THROMBOLYTIC THERAPY FOR PULMONARY EMBOLISM

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Consensus regarding the use of thrombolysis to treat acute pulmonary embolism has not yet been reached. There is good evidence that thrombolytic agents dissolve clot more rapidly than heparin. However, proving that this benefit reduces the death rate from pulmonary embolism has been difficult. Each of the 3 thrombolytic agents (tissue type-plasminogen activator, streptokinase and urokinase) is equally efficacious at dissolving clot, but all are associated with an increased risk of major hemorrhage when compared with heparin. One evolving position is that, in addition to patients presenting in circulatory collapse, for whom thrombolysis has been demonstrated to be life-saving, a subgroup of patients may be identified by echocardiography, through its ability to assess right ventricular dysfunction, who should also be considered for thrombolytic therapy. It remains to be seen whether this approach can reduce the death rate associated with pulmonary embolism.

Un consensus au sujet de l'utilisation de la thrombolyse pour traiter les embolies pulmonaires aiguës n'a pas encore été dégagé. Des données valables indiquent que l'agent thrombolytique dissout les caillots plus rapidement que l'héparine. Néanmoins, il a été difficile de prouver que cet avantage réduit le taux de mortalité par embolie pulmonaire. Chacun des trois agents thrombolytiques (l'activateur tissulaire du plasminogène, la streptokinase et l'urokinase) est également efficace pour dissoudre les caillots, mais tous sont associés avec un risque accru d'hémorragie majeure comparativement à l'héparine. Un point de vue est en train d'émerger, selon lequel en plus des patients présentant un collapsus circulatoire et pour qui il a été démontré que la thrombolyse est nécessaire à la survie, un sous-groupe de patients pouvant être identifiés par échocardiographie (puisque cette technique peut évaluer le dysfonctionnement du ventricule droit) devrait également être envisagé pour le traitement thrombolytique. Il reste à déterminer si cette approche peut réduire le taux de mortalité associé aux embolies pulmonaires.

The use of thrombolytic therapy to treat acute pulmonary embolism (PE) remains a controversial and unresolved issue more than 35 years after its first reported use.[1] There is no doubt that it can be life-saving in certain groups of patients; however, it confers a risk of severe hemorrhagic complications in many PE patients who could be safely treated with anticoagulation alone. This topic has been a focus of several recent comprehensive reviews,[2–6] and this article presents an overview of some of the key issues, highlighting the most important studies published to date.

PE is a common disorder and an important cause of morbidity and mortality. It is estimated to be the cause of death in 5% to 15% of patients who die in hospital.[7] Even this may be an underestimate because it has been reported that only one-third of patients who die as a result of PE have a

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correct antemortem diagnosis.[8] The classic triad of risk factors for venous thromboembolism proposed by Virchow — local trauma to the vessel wall, hypercoagulability and stasis — still hold true. Recognition of hypercoagulable states, however, is rapidly expanding. Only in the last few years have we learned about the Factor V Leiden and prothrombin G20210A genetic variants, which confer an appreciably increased risk of thrombosis.[9]

The clinical spectrum of PE ranges from small, incidental thrombosis to massive PE associated with sudden death due to cardiogenic shock. In the early 1960s, the efficacy of heparin plus oral anticoagulants in the treatment of pulmonary emboli was conclusively documented.[10] Anticoagulation, by neutralizing thrombin and other serine proteases halts thrombus growth and prevents clot propagation. Despite this effective therapy, results of the International Cooperative Pulmonary Embolism Registry found a 3-month death rate of 17.4% in a consecutive series of 2454 patients hospitalized with PE.[11] PE was the principal cause of death in this group. Moreover, this study demonstrated that death resulting from thromboembolism has not significantly diminished in the past 20 years.

A well-recognized limitation of anticoagulant therapy is that it cannot dissolve existing thromboemboli in either the pulmonary arteries or the deep venous system. By contrast, thrombolytic drugs such as streptokinase (SK), urokinase (UK) and recombinant tissue type-plasminogen activator (tPA) are able to induce the production of plasmin to actually dissolve thromboemboli. This offers the potential advantage of rapidly restoring pulmonary perfusion, aiding gas exchange and reversing hemodynamic abnormalities associated with pulmonary emboli. In addition, thrombolysis may dissolve much of the source of the thrombus in the pelvic or deep veins, thereby reducing the frequency of recurrent PE. Such therapy should translate into improved survival.

