Pulmonary embolism: treatment of the acute episode

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The prognosis of acute pulmonary embolism (PE) is mainly related to the clinical presentation and circulatory state of the patient: the therapeutic strategy is consequently different, ranging from an aggressive treatment in patients in life-threatening clinical conditions to a "stabilization" treatment in those hemodynamically stable. Since the majority of PE patients are clinically stable, a well conducted anticoagulant therapy, either with unfractionated or low-molecular-weight heparins together with a vitamin K antagonist, is sufficient to stop thrombus extension, to minimize the risk of recurrent embolism and prevent mortality. In about 15-20% of cases presenting with clinical instability of variable severity, prompt intravenous thrombolysis with a short-acting compound often represents a life-saving treatment and should be the first-line approach. In normotensive patients with right ventricular dysfunction at echocardiography, who represent about 30% of PE patients, the debate regarding the optimal therapy is still open and further studies are required to document a clinically relevant improvement in the benefit-risk ratio of thrombolytic agents over heparin alone: young people, with a very low risk of bleeding and a concomitant reduction of cardiopulmonary reserve might be the best candidates to systemic thrombolysis. In any case such patients should be admitted to an intensive care unit to monitor the clinical status for at least 48-72 hours and detect signs of possible hemodynamic worsening. Mechanical thrombectomy, either percutaneous or surgical, are ancillary procedures and should be reserved to a minority of highly compromised patients who are unable to receive thrombolysis.

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The aim of treatment in acute pulmonary embolism (PE) is to manage circulatory imbalance, to obtain pulmonary artery reperfusion, to interrupt progression of clot, and to prevent recurrences. A timely and appropriate approach can reduce at least 4-fold the mortality rate due to an acute PE, the incidence of subacute symptomatic events and chronic morbidity[1,2]. Antithrombotic drugs are the mainstream of treatment and these include compounds that inhibit blood coagulation, such as various heparins and heparinoids and thrombolytic agents. Direct mechanical reperfusion, as complementary or alternative option, can be performed by surgical or catheter techniques.

As the prognosis in acute PE is mainly related to the clinical presentation and circulatory state of the patient, the therapeutic strategy is consequently different: in patients presenting with hypotension, shock or cardiac arrest ("massive PE"), thrombolytic therapy is indicated as first-line treatment. In this subset of patients, non-pharmacological reperfusion can also be considered when and where available. All other symptomatic patients (more than two thirds of those presenting with PE), with hemodynamic stability and normal blood pressure, have to be treated with heparin for at least 5 days, together with vitamin K antagonists started on the first treatment day[3]. An unresolved issue remains nowadays the use of thrombolytic agents in patients with preserved systemic arterial pressure and echocardiographic signs of right ventricular dysfunction (RVD) ("submassive PE").

Heparins

Heparin is currently the standard treatment after thrombolysis and, as initial therapy, for all patients who do not have severe circulatory failure.

In hemodynamically stable patients, unfractionated heparin (UFH) has been shown to be effective in the treatment of PE in comparison to no treatment reducing both mortality and recurrences[1]. Intravenously administered UFH is started with a bolus dose followed by continuous infusion. When sufficiently high starting doses

are used, a therapeutic activated partial thromboplastin time (aPTT) is achieved quickly. Other possible routes of administration are intermittent intravenous bolus or subcutaneous calcium heparin every 12 hours; both regimens are effective but the former causes excessive bleeding and with the latter route it is difficult to reach an aPTT in the initial hours of treatment owing to the low bioavailability[4].

The efficacy of intravenous UFH therapy depends mainly on the starting dose; after an initial bolus of 80 IU/kg, a continuous infusion of 18 IU/kg/hour should be administered to achieve at least 30 000 IU/24 hours[5]. An aPTT value 1.5 to 2.5 times the control value is recommended as a target therapeutic range for heparin. A plasma heparin concentration of 0.4 to 0.7 IU/ml, measured by anti-factor Xa assay, is effective and safe and is demonstrated to have an approximately linear correlation with aPTT value over the therapeutic range; lower doses result in higher rates of recurrences[6].

The phenomenon of resistance to heparin (arbitrarily defined as the need for more than 40 000 IU/24 hours) could be related to an increased binding of heparin to different plasma proteins, including histidin-rich glycoprotein, platelet factor-4, vitronectin, fibronectin and von Willebrand factor; so monitoring heparin-resistant patients with an anti-factor Xa heparin assay is safe and effective[7], but is difficult to obtain in the current clinical practice. Alternatively, a low-molecular-weight heparin (LMWH) can be given because it has less propensity to bind to plasma proteins and is likely to eliminate heparin resistance.

