Knossos mutation are in combination with the deletion of A in codon 59 of the δ-gene in *cis* which completely inactivates the δ-gene.[12]

Other very mild mutants occasionally found in Mediterranean countries are –90 C→T[13] and IVS2-844 C→G.[14] Silvestroni Bianco suggests according to her experience, that the latter is commonly associated to a normal phenotype. Within type 2 normal HbA_2 β-thalassemia, several different defects have been observed. Many cases are likely due to the coinheritance of a defective δ gene which may occur either in *cis* or *trans* to the β-thalassemia gene, which itself may be of the β^+ or β° type.[12,15]

In populations in which α and β-thalassemias are common, such as in our country, the probability to have couples at risk remains quite high, therefore the proper identification of the carrier states is extremely important. Although the *silent thalassemia haplotypes* in combination with any severe thalassemia haplotypes are responsible for very mild thalassemia intermedia phenotypes, they have to be properly diagnosed in order to offer an adequate genetic counselling. The article by Ida Silvestroni Bianco published in this issue, due to her great hematological experience, maps the silent thalassemia phenotype in our population, drawing the attention of anyone is dealing with thalassemia.

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editorial

THE ROLE OF THROMBOLYTIC THERAPY IN THE TREATMENT OF PULMONARY EMBOLISM

The treatment of pulmonary embolism was one of the most debated subject at the *Second Winter Meeting on Basic, Laboratory and Clinical Aspects of Thromboembolic Diseases,* held in La Thuile on March 17-23, 1996. This topic will be briefly reviewed here and the pros and cons of the different thrombolytic drugs available will be discussed. In the section *Decision Making and Problem Solving* of this issue, Perrier proposes a rational strategy for noninvasive diagnosis of pulmonary embolism.

As early as 1960 the landmark study by Barrit and Jordan[1] had conclusively documented the efficacy of heparin plus oral anticoagulants in the treatment of pulmonary embolism (mortality rate 26% in the placebo group vs 0% in the heparin+acenocoumarol group) and thereby established heparin plus coumarins as the treatment of choice in this disease state. Yet we know that heparin is only able to neutralize thrombin and other serine proteases, thus halting thrombus growth and preventing recurrences, and that it cannot dissolve thromboemboli obstructing the pulmonary arteries. By contrast, thrombolytic drugs, such as streptokinase (SK), urokinase (UK), and recombinant tissue type-plasminogen activator (tPA), are able to induce the production of huge amounts of plasmin in the blood and to lyse (partially or completely) the thromboemboli. These powerful agents can therefore rapidly restore lung perfusion and reduce pulmonary hypertension, and can also attack the residual thrombus in the original site of the thromboembolism.

SK and UK, which were already on the market in the 1960's, and t-PA which became available in the 1980's, were compared to heparin in the treatment of pulmonary embolism in a number of trials. However, no reduction of mortality rate was observed in any of these studies.

In the UPET (*Urokinase Pulmonary Embolism Trial*), a multicenter American study which randomized 160 patients with angiographically proven pulmonary embolism to receive either urokinase 4400 U/kg IV in 20 min + 4400 U/kg/hour for 12 hours, or standard heparin IV infusion, mortality at 2 weeks was 7% in the UK group and 9% in the

heparin group, and there was a significant increase of bleeding complications in patients treated with UK.[2] Tibbut *et al*.[3] and Ly *et al*.[4] evaluated streptokinase vs. heparin in two small trials without observing significant differences in efficacy and safety. rt-PA was assessed vs heparin at two different doses. In a study by Levine *et al*.[5] a bolus of 0.6 mg/kg was given, followed immediately by heparin infusion, while the FDA approved dosage (100 mg given over 2-hour IV infusion) was used in the Italian PAIMS study[6] and in the study by Goldhaber *et al*.[7] Although no reduction of the mortality rate was obtained in these studies either, both the Canadian and the American trials showed a trend towards greater efficacy in patients treated with t-PA without an appreciable increase in bleeding, while serious bleeding complications in the t-PA group were recorded in the PAIMS trial.