Diagnosing pulmonary embolism

Thrombolysis carries a significant risk of major hemorrhage, so the diagnosis of PE needs to be confirmed before thrombolysis is initiated. The standard for diagnosis remains contrast pulmonary angiography. However, there is a risk of serious bleeding at the venous puncture site after this procedure if thrombolysis is used. Ideally, the diagnosis of PE should be made by noninvasive imaging techniques. A high probability ventilation-perfusion scan in the presence of suggestive clinical features is usually sufficient. Spiral CT of the chest may also be used to detect emboli in central (segmental or larger) pulmonary arteries.[11] Excellent correlation between spiral CT and angiographic findings has been demonstrated.[12]

These imaging studies are frequently unfeasible in the patient who is unstable. In such cases, diagnosis must be based on clinical evaluation supplemented by indirect evidence of PE. Bedside transthoracic echocardiography may be particularly useful in critically ill patients. The thrombus itself is rarely visualized. However, signs of acute right ventricular (RV) pressure overload may be observed and interpreted as highly suggestive of PE.[3] These include RV dilatation, RV hypokinesis, pulmonary arterial hypertension as assessed by Doppler scanning, interventricular septal flattening and displacement of the septum into the left ventricle. These signs of RV overload cannot be considered acute in the presence of RV wall hypertrophy. Echocardiography also offers the advantage of ruling out other causes of acute shock such as left ventricular failure, pericardial tamponade and aortic dissection.

Thrombolysis in acute pulmonary embolism

Multiple studies have shown that thrombolytic therapy produces more rapid clot resolution than treatment with heparin alone. However, these trials have reported no difference in the extent of clot resolution over time and no reductions in morbidity or mortality from PE. In 1970 the urokinase in pulmonary embolism trial published its results.[13] In this large, prospective, multicentre study, 160 patients with angiographically proven PE were randomized to receive either a 12-hour infusion of UK followed by heparin or heparin alone. End points included improvement in hemodynamic measurements and pulmonary blood flow at 24 hours and over time. Results showed that at 24 hours patients who had received UK had obtained significantly better results than those who had received heparin. However, the difference in the amount of resolution between the 2 groups as assessed by serial scans decreased after 24 hours, and no difference was found at 5 or 14 days or at 3, 6 or 12 months. Furthermore, no difference in mortality or the rate of recurrent PE was detected between the 2 groups.

Levine and associates,[14] in a similar randomized trial, compared a bolus regimen of tPA with heparin in patients with PE. Resolution demonstrated by lung scanning at 24 hours was significantly greater in the tPA group. However, follow-up lung scanning 7 days after treatment showed no significant difference between treatment groups.

In the plasminogen activator Italian multicenter study 2, Dalla-Volta and colleagues[15] reported that resolution of pulmonary emboli, as monitored by pulmonary artery pressure and angiographic perfusion scores, decreased more significantly 2 hours after tPA treatment than after adminis-

tration of heparin alone. Once again, however, there was no difference in the lung scans obtained 7 and 30 days after treatment.

It is also worth noting that unlike myocardial infarction, in which the therapeutic window for thrombolytic therapy is narrow (approximately 12 hours from the onset of symptoms), the benefit of thrombolytic therapy for PE even in patients presenting as long as 14 days after symptom onset has been documented.[16] However, maximal benefit is observed when therapy is administered soon after diagnosis.

A survival benefit of thrombolysis in acute PE was seen only in those presenting with acute massive life-threatening PE, defined as severe pulmonary vascular obstruction resulting in hemodynamic instability. This was demonstrated by Jerjes-Sanchez and associates[17] who in 1995 reported the results of a small study in which 8 patients with shock related to massive PE randomly received bolus SK (1.5 million units over 1 hour) or heparin therapy. All patients receiving heparin alone died, but no one in the SK group died. This trial was intended to enrol 40 patients but was stopped as a consequence of the clear survival benefit conferred by SK. On the basis of this study it is now accepted that thrombolysis is indicated for patients presenting in circulatory collapse from massive PE.

