have been 8 minor bleeds and 3 major bleeds with 3 recurrences. Three published reports have very low major bleeding complication rates with continuous heparin controlled by either Lee White clotting times (O'Sullivan et al, 1968) or APTT (Salzman et al, 1975; Glazier and Crowell, 1976). In all 3 studies the patients received approximately 24,000 to 26,000 units of heparin per day. Patients with intermittent therapy received higher 24 hour doses of approximately 32,000 to 36,000 units per day. The 24 hour dose was significantly higher for intermittent heparin for Glazier and Crowell's study. In other studies where the 24 hour dose of continuous heparin is higher, such as ours and that of Mant et al, (1975),the bleeding complication rates have been similar for continuous as for intermittent heparin. Thus, there is considerable question as to whether it is the total 24 hour dose of heparin that is important as opposed to the method of administration. Another reason for the difference may be that when patients have bolus intravenous heparin ordered they get the dose even though it may not always be exactly on schedule. However, it is a very frequent finding that patients who have continuous heparin ordered get behind schedule with malfunctioning of the pump during the night and they frequently get no more than two-thirds of the dose ordered. Salzman et al (1975) achieved their therapeutic goal only about half the time and our experience is similar.

In normal hemostatic mechanisms the first line of defense in preventing bleeding from a damaged vessel is a platelet plug. In animal models if this platelet plug is not reinforced with fibrin deposition within the platelet plug, it breaks up and bleeding occurs. (Holvig et al, 1975). If continuous heparin were really "effectively controlled" it would not surprise me if patients bleed regularly because of inability to lay down a fibrin meshwork around platelet plug as part of the normal hemostatic mechanism. This same line of reasoning may explain the higher bleeding

complication rate with bolus intravenous heparin when the dose is pushed to keep the clotting time or APTT prolonged continuously. Even though animal studies suggest that bolus intravenous heparin is less effective in preventing fibrinogen incorporation into a propagating clot (Hirsh, Chiu et al, 1977), this may not apply to propagation of a thrombus or in a human.

In summary, if it is important to push the dose of heparin it can be done more safely with continuous intravenous heparin. However, major bleeding may be more related to total 24 hour dose and to high risk patients than to the method of administration. In low risk patients bolus intravenous heparin would seem warranted because of its convenience and long standing effectiveness. It appears important to control continuous heparin with some coagulation parameter. Whether an arbitrary smaller dose of bolus heparin IV every 4 hours without laboratory control will prevent recurrence remains to be seen but is under investigation. Continuous intravenous heparin therapy with a total 24 hour dose of approximately 24,000 units in an average size person has very few major bleeding complications. I suspect that a similarly low bleeding complication rate with an acceptable measurement can be accomplished with a similar 24-hour dose of bolus intravenous heparin in divided doses every 4 hours. However, this needs further study with larger numbers of patients to be sure.

Thrombocytopenia: The possibility of heparin inducing thrombocytopenia has been known for a long time (Fidlar and Jaques, 1948; Gollub and Ulin, 1962). Marked thrombocytopenia has been reported as an occasional unexpected response in the treatment of consumptive coagulopathy (Natelson et al, 1969). The mechanism of the thrombocytopenia has been shown to be due to a heparin dependent antiplatelet antibody (Rhodes et al, 1973, Babcock et al, 1976). A prospective study of 52 patients being treated with continuous intravenous heparin (Bell et al, 1976) has demonstrated the development of thrombocytopenia with platelet counts less than 100,000 in 16 patients. Nine patients developed platelet counts less than 50,000. Five of the patients had the combination of thrombocytopenia, hypofibrinogenemia and elevated FDP. In the whole series only 2 of the thrombocytopenic patients developed excessive bleeding from venipuncture sites. There was no other major bleeding and none of the patients required transfusions. They looked for and found no increase in fragmented red blood cells. The thrombocytopenia started variably between the second and the tenth day and gradually increased for two or three days. When heparin was discontinued the platelet counts returned to normal in three to five days. There was no evidence of other thrombotic complications as suggested by one of the earlier studies (Rhodes et al, 1973). They mentioned seeing thrombocytopenia in two patients being treated with low dose subcutaneous heparin every 8 hours and that others had found the problem with bolus intravenous heparin.

It appears that thrombocytopenia during heparin therapy may be much more common than previously suspected, but apparently has no relationship to bleeding complications.

It would seem unwise to use drugs that effect platelet adhesiveness, i.e., aspirin or indocin, if they can be avoided in patients receiving heparin. However, Salzman, et al (1975), could find no association between the use of drugs that affect platelet function and bleeding complications.

RECURRENCE OF VENOUS THROMBOEMBOLISM:

Predictability use of coagulation tests. Once heparin therapy is started the rate of recurrence of venous thromboembolism is very low regardless of the method of administration of heparin when in the usual therapeutic doses of 24,000 to 36,000 units per day. Recurrence rate for venous thromboembolism based on clinical grounds varies from 2% to 5%. (Coon et al, 1969; Parakos et al, 1973). In the urokinase pulmonary embolism trial (1973) with the addition of routine follow-up lung scans, the incidence of recurrence within the first 2 weeks of treatment in heparin treated patients was 18 of 76 (24%). They had a small group of patients who were considered inadequately anticoagulated and 7 of these 16 (44%) had recurrent pulmonary embolism. Their criteria for adequate anticoagulation was as follows: For continuous IV heparin total daily dose equal to or greater than 20,000 units and/or Lee White clotting time greater than or equal to 20 minutes; for intermittent IV heparin, total daily dose equal to or greater than 30,000 units and/or Lee White clotting time greater than or equal to 20 minutes; for warfarin derivatives, one stage prothrombin time equal to or greater than 18 seconds. Unfortunately there was no breakdown as to which of the recurrences were in continuous heparin as opposed to bolus heparin. It may be more important for a minimal level of anticoagulation to be achieved with continuous infusion than for bolus infusions where at least transiently the clotting time is greatly prolonged after the injection. With continuous intravenous heparin Basu et al (1972) found a significantly higher clinically diagnosed recurrence rate if an activated partial thromboplastin time was not maintained above 50 seconds.

