Management of Thromboembolism*
Anticoagulants, Thrombolysis, or Surgical Intervention?
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It is estimated that acute pulmonary embolism is the sole cause of death in 100,000 patients and a major contributing factor in another 100,000 patients annually, making it the third leading cause of death in the United States. Since the study of Barritt and Jordan in 1960 demonstrated that therapy significantly improves survival in this disorder, it is generally acknowledged that all patients with documented thromboembolic disease should be treated. However, the optimal form of therapy for an individual patient is still controversial.

The major pathophysiologic consequence of thromboembolism is obstruction of the pulmonary vascular bed by emboli, which produces pulmonary hypertension. The degree of pulmonary hypertension is proportional to the amount of pulmonary vascular obstruction. Small emboli that obstruct a single lobar segment may produce pleuritic pain and mild ventilation-perfusion abnormalities, but rarely cause pulmonary hypertension in a previously healthy individual. An embolus large enough to occlude a lobar artery (or several small emboli which occlude an equivalent number of segmental arteries) will produce a modest rise in pulmonary artery pressure that is well tolerated by the patient free of prior cardiopulmonary disease. The same modest embolus can, however, evoke severe pulmonary hypertension in a patient with preexisting heart or lung disease. Massive emboli, which occlude more than 70 percent of the pulmonary vascular bed, will almost inevitably create a critical obstruction to right ventricular outflow with diminished left ventricular filling. This causes systemic hypotension, which decreases myocardial perfusion and further compromises right ventricular performance, leading to death within minutes or hours of the acute event. If the patient survives this critical period, his prognosis is good unless he suffers a subsequent embolic event. While the first embolus is fatal in only a minority (10 percent) of patients, the mortality of untreated pulmonary embolism has been shown to be about 30 percent. In almost all instances, these late deaths are due to recurrent emboli which could have been prevented with treatment.

Choice of Therapy in the Acute Situation
The vast majority of patients with a documented pulmonary embolism will respond to treatment with either heparin or thrombolytic therapy. Before administering either of these agents, it is important to ascertain whether any of the contraindications listed in Table 1 is present. While active bleeding is a contraindication to any form of anticoagulation, in the majority of patients, the risk of developing a bleeding complication must be weighed against the morbidity and mortality of surgical intervention to prevent recurrent emboli. Lytic therapy carries a substantial risk to the patient who has had recent surgery or trauma since, once plasmin is activated, it will lyse the normal hemostatic clot in the wound as well as the intravascular thrombus. Heparin, which acts primarily to prevent the propagation of thrombi in vivo, is preferred in these high risk patients. While thrombolytic therapy has not yet been approved for use in pregnant patients and could produce potentially lethal bleeding complications in the immediate postpartum period, heparin has been used safely in this situation. The risks and benefits of each form of therapy must be assessed in an individual patient before deciding on the appropriate course of management.

Heparin
The effectiveness of heparin in the treatment of

| Absolute | Intracranial hemorrhage, malignancy or arteriovenous malformation |
| Relative | Active internal bleeding |
|          | Recent major surgery, trauma or deep biopsy* |
|          | Pregnancy and the postpartum period |
|          | Preexisting hemorrhagic tendency |
|          | Uncontrolled severe hypertension |
|          | Other potential bleeding risks (eg, a history of peptic ulcer disease) |

*Within two weeks.
pulmonary embolism was firmly established in the only prospective clinical trial which contained untreated controls. Its immediate onset of action and antithrombotic effects make it the logical initial choice for the therapy of thromboembolic disease in most patients. In addition, heparin possesses antiplatelet activity and is a serotonin antagonist, so that it may ameliorate some of the adverse effects due to the release of serotonin and other humoral mediators from platelets adherent to the thrombus.

Heparin is a heterogenous mucopolysaccharide extracted commercially from the mast cells of many tissues including liver, lung, and intestine and standardized as to units of activity. The USP unit commercially available in this country is about 10 percent more potent than the heparin unit used in Europe. Its major action is to combine with and modify antithrombin III so that its combination with and inactivation of thrombin is virtually instantaneous. It also affects other steps in the coagulation cascade. There is controversy as to whether heparin may also have fibrinolytic activity.

Sufficient heparin should be administered to double the Lee White clotting time, or to increase the activated partial thromboplastin time (aPTT) to 1½ to 2½ times control. The need to monitor the aPTT in the patient with no risk factors for bleeding has been questioned. However, it is reasonable to monitor the aPTT and to maintain it within the recommended range, since some studies have noted a doubling of the rate of thrombosis in patients with suboptimal heparin effect whereas others have reported a higher incidence of bleeding with increased prolongation of the aPTT. The dose required to achieve the recommended aPTT varies among individual patients. While 600 U/kg/24 h represents an average dose for most patients, those with ongoing thrombosis have increased heparin requirements that diminish as the thrombotic process is brought under control. Conversely, patients with liver disease or renal insufficiency may be extremely sensitive to the effects of heparin.

