MASSIVE PULMONARY EMBOLISM

INTERNAL MEDICINE GRAND ROUNDS

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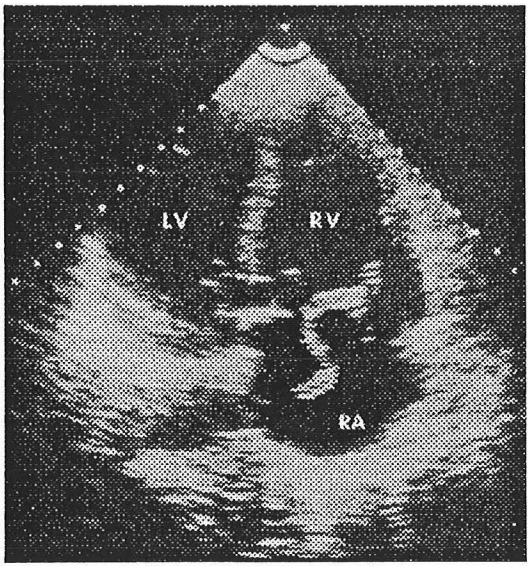

Echocardiographic demonstration of mobile clot
in right atrium prolapsing across tricuspid valve
(from Proano, et al, Mayo Clin Proc 63:1181, 1988)

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He has no financial ties to or interests in any drugs or products discussed herein.

INTRODUCTION

Thromboembolic disease continues to challenge clinicians in virtually all clinical disciplines. Fortunately, many of the principles which guide our diagnostic and therapeutic efforts have become well established (1-3). With timely diagnosis and institution of conventional anticoagulation we can expect to significantly reduce mortality with acceptable therapeutic morbidity in the majority of cases (4-6). Nonetheless, thromboembolism continues to represent a significant cause of death, especially in those sustaining acute, massive embolization to the lung (7-9). This review will focus on the differences in physiology, outcome and management in this important subgroup of patients with thromboembolic disease. In particular, the roles of echocardiography, pressor management, thrombolytic therapy, less invasive diagnostic strategies, and use of inferior vena cava (IVC) filters will be discussed.

The physiologic effects of pulmonary emboli correlate with the degree of vascular occlusion produced(10-12). Several methods have been described for quantifying the degree of vascular obstruction based on either angiographic (13,14) or perfusion lung scan findings (15-17). Traditionally, a massive embolic event is defined as one in which more than half of the pulmonary vasculature is obstructed (5,6,9,18,19). Thus, massive pulmonary emboli are those with angiographic or perfusion lung scans demonstrating > 50% vascular occlusion (corresponding to a Miller index of 17 or more out of a possible 34 points). Those with less than 50% occlusion are referred to as submassive. This categorization is not arbitrary, but rather, is based on differences in physiologic consequences. Accordingly, it may help to identify higher risk patients, as will be discussed. While the exact frequency of massive embolization is difficult to determine, this event is certainly not uncommon. Approximately half (49-56%) of all patients who survive to reach the hospital and have the diagnosis of pulmonary embolism (PE) established will meet the definition of massive PE (14,18). Indeed, many patients with high probability lung scans will fit this category.

When emboli cause an abrupt rise in pulmonary vascular resistance sufficient to produce cardiovascular embarrassment, they are referred to as hemodynamically significant emboli. These are associated with systemic hypotension (shock), clinically apparent acute right heart failure (acute cor pulmonale), and/or severe, refractory hypoxemia (high shunt fraction). Whether echocardiographic abnormalities *per se* can be used to define this group is one of the more important questions at present and will be discussed below. Hemodynamically significant PE as judged by the presence of shock occurs in 7-9% of diagnosed cases (18,20). The majority (80%) of hemodynamically significant emboli are massive, but only 12% of all massive emboli result in overt hemodynamic compromise (18,20). Thus, the two terms should not be used interchangeably.

The management of patients with submassive emboli who are hemodynamically stable is well established and there is reasonable consensus on the management of patients with clinical evidence of hemodynamically significant PE. However, the approach to patients with massive PE who are hemodynamically stable by clinical criteria remains controversial. Before further discussing the characteristics of massive and hemodynamically significant emboli, we must first understand the physiology and outcomes associated with conventional therapy.

CONVENTIONAL MANAGEMENT OF PULMONARY THROMBOEMBOLISM

The incidence of pulmonary embolism has been estimated to be 23 per 100,000 population (21). Thromboembolism may account for 4 to 5% of all hospital deaths, amounting to approximately 60,000 deaths annually in the United States (22). Dalen has estimated that 11% of patients die suddenly before reaching medical attention (5,6). Of those surviving at least one hour, the mortality when not treated is at least 30% (5,6). With appropriate therapy the mortality is reduced to 5 to 8% (4-6,8,23-27).

The signs and symptoms of PE are notoriously non-specific (28), but the diagnosis should be suspected in any patient with compatible symptoms, especially when a recognized risk factor is known to be present. Unfortunately, inherited predispositions to thromboembolism, especially factor V Leiden resistance to activated protein C, may account for 5-20% of new cases (29-31) and would be unlikely to have been diagnosed prior to the first clinical episode.

The value and limitations of ventilation/perfusion lung scanning in the diagnosis of PE has been well established through the large Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) collaborative trial (1). A high probability lung scan has a positive predictive value of 88%, and is 96% predictive of PE when there is strong clinical concordance. A normal lung scan effectively excludes the diagnosis, and a nearly normal or low probability scan where the pre-test clinical estimate of probability is very low carries a negative predictive value of 96% (1). The test is reliable in critically ill patients, including those on mechanical ventilation (32). Thus, treatment may be initiated on the basis of a high probability scan in patients at low risk for bleeding or when there is strong clinical concordance; treatment may be withheld when the lung scan is normal or when it is nearly normal or low probability with strong clinical concordance.

Unfortunately, these combinations of findings occur in only about 33% of patients suspected of having PE (12% concordant high probability scans, 14% normal scans, and 7% concordant low probability scans). The likelihood of PE varies considerably for all other combinations, ranging between 14% and 66%, with a positive predictive value of only 30% in patients with intermediate probability scans (the overall clinical positive predictive value is also only 33%; one in three patients suspected of PE were actually found to have had emboli). Therefore, in two thirds of patients the lung scan will be non-diagnostic (1).

Duplex ultrasound scanning of the lower extremities may be used in those patients with non-diagnostic scans, as a positive result is highly specific for proximal deep vein thrombosis (DVT) and would thus serve to allow the institution of conventional therapy in patients at low bleeding risk (2). However, less than half of patients with proven PE will have positive Duplex studies and an initial single negative study does not exclude the diagnosis of clinically significant thromboembolism (2,3).

Angiography should be performed in patients with non-diagnostic lung scans (most, if not all, intermediate probability scans as well as discordant high and low probability scans) who have negative Duplex ultrasound exams. The PIOPED trial also suggested that in patients with high bleeding risks, the overall complication rate was minimized

when the diagnosis was established with the highest level of certainty using angiography rather than relying on "non-invasive" techniques (33); thus, angiography should be considered in most patients with high bleeding risks, perhaps even as the initial diagnostic study.

Pulmonary angiography remains the gold standard for the diagnosis of PE. Patients who have a technically adequate study which is negative for PE and who are therefore not treated have only a 0.6 - 1.6% likelihood of experiencing a subsequent PE within one year (34,35); the risk of experiencing fatal PE recurrence is less than 0.5% (34). The specificity of pulmonary angiography is always excellent and is not dependent upon the time between the embolic event and the performance of the study. However, the natural history of emboli to the lung is gradual resolution through intrinsic fibrinolysis. Thus it might be anticipated that the sensitivity of the test would decline with increasing intervals between clinical onset and angiography. Early experimental models in dogs suggested that complete clot lysis may occur as early as 24 hours and as late as 72 hours after experimental embolization (6); however, these data are not extrapolatable to humans because the earlier studies used non-organized fresh thrombus and because the fibrinolytic activity in dogs is considerably greater than in other mammalian species (36). Studies in humans suggest that the rate of clot lysis is much slower and that emboli remain detectable for at least 48-72 hours (1,18,37-39) and probably for at least 7 days (39). Indeed, the angiogram or the lung scan can be expected to remain abnormal for weeks to months in the majority of cases (6). However, sensitivity does decline appreciably after 7 days (40). A similar diagnostic time window has been demonstrated for perfusion lung scans (41).

In patients with low bleeding risk, angiography need not be done emergently; heparin therapy may be started immediately and angiography deferred for 12 hours or so while other diagnostic studies are pursued and/or until the angiogram can be done under more less emergent conditions. The heparin infusion need only be stopped for 1-2 hours prior to the angiogram and can be resumed afterward (after repeating the bolus dose) as soon as local hemostasis is achieved (42).

With modern techniques, pulmonary angiography is safe, carrying a 0.5% risk of procedure-related death, a 1% risk of major complication, and a 5% risk of any morbidity (33,35). Major complications in 1,111 angiograms done in the PIOPED trial included death in 5, respiratory distress in 4, renal failure requiring dialysis in 3, and bleeding requiring transfusion in 2. Experience in multiple large trials shows that the study can be performed safely even in the presence of significant pulmonary hypertension if appropriate techniques are used (18,35). Technically adequate studies can be obtained in 96% of patients. These results reflect the experience in major centers with extensive interest and experience in pulmonary angiography; it is of course unclear if the these results are generalizable to all clinical situations. Nonetheless, pulmonary angiography is safe, accurate, and reliable as long as it can be done within 7 days of the onset of symptoms and is performed by a radiologist with sufficient skill and experience.

Magnetic resonance imaging (MRI) and computed tomography (CT) of the chest with IV contrast enhancement have been used to demonstrate pulmonary emboli in central pulmonary artery locations (43). CT techniques using continuous spiral volumetric

methods appear to be the most sensitive (43-46). Unfortunately, neither technique has been validated against pulmonary angiography except in small numbers of patients (46). Spiral CT still requires that the patient be transported to the radiology suite, that the patient hold their breath during imaging, and that IV contrast material be used. Further, these techniques are only capable of detecting emboli in central locations (2nd to 4th order vessels). These methods might have potentially limited application in patients with suspected massive or hemodynamically significant PE in whom thrombolytic therapy is being considered and avoidance of invasive angiography is desirable. However, at the present time CT or MRI diagnosis should still be considered experimental.

Intravascular ultrasound (IVUS) imaging has been used to detect large, central emboli in dogs (47) and in humans (48,49). While this technique is clearly in its developmental stages and not widely available, IVUS is potentially attractive for use in very unstable patients being managed in the ICU setting as it can be performed at the bedside, does not require transport to the radiology suite, and does not require iodinated contrast.

Plasma D-dimer assays to screen for thromboembolism have had varied success. Older latex agglutination methods lacked sufficient sensitivity. Newer ELISA methods appear to have excellent sensitivity (97%), but are limited primarily by their poor specificity of only 35% (50). In addition, care must be taken in interpreting these results for there is considerable variability amongst different assays. A recent report has suggested that a newer whole-blood agglutination assay (SimpliRED, Agen Diagnostics) that has higher binding specificity and can be done using a fingerstick at the bedside had an overall sensitivity of 93% for DVT. The negative predictive value of a negative D-dimer test in conjunction with a negative Duplex ultrasound was 97%. Sensitivity was 70% for calf-vein thrombosis and 93% for proximal DVT (51). Thus, newer D-dimer assays may find a role in the screening of patients (at least for DVT). It may be especially useful for those presenting in outpatient settings who have no identifiable risk factors, a low clinical suspicion for thromboembolism, and normal lower extremity Duplex ultrasound exams (2,51). The utility of D-dimer measurements in critically-ill hospitalized patients with suspected PE remains to be determined. Other novel diagnostic methods have been explored, including the use of radiolabelled tissue-type plasminogen activator (52).

The primary therapy for PE is anticoagulation to minimize further clot formation and propagation. Heparin should be started as soon as the diagnosis is entertained in patients without high bleeding risk. Treatment is initiated with an intravenous bolus loading dose followed by continuous infusion (24,26,27). The primary goal is to achieve minimum therapeutic threshold levels as rapidly as possible; failure to achieve adequate anticoagulation within the first 24 hours of therapy has been associated with a higher risk of recurrence (24,53). Avoidance of excessive anticoagulation with heparin is still desirable, but of secondary importance relative to the need to achieve rapid therapeutic threshold. While there is a clear relationship between the level of anticoagulation and bleeding complications for warfarin therapy, the data supporting a similar effect with supratherapeutic doses of heparin is less conclusive (54,55). Indeed, Hull's group has stated that there is no association between supratherapeutic activated partial thromboplastin time (APTT) responses to heparin and bleeding complications (54).

Dosing requirements vary considerably from one patient to the next, in large measure due to variable heparin binding to plasma proteins (56). As a result fixed dosing is not possible and drug administration is titrated based on monitoring of the APTT, since measurement of heparin levels is impractical. The traditional goal is to achieve a level of anticoagulation with the patient's APTT 1.5 to 2.5 times control (2,3). Unfortunately, there is significant variation in the APTT control depending upon the reagent used. Standards based on the APTT (in seconds) developed in individual centers using specific reagents are not directly translatable to other labs or centers. In fact, it has been suggested that reliance on the APTT ratio for targeting the therapeutic range could lead to underdosing in terms of actual protamine-titrated heparin levels when most commercial reagents are used (57). There is currently no standardization of APTT reagents analogous to the international normalized ratio (INR) for the thromboplastin (PT) reagents. Until such standardization is accomplished, individual labs could establish local therapeutic ranges by determining the APTT range which corresponds to heparin levels of 0.2-0.4 U/ml by protamine titration for the reagent in use locally (57). In the absence of such standardization, the goal of achieving an APTT ratio of 1.5 to 2.5 is still a reasonable (and conventional). Studies based on this goal have consistently shown acceptably low rates of recurrence when the minimal level is achieved within 24 hours.