In our own study, which includes predominantly pulmonary embolism, recurrence rate was 8 of 60 patients (13%). Comparing those with recurrence to those patients without recurrence, there is no significant difference in total daily heparin doses or Lee White clotting times. (Bynum and Wilson, 1977).

Use of by-products of thrombin and plasmin generation predict recurrence: Serial measurement of FDP and soluble fibrin complexes (SFC) show significant differences in patients who had recurrences as opposed to those who did not have recurrence. In patients without recurrence FDP and SFC declined to normal levels within 3 to 5 days with only minor and unsustained elevations (See Figures next page). In patients with recurrence FDP was significantly higher on the initial determination (Day 0) and on the second through the 10th day of treatment. Soluble fibrin complexes were also significantly higher in patients with recurrence on the initial determination and again on Day 7. The importance of this finding is that serial determination of FDP and SFC during heparin therapy may pick out the patients at little risk for recurrence. These could receive lower doses of heparin with a more convenient method such as bolus IV every 4 hours. Patients at higher risk can also be identified. These might need higher doses of continuous heparin carefully regulated to avoid bleeding complications. On the other hand, it is possible that the patients with higher FDP and SFC on

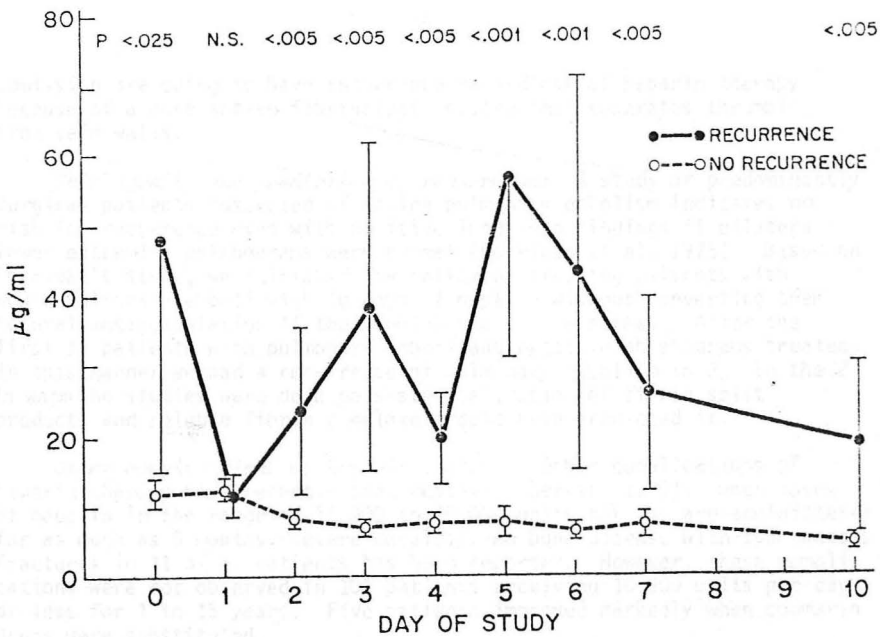


Figure 8. Fibrinogen/fibrin degradation products (FDP/fdp) during 10 days of heparin therapy in patients with pulmonary embolism. Circles represent mean values and brackets indicate the standard error of the mean. Values below 10 µg/ml are normal.

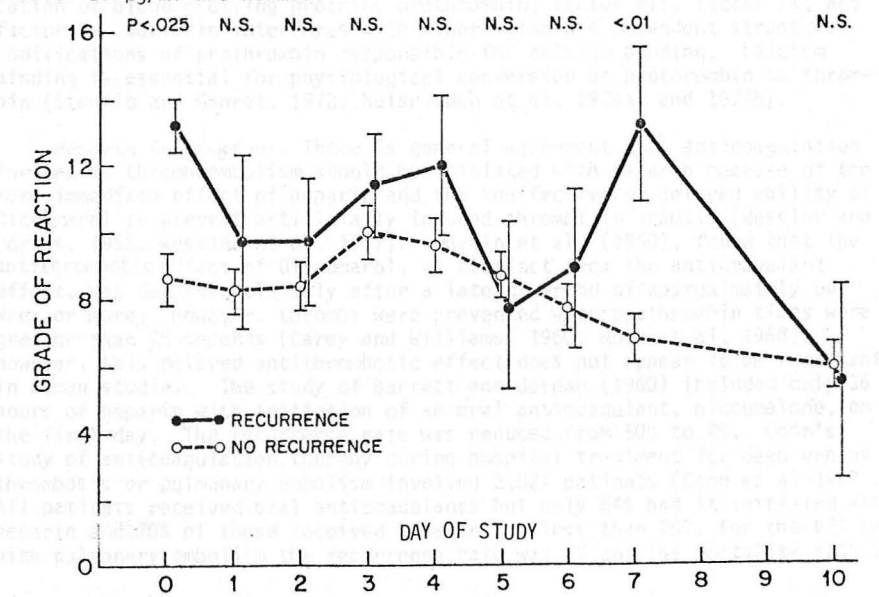


Figure 9. Soluble fibrin complexes (SFC) during 10 days of heparin therapy in patients with pulmonary embolism. Circles represent mean values and brackets indicate the standard error of the mean. Values below a grade of 10 are normal.

admission are going to have recurrence regardless of heparin therapy because of a more active fibrinolytic system that separates thrombi from vein walls.