Three of the patients who died in the study of Jerjes-Sanchez and associates underwent autopsy. All were found to have RV myocardial infarction in addition to massive PE although none had significant coronary arterial obstruction.[18] This provided further evidence that death from massive PE results from a cycle of progressive RV ischemia and failure due to acutely elevated pulmonary vascular resistance. With reduced RV output, the left ventricle underfills, leading to circulatory collapse. Such patients clearly benefit from thrombolysis, which presumably acts by lysing massive pulmonary arterial thrombus, preventing the downhill spiral of right heart failure.

Acute right ventricular dysfunction as an indication for thrombolytic therapy

Less than 5% of patients with PE present in cardiogenic shock.[11] On the other hand, nearly 50% of patients with PE and normal systemic arterial pressure have signs of RV hypokinesis as assessed by echocardiography at the time of presentation.[11] Moreover, RV hypokinesis has been associated with a significantly increased death rate resulting from PE.[11] It has therefore been postulated that thrombolytic therapy might also improve outcomes in this subset of patients.[19]

A 1993 trial by Goldhaber and colleagues[20] examined this issue. Of 101 hemodynamically stable patients having PE, half were randomized to tPA followed by heparin the other half to heparin alone. Of the 89 patients who had evaluable echocardiograms at 0, 3 and 24 hours from the time of presentation, there was a significantly greater improvement in RV function in patients treated with tPA than in those treated with heparin alone. Moreover, no patient died or had recurrent PE in the group receiving tPA. By contrast, of the 55 patients who received heparin alone, 5 had recurrent PE and 2 of these died of PE. RV hypokinesis on echocardiogram at the time of presentation was demonstrated in 40% of all patients and was present in each of the patients with adverse clinical outcomes. Results in this study approached statistical significance and suggested that patients with normal systemic pressure but with RV dysfunction should be considered for primary therapy with thrombolytic agents.

The management strategy and prognosis of pulmonary embolism registry, comprising 204 centres throughout Germany, studied the clinical course of 1001 patients with a major PE over a 15-month period.[21] In this observational nonrandomized study, it was demonstrated that as right heart failure worsened, the death rate increased. In a separate analysis, this group described a total of 719 patients presenting with RV dysfunction but preserved blood pressure.[22] Of the 719 patients, 169 received thrombolytic therapy and 550 were treated with heparin alone. The mortality at 30 days was significantly lower in the thrombolytic group than in the heparin group (4.7% versus 11.1%). In addition, recurrent PE was significantly less frequent in the group receiving thrombolytic therapy.

Grifoni and associates[23] recently published the results of a prospective clinical outcome study of 209 consecutive patients with documented PE. Among normotensive patients presenting without RV dysfunction seen on echocardiography (47% of patients), none suffered shock or died as a result of PE. Hence, the negative predictive value of echocardiography for PE-related death proved to be 100% in this patient population. Among normotensive patients with RV dysfunction (31% of patients), 6 (10%) suffered PE-related shock after admission despite adequate anticoagulation with heparin. Three of these patients died and 3 were successfully treated with thrombolytic agents. This study provides further evidence that the detection of RV dysfunction represents an important prognostic determinant specifically in patients who are clinically stable on presentation. It also supports a role for echocardiographic examination in all patients with pulmonary emboli.

There is mounting indirect evidence to support the use of thrombolytic agents in this hemodynamically stable group of patients. Certainly its use needs to be considered on a patient by patient basis, and

the risks and benefits need to be weighed. There is a definite need for a large scale, randomized clinical trial to prospectively address this issue.

