Double Thrombolysis with rt-PA in a Patient with Massive Pulmonary Embolism and Antiphospholipid Syndrome

Stavros G. Spanodimos, Dionysios G. Antonatos, Konstantinos Th. Sotirellos, Socrates P. Patsilinakos, Anastasios I. Andrikou, Efrosini Ch. Paraskevopoulou, Dimitrios L. Tsigas

Cardiology Department, Konstantopoulio General Hospital - Agia Olga, Athens, Greece

Key words: **Massive pulmonary embolism, thrombolytic treatment, antiphospholipid syndrome, antiphospholipid antibodies, anticardiolipin antibodies, lupus anticoagulant.**

A thirty-seven year old woman was admitted to our department because of syncope and severe shortness of breath. During the last month, her left lower extremity was immobilized due to Achilles tendon rupture. From her history, physical and laboratory examination (arterial blood gas, FDP, D-dimers, spiral CT, Venous Duplex, perfusion scan and Echocardiogram), massive pulmonary embolism and deep venous thrombosis was diagnosed. She underwent thrombolytic treatment with rt-PA with partial resolution of thrombi, but without significant clinical improvement. We therefore proceeded to a second thrombolytic session which resulted in significant radiographic and clinical improvement. The results of her hypercoagulable profile were positive for lupus anticoagulant and antiphospholipid antibodies. After a four-month follow-up period the patient remains asymptomatic.

Manuscript received:
May 22, 2001;
Accepted:
February 5, 2002

Address:
Stavros G. Spanodimos

5C Karkavitsa St.,
154 52, P. Psychiko,
Athens, Greece
Tel. (+30) 210-6743181

The antiphospholipid syndrome is an autoimmune disease, characterized by the presence of antiphospholipid antibodies, thromboses, repeat spontaneous abortions and thrombocytopenia. The syndrome may be encountered in patients without any clinical or laboratory indications of other systemic disease (primary), or may be encountered within the context of other systemic disease – more often with Systemic Lupus Erythematosus (secondary). The most common clinical manifestations are venous thromboses of the lower limbs, of pulmonary arteries as well as of other vessels (cerebral, renal, etc.) and repeat spontaneous abortions. The treatment of the antiphospholipid syndrome, depends on the location of the thrombosis and the severity of symptoms.

We describe a case of a patient with antiphospholipid syndrome with positive antibodies against cardiolipin and lupus anticoagulant, massive pulmonary embolism, deep venous thrombosis of the left lower limb and aggravated personal history (diabetes mellitus, hypothyroidism due to thyroidectomy, hypertension) who underwent thrombolysis treatment (with rt-PA) twice, due to insufficient clinical and laboratory improvement, following the first thrombolysis session.

Case presentation

A 37-year old woman was admitted to the emergency department of our Hospital because of a reported episode of syncope (the second within one week) accompanied by loss of urine and severe rest dyspnea. A month ago, the patient had suffered a rupture of the Achilles tendon of the left lower limb and had been immobilized (with circular plaster – initially – and later with plaster splint due to edema and pain). During this period, she presented progressively aggravating dyspnea during effort.

Her personal history included the following:

– arterial hypertension beginning 20 years ago, under pharmaceutical treatment.
– total thyroidectomy (two months earlier) due to multinodular goiter. The patient is currently on replacement therapy.
– diabetes mellitus for many years treated with antidiabetic tablets.
– hyperlipidemia (hypercholesterolemia – hypertriglycerolemia).
– history of two spontaneous abortions.
– depression syndrome.
– history of left ovariectomy and salpingectomy.

Clinical examination: the patient seemed seriously ill with obesity (height 1.65 m – weight: 95 kgr) and hirsutism. She presented tachypnea (breaths > 35/min), arterial pressure 160/100mmHg, temperature: 36.5° C, pulses: 115 /min and jugular veins dilatation. Left parasternal systolic repulsation and left lower limb edema with pain upon palpation of the collateral calf were present. On lung auscultation, diffuse reduction of the respiratory murmur was observed with expiration prolongation while upon heart auscultation, we observed increase of the 2nd tone intensity on the 2nd intercostal space, left parasternally and systolic murmur on the 4th intercostal space, left parasternally, with relevant intensity increase upon inspiration (Revero Carvallo sign).