Earlier dosing schemes tended to underdose patients and result in delays in achieving adequate anticoagulation. Several nomograms have been published which improve on earlier approaches (54,58,59). The weight-based nomogram of Raschke, *et al* (58) is one of the simpler and most broadly applicable of these published nomograms (see table 1). Thus, heparin should be initiated as soon as possible and dosing should be driven by an urgency to achieve adequate anticoagulation as quickly as possible rather than a fear of inducing bleeding complications; use of published nomograms will assist in achieving these goals.

Table 1. Weight-Based Nomogram for Heparin Administration
(from Raschke, et al, Ann Int Med 151:333, 1993)

	Dosing/Adjustment
Initial Dose	80 U/kg bolus, then 18 U/kg/hr infusion
APTT*	
< 1.2 X control	80 U/kg bolus, then ↑ infusion by 4 U/kg/hr
1.2 - 1.5 X control	40 U/kg bolus, then ↑ infusion by 2 U/kg/hr
1.5 - 2.3 X control	No Change
2.3 - 3.0 X control	↓ infusion by 2 U/kg/hr
> 3.0 X control	Hold infusion 1 hr, then ↓ infusion by 3 U/kg/hr

* The APTT is drawn q 4 hours and adjustments made until within therapeutic range on two consecutive checks.

Low-molecular weight heparin (LMWH) has been released in the United States. For the treatment of deep vein thrombosis it has been shown to be as effective and at least as safe as unfractionated heparin preparations (25,60,61). LMWH can obviate the need for IV infusions as it is given subcutaneously and does not require laboratory monitoring since reliable anticoagulation can be achieved with fixed dosing. LMWH may also be associated with a lower incidence of heparin-associated thrombocytopenia (62). It has been successfully used to treat DVT in the outpatient setting, often obviating the need for hospitalization altogether (61,63). Despite the higher cost of the drug *per se*, its other benefits are such that it may prove to be more cost effective than unfractionated heparin (57). On drawback to LMWH is that it not as readily interrupted as standadr heparin should bleeding occur. Unfortunately, there are as yet no direct comparisons of LMWH vs unfractionated heparin in the management of patients with pulmonary embolism.

Once the diagnosis of PE is made and therapeutic heparin dosing achieved, prolonged anticoagulation is maintained using oral warfarin. Heparin must be started prior to initiation of warfarin. However, warfarin can be started as soon as adequate heparin dosing is achieved (64). Warfarin is started at a dose of 10 mg/day within 24 hours of starting heparin and is monitored using the prothrombin time (PT). Adjustment of the warfarin dose to achieve a PT equivalent to an INR of 2.0-3.0 yields the optimum minimization of both recurrence and bleeding complications (2,3,65). Heparin is continued until the PT has been above the therapeutic threshold (INR > 2.0) for 2 consecutive determinations. The earlier initiation of warfarin decreases the time that heparin is required, and therefore leads to shorter hospitalizations (5 days on average, rather than 10 or more as was common in the past) with equal clinical efficacy (66). Warfarin is continued for 3 to 6 months, depending upon the patient's relative likelihood of recurrence and/or bleeding risks (2,3,65).

Treatment of thromboembolic disease with conventional anticoagulation is remarkably effective. Data pooled from over 1400 patients in trials reported over the last 30 years (13,18,24-27,61,66-71) suggest that the rate of thromboembolic recurrence is 7.9%. and the risk of major bleeding (associated with death, transfusion, operative intervention, etc.) is 4.8%. The risk of intracranial hemorrhage (ICH) during conventional therapy is 0.4%. These figures have remained fairly constant over the last 30 years.

Dalen has reported that the mortality in patients who live long enough to reach the hospital and in whom the diagnosis of PE is made is 30% without anticoagulation therapy (6). With conventional anticoagulation therapy the mortality is usually said to be 8%; most review articles on the subject continue to cite Dalen's 1975 article for this figure. While this clearly establishes the universal acceptance of the value of timely therapy in patients with PE, a more careful assessment of mortality with conventional therapy is needed, especially when considering alternative therapeutic modalities such as thrombolytic agents. Population-based studies have in fact demonstrated a trend toward improved survival in patients treated for thromboembolism over the last several decades (21). Dalen's 8% estimate is fairly consistent for reports in the 1970's; pooled data from 183 patients reported prior to 1980 gives a mortality of 8.7% (13,18,27,67,68). More recent reports, however, have suggested an improved outcome (independent of use of thrombolytics); pooled data for almost 1200 patients reported

since 1980 suggest a modern mortality of 4.5% in all patients with thromboembolism (either DVT or PE) treated with conventional heparin therapy followed by warfarin (24,25,61,66,69-71). Modern mortality for proximal DVT without PE is 5% and with PE is 7.3%.

Further, while many of the deaths associated with PE are ascribed to the original embolism or to recurrence, a substantial fraction of the total mortality relates primarily to underlying diseases. Indeed, while the short-term mortality is 5-8%, there is a 20% mortality at one year (9,21) and a mortality of 30% at 3 years (21) which is largely due to comorbid disease. Up to 15% of patients will be found to have cancer in the 12 months following an initial episode of PE (72). Thus, not all of the mortality associated with PE can be ascribed directly to the thromboembolism would therefore not be expected to be affected by additional therapy directed towards clot prevention or lysis. Although the rate of spontaneous clot regression is slow, the majority of patients will have complete or nearly complete resolution without physiologic impairment within a year of a single event (9). Only a very small minority of patients will have significant persistent occlusion leading to chronic pulmonary hypertension. Although small, this is an important group nonetheless as such patients have an excellent prognosis with pulmonary thromboendarterctomy done in experienced centers (3,73,74). Given these considerations, one would anticipate that it would be very difficult to show any incremental improvement in outcome for patients with PE as a whole beyond what can be expected with conventional anticoagulation therapy. Thus, more recent efforts have attempted to identify characteristics of subgroups of patients who are at higher risk for death to target such persons for more aggressive therapies.

PATHOPHYSIOLOGY

Hemodynamic Effects

Acute mechanical obstruction of the pulmonary vasculature immediately leads to an increase in pulmonary vascular resistance (PVR) and an increase in pulmonary artery pressure. This pressure increase is transmitted to the right ventricle (RV) which dilates, increasing right ventricular myocardial stretch. This in turn allows the right ventricle to contract with greater force, thus sustaining the increased pressure needed to maintain flow through the more resistant circuit (75). However, the degree of increased pulmonary artery pressure in response to mechanical obstruction is very modest. Experimentally induced pulmonary artery occlusion using mechanical constriction or obstruction does not result in significant pulmonary hypertension until over 60-75% of the vasculature is obstructed (75). Complete obstruction of either the right or left main pulmonary arteries through inflation of a balloon-catheter within the artery (thus producing 50% obstruction) leads to average increases in mean pulmonary artery pressure of only 3-6 mm Hg in normal human subjects (76,77). Progressive obstruction produces further right ventricular dilation. However, the non-hypertrophic right ventricle can only increase its force of contraction to mean pressures of about 40 mmHg in the acute setting (10,78). At about 60% pulmonary artery occlusion right ventricular end-diastolic pressure and systemic venous pressure begins to rise as the right ventricle begins to fail. Circulatory collapse only occurs after 75-80% of the vasculature is mechanically obstructed (75).

In both experimental and clinical settings (10,12,78-80) when pulmonary embolism rather than mechanical obstruction is the cause of vascular compromise, the degree of angiographic occlusion required to produce similar hemodynamic responses is consistendly less. That is, a given amount of vascular occlusion from thromboembolism produces a greater increase in pulmonary vascular resistance than does pure mechanical obstruction (11). This suggests that there is an additional component of reactive pulmonary vasoconstriction in the setting of PE (81,82). Reactive vasoconstriction is due in large measure to humoral substances released from thrombi, in particular serotonin and thromboxane A2 (11). It is also thought that baroreceptors in the pulmonary arteries may produce reflex vasoconstriction in response to increased PA pressure (11). Vasodilator infusion does not reliably improve pulmonary hypertension in the setting of acute pulmonary embolism (83-85), an observation which suggests that mechanical obstruction *per se* is quantitatively the primary determinant of the resulting pulmonary vascular resistance. Alveolar hypoxia and/or arterial hypoxemia also contribute to the increased vascular resistance. This contribution must be relatively small since correction of alveolar and/or arterial hypoxemia has only modest mitigating effects on PVR (77). In fact, there is evidence that the hypoxic vasoconstrictor response is actually attenuated in the setting of pulmonary embolism (86,87), even though this does not result in preservation of gas exchange and may even contribute to the development of severe hypoxemia (see below).

The site at which emboli produce occlusion is also important in determining the degree of hemodynamic impairment. A given volume of clot caught in the pulmonary artery outflow tract or in a main pulmonary artery may occlude a substantial fraction of the total cross-sectional area of the pulmonary vasculature, even though the vessel's diameter is relatively large. Conversely, the same volume of clot, if fragmented and located distally in smaller diameter vessels, will occlude a significantly smaller fraction of the total vascular cross-section (see table 2). Thus, PVR can be substantially reduced and hemodynamics improved without any significant reduction in the amount of clot (i.e., without thrombolysis) through fragmentation and peripheral migration.

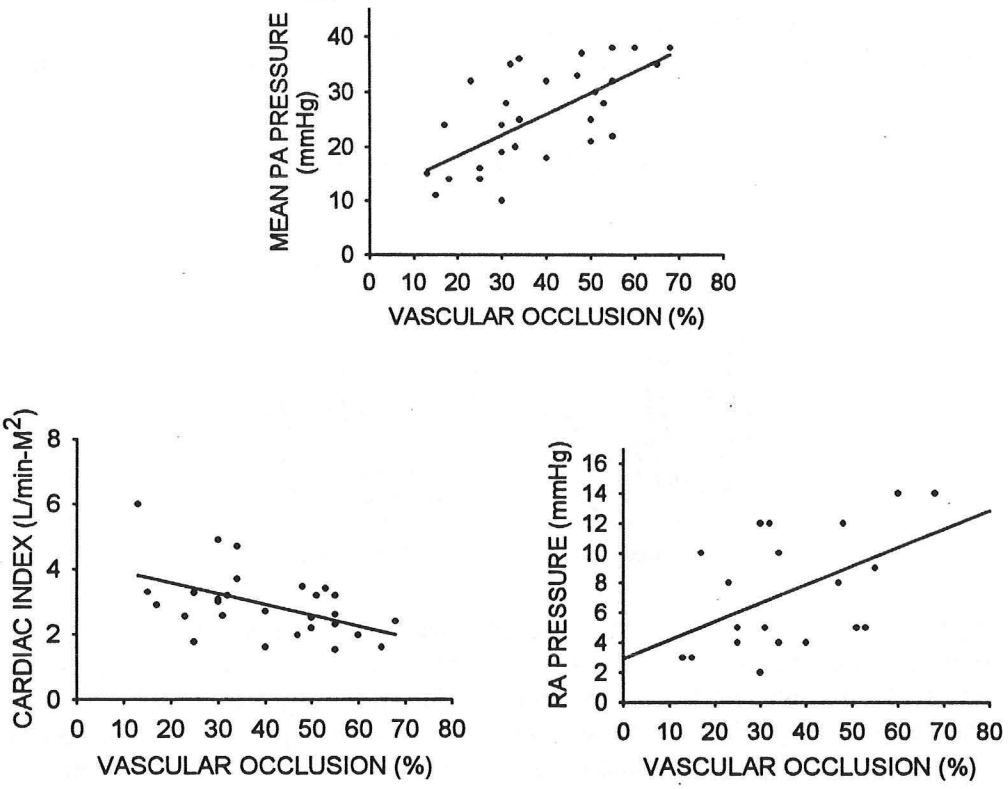
Table 2. Vessel Diameter and Cross-sectional Area with Progressive Branching of the Pulmonary Vasculature

Vessel	Diameter (mm)	Vessels (n)	Total Area (cm^2)
Pulmonary outflow	30	1	9
Main PA	15	2	10
Lobar	8	5	13
Segmental	6	19	36
Subsegmental	4	65	817

adapted from reference (88)

Studies in human subjects with acute pulmonary embolism demonstrate that the hemodynamic effects of emboli correlate with increasing degrees of vascular obstruction (10,12,78-80), as is shown in figure 1. In patients without pre-existing cardiopulmonary disease, obstruction of 50% or more is fairly consistently associated with pulmonary hypertension (mean PA pressure over 25 mm Hg). Obstruction of 60-85% is said to be required to produce shock (89), though hypotension can be seen with lesser degrees of obstruction. However, as mentioned above, the pressure response is limited in the non-hypertrophied ventricle, so that in the setting of acute embolism, even with extensive obstruction, the mean PA pressure does not exceed 40 mm Hg (10,12,80). Indeed, pressures in excess of this are generally taken to be evidence of pre-existing pulmonary hypertension, either due to prior, recurrent pulmonary emboli or to any other cause of chronic pulmonary hypertension (12).