Phlebography and prediction of recurrence: A study of predominantly surgical patients suspected of having pulmonary embolism indicates no risk for recurrence even with positive lung scan findings if bilateral lower extremity phlebograms were normal (Corrigan et al, 1975). Based on Corrigan's study, we initiated the policy of treating patients with acute pulmonary emboli with 10 days of heparin without converting them to oral anticoagulation if their phlebograms were normal. After the first 15 patients with pulmonary emboli and negative phlebograms treated in this manner we had a recurrence of pulmonary embolism in 3. In the 2 in whom the studies were done persistent elevation of fibrin split products and soluble fibrin complexes could have predicted it.

Other complications of heparin therapy: Other complications of heparin therapy have recently been reviewed (Gervin, 1975). When doses of heparin in the range of 15,000 to 30,000 units per day are administered for as much as 6 months, severe decalcifying bone disease with spontaneous fractures in 11 of 17 patients has been reported. However, these complications were not observed in 107 patients receiving 10,000 units per day or less for 1 to 15 years. Five patients improved markedly when coumarin drugs were substituted.

ORAL ANTICOAGULATION IN ACUTE PULMONARY EMBOLISM

Method of action: Vitamin K is essential for post ribosomal modification of blood clotting proteins prothrombin, factor VII, factor IX, and factor X. Warfarin interferes with minor vitamin K dependent structural modifications of prothrombin responsible for calcium binding. Calcium binding is essential for physiological conversion of prothrombin to thrombin (Stenflo and Ganrot, 1972; Nelsestuen et al, 1974a, and 1974b).

Heparin initiation: There is general agreement that anticoagulation for venous thromboembolism should be initiated with heparin because of the more immediate effect of heparin and the ineffective or delayed ability of Dicoumaral to prevent artificially induced thrombi in animals (Wessler and Morris, 1955, Wessler et al, 1957). Deykin et al, (1960), found that the antithrombotic effect of Dicoumarol, as distinct from the anticoagulant effect, was demonstrable only after a latent period of approximately one week or more. However, thrombi were prevented when prothrombin times were greater than 25 seconds (Carey and Williams, 1960; Hoak et al, 1966). However, this delayed antithrombotic effect does not appear to be important in human studies. The study of Barrett and Jordan (1960) included only 36 hours of heparin with initiation of an oral anticoagulant, nicoumalone, on the first day. The recurrence rate was reduced from 50% to 2%. Coon's study of anticoagulation therapy during hospital treatment for deep venous thrombosis or pulmonary embolism involved 2,027 patients (Coon et al 1969). All patients received oral anticoagulants but only 64% had it initiated with heparin and 70% of those received heparin for less than 48%. For the 639 patients with pulmonary embolism the recurrence rate was 5% and the mortality rate 1%. Major

bleeding occurred in only 2.4% of episodes. He later presented soft evidence supporting lower recurrence rates in patients who receive heparin during the first 7 days of oral anticoagulation. (Coon and Willis, 1972). In the urokinase pulmonary embolism trial there was no difference in recurrence rate in patients treated with heparin for 5 days during oral anticoagulation initiation as opposed to patients receiving heparin for 14 days. (UPET, 1973).

Duration of oral anticoagulation: In Coon's study (1969) the mean duration of anticoagulation therapy in the hospital was 16 + 11 days. During hospitalization there was a 5% recurrence rate (1% fatal recurrence). In the 12 weeks following hospitalization for pulmonary embolism there was again about a 5% recurrence of pulmonary embolism and a 1% fatal recurrent pulmonary embolism. In patients in whom venous oral anticoagulation was continued for 6 to 12 weeks after discharge thromboembolic complications were reduced from 7.2 to 4.6%. This almost reached significance because of the large numbers. In patients whose anticoagulation had to be interrupted in the hospital for some reason, such as a bleeding episode, the thromboembolic complication rate within the next 12 weeks was 12.5%. This study has the disadvantage of being based entirely on clinical diagnoses, but it is the only information available.

We have an on-going out patient study following patients with well documented pulmonary embolism and/or thrombophlebitis. Patients are randomly assigned the total of one month versus a total of 4 to 6 months anticoagulation. They are randomized separately according to whether their phlebograms are normal, show thrombi confined to the calf (minor DVT) or have thrombi extending above the knee (major DVT). Although the numbers are too small to reach significance the trend is that anticoagulation does reduce the incidence of recurrence in patients with pulmonary embolism and negative phlebograms, as well as patients whose thrombophlebitis is confined to the calf. In this small series once thrombi have extended above the knee recurrence rate was the same even with longer term oral anticoagulation.