Laboratory control: Ht:42.9%, WBC: 11200 (poly.: 52.5%, lympho.: 38.5%), PLT: 188000, RCSR: 14mmHg, glucose: 126mg%, urea: 27mg%, creatinine: 0.7mg%, K^+: 4,3mEq/L, Na^+:136mEq/L, SGOT: 34U/L, SGPT: 59U/L, LDH: 193U/L, CPK: 25U/L, ALP: 67U/L, γGT: 95U/L, total bilirubin: 0.43mg%, cholesterol: 272mg%, LDL: 163mg%, HDL: 67mg%, triglycerides: 209mg%. Blood gases: pH: 7.423, pO_2: 49mmHg, pCO_2: 30.3mmHg, HCO_3:20 Eq/l, O_2SAT: 86,1%. Coagulation control: PT: 16sec, APTT: 25.5sec, INR: 1.20, FDP>20μg/ml (NV: <0.5μg/ml), D-Dimers>8μg/ml (NV: <0.5μg/ml), fibrinogen: 268mg/ml.

The chest X-ray was without any specific findings from the pulmonary parenchyma and the cardiovascular system, with a slight rise of the right hemidiaphragm.

The ECG showed sinus tachycardia (120 beats/min) and negative T waves on leads III, aVF, V_1,V_2.

On the basis of history, clinical picture and laboratory findings, we considered pulmonary embolism a possible diagnosis. We immediately proceeded to a thorax CT scan (spiral technique 120KV, 200MA, section thickness: 3-5mm, pitch: 1, with

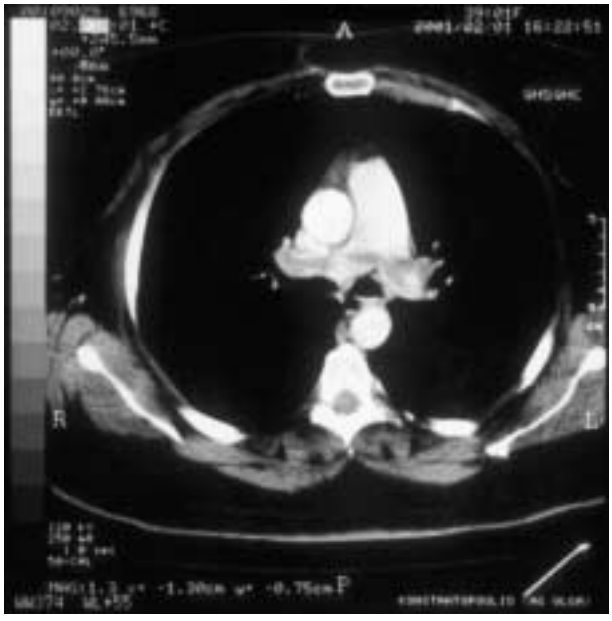

Figure 1. CT after infusion of contrast material at the level of the two main branches of pulmonary artery before thrombolytic therapy: the presence of longitudinal thrombi is obvious.

administration of contrast material 120ml, administration rate: 2,5ml/min) which verified our initial diagnosis: "presence of longitudinal thrombi on the right main branch of the pulmonary artery, 5 cm long and 1cm thick and on the left main branch 4cm long and 1 cm thick, with extension to the branches for the upper lobes and the lower lobes. Conclusion: bilateral massive pulmonary embolism" (Figure 1).

To assess the hemodynamic condition and the prognosis of massive pulmonary embolism we conducted an echocardiogram that in summary indicated the following: "Left ventricle with normal dimensions, wall thickness and function. Significant dilatation of the right ventricle with reduced motility of its entire free wall. On the short axis a leveling and projection of the interventricular septum to the left (D point) is observed. Tricuspid valve regurgitation $2^+/4^+$ with calculated RVSP:55mmHg" (Figure 2).