If we now consider cardiac and pulmonary function tests, there is no doubt that thrombolytic treatment is superior to heparin in achieving significantly greater improvement in angiographic and perfusion lung scans, and in echocardiographic parameters at early assessments.[2,5,7] However, there is some uncertainty regarding late results because in the UPET and Levine studies patients treated with heparin caught up in the perfusion lung scans executed after 2 weeks and one week, respectively. In contrast, Sharma *et al*.[8] found that in a subgroup of 40 patients enrolled in the UPET and USPET study (*Urokinase Streptokinase Pulmonary Embolism Trial*), the pulmonary diffusion capacity and capillary volume were significantly higher in patients treated with thrombolytic drugs at 2 weeks and one year after embolism; moreover, 23 of these patients were evaluated after about 7 years and those who had received heparin showed persistently higher PAP and pulmonary vascular resistance than the ones who had received thrombolytic therapy.[9]

Even though the overall results of the UPET study did not show a reduction of the mortality rate in patients treated with thrombolysis, the results obtained in the subgroup of patients with massive (two or more lobar arteries occluded) pulmonary embolism and, in particular, the clear reduction of pulmonary artery pressure and angiographic scores were taken as sufficient evidence that thrombolytic drugs should be the treatment of choice in those patients unless a compelling contraindication were present. A consensus therefore was reached after the UPET trial in favor of thrombolytic therapy in patients with massive pulmonary embolism, particularly if it is hemodynamically unstable.

Another point which can be considered settled is that there is no advantage in giving thrombolytics via locoregional infusion. In a study by Verstraete *et al.* 34 patients with PE were randomized to receive t-PA either intravenously or intrapulmonarily according to the following *two-step* dosage (first step: 10 mg bolus + 40 mg over 2 hours; 2nd step: 50 mg over 5 hours if the Miller pulmonary angiographic index was greater than 15/34). There was no difference in the angiographic scores or in the reduction of the PAP between the two groups either after the first or after the second t-PA infusion.[10]

Besides the results of clinical trials, important information also came from studies of the (natural) history of the disease, such as the one by Carlson *et al*.[11] These authors prospectively followed 399 patients with pulmonary embolism recruited from the PIOPED (*Prospective Investigation of Pulmonary Embolism Diagnosis*) project who had been treated with conventional heparin therapy (73%), vena cava interruption (10%), thrombolytic therapy (6%) and embolectomy (1 patient). Mortality at 1 year was 23.8%, with a steep rise in the curve during the first 2 weeks (23% of the deaths); in-hospital mortality was 9.5%. The one-year mortality rate was 19.2% for those treated with conventional therapy, 36.8% for those treated with vena cava interruption, and 8.7% for patients treated with thrombolytic therapy. Causes of death included: cancer (34.7%), infection (22.1%), cardiac disease (16.8%) and pulmonary embolism (10.5%). Of the 10 deaths due to pulmonary embolism, 8 occurred within one week of entry into the study. These findings have two major implications for the topic under discussion. One is that conventional heparin therapy is associated with infrequent recurrences and deaths from pulmonary embolism. The second is that since heparin therapy is associated with a mortality rate of 9% at one month (the same as acute myocardial infarction), a megatrial the size of the GISSI would have been necessary to show a statistically significant reduction of the mortality rate with thrombolytic drugs. None of the comparative studies performed so far have had enough power to detect potentially important differences; therefore we should recognize that thrombolytic therapy could save lives and that we simply do not have adequate studies to prove or disprove this possibility. A definitive answer will have to wait for such a large trial.

A number of studies have compared different thrombolytic drugs and/or different dosages. The USPET trial[12] compared 3 treatment modalities: SK 250,000 U bolus (20 min) + 100,000 U/hour for 24 hours; UK 4,400 U/Kg bolus + 4,400 U/kg/hour for 12 hours; UK same dosage for 24 hours. Each scheme obtained a significant improvement in angiographic and scintigraphic abnormalities as compared with the heparin group of the parent UPET study, but there was no difference in mortality rates, in bleeding episodes or in hemodynamic parameters among the different treatment groups evaluated. The European UKEP trial[13] compared 2 different locoregional dosage schemes of UK: 2,000 U/kg/hour for 24 hours (plus heparin) and 4,400

U/kg/hour for 24 hours (without heparin). No differences were observed between the two groups with regard to angiographic scores or PAP reduction.

Goldhaber promoted several trials comparing t-PA with different alternative treatments. One compared t-PA with the classic UK dosage in 45 patients. There were 2 deaths in each group, a similar decrease in plasma fibrinogen level, a significant difference in the angiographic score at 2 hours, similar lung scan improvement after 24 hours.[14] This study was criticized because of the time set for angiographic comparisons: after 2 hours the entire t-PA dosage had been administered versus 1/12 only of the UK dose; in another trial Goldhaber *et al*. compared t-PA with a completely new UK dosage scheme: 1 MU bolus (10 min) + 2 MU over 110 min. Angiography controls at 2 hours disclosed 66% improvement in the UK group vs 79% in the t-PA group (p= 0.19), and no differences in the other clinical or instrumental parameters either.[15]

A reduced t-PA bolus vs the standard t-PA dosage was evaluated by the *Bolus Alteplase Pulmonary Embolism Group* in a study aimed at demonstrating a reduced bleeding rate in the bolus group.[16] In a 2:1 randomization process, 60 patients with hemodynamically stable PE were treated with 0.6 mg/kg (max 50 mg) t-PA over 15 minutes, and 27 patients with 100 mg over 2 hours. No significant differences between groups were detected with respect to bleeding complications, adverse clinical events, or imaging studies.