In summary, oral anticoagulation with brief heparin initiation is very effective in preventing recurrence acutely, and there appears to be benefit of continuing oral anticoagulation for at least a month. Beyond this period of time the benefit is small, and appears warranted only if careful laboratory control is possible.

The surgical literature leads one to believe that recurrence of pulmonary embolism is more likely if there is residual deep vein thrombophlebitis extending above the knee. However, in predominantly medical patients we find that patients with pulmonary emboli and negative phlebography have significantly greater chance of recurrence than patients with pulmonary emboli and positive phlebograms. (Bynum and Wilson, 1977). This speaks for some underlying abnormality of the coagulation or fibrinolytic system in these patients.

THROMBOLITIC AGENTS

The urokinase pulmonary embolism trial (UPET) started in 1968 and was reported in Circulation in 1973. Urokinase in a standard dose was compared to heparin therapy in a carefully planned multicenter randomized trial. Urokinase resulted in significantly more improvement in patients with pulmonary emboli in terms of hemodynamic measurements as well as in angiographic and lung scan improvement within the first 24 hours. However, by the end of 7 days the lung scan improvement was similar in both groups.

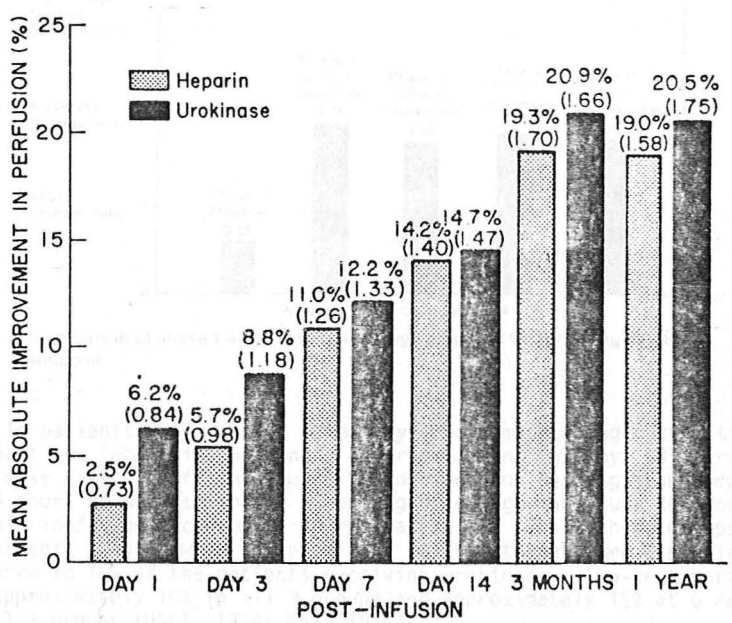
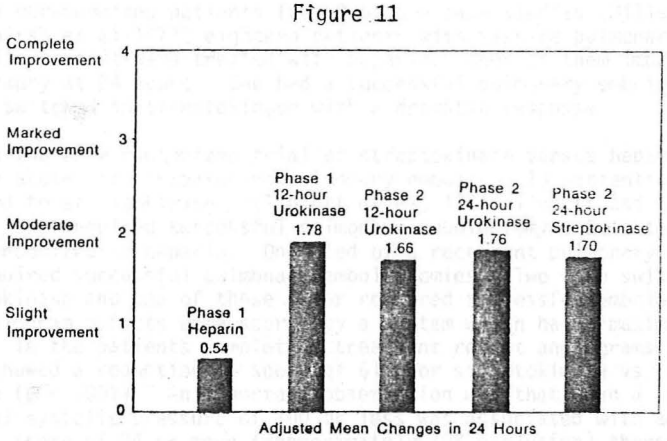


Figure 10.

Mean postinfusion absolute improvement in lung scan perfusion defect. Mean preinfusion perfusion defect was 24.8% (SD 12.3) in heparin patients and 26.5% (SD 14.8) in urokinase patients. The standard error of the measurement is given in parentheses above each column with the mean absolute improvement in perfusion.

The bleeding complication rate was 45% in the urokinase patients and 27% in the heparin patients. There was no difference in mortality. Urokinase treatment in this study was a 12-hour infusion. The study was extended into a Phase 2 study to compare 12 hours of urokinase with 24 hours of urokinase and 24 hours of streptokinase (The Urokinase-Streptokinase Embolism Trial[USET]). The angiographic improvement in 24 hours was virtually the same in all 3 groups and similar to the previous 12 hour infusion of urokinase in Phase 1 study. All three groups with thrombolytic therapy showed significantly more angiographic improvement in 24 hours than patients treated with heparin.

Figure 11



Comparison of phase 1 and 2 results with angiographic 24-hour change as an endpoint.

In patients with massive pulmonary embolism (meaning obstruction of at least two lobar size pulmonary arteries on angiography) 24 hours of urokinase gave significantly more improvement in the lung scan compared to 24 hours of streptokinase. Bleeding of enough magnitude to require blood transfusion occurred in approximately 15% of all three groups. In patients treated with streptokinase 26% had temperature elevations, compared to 16% of the patients receiving urokinase. Two-week mortality was approximately 10% in all 3 groups and approximately 15% at 6 months in all 3 groups.(USET, 1974; Bell, 1975).

Streptokinase is likely to become available in the United States for treatment of pulmonary embolism and thrombphlebitis within the year 1977. Therefore, I will review other studies evaluating its effect in massive pulmonary embolism.