The diagnosis of massive pulmonary embolism with the thorax CT and the clear picture of affected motility of the right ventricle in transthoracic ultrasound, in conjunction with the patient's clinical condition, led us to make the decision to proceed to thrombolysis. We chose to administer rt-PA (100mg Actilyse with 2 hrs infusion time), as comparative studies, have shown that it acts more rapidly compared to other specific thrombolytic preparations. Prior to thrombolysis, we administered i.v. heparin

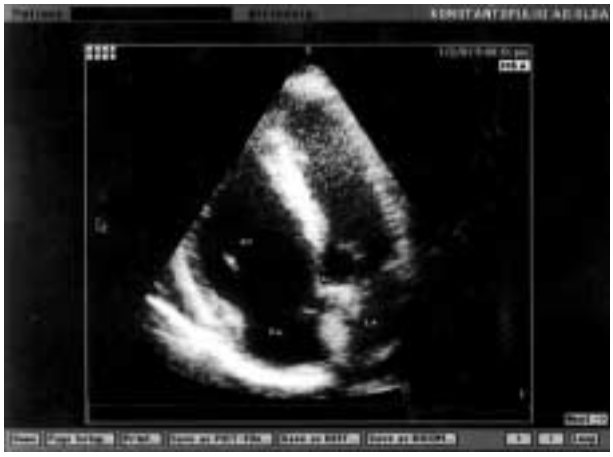

Figure 2. Echocardiogram before thrombolytic therapy: Severe dilatation of right ventricle with shifting of the interventricular septum to the left.

8000 iu bolus and following thrombolysis, at a rate of 1000 iu/hr, aiming at doubling the initial APTT.

Eighteen hours later, the patient's clinical condition had not presented significant improvement. She still presented severe dyspnea and tachypnea, while blood gases remained the same. (Blood gases with 50% O_2 oxygen mask, 12lt/min: pH: 7.389, pO_2: 52.5mmHg, pCO_2: 38.2mmHg, HCO_3: 23 mEq/l, O_2SAT: 90.2%). We then decided to proceed to a new thorax CT scan: "Improved condition with complete lysis of the thrombus of the right main branch and presence of residual thrombus in the periphery of the left main branch. A thrombotic picture remains at the central section of the branches of the upper and lower lobes on both sides". On repeated heart ultrasound, the initial picture of dilatation and dysfunction of the right ventricle and the pulmonary hypertension remained as well as the shift of the interventricular septum to the left, with slight improvement compared to the initial picture.

We thus decided to administer a 2nd session of thrombolysis with rt-PA (100mg Actilyse), again within 2 hrs, that was of course followed once more by continuous heparin infusion.

Within 6 hours from the beginning of treatment, the patient presented clear improvement of her clinical condition (decrease of dyspnea – tachypnea) and oxygenation (blood gases with nasal O_2 administration 3lt/min, pH: 7.397, pO_2: 80mmHg, pCO_2: 35.7mmHg, HCO_3: 21.9, O_2SAT: 95.9%). This improvement was also seen on the new thorax CT scan: "significant improvement of the condition. Complete lysis of the residual thrombus on the periphery of the left main branch. Small residual thrombi on the central parts of the lower lobe branches" (Figure 3), as well as on the new echocardiographic examination that followed: "clear improvement of dimensions and of the motility of the right ventricle, no tricuspid valve regurgitation is observed and the interventricular septum presents normal motility" (Figure 4).