Figure 1. Hemodynamic Effects of PE

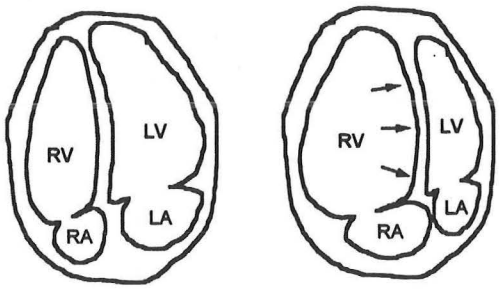


The initial right ventricular dilation in response to increasing vascular resistance is an adaptive compensation which allows the ventricle to generate the additional pressure needed to maintain forward output. However, stretch-enhanced contractility increases myocardial oxygen demand while the accompanying increase in wall tension and transmural pressure eventually lead to right ventricular ischemia (11,90-92), especially when diastolic pressure elevation ensues. This myocardial ischemia may produce typical anginal quality chest pain (90,92) and electrocardiographic evidence of ischemia (93). Though uncommon in the majority of patients with acute PE (28), these findings

are suggestive of large, central emboli with significant hemodynamic effect (90). Right ventricular ischemia in this setting is very sensitive to changes in mean systemic arterial pressure, even in the absence of right coronary occlusion. Ischemia is magnified by systemic hypotension and can be offset by increasing arterial pressure (94). This later point has important implications for hemodynamic management (see below). It is at this point that the right ventricle begins to decompensate and end-diastolic pressure and right atrial and systemic venous pressure begin to rise. Overt right ventricular failure, or acute cor pulmonale, then ensues.

In light of the forgoing it is important to emphasize that right ventricular enlargement is common with pulmonary embolism and represents a ventricular compensation for increased resistance. The right ventricle has a relatively high diastolic compliance and thus pressure elevations are very modest over a broad range of increased vascular resistance, pulmonary artery pressure, and ventricular dilation (95). Right ventricular diastolic, right atrial, and/or systemic venous pressure elevations would be expected to occur only with more severe abnormalities and thus to be more specific markers of ventricular dysfunction and failure as opposed to RV dilation *per se* (see below). Although RV dilation can be readily detected by echocardiography in patients with acute PE (96-99), it does not necessarily follow that this implies ventricular dysfunction.

Figure 2. Ventricular Interdependence

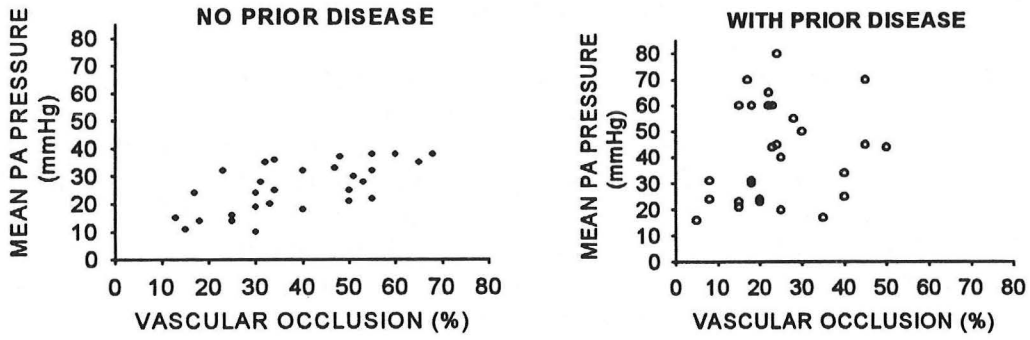


As the right ventricle begins to fail its forward cardiac output falls, decreasing left ventricular (LV) preload. In addition, as the right ventricle dilates in response to increasing PVR, the left ventricular volume is reduced during diastole (79,90,94,96,98) due to the constraining effect of the acutely non-distensible pericardium (97,99-101). This can be seen as leftward displacement of the interventricular septum and an increase in the ratio of RV/LV diameter (figure 2). While RV dilation reduces LV diastolic filling and thus LV end-diastolic volume, left ventricular end-diastolic pressure remains unchanged (102). As a consequence an apparent reduction in LV diastolic compliance (or "LV diastolic tamponade") occurs. In fact, actual LV compliance is normal, though transmural LVEDP is reduced, which is indicative of reduced LV preload (102). The net result is that ventricular interdependence further limits LV preload and contributes to declining stroke volume, systemic cardiac output, and ultimately to systemic hypotension. Systemic vascular resistance increases to compensate. Thus, the hemodynamic profile is one of cardiogenic shock.

The patient may have prominent jugular venous distention or hepatojugular reflux. With sudden, acute decompensation there is only moderate pulmonary hypertension, so that the second heart sound and tricuspid regurgitation (TR), while almost always present, are not prominent on exam. In the absence of ventricular hypertrophy there is usually no ventricular lift; dependent edema does not have time to develop immediately (28,78,90). Thus, many of the typical signs of chronic pulmonary hypertension and right-sided heart failure are absent despite the fact that the circulation may be failing.

Patients who have pre-existing cardiac and/or pulmonary disease mainfest a very different physiologic picture. The chronically loaded right ventricle will hypertrophy. Such patients may have resting pulmonary hypertension, right ventricular dilation, and clinical signs of right heart failure. Echocardiography will often show evidence of tricuspid regurgitation. In this situation, the hypertrophic right ventricle can generate mean pressures considerably in excess of what is observed in acute PE. As a result, the degree of vascular obstruction does not correlate well with the hemodynamic consequences of PE in patients with pre-existing cardiopulmonary disease (12,103), as is shown in figure 3. This lack of correlation is important as the presence of significant pulmonary hypertension may be more reflective of prior disease and could thus be misleading as a measure of the impact of an episode of PE or as a prognostic marker for therapeutic decision-making. Echocardiographic or hemodynamic features which suggest the presence of pre-existing disease as a cause of pulmonary hypertension in the setting of PE include: (a) mean PA pressure greater than 40 mmHg, (b) evidence of right ventricular hypertrophy (RVH) as indicated by RV free wall thickness of >5mm on echocardiogram, and (c) high-velocity (>3.7 m/sec) tricuspid regurgitant jet (12,103).

Figure 3. Hemodynamic Response in Patients With and Without Prior Cardiopulmonary Disease



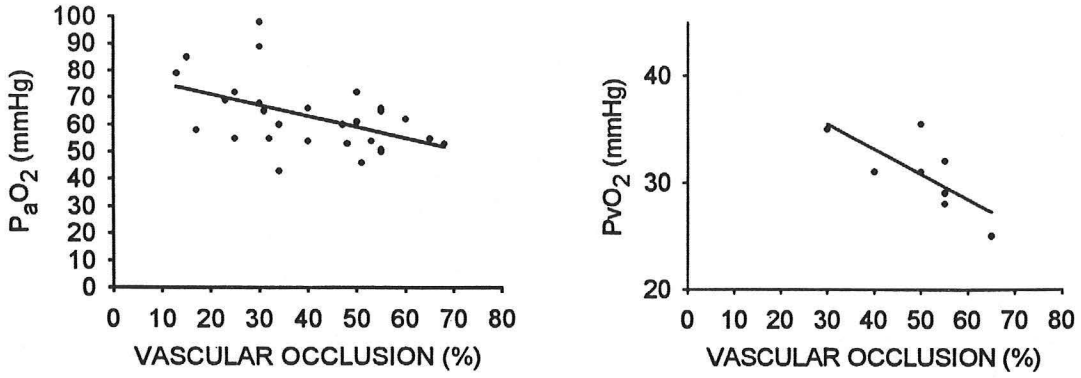
Gas Exchange

The majority of patients with PE will develop some degree of arterial hypoxemia, although an ancillary report from the PIOPED trial clearly demonstrated that a normal PaO_2 or even normal A-a O_2 gradient does not rule out the possibility of clinically significant PE (104). The cause of hypoxemia is multifactorial and depends in large measure on co-existing lung disease. The distribution of both ventilation and perfusion are altered after a PE. Obstruction of blood flow leads to regional areas of underperfusion (relative dead space or high ventilation/perfusion ratios, V/Q). This increased dead space is usually compensated by an increase in total minute ventilation, though in patients with a fixed minute ventilation it will lead to hypercapnia. Sensitive measures of gas exchange such as the multiple-inert gas elimination technique (MIGET) usually demonstrate only minor increases in true dead space (80,105-109).

More importantly, the mechanical obstruction and reactive vasoconstriction which accompany PE (see above) require that the cardiac output be redistributed to other lung regions. The normal lung has a marked capacity to redistribute blood flow without significant impact on gas exchange. Such redistribution, however, might have adverse consequences on gas exchange if the result is excess blood flow to areas with relatively poor ventilation. This scenario would be expected in patients with underlying pulmonary disease. In addition, patients will develop new regional areas of reduced ventilation due to: reflex bronchoconstriction from humoral substances released from embolized clot (11,108); atelectasis (110); or overt lung infarction (11). When significant flow redistribution occurs and pulmonary hypertension begins to develop, the normal reflex hypoxic pulmonary vasoconstrictor response is overcome (86,87). The net result is that the redistributed blood flow may be directed to areas with poor ventilation (86). Thus, redistribution of a significant amount of blood flow, as might occur with large occlusions, would be expected to actually shift many lung units in non-embolized regions to a much lower ventilation/perfusion ratio. Numerous studies using MIGET have shown that, in fact, the major mechanism for hypoxemia with PE is a shift in the relative proportion of blood flow to low or very low V/Q units (80,105-109). Others have also suggested that diffusion limitation may play a role (111).

Most studies of gas exchange in patients with PE do not detect the presence of significant right-to-left shunt. Nonetheless, intra-pulmonary shunt may develop in areas of atelectasis (110). In addition, as the right ventricle begins to fail and diastolic pressure elevation ensues, the increase in right atrial pressure (with normal left atrial pressure) may lead to significant right-to-left shunting through a patent foramen ovale (112-114). If PE produces a decrease in cardiac output, then the mixed venous oxygen saturation will fall as peripheral O_2 extraction increases. In any situation where there is significant venous admixture (due to either to low V/Q distribution or shunt), mixed venous hypoxemia may contribute to or exacerbate arterial hypoxemia (115). Indeed, mixed venous hypoxemia correlates very well with the degree of vascular obstruction (80). Thus, the cardiac effects of large emboli may actually contribute to deteriorating gas exchange through creation of right-to-left shunts through a patent foramen ovale as well as through mixed venous hypoxemia and venous admixture.

Figure 4. Effects of PE on Gas Exchange



The degree of gas exchange abnormalities and resulting hypoxemia tend to correlate fairly well with the degree of vascular obstruction in PE (10,80,105), except in patients with underlying lung disease (116). The degree of V/Q inequality and/or shunt is generally greatest with larger, more centrally placed emboli (81) and in those with hemodynamic compromise. Thus, significant hypoxemia might be expected to be indicative of more advanced degrees of embolism. Severe dyspnea and refractory hypoxemia (suggesting shunt physiology) are clearly markers for very severe physiologic derangement, including hemodynamic alterations.

HEMODYNAMIC MANAGEMENT

Consideration of the underlying physiologic derangements which occur when PE produces hemodynamic abnormalities underscores the need for rapid restoration of adequate arterial blood pressure and cardiac output through appropriate hemodynamic management. As discussed above, myocardial ischemia is particularly sensitive to decreases in systemic arterial pressure and can be abrogated by restoring arterial perfusion pressure (90,94). Given the underlying physiology, one could hypothesize that hemodynamics might be improved through strategies aimed at: (a) increased preload, (b) pulmonary vasodilation, (c) systemic vasoconstriction, or (d) increased myocardial contractility.

Conventional wisdom has suggested that the primary thrust of hemodynamic support is to increase preload through volume expansion (95). However, there is now significant evidence that this approach not only may not work, but may actually cause hemodynamic deterioration. Several studies have used glass beads or autologous clot to embolize euvolemic dogs and create acute pulmonary hypertension with low cardiac output and hypotension. Three such studies demonstrated that volume administration did not reverse this hemodynamic state and led to deterioration, and ultimately, to death (84,117,118). This poor outcome is largely due to accentuation of ventricular interdependence together with the constraining influence of the pericardium. With volume expansion, the right ventricle dilates further with accentuated left-ward shift of the septum, causing more extreme encroachment on left ventricular filling (118). Volume expansion only improved cardiac output when the pericardium was opened

(101). One study is usually cited for purportedly demonstrating that volume expansion can restore hemodynamics (119). However, volume administration in this animal model only raised mean arterial pressure from 69 mm Hg post-embolization to 77 mm Hg; norepinephrine increased mean pressure to 110 mm Hg and had the greatest effect on cardiac output. Thus, contrary to conventional wisdom, volume administration should only be given to correct volume deficits.

Although isoproterenol can decrease pulmonary vascular resistance (81), the effect is very modest and in most instances cardiac output and systemic blood pressure either do not increase or actually decrease (81,84,85). In addition, Rosenberg reported that isoproterenol potentiated myocardial ischemia as myocardial oxygen demand/work increased without a concomitant increase in oxygen supply (85). Other attempts to produce pulmonary arterial vasodilation with hydralazine, nitroglycerin, or nitroprusside have had similar effects (83,119,120).

Phenylephrine can restore systemic arterial blood pressure, but does not reliably increase cardiac output although it does tend to increase myocardial oxygen demand (83,121). In one report amrinone increased both systemic blood pressure and cardiac output in a canine model (122). There is only a single case report of its use in a human subject with massive PE (123) and its longer half-life limits its use (90). Both dopamine and dobutamine have been shown to increase cardiac output (119,124,125) though dobutamine has variable effects on systemic blood pressure (124), presumably through its tendency to cause peripheral vasodilation (83). Increasing cardiac output with these agents is often associated with worsening of oxygenation, suggesting that increased pulmonary blood flow causes worsening V/Q mismatch since mixed venous saturation improves as expected (83,115).