STREPTOKINASE IN MASSIVE PULMONARY EMBOLISM

In massive acute pulmonary embolism with more than 50% occlusion

of the pulmonary vascular bed on angiography streptokinase treatment resulted in marked or moderate lysis demonstrated with repeat angiography 24-72 hours later in 44 of 61 patients from six studies (Hirsh et al, 1968, Miller et al, 1969; Kakkar and Rafferty, 1970; Miller et al, 1971, Hirsh et al, 1971; and Strickland et al, 1973). Only 2 patients died (Kakkar and Rafferty, 1970) and these could have been identified by the markedly poor peripheral perfusion on the pulmonary angiogram. When commented upon, bleeding occurred in 21 of 36 patients but was major in only 6 and caused death in none.

In unrandomized patients from 2 of the same studies (Miller et al, 1971; Hirsh et al 1971) eighteen patients with massive pulmonary emboli of similar extent were treated with heparin. None of them improved by angiography at 24 hours. One had a successful pulmonary embolectomy and 8 were switched to streptokinase with a dramatic response.

In the only randomized trial of streptokinase versus heparin in massive acute life threatening pulmonary embolism 13 patients were assigned to streptokinase. (Tibbutt et al, 1974; Tibbutt and Chesterman 1976). Two required successful pulmonary embolectomy. Seventeen patients were randomized to heparin. One died of a recurrent pulmonary embolus. Two required successful pulmonary embolectomies. Two were switched to streptokinase and one of these later required successful embolectomy. The angiogram defects were scored by a system which has a maximal score of 34. In the patients completing treatment repeat angiograms at 72 hours showed a reduction in score of 61% for streptokinase vs 15% for heparin ($p < .001$). An important observation was that when a systemic arterial systolic pressure of 100 or less was associated with an angiographic score of 24 or more (approximately 70% occlusion) there was a 70% chance of death or need for a pulmonary embolectomy. Unfortunately, of the 7 patients that met these criteria, 6 were randomized to heparin. Thus, even though streptokinase improves early lysis of massive life threatening pulmonary emboli significantly better than heparin, no study has demonstrated a better survival rate with streptokinase.

An alternative to high dose streptokinase therapy is thrombolysis with a combination of small doses of streptokinase and full doses of heparin. They appear to have a synergistic effect (Gallus et al, 1975). This observation warrants further study.

Streptokinase has been demonstrated to frequently cause prompt lysis with preservation of venous valve in deep vein thrombosis that extends above the knee. Such lysis rarely happens with heparin alone (Kakkar et al, 1973; Tsapogas et al, 1973; Tibbutt et al, 1974).

VENA CAVA INTERRUPTION

Some institutions are very liberal in their indications for vena cava interruption. In a series of 60 consecutive patients treated for pulmonary embolism at the Peter Bent Brigham Hospital 75% of them had a vena cava interruption procedure (Paraskos et al, 1973). However, a series from Duke University (Silver and Sabiston, 1975) reported 60 patients with well documented moderate to severe pulmonary embolism managed primarily with anticoagulation or lytic-anticoagulation therapy. The in-hospital mortality rate from embolization was 5%. Recurrent pulmonary embolism was documented in only 2 patients (3%). Three patients (5%) required caval ligation because of a profound heparin sensitivity, peptic ulcer, bleeding, and recurrent embolization while adequately anticoagulated. This agrees with most other studies that anticoagulant treatment alone is adequate therapy for most patients and is associated with a low incidence of recurrent embolism.

After a critical review of venous interruption, Bernstein (1975) recommended inferior vena caval ligation only for:

(1) septic pulmonary emboli
(2) multiple small emboli and pulmonary hypertension

He recommended inferior vena cava plication or clips for:

(1) patients in whom anticoagulation is contraindicated
(2) for recurrent pulmonary embolism, despite adequate anticoagulation
(3) following pulmonary embolectomy

Vena Caval Ligation: Vena cava ligation in patients with Class IV heart failure carries a very high nortality rate of 55% related deaths (Amador et al, 1968). Mortality from related causes was 6% in patients without heart disease and 11% in patients with mild heart failure. When vena caval ligation is performed on the basis of strict criteria (Piccone et al, 1970) reported a disturbing 36% instance of recurrent pulmonary emboli in 72 patients. Recurrent pulmonary embolism was the cause of death in 7 of these patients. Inferior vena cavograms were done in 16 of the patients and 11 of them had collaterals at least 15 mm in diameter.

Vena Cava Clip: In an institution that carefully documents pulmonary emboli, but is very liberal with the use of vena caval interruption, follow up of patients that were treated with inferior vena cava clips was as follows:

TABLE 19

LATE LEG FINDINGS FOLLOWING
VENA CAVA CLIPS

TYPE SYMPTOM	NUMBER OF PATIENTS (%)
NONE	48 (58%)
CONTROLLABLE SWELLING	23 (28%)
SEVERE (ULCER, ETC.)	12 (14%)

Couch, et al SURGERY 1975

From the same institution recurrent embolism was detected in only 8 (1.8%) of 447 patients having inferior vena cava interruption (Dexter et al, 1969).