Hemorrhagic complications during heparin therapy are infrequent, unless the patient has a potential risk of bleeding, and approximately 3% of patients receiving treatment have immune, IgG-mediated thrombocytopenia.

LMWHs are progressively replacing standard UFH for treatment of venous thromboembolism. A meta-analysis of studies in patients with non-massive symptomatic PE or with asymptomatic PE in the context of symptomatic deep venous thrombosis has shown that LMWHs administered subcutaneously, in doses adjusted to body weight, are at least as effective and safe for initial treatment as intravenous, dose-titrated UFH[8]. As a result, the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy recommends LMWHs over UFH for the initial treatment of patients with acute non-massive PE (grade 1A)[3].

LMWHs have several advantages over UFH. Their half-life is longer so that twice or once-daily subcutaneous treatment can be effective; the anticoagulant response is more predictable so the drug can be administered in fixed body-weight adjusted doses without laboratory monitoring. LMWHs reduce the incidence of heparin-dependent antibody and the activation of osteoclasts, allowing a lower incidence of heparin-induced thrombocytopenia and osteopenia[9]. In laboratory animals, LMWHs cause less bleeding with equivalent antithrombotic effect[10]. Finally, the treatment is cost-effective (despite the higher cost of LMWHs) since it allows early mobilization and requires less nursing and laboratory monitoring. In severely obese patients (body mass index > 50 kg/m^2), scheduled for LMWH treatment, it is reasonable to consider anti-factor Xa testing 4 hours after subcutaneous administration (range 0.6-1 IU/ml for a twice-daily regimen) to avoid over- or underdosing because of an uncertain volume of distribution; in subjects with a body mass index > 30 kg/m^2 but < 50 kg/m^2, it seems safe to administer LMWHs in doses based on total body weight, without the need of anti-factor Xa testing. Similarly, in patients with severe renal insufficiency, monitoring of therapeutic anti-factor Xa activity should be performed, due to the increased risk of bleeding: in such a situation, UFH should be preferred to provide full therapeutic anticoagulation therapy[9].

Preliminary data suggest that LMWHs may be used for out-of-hospital treatment of patients with non-massive PE[11], but the safety and the opportunity of this approach need to be further evaluated. The characteristics and the therapeutic doses of the LMWHs available in Italy are described in table I.

What is the future of antithrombotic therapy for venous thromboembolism? The new selective factor Xa inhibitor fondaparinux (a synthetic analog of the pentasaccharide sequence in UFH and LMWHs) administered subcutaneously once daily has recently been shown to be at least as effective and safe as UFH and

Table I. Low-molecular-weight heparins commercially available in Italy.

Drug	Commercial name	Molecular weight (dalton)	Anti-Xa/lla activity	Dosage
Enoxaparin	Clexane	4500	3.7	100 IU/kg × 2 150 IU × 1
Nadroparin	Fraxiparina Seleparina	4500	4	93 IU/kg × 2 171 IU × 1
Dalteparin	Fragmin	5000	2.6	100 IU/kg × 2 200 IU × 1
Reviparin	Clivarina	3900	4	87 IU/kg × 2 0.125 ml/10 kg × 2
Bemiparin	Ivor	3600	8	115 IU/kg × 1

enoxaparin for the initial management of both symptomatic PE and deep vein thrombosis patients in two recent trials[12,13]. Fondaparinux not only shares all the advantages of LMWHs over UFH, but also has the added feature that it does not cause heparin-induced thrombocytopenia. A modified version of fondaparinux, known as idraparinux, has a longer half-life that permits once-weekly subcutaneous injections. Since these new compounds have been registered just for prophylaxis of deep vein thrombosis in some particular clinical settings, and not for treatment of venous thromboembolism, no recommendations are made at present.

Ximelagatran, an oral direct thrombin inhibitor with a rapid onset of action and predictable antithrombotic effect, has the potential to be a simple therapeutic alternative to current standard treatment of venous thromboembolism; administered in a fixed dose of 36 mg twice daily, this drug proved to be as effective as enoxaparin/warfarin for treatment of deep vein thrombosis with or without PE and showed similar, low rates of bleeding[14]. Unfortunately, the finding of increased levels of liver enzymes in almost 10% of ximelagatran-treated patients requires further studies about the safety of the drug.