Norepinephrine has consistently been shown to increase cardiac output, raise systemic arterial pressure, and reduce pulmonary vascular resistance (84,85,117,119,121). In addition, right ventricular stroke volume is increased and end-diastolic pressure reduced. These effects have been demonstrated in both animal models and in human subjects. Norepinephrine increases right ventricular work and oxygen consumption with concomitant increases in right ventricular blood flow (121), though some have raised concerns that the increase in myocardial oxygen demand is disproportionate and potentially deleterious (19). In direct comparative trials norepinephrine produced superior results to isoproterenol (84,85,119), phenylephrine (121), dopamine (119), nitroglycerin (119) and volume expansion (84). Molloy found that in a canine model using autologous clots, norepinephrine restored hemodynamics and improved survival; none of the animals in control, isoproterenol, or volume-expansion groups showed hemodynamic improvment and all died (84). Interestingly, there have been no trials directly comparing the effects of dobutamine and norepinephrine.

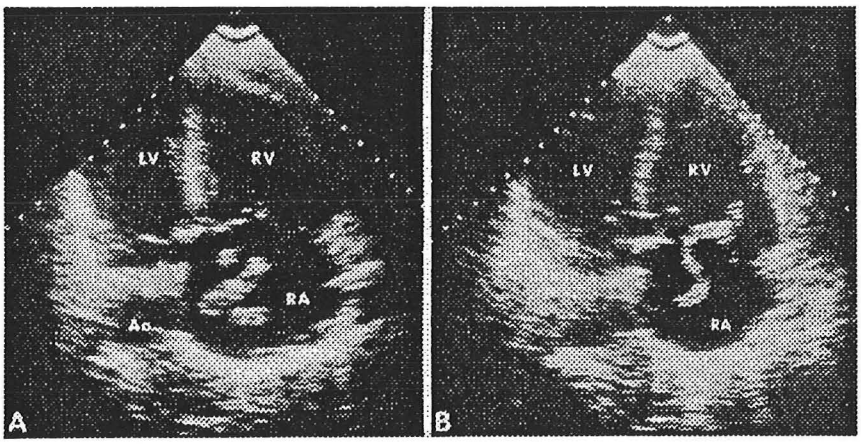
While some authors recommend dobutamine as the first-line agent in managing patients with massive PE (19,90), the consensus opinion is that norepinephrine is the agent of choice, especially for patients with systemic hypotension (7,83,126). All would currently agree that fluids should be administered judiciously in this setting, primarily to correct volume deficits.

ECHOCARDIOGRAPHY

Echocardiography has been used to assist in the diagnosis of PE through direct visualization of clot, demonstration of compatible physiologic changes, and by detection of other conditions which might mimic PE. Echocardiography has also helped define our current understanding of the physiology of acute PE, especially with regard to ventricular interdependence (see above). Physiologic responses to therapy can be assessed and documented. Pulmonary artery systolic pressure can be estimated using Doppler echocardiography whenever tricuspid regurgitation is present. A variety of echocardiographic indices of the right ventricular response to vascular occlusion have been described; these have been used in an attempt to risk-stratify patients with massive PE.

There are numerous reports of echocardiography being used to detect large emboli in the right atrium (127-135). While some of these are thought to arise in dilated, hypokinetic chambers, the majority likely arise from systemic veins and represent "emboli-in-transit" or "mobile emboli" which are caught in the right atrium. These emboli may migrate to the lungs or cause sudden outflow obstruction and death (131,132,134). Indeed, the mortality with these lesions is exceedingly high. These are almost uniformly fatal without treatment and carry an approximate 50% mortality with anticoagulation (136-138). Although the infrequent nature of the lesion makes comparative trials impossible, recent experience would suggest that thrombolytic therapy is effective at resolving clot and improving outcome (139-146). Surgery should be performed for patients who fail or cannot receive thromobolytic therapy. The operative mortality is still approximately 15% (138), but is decidedly better than that seen with emergent pulmonary embolectomy (see below).

Figure 5. Mobile Clot in Right Atrium (RA)



From reference (139)

The usual diagnostic difficulty is distinguishing these emboli from other right atrium masses such as myxomas or large vegetations. The echocardiographic characteristics of each have been described (137,138). Emboli are said to be more often elongated, cylindrical, serpiginous, and free-floating. They may change configuration from one

frame to the next, and often prolapse across the tricuspid valve (see figure 5). In contrast, atrial tumors are more rounded and sessile. Unfortunately, these characteristics are not uniform and reports of mis-diagnosis exist. The frequency of these abnormalities among all patients with PE is not known, but must be relatively small since most reports are small series or single case reports. In two large series comprising 165 patients with PE who were referred for echocardiography (and thus a highly selected group), clots were detected in 14% (98,147). Clots can also be visualized in the central pulmonary arteries and pulmonary outflow tract, especially if transesophageal echocardiography is used (144-146,148). Thus, the sensitivity is quite poor and the specificity imperfect for direct echocardiographic diagnosis of thromboemboli; however, echocardiographic detection of clot appears to identify a high-risk group that would benefit from more aggressive therapy.

Echocardiography is probably most useful in hemodynamically unstable patients to exclude other conditions such as aortic dissection, interventricular sepal rupture, or cardiac tamponade (149). Evidence of right ventricular hypokinesis or dilation may be clues to PE (see below), but can also be seen with right ventricular infarction and other conditions. Right ventricular hypertrophy is a marker of pre-existing disease as discussed above. The typical findings of a patient with PE are listed in table 3. While these findings are typical, they are nonetheless not pathognomonic for PE and do not allow for the diagnosis to be established solely on echocardiographic criteria (except perhaps for the rare patient who is judged to be too unstable to undergo any diagnostic studies outside of the ICU). Thus, these findings may help steer the clinician toward the diagnosis of PE, but should not be relied upon in the majority of cases.

Table 3. Echocardiographic Findings in Pulmonary Embolism

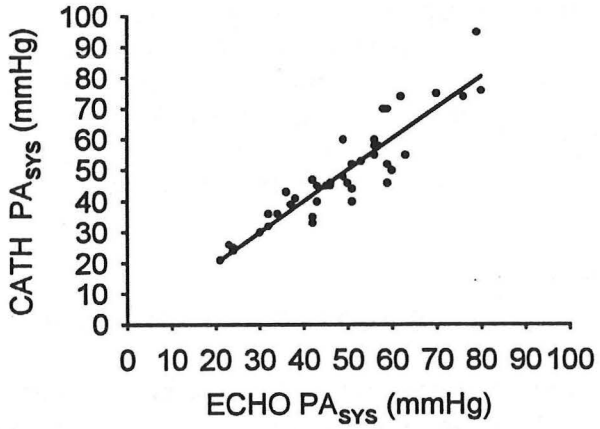
Thromboemboli within the right heart or pulmonary artery
Right ventricular dilation
Right ventricular hypokinesis
Abnormal septal position and paradoxical systolic motion
Reduced left ventricular size
Increased right ventricular/left ventricular diameter ratio
Pulmonary artery dilation
Unusual degree of tricuspid or pulmonary regurgitation
Increased flow velocity within tricuspid regurgitant jets

Tricuspid regurgitation is present to some degree in many patients with significant PE. Estimation of the systolic-diastolic pressure gradient (ΔP) across the tricuspid valve has been used to derive an estimate of RV systolic pressure (and thus PA systolic pressure, in the absence of pulmonic stenosis). This can be done using Doppler echocardiography by assessing the maximum flow velocity (V) of the regurgitant jet. It is calculated using the modified Bernoulli equation as:

$$\Delta P = 4 \times V^2$$

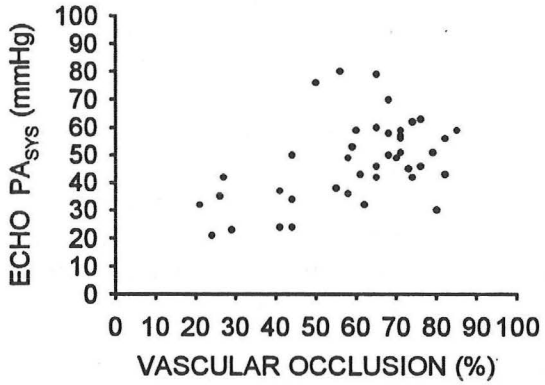
This value is then added to the CVP/RA pressure (either assumed or estimated clinically) to derive RV and PA systolic pressure (150). Studies comparing this estimate of PA systolic pressure to that measured by catheterization (figure 6) have shown excellent correlation (with r values of .92 to .97) in patients with pulmonary hypertension from a variety of causes (150-153). The estimate can be made when adequate visualization and velocity profiles are present. Measurable tricuspid regurgitation will be seen in almost all patients with PA systolic pressures in excess of 35 mmHg and in about half of those with pressures over 25 mm Hg; only about 25% of these will have clinically apparent tricuspid regurgitation(150). However, echocardiographic TR may be present in as many as 40% of normals (154). Saline contrast enhancement of trivial TR velocity profiles can increase the number of studies in which PA systolic pressure estimates can be made (154). In a very selected group of patients with suspected PE who were referred to an echocardiography lab, 90% had TR in one study (79). The actual negative predictive value of echocardiographic TR as a screening tool for PE is not known, however. As noted earlier, patients with chronic pulmonary hypertension and/or RVH may have measurable TR and high estimates of PA pressure independent of acute PE; indeed, PA pressures in excess of 40 mm Hg or very high-velocity TR jets suggest chronic disease (96,103). Thus, the presence of tricuspid regurgitation is a sensitive, but non-specific, marker for PE and allows for the non-invasive estimation of PA systolic pressure in many patients with pulmonary embolism.

Figure 6. Echocardiographic Estimation of PA Systolic Pressure



Echocardiographic alterations have been used to assess physiologic and therapeutic responses to acute PE. Any number echocardiographic criteria, both qualitative and quantitative, have been used in this context. The anatomy of the right ventricle and technical difficulties in its visualization significantly limit the accuracy of quantitative derivations, especially of volume, but also of diameter, thickness, and area (96). Thus, most of the echocardiographic assessments of right ventricular performance rely heavily on subjective grading (96). Of the criteria reported, many show considerable measurement variation and inter-observer variability. Nonetheless, echocardiographic changes demonstrate a general (but imperfect) correlation with the degree of vascular obstruction (see figure 7).

Figure 7. Degree of Vascular Occlusion and Echocardiographic Estimate of PA Systolic Pressure



Of the echocardiographic criteria reported, those which seem to correlate best with vascular obstruction are RV end-diastolic diameter and the end-diastolic RV/LV diameter ratio (79,98,155). Numerous studies have shown improvement in one or more of these echocardiographic criteria after thrombolytic therapy or mechanical removal of clot (71,139-146,148,155,156).

It is thus clear that echocardiography can identify alterations in right ventricular behavior in the setting of PE and can be used to document response to therapy. Some have suggested that these echocardiographic alterations imply ventricular dysfunction and identify a high-risk subgroup of non-hypotensive patients with PE who would benefit from thrombolytic therapy (42,71,155). The use of echocardiography for treatment stratification is controversial (149), to say the least, and will be discussed in greater detail below.

PROGNOSIS AND RISK STRATIFICATION

From the previous discussion, there would appear to be a general continuum of physiologic severity in patients with thromboembolic disease. At one end of the spectrum is the patient who sustains such sudden, overwhelming obstruction that death occurs rapidly, before medical intervention would be possible (except, of course,

a priori prophylaxis). At the other end is the patient with DVT who has not yet experienced pulmonary vascular obstruction, but who is at risk. In between are all patients with PE who survive to reach medical attention.

Those with relatively minor pulmonary vascular occlusion (submassive) will, in general, have only minor alterations in RV function, hemodynamics, or gas exchange. Those with more extreme obstruction (massive) will generally have evidence of RV alteration (especially RV dilation) and some of these will develop overt hemodynamic compromise with hypotension, shock, syncope, or refractory shunt-like hypoxemia.

This view of the pathophysiologic consequences of PE is supported by the observations cited earlier showing that, in general, the degree of vascular occlusion will correlate with such physiologic endpoints as mean PA pressure, RV dilation, arterial PO_2, mixed venous PO_2, and cardiac output. In recognition of these observations it has been traditional to categorize patients with PE on the basis of degree of vascular obstruction (i.e. massive vs submassive). Thus, one of the commonest clinical markers which has been used to estimate prognosis has been degree of vascular obstruction.

How good is the degree of vascular obstruction, especially the distinction between massive (>50%) and submassive (<50%), as a prognostic marker? While we have seen that a general correlation between vascular occlusion and physiologic alterations exisits, close inspection shows that there is considerable inter-patient variability (figures 1,3,4). Indeed, while patients with >50% vascular obstruction often have significant physiologic derangements (PA hypertension, hypoxemia, etc.), there are many with submassive obstruction who have similar degrees of physiologic compromise. Thus, degree of vascular obstruction does not reliably predict severity of physiologic effect in individual patients. As noted earlier, 49-56% of pulmonary emboli will be massive (14,18). Accordingly, strategies targeted simply by degree of obstruction to massive PE will include at least half of all patients (some of whom have few or minor physiologic changes) and will still miss a significant number of patients who have important physiologic alterations despite having quantitatively submassive PE. Thus, the "massive" designation is not entirely specific, nor sensitive, for categorizing the true endpoint, physiologic abnormality.

Despite these limitations, patients with massive PE as defined by vascular obstruction are generally thought to have a worse prognosis as a group. Table 4 represents a summary of mortality in a number of studies. They are grouped by average degree of vascular obstruction in each study. The DVT group includes only patients from studies with proximal DVT, who presumably have no pulmonary vascular obstruction. The "submassive" studies are those in which the mean vascular obstruction scores are <50%, while the "massive" studies have mean scores >50%. Since this categorization is limited to mean data, obviously significant numbers of individual patients in the "submassive" studies had massive PE and vice-versa for the "massive" groups. This analysis suggests a trend towards higher mortality with increasing degree of vascular obstruction (5.3% for DVT, 6.1% for submassive PE, 7.3% for massive PE). A similar analysis (table 5) suggests that there is also a trend towards higher recurrence rates with increasing vascular obstruction (6.1% for DVT, 9.1% for submassive PE, and 17.6% for massive PE).