THROMBOLYTIC AGENTS

The mechanism of action of all 3 thrombolytic agents (UK, SK and tPA) is to convert, either directly or indirectly, the plasma protein plasminogen to plasmin,[2] which in turn rapidly breaks down fibrin, leading to clot lysis. In addition, by cleaving and inactivating fibrinogen and Factors II, V and VIII, systemic plasminogen activation also interferes with blood coagulation. Elevated levels of fibrinogen degradation products contribute to the coagulopathy by inhibiting the conversion of fibrinogen to fibrin and interfering with fibrin polymerization.[2]

The 3 thrombolytic agents appear to be equally effective and safe when equivalent doses are delivered at the same rate over a short time. The urokinase-streptokinase embolism trial reported no significant difference in the efficacy of urokinase and streptokinase for the treatment of acute PE.[24] Several trials have compared tPA with urokinase. Goldhaber and associates[25] compared 100 mg of tPA infused over 2 hours with urokinase treatment infused for 24 hours. At 2 hours after the onset of treatment, more significant embolic resolution was observed angiographically in the tPA group. However, lung scans obtained 24 hours after treatment were the same in both groups. A second study by Goldhaber's group[26] compared the results of 100 mg of tPA infused for 2 hours to those of 3 million IU of UK infused over 2 hours. This time there was no difference in either angiographic evidence of resolution on scans obtained 2 hours after treatment or in lung scan findings 24 hours after treatment. Meneveau and colleagues[27] compared the efficacy and safety of 2-hour infusions of tPA and SK in acute massive PE and found no significant difference in the extent of clot resolution 36 to 48 hours after the start of therapy.

LOCAL VERSUS SYSTEMIC ADMINISTRATION OF THROMBOLYTIC AGENTS

The local administration of thrombolytic agents directly into the pulmonary artery has several potential theoretic advantages over systemic administration. Clot lysis may be more efficient and, because of high local drug concentrations, lower total doses of thrombolytics may be required. Against the use of local therapy is the need to perform pulmonary artery catheterization. This procedure prolongs the time for drug administration and increases the risk of bleeding from vascular access sites.

The limited available data do not support the use of intrapulmonary thrombolytic therapy over systemic therapy. In a study by Verstraete and colleagues,[28] 34 patients with PE were randomized to receive tPA either intravenously or intrapulmonarily in a dose of 50 mg over 2 hours. Both groups demonstrated rapid, significant improvement in pulmonary artery pressure and pulmonary perfusion. No significant differences were found between the 2 groups with respect to angiographic scores, reduction of pulmonary arterial pressures or risk of major hemorrhage.

COMPLICATIONS OF THROMBOLYTIC THERAPY

The major drawback of thrombolytic treatment is an increased incidence of severe bleeding complications compared with the use of heparin. The most commonly reported sites of bleeding are vascular puncture sites. More serious bleeding may spontaneously occur throughout the gastrointestinal tract, in the retroperitoneum and intracranially. Studies differ with respect to frequency of hemorrhagic complications because of differences in definitions of major hemorrhage. If major hemorrhage is arbitrarily defined as fatal he-

Table I

Summary of Contemporary Concepts in Thrombolytic Therapy for Pulmonary Embolism

Issue	Comment
Indications	
Normotensive patient with no evidence of RV dysfunction	Thrombolytic therapy **not** indicated
Hypotensive, hypoperfused patient	Thrombolytic therapy indicated
Normotensive patient with evidence of RV dysfunction	Consider thrombolytic therapy
Diagnosis of pulmonary embolism	May be based on V/Q, spiral CT or transthoracic echocardiography
Thrombolytic agents	tPA, SK and UK all equally effective
Route of administration	Peripheral vein
Time window for therapy	Up to 14 d after symptom onset
Complications	Risk of major hemorrhage increased threefold v. heparin Risk of intracranial hemorrhage 1.2%

RV = right ventricular, V/Q = ventilation-perfusion, tPa = tissue-type plasminogen activator, SK = streptokinase, UK = urokinase.

morrhage, intracranial hemorrhage (ICH) or bleeding that requires either surgery or transfusion, pooled data suggest a risk of 6.3% with thrombolytic agents versus 1.8% with heparin therapy.[2] The rates of major hemorrhage were similar among the 3 thrombolytic agents.[2]

Of primary concern is the incidence of intracranial hemorrhage in patients with PE treated with thrombolytic agents. Pooled data from 18 randomized studies involving 896 patients revealed an overall incidence of ICH of 1.2% (11 of 896), with death occurring in about half of these patients.[2] The incidence of ICH in these studies was 1.3% and 1.6% for UK and tPA respectively. ICH was not reported in the relatively small number of patients treated with SK. Spontaneous ICH did not occur in any patient treated with heparin.