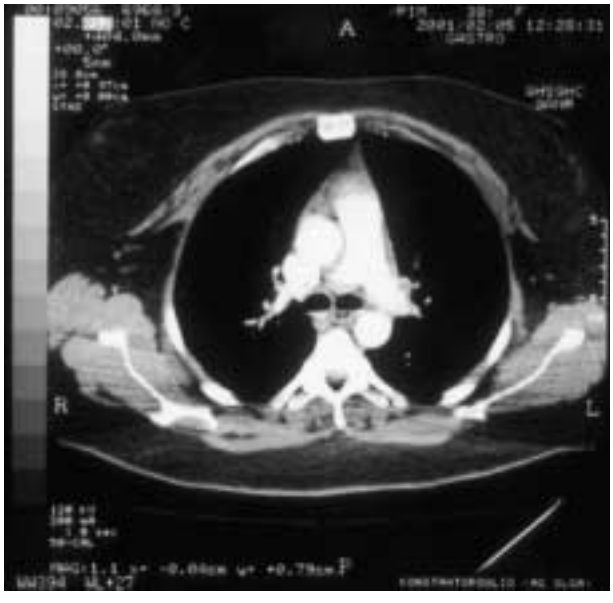

Figure 3. CT after infusion of contrast material at the level of the two main branches of pulmonary artery after the second thrombolytic therapy: Total resolution of the existing thrombi.

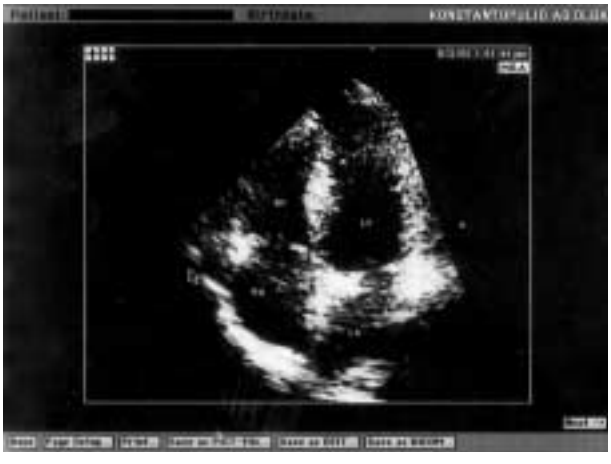

Figure 4. Echocardiogram after second thrombolytic therapy: Significant improvement of right ventricle dimensions with normal position of the interventricular septum.

Lung perfusion scintigraphy scan that was conducted two days later indicated changes compatible with the findings of the 3rd thorax CT-scan.

We did not proceed to lung ventilation scintigraphy scan since chest X-rays were normal.

Concurrently with IV heparin (that lasted 7 days) we administered anticoagulant treatment to the patient with acenocoumarol per os (overlap time 5 days) with coagulation time monitoring (target INR >2.5). Moreover, due to obesity, hyperlipidemia, mild diabetes mellitus and hypothyroidism, the patient was under dietary and pharmaceutical treatment (to restore thyroid function and achieve hypolipidemia).

Simultaneously, we began examinations to find the cause of pulmonary embolism. The recent history, of course, of Achilles tendon rupture, of immobilization of the left lower limb with circular plaster initially and the history of pain and edema thereafter, that led the orthopedic surgeon to place a plaster splint, easily led us to the suspicion of deep venous thrombosis (DVT). Indeed, color venous Duplex of the lower limbs indicated thrombosis with complete re-cavernization of the posterior tibial vein of the left calf.

The gynecological history of the patient however (two spontaneous abortions) made us suspect the presence of antiphospholipid syndrome and we directed our examination towards this direction.

Table 1 indicates all the causes of thrombotic syndromes that may lead to deep venous thrombosis (on the left column) and to pulmonary embolism, while the right column presents all the respective laboratory examinations to which we subjected our patient and we underline the pathological values. As is shown from the results of this control, our patient was at high risk for DVT because aside from obesity and immobilization of the left lower limb, she also suffers from primary antiphospholipid syndrome with positive antiphospholipid antibodies (IgG antibodies vs. cardiolipin and lupus anticoagulant). In the discussion that will follow, we will further examine the antiphospholipid syndrome in detail. As far as the per os anti-coagulant treatment duration is concerned, there is no consent. However, since according to international literature[1-5], the risk of recurrence is high, particularly in patients with additional predisposing factors, we are considering coumarin administration for life for our patient. Our patient is completely asymptomatic four months after her hospitalization.