Heparin must be given parenterally to achieve a reliable anticoagulant effect. Intramuscular injections are to be avoided because of local bleeding. While the subcutaneous administration of heparin is possible, most physicians prefer the more reliable intravenous route of administration during hospitalization. The continuous infusion of heparin after an initial loading bolus appears to provide reliable anticoagulation with a decrease in the incidence of major bleeding episodes when compared to the intermittent intravenous administration of heparin. The incidence of major, clinically significant bleeding during intermittent heparin therapy is roughly 12 percent while the administration of heparin by continuous infusion has reduced this risk to 5 percent. Patients receiving intermittent therapy generally receive a higher total daily dose of heparin which may account for the higher incidence of bleeding with this form of therapy. It is reasonable to avoid drugs such as aspirin and indomethacin that alter platelet function during heparin therapy, though Salzman was unable to demonstrate any adverse effects from these agents.

Recurrent thromboembolism may occur during the first few days of heparin therapy before the clot becomes adherent to the vascular endothelium and does not constitute a therapeutic failure. About 40 percent of patients who suffer recurrent embolism while receiving heparin therapy will be found to be inadequately anticoagulated as reflected by an aPTT below the therapeutic range. Increasing the dose of heparin to maintain the aPTT at the upper end of the therapeutic range should be the initial alteration in therapy in these patients. The documented recurrence of clinically significant emboli after several days of adequate anticoagulant therapy is an indication for interruption of the inferior vena cava.

The major complication of heparin therapy for pulmonary embolism is serious bleeding. Hemorrhage that occurs when the aPTT is excessively prolonged can usually be managed by interrupting therapy for a few hours and then resuming the heparin at a lower dose, maintaining the aPTT in the lower end of the therapeutic range. Life-threatening hemorrhage and major bleeding when the aPTT is barely therapeutic are indications for the cessation of therapy and surgical intervention.

Another common side effect of heparin is thrombocytopenia, which may develop in 2 percent to 30 percent of patients receiving therapy. One prospective study noted a drop in the platelet count to less than 100,000 in 16 of 52 patients, none of whom manifested clinically significant bleeding despite continuation of therapy. When the therapy was completed and heparin was discontinued there was a prompt rise in the platelet count to normal. Others have reported a high incidence of arterial and venous thrombosis in these patients, and it would seem prudent to monitor platelet counts during heparin administration and to choose another form of therapy if thrombocytopenia develops. Osteopenia has been reported in 10 percent of patients treated with more than 15,000 U per day for longer than six months.

**Thrombolytic Therapy**

Although thrombolytic agents have been recognized for years, it was not until the late 1960s that a large multicenter study of thrombolytic therapy was initiated. This study randomly assigned 160 patients with angiographically-documented pulmonary embolism to receive 12 hours of either urokinase or heparin by infusion, followed by conventional heparin therapy.
Repeat angiography and perfusion lung scanning upon completion of the infusion demonstrated significantly greater early improvement in pulmonary perfusion in the urokinase group. The greater resolution of the clot was associated with a significant reduction in pulmonary artery pressure and an increase in cardiac output in the thrombolytic group. However, after the first week, the perfusion defect on lung scan was similar in both groups. Despite the more rapid improvement in the pulmonary circulation of the urokinase group, there was no difference in mortality, and this more rapid resolution of the thrombus was achieved at the expense of nearly doubling the incidence of bleeding complications. Most of the excessive bleeding in the urokinase group occurred at the catheter cut down site. In the second phase of this study, the effect of the original 12 hours of urokinase was compared to a 24 hour infusion of either urokinase or streptokinase.83 No additional beneficial effect of therapy could be demonstrated when the period of the infusion was extended.

At the present time, thrombolytic therapy is recommended for the patient with a massive embolus that has produced systemic hypotension or created such a critical (50 percent) degree of obstruction in the pulmonary vascular bed that a small subsequent embolus could be fatal. The more rapid resolution of the clot by thrombolytic therapy will hopefully improve the hemodynamic status and provide a margin of reserve in case of subsequent emboli. Even though, after the first few days, the degree of thrombus resolution as determined angiographically or by perfusion lung scanning is similar in heparin treated patients and those who receive thrombolytic therapy, there may be important changes in the microcirculation. Sharma et al84 have demonstrated a reduction in the diffusing capacity of the lung and the pulmonary capillary blood volume in heparin-treated patients which persists for as long as 12 months after the acute embolic episode, whereas these values were normal in individuals who were treated with thrombolytic therapy. If these physiologic alterations are shown to be clinically significant in future studies, thrombolytic therapy may become the preferred treatment in patients with pulmonary emboli.