Table 4. Mortality and Degree of Vascular Obstruction for Patients Treated with Heparin

	Vascular Obstruction (%)	Mortality	
Proximal DVT			
Salzman (27)	---	6/69	
Hull '86 (24)	---	3/58	
Hull '90 (54)	---	10/219	
Hull '92 (25)	---	10/199	
		29/545	5.3 %
Submassive PE			
Goldhaber (71)	36 ± 21	2/55	
Arnesen (68)	49 ± 22	2/11	
		4/66	6.1%
Massive PE			
Tibbutt (67)	55 ± 17	1/17	
Miller (13)	70 ± 10	0/8	
UPET I (18)	67 ± 18	7/78	
PAIMS 2 (70)	74 ± 16	1/16	
PEOPED (69)	84 ± 14	0/4	
		9/123	7.3 %
All PE		13/179	7.3 %

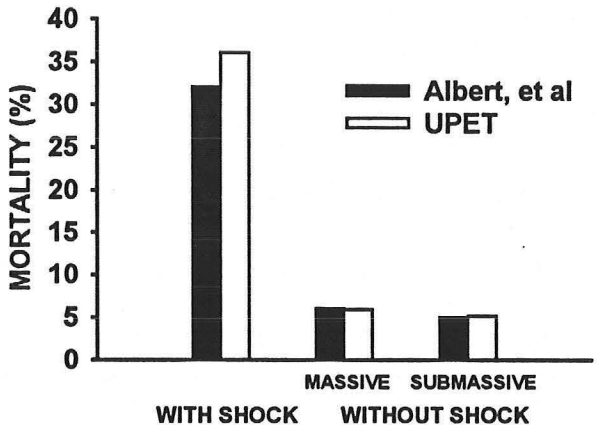
Table 5. Recurrence and Degree of Vascular Obstruction for Patients Treated with Heparin

	Vascular Obstruction (%)	Recurrence	
Proximal DVT			
Salzman (27)	---	1/69	
Hull '86 (24)	---	3/58	
Hull '90 (54)	---	15/219	
Hull '92 (25)	---	14/199	
		33/545	6.1 %
Submassive PE			
Goldhaber (71)	36 ± 21	5/55	
Arnesen (68)	49 ± 22	1/11	
		6/66	9.1%
Massive PE			
Tibbutt (67)	55 ± 17	1/17	
Miller (13)	70 ± 10	2/8	
UPET I (18)	67 ± 18	15/78	
PAIMS 2 (70)	74 ± 16	3/16	
		21/123	17.6 %
All PE		27/185	14.6 %

Hall reported that the overall mortality in a group of 88 patients who all had massive PE was 18% (9). Albert reported a mortality of 16% in 50 patients who all had massive PE (8). On the other hand, the mortality for all patients with massive PE in the Urokinase Pulmonary Embolism Trial (UPET I) trial was 6.7%, no different from the usual 5-8% mortality for all patients with PE (18). Thus, the combined mortality for those patients who all had massive PE (n=227) in these three studies was 13.2 %.

Importantly, in Albert's study all of the excess mortality was in the subgroup of patients with shock on presentation (8). The mortality in the group with shock was 32%; the mortality in patients without shock was no different whether they had massive (6% mortality) or submassive (5% mortality) PE. Similarly, in UPET I the mortality for patients with shock was 36% while it was 5.1% for submassive PE without shock and 5.9% for massive PE without shock (18). The combined mortality for 33 patients reported in these studies who had shock was 33% (figure 8).

Figure 8. Prognostic Significance of Shock in PE



The presence of shock at presentation is therefore clearly a better marker for poor prognosis than is the designation of "massive" based solely upon degree of vascular obstruction. Indeed, in experimental models of PE, shock is clearly the best predictor of mortality (157). As noted earlier, approximately half of all patients have massive PE; however, shock is found in only 7-9%, 80% of whom have massive PE. Therapeutic strategies would therefore be expected to either greatly limit or expand the number of patients targeted for more aggressive treatment depending upon whether discrimination is based on degree of vascular obstruction or on hemodynamic compromise.

There are a number of clinical markers which correlate very well with this subgroup of patients with overt hemodynamic alteration (table 6). Central, anginal-quality chest pain is more common in patients with hemodynamically significant PE and correlates with RV ischemia which will occur with marked RV dilation along with increased right-sided diastolic pressure elevations as discussed earlier. Unfortunately, the ECG findings are not very sensitive, nor highly specific in this regard (93). Lateral pleural chest pain and hemoptysis are more indicative of smaller, more peripheral emboli with infarction (21,28,78). Syncope is an excellent marker for hemodynamic compromise (158).

Clinical evidence of acute right heart failure (especially jugular venous distention, hepatojugular reflux, right-sided S3) in a patient without pre-existing cardiopulmonary disease also indicates overt hemodynamic compromise independent of shock (21,28,78). For the reasons discussed earlier, the presence of refractory, shunt-like hypoxemia is often used as a reliable surrogate for hemodynamically significant PE (159). Although rare, the identification of a patient with a right atrial mobile thrombus, or clot-in-transit, carries a very high mortality, approximately 50% with anticoagulation therapy alone (136,138,145).

Table 6. Hemodynamically Significant PE

Shock (systolic BP <90 mm Hg)
Syncope
Ischemic chest pain
Acute RV failure*
jugular venous distention
hepatojugular reflux
right-sided S3 gallop
Refractory hypoxemia
Right heart clot in-transit
Severe RV hypokinesis on Echo (?)

*in the absence of prior right heart failure

Thus, the presence of clinical signs of hemodynamic compromise, rather than the designation of "massive" based solely upon degree of vascular obstruction, are the best markers of poor prognosis. As will be seen, it is this group for whom most would agree the higher expected mortality justifies the use of more aggressive (and higher risk) management strategies such as thrombolytic therapy (149,159).

As noted earlier, numerous investigators have reported that many patients without clinical evidence of hemodynamic compromise will have echocardiographic changes including RV dilation, RV hypokinesis, or distortion of the interventricular septum. Goldhaber, *et al* have argued that these echocardiographic features are evidence of RV dysfunction (71,155) and that the presence of these findings in patients with PE, even without evidence of hemodynamic instability, suggests a higher potential mortality and rate of recurrence. This argument is based upon a subgroup analysis arising from a randomized trial of thromobolytic therapy using recombinant tissue plasminogen activator (r-TPA) 100 mg over 2 hr vs heparin alone in 90 hemodynamically stable patients with PE in which the principal endpoints were echocardiographic improvement and clinical recurrence (71). There were no significant differences observed in outcome between the two treatment groups as a whole. The authors went on to look at treatment outcomes when patients were subgrouped by echocardiographic criteria.

The echocardiographic findings for the same patients have been reported in two separate publications (71,155). Using *post-hoc* analysis, the investigators noted that qualitatively assessed of RV hypokinesis was observed on pre-treatment echocardiogram in 38 (42%) patients. Of the patients with RV hypokinesis on

echocardiogram, 20 were treated with heparin; there were 5 clinical episodes of recurrence (25%) and 2 deaths (10%) in the heparin group as opposed to no recurrences or deaths in 18 patients who received r-TPA. The authors concluded that the presence of echocardiographic evidence of RV hypokinesis therefore is a marker for patients with a higher risk for both recurrence and death among those with hemodynamically stable PE. They have argued that these patients do better when treated with thrombolytic therapy.

Unfortunately, there are a number of problems with accepting these conclusions at face value. The small sample size and need for *post-hoc* analysis to find apparent differences are problematic in themselves. Recurrence was based on clinical grounds only. The study found a rough correlation with its principal quantitative measure of RV alteration (i.e. RV diameter) and other measures such as RV hypokinesis and perfusion defect, but not with outcome. This is not surprising since as noted earlier, RV dilation is the expected physiologic adaptation to increased PVR and would not necessarily be a marker of RV dysfunction *per se*. Further, the only echocardiographic predictor of any value was the qualitative assessment of RV hypokinesis, which was judged to be mild to moderate in the 3 patients with non-fatal recurrence. Only severe hypokinesis predicted fatal recurrence and the incidence of this finding is not given, but by inference was small. No information is given in the study about the presence or absence of overt clinical markers of RV dysfunction independent of shock. Further, in order to identify the patients with any degree of RV hypokinesis the study suggested that echocardiography would have to be done on patients with estimated vascular occlusions over 30%. Thus, to be used as suggested, echocardiography would need to be performed on almost all patients with high probability lung scans.

Figure 9. Mortality with Thromboembolism.

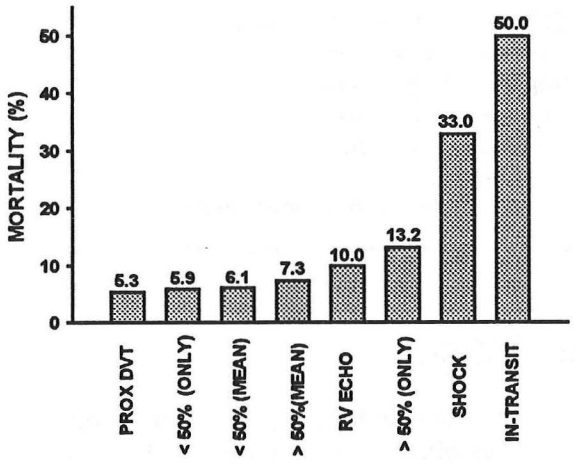


Figure 9 is a summary of mortality data presented thus far in this discussion for patients treated with conventional anticoagulation therapy. The mortality for the 20 patients from the Goldhaber study with RV hypokinesis who were treated with heparin is 10%, which is clearly in the range expected for patients with massive PE. Thus, the limited data available from this single study do not appear to demonstrate a significant, independent discriminate value for this particular qualitative echocardiographic finding.

THROMBOLYTIC THERAPY

The preceding discussion suggests that therapy with conventional anticoagulation provides effective therapy, reduction in recurrence, and improved survival, all with acceptable risk. This is particularly true for those with isolated proximal DVT and those with hemodynamically stable submassive PE. In addition, these data also demonstrate a trend towards higher recurrence and death with increasing evidence of disease severity. This is clearly evident in those patients with hemodynamically significant PE or emboli-in-transit. The trend may also include (though to lesser extent) those with massive PE as defined by extent of vascular obstruction and, perhaps, those with echocardiographic evidence suggesting alterated in RV function.

The goal of conventional anticoagulant therapy is to arrest further clot formation and to then allow natural thrombolytic mechanisms to remove clot and ameliorate physiologic abnormalities. This therapeutic stategy would likely be expected to work well as long as the patient tolerates the initial insult and does not sustain recurrence prior to clot resolution and organization. Enhancing the rate of clot resolution through thrombolytic therapy clearly has powerful theoretical advantages. Balancing this expected benefit with the intrinsic added risk of bleeding has been the difficulty facing clinicians for decades. This debate has centered on several related questions: Does thrombolytic therapy work? What is the best way to deliver thrombolics? How much greater are the risks associated with thrombolytic therapy? Are there ways to use our understanding of the pathophysiology of the disease to identify subgroups of patients in whom the benefit outweighs the additional risk?

Table 7. Potential Benefits of Thrombolytic Therapy

Enhance rate of clot resolution
Improve hemodynamics
Improve RV function
Reduce in clot burden
Reduce recurrence
Improve survival
Minimize long-term functional sequelae

Efficacy of Thromolytic Therapy

In reviewing the data on thrombolytic therapy for PE it is very important to keep in mind that the underlying pathophysiology is quite different than with other situations in which thrombolytics are employed. For instance, the clot associated with acute myocardial or cerebral infarction is causing an ischemic injury to a critical organ in which oxygen needs and supply are delicately balanced; it is crucial to restore blood flow within minutes to hours if organ dysfunction and death are to be prevented. The clot is usually fresh and thus more responsive to thrombolysis. The same situation clearly does not exist with respect to the pulmonary circulation. Thus, extrapolation of outcome or even

strategy from studies involving myocardial or cerebral infarction is not possible. Indeed, even the treatment protocols are considerably different in the setting of PE.

The use of thrombolytic therapy in PE has been in continual evolution since the late 1960's. The result is that there are currently three FDA-approved thrombolytic regimens for PE involving the use of streptokinase (SK), urokinase (UK), and recombinant tissue plasminogen activator (r-TPA). Trials in which the combination of thrombolytic therapy and anticoagulation has been compared to standard heparin therapy using prospective, randomized methods have consistently shown that thrombolytic therapy increases the rate of clot resolution. This result has been shown with urokinase (18,160), streptokinase (67,68), and r-TPA (69-71,161).

The first urokinase pulmonary embolism trial (UPET I) compared heparin therapy to a 12-hour infusion of urokinase (4,400 U/kg bolus followed by 4,400 mg/kg/hr infusion) in 160 patients with angiographically proven PE (18). Patients had follow-up angiograms and lung scans at 24 hours. There was greater improvement in angiographic score for the urokinase group; lung scans showed 8.1% improvement from baseline for heparin as compared to 22.1% improvement at 24 hours for urokinase. No patient in either group had complete resolution over the first day, and there were significantly more patients treated with urokinase than with heparin alone whose angiograms were judged to be moderately or markedly improved. Significantly more heparin-treated patients were felt to have had minimal or no perfusion improvement. All studies to date in which thrombolytic therapy has been compared to heparin have shown enhanced clot resolution.