Kanter and associates[29] in a retrospective analysis that looked at risk factors for ICH in patients treated with thrombolysis for PE found a significantly increased risk in patients presenting with diastolic hypertension on hospital admission. It also revealed that younger patients appear to be at very low risk, and there was a trend of increasing risk with advancing age.

The relative contraindications to thrombolytic therapy for fear of bleeding include recent cerebrovascular accident or intracranial surgery (within 2 months), active intracranial disease (aneurysm, vascular malformation or neoplasm), major internal bleeding within the past 6 months, uncontrolled hypertension, recent major surgery or trauma, pregnancy pericarditis and hemorrhagic retinopathy.

CONCLUSIONS

Contemporary opinions on the use of thrombolytic therapy for pulmonary embolism are outlined in Table I. Risk stratification is crucial in determining which patients presenting with pulmonary emboli will do well with anticoagulation alone and which patients should be considered candidates for primary treatment with thrombolysis. For those without hemodynamic disturbance, especially those without evidence of RV dysfunction on echocardiography, thrombolysis is not indicated and they may be safely treated with heparin and warfarin alone. In patients with circulatory shock due to massive PE, the benefits of thrombolysis clearly outweigh the risks. It is for patients in between that a large randomized trial is required to prospectively evaluate outcome in those presenting with PE who are hemodynamically stable yet demonstrate evidence of RV dysfunction.

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Notices
Avis

Mayo interactive surgical symposium

From Mar. 1 to 3, 2001, the Mayo Clinic Scottsdale will conduct a Mayo interactive surgical symposium — an interactive update for surgeons — at the Marriott's Camelback Inn Resort, 5402 East Lincoln Dr., Scottsdale, Ariz. The course directors are Drs. John H. Donohue and William M. Stone. Credit: AMA Category 1 (to be announced). For information contact Sarah Dorste, Mayo School of CME, Mayo Clinic Scottsdale, 13400 East Shea Blvd., Scottsdale AZ 85259; tel 480 301-4661, fax 480 301-8323

EGE Society for Pediatric Thorax

The 2nd World Congress of the Pediatric Thoracic Disciplines will be held from Apr. 26 to 28, 2001, in Izmir, Turkey. For further information contact Professor Oktay Mutaf, Ege University, Faculty of Medicine, Pediatric Surgery Department, Bornova 35100 Izmir, Turkey; fax +90 232 3751288, email omutaf@med.ege.edu.tr

Hepatology and liver transplantation

On Mar. 29 and 30, 2001, the Mayo Clinic Scottsdale will host a course entitled "Update in Hepatology and Liver Transplantation" at the Embassy Suites at Stone Creek Golf Club, 4415 East Paradise Valley Parkway S, Paradise Valley, Ariz. This course, an update for primary care physicians and gastroenterologists, is directed by Dr. David D. Douglas. Credit: AMA Category 1 (to be announced). Contact Sarah Dorste, Mayo School of CME, Mayo Clinic Scottsdale, 13400 East Shea Blvd., Scottsdale AZ 85259; tel 480 301-4661, fax 480 301-8323

Urogynecology and disorders of the female pelvic floor

The Mayo Clinic Scottsdale will hold its 10th annual course on urogynecology and disorders of the female pelvic floor from Apr. 5 to 7, 2001, at Mariott's Camelback Inn Resort, 5402 East Lincoln Dr., Scottsdale, Ariz. The course, which will provide physicians with an update of the newest treatment options and surgical modalities of pelvic floor disorders, is directed by Dr. Jeffrey L. Cornella. Credits: AMA Category 1 (to be decided) and ACOG (to be decided). For information contact Sarah Dorste, Mayo School of CME, Mayo Clinic Scottsdale, 13400 East Shea Blvd., Scotts-