Thrombolytic therapy

Nowadays three drugs (streptokinase, urokinase and recombinant tissue-type plasminogen activator-rt-PA) are approved for the systemic treatment of acute PE that share similar thrombolytic effect but have different administration modalities. rt-PA is generally preferred due to its more rapid effect and should be administered in a 2-hour regimen, in a dosage according to body weight (as in myocardial infarction) to minimize the risk of bleeding. Heparin should not be infused concurrently with streptokinase or urokinase; for rt-PA patients, concurrent use of heparin is optional. Despite more than three decades of experience with thrombolytic agents and several randomized clinical studies, yet enrolling a relatively small number of patients, their role in the treatment of acute PE remains controversial: in comparison to heparin, these drugs produce a more rapid rate of resolution of pulmonary embolic obstruction, documented by angiography, lung scans and echocardiography[15], but this effect does not result in a significant reduction in mortality or recurrence of PE. On the other hand the most important disadvantage of thrombolysis is the increased rate of bleeding complications, especially intracranial hemorrhage, with death occurring in about half of these patients. Two recent meta-analyses of the pooled data from the same 9 randomized trials including 461 cases came to conflicting conclusions about the benefits of thrombolysis compared with heparin for the initial treatment of PE: no benefits on mortality or PE recurrence, but a significant increase in major bleeding was stressed by Thabut et al.[16], while a significant benefit ($p < 0.03$, number needed to treat = 14.5) was described by Agnelli et al.[17] when death and recurrence were considered together. The latest meta-analysis, published by Wan et al.[18] in 2004, reported on 11 randomized trials involving 748 patients with PE, including the largest randomized study by Konstantinides et al.[19]; indeed, among them, only 5 studies enrolled cases with hemodynamic instability. As shown in figure 1, compared with heparin, thrombolytic therapy was associated with a non-significant reduction in recurrent PE or death. A non-significant increase in major bleeding and a significant increase in non-major bleeding were also found (Table II). Interestingly, in a subgroup analysis, thrombolytic therapy was associated with a significant reduction in recurrence or death in the 5 trials that included patients with hemodynamic instability and therefore the highest risk of death or recurrence, but no benefit in the 6 trials that excluded these patients (Table III). Taking into consideration the modest number of patients

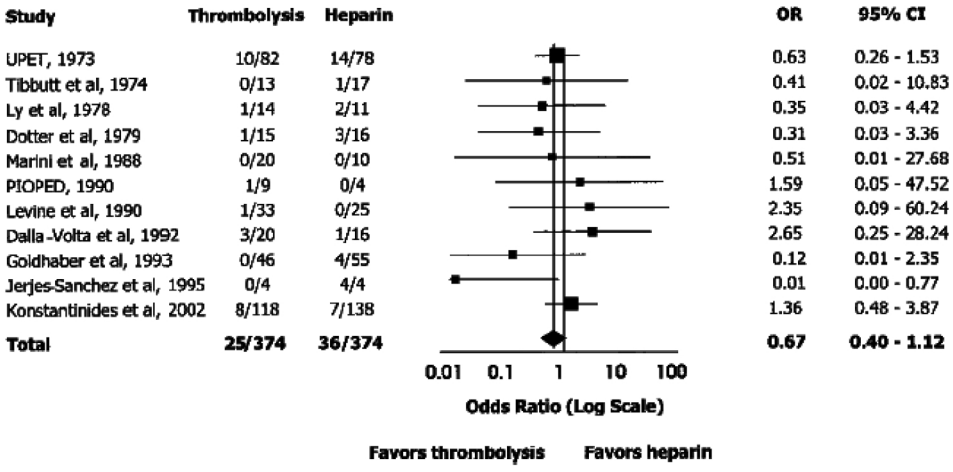

Figure 1. *Recurrent pulmonary embolism or death in trials comparing thrombolysis with heparin for the initial treatment of acute pulmonary embolism[18]. CI = confidence interval; OR = odds ratio.*

Table II. Major and non-major bleeding and intracranial hemorrhage in patients randomized to thrombolysis compared with heparin[18].