In comparing these various trials it is clear that the relative amount of clot resolution observed with thrombolytics is in part determined by the degree of baseline vascular occlusion; i.e. there is generally a greater difference in rate of clot resolution with thrombolytic therapy in patients/studies with the greatest degree of initial vascular obstruction. Figure 10 represents the combined data from studies which have evaluated the rate of thrombolysis when the average initial vascular obstruction was >50% (i.e. massive PE). This analysis incorporates data from 112 heparin treated patients and 160 patients treated with streptokinase, urokinase, or r-TPA for whom angiographic or lung scan data were available at 2, 24, or 72 hours after initiation of therapy. Only studies using thrombolytic protocols which would be considered acceptable by current recommendations were included (13,67-70,162,163). As the figure demonstrates, there is consistently greater improvement at each time point with thrombolytic treatment. It is important to note that there is usually little improvement (in fact, often some deterioration) in heparin-treated patients at 2 hours, whereas there is significant improvement as early as 2 hours with thrombolytics. Although the degree of improvement at 2 hours seems modest (15%), these data coupled with hemodynamic data (see below) suggest that even this degree of improvement can be physiologically important.

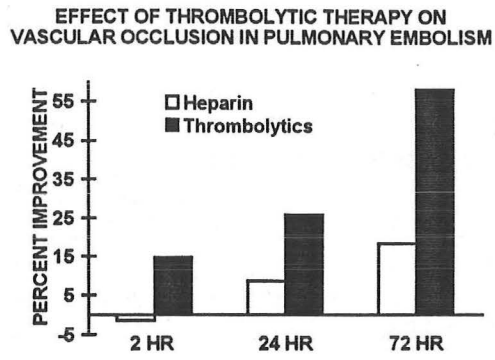


Figure 10. See text for references

Thrombolytic therapy has likewise consistently been associated with more rapid improvement in hemodynamic abnormalities than is standard heparin therapy (67,69,70,162). An similar analysis of the effect of thrombolytic therapy on improvement in mean pulmonary artery pressure was done involving 37 heparin-treated patients and 117 treated with streptokinase, urokinase, or r-TPA for whom hemodynamic measurements were obtained. The results of that analysis are shown in figure 11. Patients treated with heparin had little improvement in PA pressure within the first 24 hours, in fact, there was often slight deterioration. Patients who received thrombolytic therapy had significant improvement which was evident as early as 2 hours after initiating therapy.

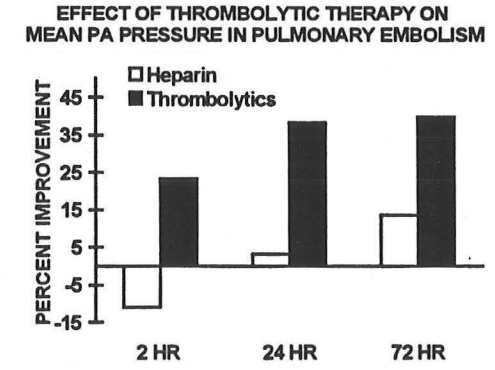


Figure 11. See text for references

In the Plasminogen Activator Italian Multicenter Study (PAIMS 2), r-TPA (100 mg total over 2 hours) was compared to heparin alone in patients with acute PE (70). There was greater angiographic improvement in the thrombolytic group. Hemodynamic monitoring also showed that mean PA pressure increased (11%) in the heparin treated patients while there was a significant (29%) reduction in pulmonary artery pressure at two hours in the r-TPA group (figure 12).

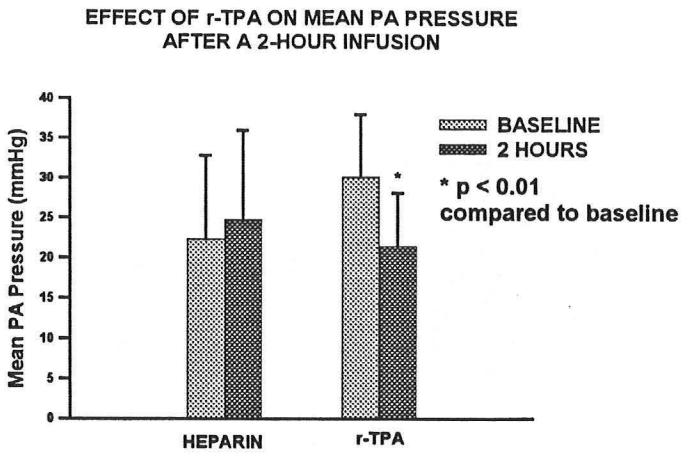


Figure 12. From reference (70)

Several studies have not only shown that thrombolytic therapy enhances the rate of improvement in hemodynamics, but that the effects may occur within 1-2 hours of initiating therapy. The time course for improvement in total pulmonary resistance (TPR) after a 2-hour infusion of r-TPA (100 mg) is shown in figure 13 (163).

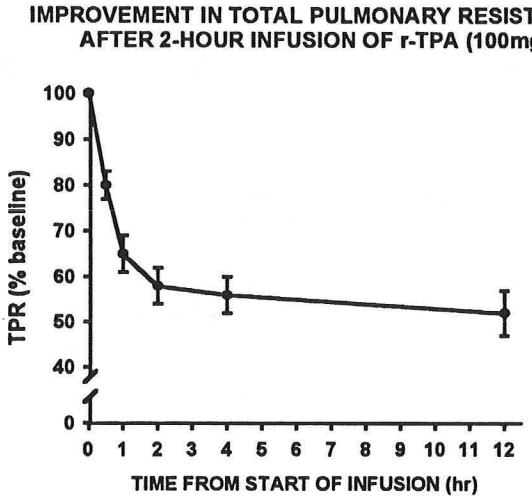


Figure 13. From reference (163)

A number of reports have shown that thrombolytic therapy is associated with early reversal of echocardiographic indicators of RV functional alteration (71,96,156,164,165). Goldhaber, *et al* studied serial echocardiographic indices of RV function in 89 patients who had been randomly assigned to receive heparin alone or r-TPA 100 mg over 2 hours (71). They reported that qualitative assessment of RV wall motion was improved in 39% of r-TPA patients as compared to 17% of heparin patients; the echocardiographic findings were unchanged at 24 hours however in 59% of r-TPA and 66% of heparin patients. There was said to be worsening of RV motion in 17% of heparin and only 2% of r-TPA patients (figure 14). However, only about half of the patients in this study had any qualitative evidence of abnormal RV function at the time of enrollment.

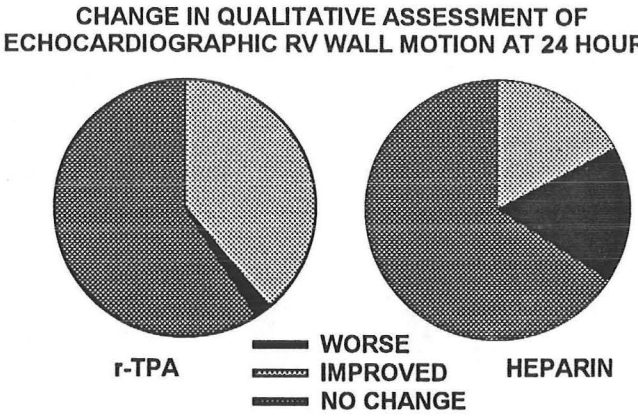


Figure 14. From reference (71)

The authors also used a semi-quantitative assessment of RV dilation, the right ventricular end-diastolic area from an apical four-chamber 2-D echocardiogram view. These data are shown below in figure 15. The authors reported that the rate of change in RV area (as determined by a repeated measures ANOVA technique) showed significant improvement for the r-TPA group; there was said to be no change from baseline in the heparin group. Unfortunately, the degree of RV enlargement in both groups was very modest at entry and the degree of improvement in the r-TPA group only succeeded in bringing the RV area to about the level at which the heparin group began.

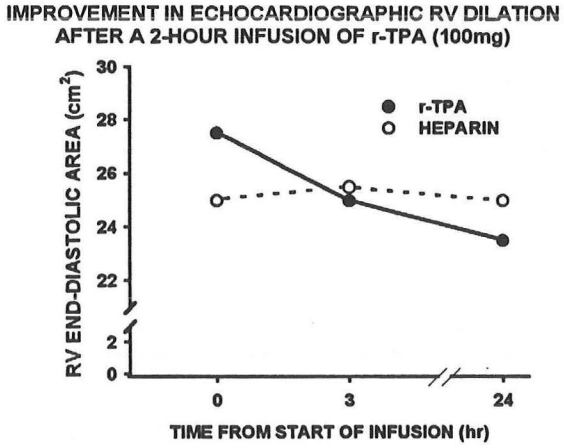


Figure 15. From reference (71)

As discussed earlier, echocardiography occasionally demonstrates the presence of mobile clots in the right atrium or pulmonary outflow tract (figure 5). These emboli-in-transit are associated with a very high mortality (up to 50%), even with anticoagulation. Though no large series of these patients exists, there are numerous reports in the literature in which rapid echocardiographic resolution of these emboli-in-transit has followed thrombolytic therapy (132,135,141,143,145,146,148).

Thus, the data available demonstrate that thrombolytic therapy clearly increases the rate of clot resolution, improves hemodynamic measures, and may be associated with improvement in RV function as assessed echocardiographically. However, as noted above, the magnitude of these changes may be quite modest, though the effects seem to be greatest in those with the greatest physiologic abnormalities prior to therapy.

Thrombolytic Stategy

Early experimental work in dogs by Cade demonstrated that the administration of an infusion of streptokinase (SK) resulted in significantly more thrombolysis than did heparin alone (166). Based on these early results, SK was given to patients with massive PE with enhanced thrombolysis, as noted earlier (13,67,68). These early trials relied on very long 72-hour infusion durations. The second urokinase trial (UPET II) demonstrated that SK given as a 250,000 U loading dose followed by 100,000 U/hr for 24 hours also achieved acceptable thrombolysis (20). This shorter SK infusion gained FDA approval in 1977 and is the current SK regimen used in North America.

The initial urokinase trial, UPET I, demonstrated that UK achieved more rapid clot lysis than did heparin alone, as was discussed earlier (18). The UPET II trial was primarily designed to compare several UK dosing regimens with the "short" 24-hour SK regimen. This trial showed that UK given as a loading dose of 4,400 U/kg followed by an infusion of 4,400 U/kg/hr gave similar results whether given for 12 or 24 hours (20). In addition, both of these were comparable to the 24-hour SK regimen. This led to FDA approval for this regimen in 1978 (the FDA recommendation actually allows for the infusion to be given for 12 to 24 hours, depending upon clinical response). While these regimens were thought to have similar efficacy with respect to thrombolysis, their lack of proven significant impact on overall outcome along with the attendant bleeding complications and complexity of administration and monitoring has severely limited their use (see below). Other UK dosing regimens have been used in Europe with varying results, but have not gained widespread acceptance in North America (160,167).

A Belgian study by Verstraete, *et al* compared r-TPA given either through a central pulmonary artery catheter or peripherally (168). They showed that similar doses of r-TPA achieved equivalent degrees of thrombolysis, but that there were more bleeding complications with the use of central catheters. Further, there is systemic evidence of fibrinolysis whether the drug is given peripherally or centrally. Other studies have also failed to show any advantage to delivering thrombolytics centrally as opposed to peripherally (167,169). Thus, current recommendations are to deliver thrombolytic therapy via a peripheral vein, even when a central catheter has been placed for other reasons.

When recombinant tissue plasminogen activator (r-TPA) was developed it was reported that it produced a superior thrombolytic response compared to heparin in animals (170). Cases were reported of its successful use in humans (171,172) and an open-label trial was performed which demonstrated its feasibility as a treatment for PE (173). As noted earlier, r-TPA has been consistently shown to enhance thrombolysis compared with heparin (69-71,161).

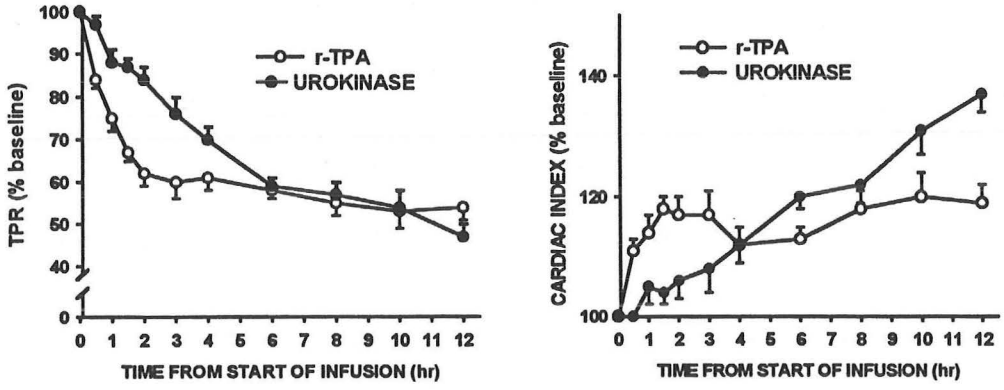
Experimental work rapidly led to the concept that therapeutic effect could be achieved with relatively high doses given over a shorter interval with r-TPA. It had been observed that significant thrombolysis persisted long after the drug had been cleared from plasma (174-176), an effect which was attributed to enhanced binding directly to clot (174). It was also noted that r-TPA given over fairly short intervals achieved better thrombolysis than the same dose given over longer duration, and actually induced less bleeding in animal studies (175-177).

Other experimental studies demonstrated that very high doses of r-TPA not only failed to achieve greater thrombolysis compared to conventional dosin, but in some situations actually led to less effect (178). Verstraete's Belgian study in patients wit PE demonstrated that a low dose of r-TPA (50 mg) was not as effective as the higher, and now accepted, dose of 100 mg given over 2 hours (168).