MOBIN-UDDIN UMBRELLA: When vena cava interruption is needed in critically ill patients the umbrella design by Mobin-Uddin is very safe and effective (Mobin-Uddin et al, 1969a and 1969b). In a nationwide survey of use of the umbrella in more than 2,000 patients (Bohling et al, 1974) the operative mortality was less than 1% as was fatality due to recurrent embolism. There was a 2.4% instance of non-fatal pulmonary embolism and edema or phlebitis occurred in 5% of the patients. Despite the safety of the procedure, when the indications were primarily pulmonary emboli superimposed on severe heart failure or cor pulmonale, only 58% of the patients survive for more than 6 months (Orvald et al, 1973). The late sequelae in these 87 survivors were swelling in 38%, phlebitis in 18%, pain or fatigue in 6% and ulcer in 2%. There are no 5-10 year follow up studies reported. Migration of the filter is known to occur in 1%.

PULMONARY EMBOLECTOMY

Almost all deaths due to pulmonary embolism are on a mechanical basis and require greater than 50% occlusion of the lungs. There is little evidence to support a reflex mechanism as a cause of death in pulmonary embolism (Gorham 1961). Of the patients who die of pulmonary embolism two-thirds are dead within the first 1 to 2 hours making pulmonary embolectomy virtually impossible (Gorham 1961a; Coon and Collier 1959; Donaldson et al, 1963; Tibbut and Chesterman, 1975). The overall surgical mortality for pulmonary embolectomy by surgeons surveyed in 1967 was 57% (Cross and Mowlem, 1967). In series with lower mortality rate the average time from onset of symptoms to embolectomy was much longer and the patients probably did not need the operation (Sautter et al, 1975). In patients treated medically, even those with massive pulmonary emboli (demonstrated angiographically) with hypotension have 65% survival rate. A massive embolus will initially cause more obstruction when it is in the main pulmonary artery, than when it moves peripherally with or without fragmentation (Sautter et al, 1975). Evidence has been presented that external cardiac massage can effectively produce fragmentation of massive pulmonary emboli (Oakley, 1968; Heimbecker et al, 1973). In the survey by Cross and Mowlem (1967) nine patients had attempted embolectomy for an incorrect diagnosis and all 9 patients died, mostly of myocardial infarctions.

Indications for pulmonary embolectomy are modified from 3 sources (Cross and Mowlem, 1967; Sasahara and Barsamian, 1973; DelGuercio et al, 1964).

1) A deteriorating clinical course requiring vasopressors and maximal medical management with:
   (a) the systolic blood pressure less than 90 mm Hg
   (b) urine output less than 20 cc per hour and
   (c) arterial PO_2 less than 60 mm Hg on oxygen
2) Angiographic evidence of at least 50% occlusion of the pulmonary vascular tree.
3) Associated elevation of the right sided pressures

DelGuercio reported that patients with right ventricular mean pressure in excess of 30 cms of saline had a very poor prognosis, whereas 13 hypotensive patients with a documented pulmonary embolus survived and all but one had a right ventricular mean pressure of less than 30 cms of water. Exceptions to these mean right ventricular pressure guidelines can be found (Sautter et al, 1975).

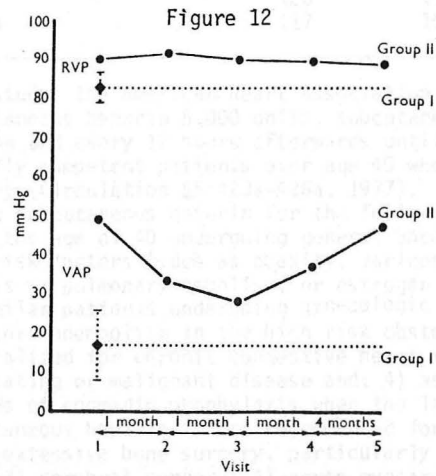
Portable partial cardiopulmonary bypass. A self contained portable pump oxygenator connected from femoral vein to femoral artery can be very effective in stabilizing patients while performing pulmonary angiography or waiting a few hours while emboli move or fragment (Beall and Cooley, 1965).

PROPHYLAXIS

STOCKINGS

Elastic stockings are not effective in preventing post-operative deep venous thrombosis detectable by 125 I fibrinogen technique (Rosengarter et al, 1970). In ambulatory patients with varicose veins elastic stockings significantly reduce the venous ambulatory pressure measured with a needle in a vein on the dorsum of the foot. The pressures were made with the stockings off. Presumably, chronic pressure from the stockings prevented chronic dilatation of veins and made the valves more competent by avoiding chronic distention of the veins (Somerville et al, 1974).

Figure 12



Changes in resting venous pressure (RVP) and venous ambulatory pressure (VAP) during the study period.

The use of elastic stockings was discontinued on the third visit.

LOW DOSE SUBCUTANEOUS HEPARIN

Various methods of prophylaxis for venous thromboembolism have been reviewed extensively (Kakkar 1975; Claggett and Salzman 1975). The most promising is low dose subcutaneous heparin. The rationale is to potentiate the naturally occurring antithrombin III so that the rate of neutralization of activated factor X is greatly accelerated (Wessler and Yin, 1973). The International Multicenter Trial of low dose subcutaneous heparin in post operative patients (1975) has demonstrated a significant reduction in deaths due to pulmonary emboli as well as a significant reduction in deep vein thrombophlebitis diagnosed by various methods.