The *European Study Group for Pulmonary Embolism*[17] randomized 60 patients with acute massive pulmonary embolism to either t-PA (10 mg bolus + 90 mg over 2 hours) or to UK (standard dosage), using total lung vascular resistance as a parameter of efficacy. There was a non significant trend in favor of t-PA at the early assessments, but this vanished at the determinations performed after 12 hours. More importantly, there were 4 deaths in the t-PA group due to hemorrhagic complications vs 1 in the UK group.

Among the lessons learned from this (and other) trials is that if one is considering thrombolytic therapy for a patient with suspected PE, in order to reduce the probability of serious or even fatal bleeding due to angiographic procedures, he (or she) should:

1) order pulmonary angiography only in cases in which this procedure is an essential diagnostic step;[18]

2) use a pigtail catheter.

Returning to the topic of this discussion, we should consider massive and submassive pulmonary embolism separately. Cases of massive PE, particularly those hemodynamically unstable, are candidates for thrombolytic therapy unless contraindications such as an uncompressible source of bleeding or an increased risk of fatal cerebral or spinal hemorrhage are present. In this case surgical embolectomy can be considered, provided that the patient is hemodynamically unstable and the diagnosis has been documented by pulmonary angiography.[19,20] Age *per se* cannot be considered a contraindication, as demonstrated in a study by Meneveau *et al.*, who reported about hemorrhagic complications observed in 89 consecutive patients with massive PE who were treated with SK (a few cases with UK). There was no significant difference in bleeding rates in 36 patients over 70 years of age compared to 53 patients under 70; therefore the authors concluded that thrombolysis should not be denied to elderly patients with massive PE unless other contraindications are present.[21]

Let us now consider the subset of patients with submassive pulmonary embolism, i.e. those with ecocardiography features indicating pulmonary artery hypertension, such as paradoxical movement of the interventricular septum, tricuspid reflux, right atrial enlargement or hypokinesis of the right ventricle. These patients could be considered potential candidates for thrombolysis on the basis of the results of the already cited study by Goldhaber *et al.*[7] Here 101 patients with hemodynamically stable PE were randomized to either t-PA, 100 mg over 2 hours (n = 46) or heparin treatment (n = 55). Right ventricular wall motion 24 hours after from the start of treatment improved from baseline in 39% and worsened in 2% of the patients treated with t-PA vs 17% improvement and 17% deterioration in the heparin controls (p < 0.01). There was no clinical recurrence of PE in the t-PA patients vs 5 in the heparin group, 2 of which fatal (p= 0.06).

Patients with submassive but severe PE can therefore be considered as potential candidates for thrombolysis provided they have no contraindications to treatment, such as recent (10 days) surgery, biopsy, resuscitation maneuvers, recent (4 months) internal bleeding, anemia, hemostatic defects, abnormal liver function tests, active peptic ulcer, pancreatitis, esophagitis, ulcerative colitis, pericardial effusion, endocarditis, severe hypertension, pregnancy or hemorrhagic retinopathy. Considering the clinical spectrum of pulmonary embolism, this is the subset of patients for whom the decision to give or not to give thrombolytic drugs is most problematic. In the absence of contraindications, I would prefer thrombolysis to heparin for a patient with PE who shows clearcut ecocardiographic signs of pulmonary hypertension.

We have already seen that there is no clear advantage to one thrombolytic drug versus another in terms of efficacy and safety. In favor of t-PA are its higher catalytic potency, higher fibrin specificity and absence of antigenicity; however, cost considerations tend to favor streptokinase. The standard

SK dosage in PE is still the old 250,000 U bolus (20 min) followed by 12 hours of 100,000 U/hour IV infusion. Unfortunately there are only anedoctal reports of high-dose scheme such as the one used in the treatment of MI.[22,23] However, these reports are promising and are backed by the good results obtained in MI, and one finds it hard to understand why this new dosage has not been formally evaluated in a randomized trial.

Lastly, we should not to forget that, even if the initial choice is thrombolysis, there is no doubt that heparin and oral anticoagulants should follow.[24-26]

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