Some animal studies suggested that the enhanced binding of r-TPA conferred a degree of "clot specificity" that was associated with less evidence of bleeding (179). Unfortunately, it has subsequently been established that the prolonged thrombolytic effect is due, at least in part, to the generation and persistence of circulating, systemic fibrin degradation products (180,181). Thus, the drug is not as clot-specific as was initially anticipated. This has been borne out by human studies which have not demonstrated significant reduction in bleeding complications with r-TPA (see below).

These studies along with a number of early clinical trials (71,163,182,183) culminated in the fixed-dose regimen for r-TPA which gained FDA approval in 1990: r-TPA 100 mg given as a peripheral IV infusion over 2 hours without loading dose or bolus. Other regimens have been used in Europe (163,184), but have not gained widespread acceptance in North America.

Figure 16. Time Course of Early Hemodynamic Improvement with Urokinase and r-TPA
from reference (185)



When compared to UK, r-TPA has similar efficacy and morbidity (182,185). Meyer, *et al* have examined the short-term thrombolytic effect of UK and r-TPA (185). Both demonstrated relatively rapid improvement in pulmonary resistance; there was a trend in favor of a more rapid restoration of hemodynamics for r-TPA (figure 16). There have

been no recent trials using SK and there are no data available on the early (< 2 days) rate of thrombolytic or hemodynamic response to SK. Comparative trials between SK and r-TPA have not been conducted for pulmonary thromboembolism.

There are now trials demonstrating that a single "bolus" infusion of r-TPA (0.6 mg/kg given peripherally over 10 minutes) achieves significantly greater thrombolysis than heparin (161) and has equivalent efficacy when compared to standard (100 mg over 2 hours) r-TPA (183).

Complications of Thrombolytic Therapy

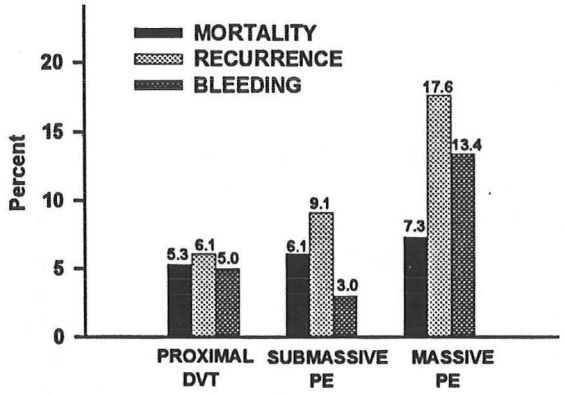
As was done earlier for mortality and recurrence (tables 4 and 5), the risk of bleeding complications with conventional anticoagulation therapy was assessed (table 8). Studies were categorized into three groups: (a) "DVT" studies including only patients with proximal DVT, (b) "submassive" studies in which the mean vascular occlusion was <50%, and (c) "massive" studies in which the mean vascular occlusion was >50%. Major bleeding complications were included in this analysis if they required transfusion, necessitated operative intervention, or resulted in death. The rates of major bleeding complications with heparin anticoagulation are 5.0% for DVT, 3.0% for submassive PE, and 13.4% for massive PE.

Table 8. Bleeding Complications for Patients Treated with Heparin

	Any Bleeding (%)		Major Bleeding (%)	
Proximal DVT				
Salzman (27)	18/69		1/69	
Hull '86 (24)	4/58		2/58	
Hull '90 (54)	18/219		11/219	
Hull '92 (25)	21/199		13/199	
	61/545	11.2 %	27/545	5.0 %
Submassive PE				
Goldhaber (71)	---		1/55	
Arnesen (68)	4/11		1/11	
	4/11	36.4 %	2/66	3.0 %
Massive PE				
Tibbutt (67)	12/17		1/17	
Miller (13)	4/8		2/8	
UPET I (18)	21/78		11/78	
PAIMS 2 (70)	6/16		2/16	
	43/119	36.1 %	16/119	13.4
All PE	47/130	36.1 %	18/185	9.7 %

Thus, as there was for recurrence and mortality, there is a trend toward worse outcome with increasing degrees of pulmonary vascular obstruction (figure 17). For all patients with PE (massive or submassive), the risk of major bleeding is 9.7%. The risk of intracranial hemorrhage in 730 patients treated with heparin therapy in these studies is 0.4%.

Figure 17. Summary of Outcomes in Subgroups of Patients with Thromboembolism



Excessive bleeding complications have plagued the use of thrombolytic therapy. Although the UPET trial convincingly showed that urokinase enhanced clot resolution, there was twice as much major bleeding in the UK group as compared to heparin treated patients (27% vs 14%). This excess bleeding occurs even though patients with excess bleeding risks are consistently excluded. A list of contraindications to thrombolytic therapy is shown in table 9.

Table 9. Contraindications to Thrombolytic Therapy

Absolute

- Active or recent internal bleeding
- Prior hemorrhagic stroke
- CNS neoplasm
- Recent CNS surgery/trauma
- Suspected aortic dissection

Relative

- Major surgery or trauma within 10 days
- Uncontrolled, severe hypertension
- Recent CPR
- Severe bleeding diathesis
- Non-hemorrhagic stroke
- Biopsy/invasive procedure at site inaccessible to external compression
- Hemorrhagic ophthalmologic lesion
- Allergy to SK, UK
- Pregnancy
- Active peptic ulcer disease

There does not appear to be an independent effect of age on the risk of bleeding complications in patients with PE (186). While these conditions should be considered strong contraindications to thrombolytic therapy, there are case reports of the successful use of thrombolytics in "life-threatening" situations during pregnancy (165,187), immediately after major surgery (188,189), following GI hemorrhage associated with a Dieulafoy's lesion (190), in the context of acute spinal injury (191), and 7-34 days following neurosurgery (192). (These reports are included here for reference and should not be taken as indicating the safety of thrombolytics in these situations.) It is important to note that angiography or PA catheterization per se are not contraindications to the use of thrombolytics, though they do confer a higher risk of local bleeding. Significant contraindications to thrombolytic therapy are common; one survey suggested that almost 50% of patients with proven PE have one or more of these contraindications (170).

The combined outcomes of 844 patients in 15 studies employing thrombolytic therapy for PE (13,18,20,67,68,70,71,161-163,167,182-185) were analyzed with respect to recurrence of PE, mortality, major bleeding, and intracranial hemorrhage. Studies using SK, UK, or r-TPA were included. The results of this analysis are shown in table 10 along with similar data from the previous 185 patients with either massive or submassive PE treated with conventional heparin therapy. Overall, the risk of major bleeding with thrombolytic therapy is about 14%, as compared to 10% for heparin alone. When comparing individual thrombolytic agents (SK, UK, r-TPA) there does not appear to be any significant difference in major bleeding rates among them.

Table 10. Comparison of Patients with PE Treated with Heparin Alone or with Thrombolytic Therapy

	Heparin Alone (n=185)	Thrombolytics (n=844)
Recurrence (%)	**14.6**	**5.8**
Mortality (%)	**7.3**	**5.3**
Major Bleeding (%)	**9.7**	**13.7**
Intracranial Hemorrhage (%)	**0.4**	**1.2**

References: (13,18,20,67,68,70,71,161-163,167,182-185)

Many of these hemorrhagic complications have been associated with bleeding at sites of catheterization (angiography, PA catheterization), especially in patients receiving thrombolytics. It has been suggested that when vascular manipulations can be avoided, the rate of major bleeding with thrombolytics is reduced (42,193). The PIOPED investigators reported that major bleeding occurred in 14% of all patients receiving thrombolytic therapy, while only 4% had similar bleeding if angiography was not done. Levine has estimated that the risk of bleeding is 20% with angiography and

thrombolytics. More recent trials in which proportionately greater numbers of patients were diagnosed non-invasively have major bleeding risks of 5-10% (194).

It has been argued that using noninvasive strategies should reduce the risk of major bleeding with thrombolytics to an acceptable level and allow for their more widespread use. However, a similar argument can be made for the use of heparin alone. Strategies for minimizing bleeding risk when angiography is necessary have been described (195) and recent experience has shown that angiographic confirmation of PE is not mandatory for the institution of thrombolytic therapy if a patient has a high clinical likelihood of PE , a high-probability lung scan, and low bleeding risk (3,42). Use of such "noninvasive" diagnostic strategies is obviously ideal when appropriate, whether one is contemplating using thrombolytics or heparin alone, and would be expected to minimize bleeding risks. However, it should be recalled that up to two thirds of patients with PE may require pulmonary angiography to establish the diagnosis (see above).

As has been seen in other applications of thrombolytics (196,197), one of the most serious complications is intracranial hemorrhage. In the above analysis, intracranial bleeding occurred in 1.2% of 844 patients receiving thrombolytics as compared to 0.4% for 1410 patients treated with heparin. Goldhaber has reported that the combined experience of his group in Boston has found an incidence of 1.6% for all ICH, 0.5% for fatal ICH. As might be expected, there is no relationship between degree of vascular occlusion and ICH. As has been observed in the cardiology literature, the higher incidence of ICH persists even when "non-invasive" strategies are employed (193,196,197). Overall, it has been estimated that the risk of fatal hemorrhage is 1-2% with thrombolytic therapy (194). No convincing data exists regarding the relative risk of ICH when comparing various thrombolytic agents in the treatment of PE.

A number of trials have reported treatment complications and outcome in patients randomly assigned to conventional heparin therapy vs streptokinase (13,67,68), urokinase (18,160), or r-TPA (69,71,161). None of these trials demonstrated statistically significant differences in recurrence or mortality among treatment groups. The analysis of combined trials using heparin or thrombolytics described above yielded an overall rate of recurrence of 14.6% with heparin alone and 5.8% with thrombolytics. Some have argued that this represents a significant reduction in recurrence and thus a reason to use thrombolytics. Few of the comparative trials have included sufficient numbers of subjects to conclusively show a difference in recurrence. Goldhaber, *et al* studied 101 patients randomly assigned to receive heparin alone or r-TPA 100 mg over 2 hours (71). They found no recurrences in those receiving r-TPA; there were 5 recurrences (2 fatal) in the heparin-alone group ($p=0.06$). At the same time, there were 3 major bleeding episodes (including 1 with ICH) with r-TPA and only 1 bleeding episode with heparin.

Another interesting observation is that the overall rate of recurrence associated with thrombolytics noted above (5.8%) comes from studies which include substantial numbers of patients with non-massive, non-hemodynamically significant PE. In fact, in two of the larger trials in which r-TPA was compared to heparin the degree of vascular obstruction was very modest. In Levine's study the mean vascular occlusion was 21.3 ± 3.7 for the heparin group and 27.4 ± 3.6 for r-TPA (161); Goldhaber's patients had mean scores of 36.0 ± 20.8 for heparin and 42.9 ± 20.7 for r-TPA (71). Thus, the

majority of patients treated in these trials have submassive PE, which as we have seen, usually has a lower incidence of recurrence. When compared to studies with comparable degrees of vascular obstruction (see table 5), the apparent difference in recurrence rates is more modest (9.1% for heparin vs 5.8% for thrombolytics).

Patient Selection

The analysis of combined trials described above (table 10) shows that the overall mortality in patients treated with thrombolytic therapy is 5.3% as compared to 7.3% for heparin-alone treatment. No individual study to date has shown a significant difference in mortality in favor of thrombolytics. The original urokinase trial (UPET) did suggest that there was a trend towards improved survival in patients with shock; the difference was not statistically significant as would be expected for the small number of patients in those subgroups. Although there is an expected mortality of 33% in patients with shock, these patients comprise less than 10% of patients with proven PE and almost 50% would have contraindications to thrombolytic therapy; thus, it would require a study population of thousands of patients with proven PE, randomly and prospectively analyzed to definitively address the issue of a beneficial effect of thrombolytic therapy on mortality in the subgroup of patients with shock or its physiologic surrogates. Such a study is highly unlikely to be done.

Nonetheless, the physiologic abnormalities present in patients with hemodynamically significant PE clearly identify a high-risk group. It has been shown in animal models that persistence of these abnormalities is associated with death and that their rapid reversal improves outcome. Thrombolytic therapy clearly does cause accelerated thrombolysis which is associated with restoration of hemodynamic function, and this improvement has be shown to occur within hours of therapy (especially with r-TPA or UK). Therefore, there is clearly a strong physiologic rationale for the use of thrombolytic therapy in the subgroup of patients with hemodynamic compromise. The consensus in the literature is thus that thrombolytic therapy should be given to patients with proven PE (either angiographically or with a high-probability scan coupled with strong clinical suspicion) who have hemodynamically significant PE and who do not have a contraindication to its use (2,3,149,159,198). A hemodynamically significant PE is one which is associated with one or more of the conditions listed in table 6.

Accordingly, the current literature does not support the use of thrombolytic therapy in any patient with submassive, non-hemodynamically significant PE. There is clearly a subgroup of patients with massive PE, as defined by degree of vascular occlusion, who are at somewhat higher risk but do not meet the criteria for hemodynamically significant disease. This group is particularly difficult to define operationally. For the reasons detailed above, the presence of >50% obstruction of the pulmonary vasculature in and of itself is not a sufficiently strong indication to justify the added risks of thrombolytic therapy.

Other markers for enhanced risk may be available, such as certain echocardiographic findings or the presence of demonstrable residual thrombus in the lower extremities. Unfortunately the data available at present are not sufficiently compelling to use the

broad and largely qualitative definitions of RV functional abnormality described by Goldhaber, *et al* as indications for thrombolytic therapy. As noted earlier, it is possible that certain more restrictive echocardiographic criteria, for example the presence of severe RV hypokinesis coupled with demonstrable TR, significant pulmonary hypertension and the absence of other abnormalities suggestive of chronic disease might have discriminate capability. It seems unlikely that use of any degree of RV ventricular motion abnormality (especially mild or moderate changes) and/or RV dilation will serve this purpose.