TABLE 20

	Control	Heparin	P value
Number of Patients	2076	2045	
Deaths from all causes	100	80	
Autopsies performed	72%	66%	
Deaths due to Pulmonary Emboli	16	2	< 0.005
Pulmonary emboli contributing to death	6	3	
^{125}I fibrinogen detected DVT	24.6%	7.7%	< .005
DVT at necropsy	24	6	< .005
Rx for Clinical DVT Confirmed by ^{125}I fib or phlebography	122	23	< .005
Rx for clinically suspected P.E.	24	8	< .005
Death from hemorrhage	5	4	
Excessive blood loss during surgery	126	182	
Wound hematomas	117	158	< .01

Based on this study the American Heart Association has recommended low dose subcutaneous heparin 5,000 units, subcutaneously, 2 hours before operation and every 12 hours afterwards until hospital discharge in hemostatically competent patients over age 40 who undergo abdominothoracic surgery (Circulation 55:423a-426a, 1977). Sherry (1976) recommended low dose subcutaneous heparin for the following high risk groups: 1) those above the age of 40 undergoing general abdominothoracic surgery or with other risk factors (such as obesity, varicose veins, previous thrombophlebitis or pulmonary embolism, or estrogen or anovulatory therapy); 2) similar patients undergoing gynecologic surgery, and for the prevention of thromboembolism in the high risk obstetric patient; 3) patients hospitalized for chronic congestive heart failure, strokes, and chronic debilitating or malignant disease and; 4) as an alternative to extended periods of coumadin prophylaxis when the latter is containdicated. Low dose subcutaneous heparin is not recommended for the following conditions 1) extensive bone surgery, particularly on the hip; 2) abdominal prostatectomy; 3) cerebral surgery; 4) acute myocardial infarction. Although venous thromboembolism appears to be prevented, no data are available as to heparin's ability to prevent endocardial muralthrombosis and systemic embolism, both of which are controlled by conventional anticoagulant prophylaxis.

RECURRENT VENOUS THROMBOEMBOLISM

Patients with pulmonary embolism or venous thrombosis who have had a history of a previous episode of venous thromboembolism are significantly more likely to develop recurrent thromboembolism (about twice the incidence) than matched controls who have their first episode of venous thromboembolism. (Coon and Willis, 1973). Some of these recurrences are related to underlying varicose veins or residual deep vein thrombosis with stasis. Other identified problems related to abnormalities of coagulation or fibrinolysis are as follows.

DISORDERS OF PLATELET ADHESIVENESS.

Hirsh and McBride (1965) performed platelet adhesiveness studies in 9 patients with recurrent venous thromboembolism. Platelet adhesiveness was determined by the percent decrease in platelet count after passage of the blood through a column of glass beads. Patients with recurrent venous thromboembolism had increased adhesiveness with little overlap with normal controls or hospital controls. Harker and Slichter (1972) found decreased survival of both platelets and fibrinogen in venous thrombotic disease but did not state whether these were patients with recurrent venous thromboembolism. Interestingly, patients with arterial thromboembolism or prosthetic heart valves had decreased platelet survival with little increase in fibrinogen destruction. In a population of 28 patients with severe idiopathic recurrent venous thromboembolism (Steel et al, 1973), 15 of the patients had episodes of venous thromboembolism while effectively anticoagulated or also had arterial thrombosis. All but one of these had decreased platelets survival with ^{51}Cr labeled platelet technique. Seven of their patients with decreased platelet survival were treated with an antiplatelet agent, sulfinpyrazone, 800 mgms per day, along with continued heparin therapy, as an out patient. Platelet survival significantly increased and there was a dramatic reduction in the incidence of arterial and venous thrombosis. These patients had no more episodes during 12 to 18 months' follow-up. All patients in the year before had experienced at least 4 episodes of venous thrombosis. This study was uncontrolled and the recurrences were not confirmed by any objective method. However, it demonstrates the possibility of a small subgroup of patients who can be identified, by platelet survival studies, as patients likely to respond to antiplatelet agents.

Wu et al, (1976) studied 30 patients with recurrent deep vein thrombosis documented at least once by acceptable methods and having at least 3 episodes in the previous 3 years without an evident precipitating cause. In almost half of these patients spontaneous platelet aggregation and circulating platelet aggregates could be demonstrated and persisted for weeks to months. The abnormal platelet function disappeared when dipyridamole and/or aspirin were given. Nine patients had platelet survival studies and of these 7 were shortened. All 7 patients had increased circulating platelet aggregates and 6 had increased spontaneous platelet aggregates. The study also gives hope that a simple test (Wu and Hoak, 1974) could identify a small subgroup of patients with recurrent venous thromboembolism who might respond to antiplatelet agents.

ABNORMALITIES OF THE COAGULATION CASCADE.

An increased tendency to thrombosis has been found in families with abnormally high concentrations of Factor V (Gaston 1966) or Factor VIII (Penick et al 1965). They had shortened activated PTT and PTT. A fibrinogen which reacts pathologically fast to thrombin has been identified (Egberg 1967) in a family with recurrent venous thromboembolism and epilepsy. Many had short plasma thrombin times.

Malignancy: The thrombophlebitis seen in patients with cancer is characterized as recurring and migrating with involvement of multiple sites including upper trunk and arms. Tumors of the lung, ovary, stomach and pancreas are believed to be most commonly associated with a thrombotic tendency. However, the incidence of thrombophlebitis in patients with malignant disease is low. Thromboembolism occurred in 9% of patients with lung cancer (Silvis et al 1970). Conversely, only 3-5% of patients with evidence of thrombosis have cancer (Levin and Conley, 1964; Isacson and Nilsson,1972). There is a 40-60% incidence of thrombocytosis in patients with a variety of carcinomas, but the thrombocytosis did not correlate with the development of thrombosis.