Streptokinase, which is as effective but considerably less expensive than urokinase, is administered in a loading dose of 250,000 units over 30 minutes and then infused at 100,000 units per hour for 24 hours.85,86 Anticoagulants must be discontinued, and the aPTT must be within the normal range before lytic therapy is begun. Prior to initiating therapy, routine coagulation tests (platelet count, aPTT, prothrombin time, thrombin time and fibrinogen level) should be performed to detect any potential bleeding diathesis and provide a baseline for comparison. After four hours of thrombolytic therapy, a lytic state should be present, manifested by a prolongation of the thrombin time and aPTT to twice the control values, a fall in the fibrinogen level, and a rise in the concentration of fibrin degradation products. Some patients with previous streptococcal infection may have high titers of anti-streptococcal antibodies with partial resistance to streptokinase. The loading done of 250,000 units is sufficient to overcome this resistance in most patients but, if a lytic state is not achieved after four hours, the patient should either receive another loading dose of streptokinase or should be switched to urokinase. Once a lytic state is achieved, further laboratory monitoring is not necessary since the optimal method of monitoring thrombolytic therapy has not yet been established. The laboratory markers of fibrinolytic activity do not correlate with either the tendency to bleed or the rate of clot resolution.10,16 During streptokinase therapy, invasive procedures such as arterial punctures, cutdowns and biopsies should be avoided. If the number of invasive procedures is minimized, the risk of major bleeding during thrombolytic therapy can be reduced to 4 percent or less.90 When the streptokinase infusion is stopped, anticoagulants are withheld for an additional two to four hours to allow the plasmin effect to dissipate, after which heparin is administered in conventional doses.

Surgical Intervention

Surgical intervention in pulmonary embolism can be divided into two broad categories: maneuvers designed to prevent the propagation of future thrombi to the lungs and procedures to remove clots already present in the pulmonary vascular bed. Patients with contraindications to anticoagulant therapy and those who experience significant bleeding or recurrent embolism on appropriate anticoagulant therapy are all candidates for interruption of the inferior vena cava. In addition, patients with a continued predisposition to recurrent embolism who are candidates for lifelong anticoagulation might well benefit from venous interruption, particularly if they have a relative contraindication to anticoagulation such as uncontrolled hypertension or alcoholism.

The majority (90 percent) of all pulmonary emboli arise from thrombi within the deep venous system of the legs.87 Interruption of the inferior vena cava should prevent these thrombi from reaching the lung. This can be accomplished via a direct surgical approach or by the transvenous placement of a filter below the renal veins under fluoroscopic guidance. Clips that reduce the size of the caval lumen or complete ligation below the renal veins will prevent the passage of large emboli to the lungs. In general, the insertion of a serrated Teflon clip or similar device to create a number of 4 mm channels in the caval lumen is preferred, since venous flow through the interruption is
preserved and the incidence of venous sequelae reduced. However, septic embolism or paradoxical emboli to the arterial circuit via a patent foramen ovale are indications for ligation of the inferior vena cava. Collateral flow through the superficial abdominal, deep circumflex iliac, iliolumbar, ascending lumbar, and gonadal vein are potential routes for recurrent emboli. However, in actual practice this appears to be a rare occurrence. The area of stasis above the interruption can promote the formation of new thrombi. More important is the risk of general anesthesia and operative intervention in a patient with an already compromised cardiopulmonary status. The operative mortality in these seriously ill patients is generally about 12 percent. To circumvent this high operative mortality, the umbrella filter (and its modifications) have been developed. These filters, which can be inserted percutaneously under local anesthesia, are an effective method of preventing emboli. The major drawback to this less invasive approach to caval interruption is a 2 percent incidence of filter dislodgement. In about half of these cases, the filter will migrate proximally to the right ventricle or pulmonary artery, and, if not immediately fatal, require surgical intervention. Regardless of the method employed, caval interruption will produce the venous sequelae of edema in 20 percent to 40 percent of patients and ulcerations and phlebitis in 2 percent to 10 percent.

Pulmonary embolectomy is rarely indicated in the management of acute pulmonary embolism. In lethal pulmonary embolism, death occurs in the immediate postembolic period. The patient who survives long enough to undergo embolectomy will probably survive without operative intervention. Since the capacity of the body’s fibrinolytic system to reabsorb thrombi is enormous, the late prognosis of these patients is excellent. Miller et al compared the efficacy of thrombolytic therapy with emergency embolectomy. In their study, only one of eight patients with hypotension secondary to a massive embolism deteriorated hemodynamically while receiving streptokinase, whereas six of 23 hypotensive patients subjected to embolectomy failed to recover. Embolectomy should be reserved for the rare patient with postembolic systemic hypotension who has an absolute contraindication to anticoagulation. It remains to be seen if the development of transvenous embolectomy catheters, which allow the removal of thrombi from the pulmonary arteries under fluoroscopic guidance without general anesthesia, will increase survival in this desperately ill group of patients.