Discussion

We will limit ourselves to what we deem as the two most interesting points of this case: the presence of antiphospholipid syndrome and the use of thrombolysis to treat pulmonary embolism.

A) The antiphospholipid syndrome is an autoimmune disorder that is characterized by the presence of antiphospholipid antibodies (APA), thromboses, repeat spontaneous abortions and thrombocytopenia. This syndrome may be observed in patients without clinical or laboratory indications of another systemic disease and is then characterized as primary, or may be observed within the context of another disease and is then characterized as secondary antiphospholipid syndrome (Table 2).

Antiphospholipid antibodies (APA) constitute a heterogeneous group of immunoglobins IgG, IgM, IgA or a mixture of them, that recognize phospholipid and protein complexes. APA are usually measured with three tests:

a) Coagulase reaction VDRL (Venereal Disease Reference Laboratory test) that is the oldest test. This test has the disadvantage of being non-specific, is semi-quantitative and does not provide the possibility of distinguishing between classes of antibodies.

b) Lupus anticoagulant (LA or dRVVT). This test presents many disadvantages because it completely depends on the subjective evaluation of the examiner (since it is not automated), cannot be quantitative since it is based on coagulation times and not on units, cannot be measured in plasma of patients who are already on some kind of anti-coagulant treatment and finally cannot distinguish and determine the isotypes of the antibodies.

c) Antibodies count against cardiolipin with the ELISA method. The main advantage of this method[6] is that it is quantitative, specific, with high reproducibility. It also allows for the control of a high number of samples in a small period of time, it can be used both in plasma as well as in blood serum and finally it can distinguish the isotype of the anticardiolipin antibody IgG, IgM or IgA. The IgG isotype is more often accompanied by the antiphospholipid syndrome[7] whereas the IgM and IgA isotypes less often. Research in the last years has shown that some APA do not actually recognize phospholipids but rather proteins in plasma that bind phospholipids and more specifically b_2-glycoprotein I[8] and prothrombin[9] or protein complexes with phospholipids.

Table 1. Thrombotic syndromes and relative laboratory tests. The pathological findings are underlined.

THROMBOTIC SYNDROMES	
CAUSES	**PATIENT RESULTS**
1. FAMILIAL (HEREDITARY)	
A. Insufficient inhibition of coagulation factors	
i. Antithrombin III deficiency	antithrombin III:88% (n.v. 85-111)
ii. Protein C deficiency	protein C:103% (n.v. 78-134)
iii. Protein S deficiency	
iv. Leiden V factor	negative
B. Fibrinolysis disorders	
i. Fibrinogen disorder	fibrinogen:268mg/dl (n.v. 146-380)
ii Plasminogen deficiency	plasminogen: 130% (n.v. 75-128)
C. Unclear mechanism	
i. Homocystinuria	homocystein :14μmol/l (nv. 9.40-14)
2. ACQUIRED	
A. SYNDROMES OR DISEASES	
i. Cardiolipin syndromes	– anti-Cardiolipin (ACA): **IgM:329 U/ml (n.v. 0-100)** IgG:28 U/ml (n.v. 0-100) – B2-GPI: IgM:55 U/ml (n.v. 0-100) IgG:50 U/ml (n.v. 0-100) – DRVVT: **Positive for LA (Lupus anticoagulant)**
ii. Malignancies	– Thorax, lower / upper abdomen CT: negative tumor markers :negative
iii. Hyperlipidemia	**hypercholesterolemia, hypertriglyceridemia**
iv. Diabetes mellitus	**yes**
v. Collagenoses	– Antinucleic ANA, anti-n-DNA: negative C3:1.664 g/l (n.v. 0.50-0.90) C4:0.250 g/l (n.v. 0.10-0.40) – Ra-test: <9.6 IU/ml (n.v. 0-15) – CRP: 9.3 mg/l (n.v. 0-5)
vi. Multicystic Ovaries syndrome	– intravaginal ECHO: negative – progesterone: 4.7nmol/l (n.v. 0.85-8.3) – FSH: 4.2 mIU/l (n.v. 4-13) – LH: 2.8 mIU/l (n.v. 1-18) (hormonal measurements during the 1st phase of the menstrual cycle)
B. PHYSIOLOGICAL CONDITIONS	
i. Obesity	**yes**
ii. Immobilisation	**one month due to Achilles tendon rupture**