Warren (1974) reviewed the evidence for platelet aggregation around tumor cells and shortened platelet survival in patients with metastatic cancer. Normal tissue cells mixed with dilute plasma either do not induce clotting or the clot is promptly lysed. Tissue from a wide variety of carcinoma induces clotting of dilute plasma without subsequent lysis (O'Mera, 1958).

Homocystinuria is associated with a very high incidence of arterial and venous thromboembolism at an early age (Carson et al 1965, Schimke et al 1965). Homocystine in concentrations similar to those in patients activates Hageman factor in vitro (Ratnoff 1968). Children with homocystinuria were found to have increased stickiness of their platelets and homocystine added to normal platelets increased platelet stickiness (McDonald et al 1964).

Antithrombin III: Families with dominantly inherited deficiencies of antithrombin III have been identified and affected members are plagued with recurrent venous thromboembolism starting at aboutage 20 (Egberg, 1965, Meer et al, 1973, Marciniak et al, 1974). Von Kaulla and Von Kaulla (1967) found antithrombin III levels depressed in non-familial venous thromboembolism and proposed this as a means of identifying a hypercoagulable state. However, in a larger series there was no deficiency of antithrombin III in patients with recurrent venous thromboembolism (Headener and Nilsson, 1973).

The defect is inherited as an autosomal dominant trait. The severe tendency for venous thrombosis appears correlated with antighrombin III levels less than 50% of normal (Egberg 1965). Plasma deficient in antithrombin III requires 40 times the usual amount of heparin to prevent the interaction of thrombin on fibrinogen in an *in vitro* heparin resistance test. In a patient with antithrombin III deficiency the *in vivo* heparin resistance was corrected for about 4 days following transfusion with fresh normal plasma. The patient then remained well for 2 years following intensive fever therapy with typhoid vaccine; he showed a normal response to

heparin *in vitro* and *in vivo* on repeated studies (Koszewski and Vahabzadeh, 1964). The heparin resistance can be corrected *in vitro* by small amounts of normal plasma but not serum, indicating that antithrombin III is consumed in the process of clotting. When continued thrombosis is prevented by oral anticoagulation with coumarin drugs the antithrombin III levels frequently returned to normal (Marciniak et al 1974). When antithrombin III did not return to normal on oral anticoagulants thromboembolic episodes continued. In these patients subcutaneous heparin prevented further clotting episodes (Von Kaulla and Von Kaula 1972).

DEFECTIVE FIBRINOLYSIS.

Astrup (1958) proposed that thrombosis was related to a problem of imbalance between coagulation and naturally occuring fibrinolysis.

Plasminogen Activator Release: Isacson and Nilsson (1972) studied 91 patients with phlebographically verified idiopathic deep vein thrombosis and 26 with recurrent histologically verified idiopathic superficial thrombophlebitis. They demonstrated defective release of plasminogen activators in blood samples obtained during venous occlusion in 38% and decreased plasminogen activator in the walls of superficial veins biopsied and placed on fibrin plates in 55%. 73% of the patients had one or both abnormalities. Other abnormalities of the fibrinolytic system studied were rare. Plasminogen was increased in 8 of 109, urokinase inhibitors were increased in 16 of 101 and antiplasmin was increased in 4 of 13. 75 similar patients (Nilsson et al, 1975) were studied to see if plasminogen activators could be pharmalogically increased with phenformin 100 mgms per day and ethyloestrenol 8 mgms per day. There was an impressive and significant increase in local fibrinolysis during occlusion and plasminogen activator content of hand-vein biopsies evident at 3 months that persisted for 12 months during continued treatment. Recurrences were in the range of 5 per year of follow-up during treatment compared to more than 30 recurrences per year for the group prior to treatment. No controlled study comparing this form of treatment in recurrent venous thromboembolism has been recorded. It is interesting that prenisolone decreases the plasminogen activator content of vein walls in normal people (Isacson 1971).

Increased inhibitors of plasminogen activators (Nilsson et al 1961) and of plasmin (Naye 1961) are very rare causes of recurrent thrombosis.

We have recently reported that patients with early recurrence of pulmonary embolism within one month of the onset of anticoagulation have significantly higher FDP on the first day seen than other patients who do not recur during the first month of anticoagulation (Bynum and Wilson, 1977). An equally interesting observation is the fact that patients who recur later had very low FDP when first seen:

TABLE 21

FDP ON FIRST SAMPLE AFTER DIAGNOSIS
OF PULMONARY EMBOLISM OR THROMBOPHLEBITIS

RECURRENCE	NO. OF PATIENTS	MEAN FDP (μg/ml)
EARLY	11	40
NONE	65	20
LATE	7	7

This prompts the speculation that there is bell shaped normal distribution of fibrinolytic activity. When patients develop thrombosis some with increased fibrinolytic activity may lyse the thrombus completely and remain asymptomatic. Others with the proper degree of increased fibrinolytic activity may lyse around thrombi sufficiently to avoid adherance to the vein endothelium and promote pulmonary embolism followed by early recurrence. Patients with venous thrombosis and average fibrinolytic activity may develop symptomatic DVT or pulmonary emboli but lyse the residual thrombi slowly enough that adherence to the vein wall occurs. Patients who develop venous thrombosis and have low spontaneous fibrinolytic activity may be prone to continued propagation of thrombi because of imbalance of the normal relationship of thrombosis and lysis.

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