Some clinicians consider the combination of massive PE (>50% vascular occlusion) and a positive non-invasive study showing persistent lower extremity thrombus to be indicative of a high risk group with significant "clot burden". Under very rare circumstances, thrombolytic administration may be defensible for the patient who is very unstable (i.e., pressor dependent) and thus too high risk to leave the ICU for whom there is compelling echocardiographic suggestion of massive PE (i.e., absence of other explanation for the hemodynamic profile; significant TR and systolic PA hypertension in the absence of RVH; RV dilation and hypokinesis; and septal deviation) especially if there is evidence of diastolic pressure elevation (such as failure of vena cava to collapse during negative-pressure inspiration). While there may be intuitive logic to these strategies, they have not been systematically tested. Anecdotal reports of thrombolytic therapy being used in the setting of CPR do not justify their use for this indication (199,200), nor would they be expected to be of benefit given the time-course of their action (hours, not minutes).

Current Thrombolytic Regimens

When the physician determines that thrombolytic therapy is indicated, there are several treatment regimens available. The four commonest regimens used in North America are outlined in table 11; three of these are FDA approved. All current regimens appear to have similar efficacy with respect to total thrombolytic effect; all appear comparable with respect to bleeding complications. Streptokinase is relatively inexpensive (direct drug cost). In addition to bleeding complications, allergic reactions can occur. Although they are generally not severe, one concern is that such reactions might limit efficacy. Most importantly, in the setting of hemodynamically significant PE, no data exists on the early (first few hours) rate of improvement for vascular occlusion and hemodynamics with SK. Streptokinase also requires a long infusion time (24 hours). Urokinase is considerably more expensive, has some potential for allergic reactions, and requires prolonged infusion (12-24 hours). Unlike SK, there is clear evidence of significant clot lysis and hemodynamic improvement in the first one to two hours with UK. Both SK and UK require loading doses; SK is a fixed dose regimen, while UK is weight-based.

Table 11. Current Thrombolytic Regimens for Hemodynamically Significant PE

Regimen	Dosing/Administration	FDA Approved
Streptokinase	250,000 U loading dose over 30 min, then 100,000 U/hr for 24 hr	Yes
Urokinase	4,400 U/kg loading dose over 10 min, then 4,400 U/kg/hr for 12-24 hr	Yes
r-TPA infusion	100 mg infused over 2 hours	Yes
r-TPA bolus	0.6 mg/kg infused over 2-10 minutes	No

Recombinant TPA is also expensive, but usually comparable to UK in regimens for PE. It has virtually no immunogenic potential, thus allergic reactions should not occur to the drug itself. One advantage of r-TPA is its very short infusion time (2 hours) and simple protocol (100 mg fixed dose given as a continuous infusion over 2 hours without loading dose). This clearly simplifies its administration; however, it must be recalled that the lytic effect persists for many hours after the infusion is stopped. When immediate effect is desirable, especially in the setting of hemodynamically significant PE, r-TPA has proven early response for both thrombolysis and hemodynamic improvement. As noted earlier, r-TPA may provide somewhat more rapid early effect than UK. The bolus r-TPA regimen has the advantage of being very easy to administer (a single dose over 2-10 minutes) and probably is as effective as 2-hour r-TPA. The total dose (0.6 mg/kg) is usually less than with the 2-hour regimen (100 mg); as such, the total drug cost may be significantly less with the bolus regimen. The bolus regimen, while often recommended, is not formally FDA approved.

Heparin is stopped prior to giving thrombolytics. In general, vena caval filters should not be placed prior to thrombolytic therapy (see below). The drugs are given via a peripheral IV line, even when a central line is present. Early recommendations for thrombolytic therapy required angiographic confirmation of PE and frequent monitoring of complex hemostasis parameters; this is no longer the case. As indicated above, thrombolytic therapy may be given on the basis of a high probability lung scan with strong clinical suspicion, when there is echocardiographic evidence of clot in-transit, or in the rare unstable patient with compelling echocardiographic changes (see above). Indeed, minimization of invasive procedures is a desirable goal, when possible. Nonetheless, angiography or central line placement is not a contraindication to thrombolytic therapy, especially when the indication is hemodynamically significant PE. If the patient undergoes angiography, it is desirable to perform the procedure through a Cordis sheath which can be left in place to allow for blood draws. The sheath is then removed the day following therapy (201). It is not necessary to monitor coagulation studies during therapy. The APTT is checked immediately after cessation of the thrombolytic infusion. Heparin is resumed (**without** loading dose) if the APTT is less than twice the upper limit of normal; if not, the APTT is checked every 4 hours this value is achieved (201).

VENA CAVAL FILTERS AND TRANSVENOUS CLOT MANAGEMENT

The major cause of death in patients with PE who do not succumb to the initial event is embolic recurrence, usually from the deep venous system of the lower extremities. As noted earlier, the primary goal of anticoagulation is to minimize this risk. However, a significant number of patients cannot receive anticoagulant therapy or suffer a major bleeding complication during therapy. For these patients, a mechanical filter is usually placed in the inferior vena cava, ideally below the level of the renal veins.

The best studied of these is the standard stainless steel Greenfield filter (24F with 26F to 28F insertion catheter, which requires surgical placement) and its more recent percutaneous analogues (the smaller 12F carrier system stainless steel filter and the 12F titanium filter using a 14F sheath). Clinical recurrence rates with the Greenfield filters are said to be 2-4% and long-term patency rates 95-98% (30,202,203). While the filters appear to be fairly effective at preventing recurrence, they are, of course, not protective against recurrence from upper extremity sources or from clot in-transit. Complications are said to be infrequent, but certainly do occur. Misplacement (into renal veins, iliac veins, or the heart) occurs in 5-7% (30,202,203). Migration of the device is common, occurring in up to 53%; however, this movement is usually only a short distance and usually is of no clinical significance (30). The device has anchoring hooks to minimize movement. These can be shown to penetrate the caval wall in 14-24% (30). This is usually only apparent radiographically; Greenfield reports that the incidence of hemorrhagic complications from penetration is rare, occurring in only 0.9%. The use of filters can also be associated with catheter-site venous thrombosis (in up to 43%) and later symptomatic DVT or post-phlebitic syndrome. Clot may develop on the device or within the cava (either proximal or distal). This causes radiographic occlusion of the cava in about 4-5% of cases. Because of these thrombotic complications, it is recommended that anticoagulation be continued (unless contraindicated) for a duration predicated on the patients original indication. Other complications include air embolism and insertion-site wound infection. Fatal complications are said to have occurred with 0.16% of insertions (30).

The usual indications for caval filter placement would be as an alternative in patients with contraindications to anticoagulant therapy, failure of anticoagulant therapy (documented recurrence during "therapeutic" anticoagulation), or severe complications of anticoagulant therapy (table 12). However, some clinicians have advocated the use of filters as adjunctive therapy in high-risk patients. Defining these patients, however, has been problematic. Patients for whom this strategy may be appropriate based on our understanding of the pathophysiology of PE certainly include those with hemodynamically significant PE who cannot receive thrombolytic therapy. In addition, filter placement may be considered for those who do not meet the criteria for thrombolytic therapy but who nonetheless appear to be in a higher risk group (e.g. patients with massive, but not hemodynamically significant PE, and either significant echocardiographic RV dysfunction or residual lower extremity thrombus). For the reasons cited earlier, these patients do appear to have a significantly higher risk of both death and early recurrence. While the current evidence does not appear to justify the added risks of thrombolytic therapy in these patients, the relative safety of caval filter placement makes it a reasonable alternative as an adjunct to anticoagulation in these subgroups of patients with massive PE.

Table 12. Indications for IVC Filter Placement

Alternative Therapy
Contraindication to anticoagulation therapy
Major complication of anticoagulation therapy
Adjunctive Therapy
Failure of anticoagulation therapy
Hemodynamically significant PE with contraindication to thrombolytic therapy
Non-hemodynamically significant massive PE with RV dysfunction on Echo (?)
Non-hemodynamically significant massive PE with persistent lower extremity thrombus (?)

There are a number of devices available other than the Greenfield filters, although they are less well characterized. Each has its potential advantages and drawbacks. The stainless steel Greenfield is large enough to be used in patients with a large diameter vena cava and is the only device for which there is considerable experience when circumstances require suprarenal placement (e.g. extensive clot in the distal vena cava). The Bird's nest filter is relatively easy to insert and appears to have a comparable efficacy and complication rate. It requires some experience to prevent premature extrusion of the device at the time of deployment, which can result in suprarenal prolapse (202). The Simon-Nitinol filter can be relatively small because its nickel-titanium composition allows it to be carried in a small sheath while maintaining its tensile characteristics. However, it has a somewhat higher rate of caval occlusion. There are newer filters (the Gunther and the Prothia) which are designed to be anchored without struts protruding into the caval wall and to be retrievable. Thus, they could be used as temporary adjuncts in patients receiving thrombolytics (202). The exact clinical advantage of this in practice is not entirely clear, however; their reported experience to date has been limited.

There are a number of devices which have been described that would allow for the transvenous catheter removal of clot from the pulmonary arterial circulation (204-207). While these methods have been shown to successfully remove clot and restore hemodynamics, the hemodynamic effects are often transient (especially in animal studies) and recurrence is common (205). Indeed, Greenfield developed his filter primarily as an adjunct to transvenous vacuum-cup catheter clot removal (206) for patients who would otherwise have been treated with surgical embolectomy in the pre-thrombolytic era. Further, the technique is not commonly used and therefore not readily available. There have been several reports of using standard cardiac catheterization methods to mechanically fragment clot in the central pulmonary arteries and thus improve hemodynamics through distal migration of the clot fragments (207-210). This might be an alternative in the patient with hemodynamically significant PE who fails or cannot receive thrombolytic therapy and for whom surgical embolectomy is not

possible. There are also anecdotal reports of the use of percutaneously placed self-expanding Wallstent endovascular stents inserted in the pulmonary artery at the site of embolic occlusion (211) or of attempted instillation of thrombolytic agents directly into the emboli (212,213).

SURGICAL EMBOLECTOMY

Emergent surgical removal of massive PE is generally considered to carry a very high surgical mortality. In the pre-thrombolytic era, the overall mortality was thought to be high, but better than with heparin alone in those presenting with shock. Since the advent of thrombolytic therapy, however, there has been debate about whether the use of surgical embolectomy is beneficial or even harmful (18). The mortality is based on uncontrolled surgical series and varies widely in the reported literature, from as low as 16% to over 80%, with most being in the range of 25-35% (214-222). Mortality is clearly influenced by whether the patients were actually in shock at the time of surgery (219), whether the surgery was done during or following CPR (214), or whether surgery could be done with or without cardiopulmonary bypass (216,221). Results could well be expected to depend upon local experience and immediate availability of surgery, as well as patient selection. Given these uncertainties, it would seem that medical thrombolytic therapy would be preferable in those patients with hemodynamically significant PE as defined earlier. Emergent surgical embolectomy should be used only in those centers where it is readily available and only for patients who are reasonable operative risks and who have failed thrombolytic therapy or are not candidates for medical thrombolysis.

Emergent surgical embolectomy should not be confused with the procedure which is referred to as pulmonary thromboendarterectomy by the San Diego group who have the largest reported experience (73,74). This procedure involves the surgical removal of residual, large thromboemboli which are found to persist in a small number of patients who have experienced prior massive PE. These patients have clinical findings of severe chronic pulmonary hypertension and have major vessel emboli on lung scan and angiography. Unlike the majority of patients, even with massive PE, these clots fail to lyse over time, even with appropriate and prolonged anticoagulant therapy. In patients with this disorder (referred to as chronic major-vessel thromboembolic pulmonary hypertension) who are otherwise in good condition to undergo elective surgery with cardiopulmonary bypass, pulmonary thromboendarterectomy has a mortality of 13% in the experience of the San Diego group. Nonetheless, the results can be striking. Their results in 250 patients reported in the literature show a reduction in systolic PA pressures from 74.8 ± 19.8 to 44.8 ± 14.0 mm Hg with the surgery (73,74)

CONCLUSIONS

- Conventional anticoagulation therapy is very effective for patients with proximal DVT and for the majority of patients with non-hemodynamically significant PE.

- Clinical markers of hemodynamically significant PE include hypotension, syncope, signs of acute right ventricular failure, refractory hypoxemia, and echocardiographically visualized clot-in-transit.

- Hemodynamic management of patients with hemodynamically significant PE should include the judicious use of fluids and the rapid restoration of systemic blood pressure, which is best accomplished with norepinephrine.

- Thrombolytic therapy should be administered to patients with hemodynamically significant PE who do not have contraindications.

- The determination of "massive" PE based solely on degree of vascular obstruction does not independently identify patients with sufficiently worse predicted outcome to warrant institution of thrombolytic therapy.

- Echocardiographic criteria relying upon indices of RV dilation and/or hypokinesis have not yet been demonstrated to independently identify patients with PE with sufficiently worse predicted outcome to warrant thrombolytic therapy.

- The combination of massive PE with either persistent thrombus in the lower extremities or severe RV hypokinesis on echocardiogram may identify a group of patients with PE with somewhat worse prognosis. The magnitude of enhanced risk in these subgroups does not warrant the considerable additional risk of thrombolytic therapy, but should lead to consideration of adjunctive IVC filter placement.

- "Noninvasive" strategies are intuitively desirable regardless of whether heparin is used alone or in combination with other therapy. The use of noninvasive methods, while desirable, frequently does not provide a definitive diagnosis. Invasive diagnostic studies such as pulmonary angiography should always be used when the diagnosis remains uncertain.

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