Thrombolytic Therapy in Acute Pulmonary Embolism

G. Simonneau, P. Petitpretz, and P. Girard

The primary therapy used by nearly all physicians in the management of acute pulmonary embolism is anticoagulation. Although fibrinolytic agents have been available for over 15 years, their indication and degree of usefulness in pulmonary embolism are still not completely established. In acute pulmonary embolism, the action of heparin is only preventive by drastically reducing the risk of further emboli while natural lytic process removes thrombi from pulmonary and venous circulation. Thus, the clinical need does persist for an agent that would act safely on the morbid event, i.e. that would dissolve thromboemboli.

When used in conjunction with anticoagulation, thrombolytic therapy can achieve the following objectives of ideal management:

1. to quickly dissolve massive pulmonary emboli and promptly reverse acute pulmonary hypertension, and thus to reduce early mortality in life-threatening pulmonary emboli;
2. to remove massive or submassive pulmonary emboli more completely than heparin and anticoagulants;
3. to prevent deep venous vascular damage and subsequent venous hypertension in the lower extremities and thus to prevent the postphlebitic leg syndrome.

Indications of Thrombolytics in Patients with Life-threatening Pulmonary Emboli

Mortality due to the direct effects of pulmonary embolism usually occurs within one hour of the onset of symptoms [1]. These deaths occur before the diagnosis can be confirmed, and fibrinolytic therapy is not feasible in such cases. In hospitalized patients with massive pulmonary emboli who survive long enough for the diagnosis to be confirmed, the prognosis is quite good [2]. Nevertheless, a subgroup of patients at high risk of death has been individualized [2]. Such patients have massive pulmonary emboli (defined angiographically by an obstruction of more than 50 per cent of their pulmonary circulation) associated with hypotension, shock or acute right ventricular failure. In this small group of patients, a prompt definitive treatment either by fibrinolytic therapy or pulmonary embolectomy might be indicated. Randomized trials comparing heparin and thrombolytic treatment have conclusively shown that emboli disappear more rapidly in patients receiving thrombolytic therapy [3], but there was no significant difference in mortality between the two treatment groups [3]. This may be
because these is no real benefit or because the design of these trials could not produce an answer. The latter explanation is probably correct if we consider that only 13% of patients of NIH trials had massive pulmonary embolism with shock [3].

A large trial limited to patients with life-threatening pulmonary emboli might show a significant difference in mortality between heparin and thrombolytics. Moreover, it has been shown [4] that in life-threatening pulmonary emboli, the incidence of treatment failure is much higher in patients receiving heparin (30%) than in patients receiving thrombolytic treatment (15%). Under these emergency conditions where a prompt decrease of right ventricular strain must be obtained, the bolus technique proposed by Dickie [5] and further evaluated by Petitpretz et al. [6] is probably the most appropriate method of administering thrombolytics agents; the bolus injection of 15 000 IU/kg bodyweight of urokinase (urinary source) administered in ten minutes in the right atrium and followed by continuous intravenous full dose heparin therapy, induced a marked rapid improvement in clinical and hemodynamic status; the greatest hemodynamic improvement occurred within three hours after bolus injection. This prompt reduction of the right ventricular afterload is of utmost importance in life-threatening pulmonary emboli. Furthermore, with this technique, the prompt recognition of thrombolytic therapeutic failure can orient to complementary pulmonary embolectomy.

Indications of Fibrinolytic Therapy in Patients with Submassive or Massive Pulmonary Emboli Without Shock and Right Ventricular Failure

A more questionable beneficial effect of thrombolytic therapy concerns their ability to induce more complete resolution of pulmonary emboli than do heparin and anticoagulants. Investigations in the dog have demonstrated that pulmonary vascular patency is usually restored to normal within a few days after acute pulmonary embolism. This rate can be accelerated by heparin administration [7]. Observations in humans are considerably less precise and the true course of resolution after embolization remains to be fully defined. However, nearly all patients who recover from acute pulmonary embolism do so without apparent sequelae; their lung scans and pulmonary angiograms generally show a complete resolution of pulmonary vascular obstruction over the ensuing weeks or months. In the NIH trials [3], approximatively 85% of patients had either normal lung scans or minimal residual defects at one year after embolization; there was no significant difference between the heparin and the urokinase group. However, neither perfusion lung scan nor conventional pulmonary angiography is a sensitive indicator of changes in the pulmonary microcirculation.

Chronic cor pulmonale resulting from unresolved pulmonary embolism is a rare event with a frequency of less than 1 per cent [8]. The incidence of chronic pulmonary hypertension is less well established; In most cases, long term hemodynamic results after acute pulmonary embolism are obtained at rest and hemodynamic exercise response is rarely evaluated. An abnormal increase of pulmonary artery pressure during exercise has previously been documented late after