Outcome	Thrombolysis	Heparin	OR (95% CI)
Major bleeding	34/374 (9.1%)	23/374 (6.1%)	1.42 (0.81-2.46)*
Non-major bleeding	53/233 (22.7%)	22/221 (10.0%)	2.63 (1.53-4.54)**
Intracranial hemorrhage	2/374 (0.5%)	1/374 (0.3%)	1.04 (0.36-3.04)***

CI = confidence interval; OR = odds ratio. Heterogeneity, * p = 0.92, ** p = 0.53, *** p = 1.00.

involved in randomized trials to date, this study was in agreement with previous meta-analyses in advocating a new, large, randomized clinical trial employing a modern thrombolytic agent to address this central issue: in which patients with acute PE would the benefits of thrombolysis overweigh the increased hemorrhagic risk in terms of total adverse events? In other words, is there a subset of patients with PE, besides those with severe hemodynamic instability, who are at such a higher risk of death as to benefit from thrombolytic therapy? Does this subset coincide with patients showing echocardiographic signs of RVD? Data from a large multicenter German registry[20] quoted a significant reduction in mortality and recurrences in patients hemodynamically stable with RVD and major PE, but another registry in France[21] reported quite different results: there were no deaths in the heparin group vs a 6.25% mortality in those treated with thrombolysis, with a 4.7% of intracranial bleeding (but all cerebral bleedings occurred in patients with relative contraindications to thrombolytic treatment!). Unfortunately, the sole recent randomized study including patients with "submassive PE"[19] remains underpowered to reliably answer the question[22] and the only significant result was the benefit of thrombolysis in preventing clinical deterioration requiring the escalation of treatment (catecholamine infusion, secondary thrombolysis, cardiopulmonary resuscitation). Furthermore, this trial reports different results in comparison with previous randomized studies or registries[22]: an overall mortality rate extremely low (< 3%) and no intracranial hemorrhage in the arm of 118 patients receiving thrombolytics; are these data representative of the real world?

At present, the international scientific associations have to face many economic and logistic problems in order to plan a new trial of adequate proportion (2000 people?) and no new projects seem predictable in the near future until the completion of the ongoing TIPES study. The Tenecteplase Italian Pulmonary Embolism Study is designed as a superiority study and 180 patients (90 tenecteplase + UFH vs 90 placebo + UFH) will be randomized. The primary efficacy endpoint cannot be based on clinical outcome, but only considers an echocardiographic parameter, namely a clinically relevant reduction of RVD at 24 hours from tenecteplase or placebo injection. The first patient was enrolled in September 2004 and the study period, initially planned in 18 months, will probably be much longer.

The best therapy of patients showing free floating right heart thrombi at echocardiography is still uncertain due to impossibility of planning a randomized trial in such patients who present in critical conditions and in whom the mortality rate, reported in a recent meta-analysis by Rose et al.[23], is up to 27%. The available data from small series of patients and the above-mentioned meta-analysis are consistent with a better outcome with thrombolytic therapy, which rapidly facilitates both the intracardiac and intrapulmonary clot dissolution. Based on our experience[24,25], we suggest a first-line thrombolytic treatment in the presence of hemodynamic instability and of a large right atrial clot prolapsing into the right ventricle: in such a condition we cannot afford any delay due to the impending migration of the thrombus into the pulmonary arteries and the risk of sudden death. An emergent surgical approach should be preferred in case of impending paradoxical embolism when a wide patent foramen ovale or a thrombus overridding the interatrial septum can be demonstrated by transthoracic or transesophageal echocardiography.

Non-pharmacological therapy

PE has been shown to have a mortality rate > 30% in patients with severe hemodynamic instability. As pharmacological thrombolysis may be ineffective or contraindicated in up to 40% of patients[26], percutaneous mechanical thrombectomy may be considered a valuable option in this clinical scenario compared to surgical embolectomy that is associated with a high intraoperative mortality and is often unavailable within a short period of time. In comparison to surgery, percutaneous embolectomy has important advantages including: a) short procedural time with faster pulmonary reperfusion; b) availability for patients with high surgical risks or surgical contraindications; c) no need of a cardiac surgery team on site, because it can be performed in the catheterization laboratory. Several devices for percutaneous thrombectomy with large differences regarding design, effectiveness, and cost are commercially available[27]. On the basis of the mechanism of action, they may be classified as follows: 1) aspiration devices, 2) fragmentation devices, and 3) rheolytic devices[28]. Nowadays there are no evidences supporting the superiority of one device compared with an-

Table III. Subgroup analysis of trials that included hemodynamically unstable pulmonary embolism (PE) patients compared with those that excluded them[18].