Whenever it is attempted, embolectomy should always be accompanied by inferior vena caval interruption to prevent recurrent emboli.

**Long-Term Management**

Most patients who complete a course of heparin therapy for acute pulmonary embolism without incident are continued on anticoagulants for four to six months after hospital discharge. The rationale for this is derived from the studies of Coon et al which showed a protective effect of anticoagulant therapy for the first four months after hospital discharge. Beyond this time, the potential beneficial effects of anticoagulation must be weighed against the risk of bleeding complications (Fig 1). The risk of recurrent thromboembolic disease is highest in those with previous episodes of the same phenomena.

Generally, oral anticoagulation therapy with sodium
warfarin or similar agents is begun after the first week of heparin therapy, which corresponds to the time required for the thrombus to become adherent to the vascular endothelium. Heparin is continued while the patient is begun on an average maintenance dose of warfarin, eg, 10 mg/day. After a few days of combined therapy, once the prothrombin time (PT) is prolonged to twice the control value, the heparin can be discontinued. The dose of warfarin is adjusted to maintain the PT 1½-2 × control. The majority of bleeding complications during long-term anticoagulation occur when the PT is greater than this, while the majority of thromboembolic events occur when the PT is suboptimal.

One would like to maintain outpatient therapy for four to six months in patients who have experienced their first episode of thromboembolic disease, and indefinitely in those who have had recurrent events and continued risk factors. However, the incidence of serious bleeding complications while receiving warfarin therapy ranges from 2.4 percent to 10 percent in most series. The risk is greater for those patients older than 60 years, particularly women; those with bleeding tendencies, severe diastolic hypertension or structural lesions (eg, peptic ulcer disease); and those receiving medications which alter coumadin metabolism.

Several recent studies have used subcutaneously administered heparin as an alternative to warfarin after hospital discharge. Two studies compared 5000 U q 12 h of heparin to conventional warfarin therapy. While both agreed that the incidence of bleeding was significantly reduced on heparin therapy, the incidence of recurrent thrombosis on this low dose heparin regimen was unacceptably high. Hull et al subsequently reported that a higher dose of subcutaneous heparin, 10,000 U q 12 h, afforded excellent protection against recurrence with significantly less bleeding than conventional warfarin therapy. However, for most patients, it is easier and more economical to take an oral anticoagulant. A month's supply of warfarin costs less than ten dollars, whereas an equivalent amount of heparin, which must be injected twice daily, will cost several hundred dollars. To some extent, this greater expense is offset by the need for frequent, often weekly, monitoring of the PT on warfarin therapy, since laboratory monitoring of outpatient heparin therapy is not required. Thus, it appears that subcutaneously administered heparin provides an acceptable alternative to warfarin therapy, particularly in high risk patients and those who cannot have their PT monitored for geographic reasons.

Finally, there is a small group of patients who will have recurrent thromboembolic events, even while fully anticoagulated. Many of these patients have an increased platelet adhesiveness. Administration of the antiplatelet agent, sulfinpyrazone, will increase their platelet survival time. In one study, none of 14 patients who completed three months of therapy with sulfinpyrazone had recurrent thromboembolism, whereas four of 11 patients treated with placebo experienced recurrent thrombotic phenomena. In other individuals, a deficiency of antithrombin III has been implicated in the genesis of their thromboembolic events. Restoration of antithrombin III may play a key role in the management of these patients.

**Conclusions**

An approach to managing the patient with an acute pulmonary embolism is presented in Figure 2. The vast majority of patients can be treated with a 10 to 14 day course of intravenously administered heparin followed by four to six months of outpatient anticoagulation with warfarin or subcutaneous heparin. Patients with postembolic systemic hypotension and those with a massive embolus that obstructs more than 50 percent of the pulmonary vascular bed should receive 12 to 24 hours of thrombolytic therapy followed by two weeks of intravenously administered heparin, after which their anticoagulation therapy should be continued on an outpatient basis. Complications of therapy are bleeding and recurrent emboli. Bleeding that occurs in the presence of excess anticoagulation, or recurrence when the anticoagulation is inadequate, can frequently be managed by adjusting the dose of anticoagulant. When anticoagulation is contraindicated, or if complications develop when the anticoagulant dose is therapeutic, surgical interruption of the inferior vena cava is indicated. The type of surgical

![Figure 2: Schematic for the management of the patient with pulmonary embolism.](image-url)
intervention chosen depends primarily upon the skills and preferences of the surgeon and the severity of the patient’s condition.

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