Outcome	Trials that included patients with major PE			Trials that excluded patients with major PE			p for heterogeneity between subgroups
	Thrombolysis (n=128)	Heparin (n=126)	OR (95% CI)	Thrombolysis (n=246)	Heparin (n=248)	OR (95% CI)	
Recurrent PE or death	12 (9.4%)	24 (19.0%)	0.45 (0.22-0.92)	13 (5.3%)	12 (4.8%)	1.07 (0.50-2.30)	0.10
Recurrent PE	5 (3.9%)	9 (7.1%)	0.61 (0.23-1.62)	5 (2.0%)	7 (2.8%)	0.76 (0.28-2.08)	0.71
Death	8 (6.2%)	16 (12.7%)	0.47 (0.20-1.10)	8 (3.3%)	6 (2.4%)	1.16 (0.44-3.05)	0.13
Major bleeding	28 (21.9%)	15 (11.9%)	1.98 (1.00-3.92)	6 (2.4%)	8 (3.2%)	0.67 (0.24-1.86)	0.12

CI = confidence interval; OR = odds ratio.

other and the operator's preferences, experience, and geographical availability determine the choice.

Actually, percutaneous embolectomy may be employed not only in patients with contraindicated or ineffective thrombolysis, but also as adjunctive therapy to standard thrombolysis[29]. In fact, the thrombotic occlusion of pulmonary artery branches may cause flow alterations so that only a minimal quantity of the thrombolytic agent can enter the thrombus. Fragmenting the thrombus or creating multiple channels inside it allows for a better exposition of the clot to the drug, therefore increasing its lytic effect. Hemodynamic and clinical improvements seem to be linked to both volume of thrombus removed and to the time interval between symptoms and pulmonary revascularization[30]. Generally, 3 weeks is the age limit of thrombus when considering the option of a mechanical or rheolytic thrombectomy device. Based on history, angiography, outcomes and follow-up data of patients undergoing pulmonary thrombectomy, three groups have been identified. Type I patients, with fresh clots that have recently embolized are the best candidates to the procedure with a high success rate; type II patients, with older, more organized clots, that have recently embolized, respond to a lesser degree to thrombectomy; type III patients, with a history of old, organized chronic PE and recent worsening due to recurrent PE are bad candidates and thrombectomy is likely to be ineffective[31].

Although mechanical reperfusion therapy in PE patients is gaining increasing acceptance and is described after ineffective or contraindicated thrombolytic therapy as a potential life-saving procedure, the level of recommendation is still low (grade 2C)[3], due to the lack of randomized clinical trials or meta-analyses of homogeneous populations of sufficient proportions.

As regards surgical pulmonary embolectomy, despite some recent reports suggesting a more extensive utilization of surgical approach including cases hemodynamically stable with RVD[32], the ACCP guidelines[3] recommend against this procedure that should be reserved to selected highly compromised patients who are unable to receive thrombolytic therapy.

Conclusions

Since the landmark study by Barritt and Jordan[1] 45 years ago, anticoagulants remain the cornerstone of treatment of PE. Patients with PE should be treated with UFH or LMWHs as soon as the diagnosis is confirmed by objective testing. If the clinical suspicion is high and there is a delay before confirmation, the treatment should be started while awaiting objective examinations and should be continued only if the diagnosis is ascertained. In the vast majority of PE patients, a well conducted heparin therapy, together with a vitamin K antagonist, is sufficient to stop thrombus extension, to minimize the risk of recurrent embolism and prevent mor-

tality. In about 15-20% of cases presenting with clinical instability of variable severity, prompt intravenous thrombolysis with a short-acting compound often represents a life-saving treatment. In normotensive patients with RVD at echocardiography, the debate regarding optimal therapy is still open and further studies are required to document a clinically relevant improvement in the benefit-risk ratio of thrombolytic agents over heparin alone: young people, with a very low risk of bleeding, and a concomitant reduction of cardiopulmonary reserve might be the best candidates to systemic thrombolysis[25]. In any case such patients should be admitted to an intensive care unit to monitor the clinical status for at least 48-72 hours and detect signs of possible hemodynamic worsening. Mechanical thrombectomy, either percutaneous or surgical, is an ancillary procedure and should be reserved to a minority of highly compromised patients who are unable to receive thrombolysis.

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