The incidence of APA found in systemic lupus erythematosus and in the lupus-like syndrome ranges in various studies[10] from 18%-61%, while in the general population it ranges between 2%-4%.

Depending on the thrombosis site, the antiphospholipid syndrome is divided into the following types:

- type I: pulmonary embolism and deep venous thrombosis
- type II: coronary or peripheral arteries thrombosis
- type III: cerebral or renal vessels thrombosis
- type IV: thrombosis in several points
- type V: patients with repeated spontaneous abortions and APA

Table 2.

CLINICAL CONDITIONS ASSOCIATED WITH SECONDARY ANTIPHOSPHOLIPID SYNDROME

i. Rheumatological diseases	Systemic Lupus Erythematosus (SLE) Rheumatoid Arthritis Primary Sjogren's syndrome Dermatomyositis, polymyositis Psoriasic arthropathy Ankylotic spondylitis
ii. Vascular diseases	Giant – cell arteritis Adamantiadis – Bechet syndrome Takayasu arteritis
iii. Infectious diseases	Viral infections (HIV-1, Hepatitis-C) Protozoa infections (Pneumocystis carinii) Syphilis, leprosy Tuberculosis Lyme disease Q fever
iv. Malignancies	Lung cancer, ovarian cancer, prostate cancer Leukemias, Lymphoproliferative syndromes Hypenephroma, Paraproteinemias, Thymoma
v. Administration of drugs	Phenothiazines, procainamide, contraceptive pill
vi. Diabetes mellitus	
vii. Megaloblastic anemia	
viii. Healthy individuals	
ix. Patients on renal dialysis	

– type VI: asymptomatic patients with APA.

Thus, the clinical manifestations of the antiphospholipid syndrome may be the following:

1. *Pulmonary embolism due to deep venous thrombosis.* It is the third most common cardiovascular disease following acute ischemic syndromes and strokes. Its incidence in the United States is calculated at approximately 350,000 hospitalized patients/per year among which 50,000 deaths/year. The morbidity increases depending on age and gender (ratio of men/women: 1.24).
2. *Obstetrical complications.* The incidence of APA in the general obstetrics population ranges from 2.2-6.1%. Initially, the presence of placenta infarctions was indicated as the cause of spontaneous abortions. In many cases, the placenta damage induced by the infarcts is not sufficient on its own to justify the death of the embryo. Reduced prostacyclin (PGI_2) in embryonic and maternal tissue has been proposed as an explanation.
3. *Hematological complications.* The presence of APA is associated with autoimmune hemolytic anemia and autoimmune idiopathic thrombocytopenic purpura.
4. *Dermatological complications.* They present a wide spectrum of manifestations from livedo reticularis to extensive skin necroses, e.g. Sneddon Wilkinson syndrome (vascular cerebral episodes and livedo reticularis in young persons), Degos disease and Adamantiadis-Bechet syndrome.
5. *Rheumatological complications.* Systemic lupus erythematosus and its variations (discoid lupus, subacute dermatological lupus), Sjogren's syndrome.
6. *Gastrointestinal complications.* Budd-Chiari syndrome, intestinal ischemia and hepatic circulation thrombosis.
7. *Neurological complications.* Transient ischemic cerebral episodes, dementia due to multiple infarcts, chorea, migraines, epilepsy, transverse myelitis, etc.

8. *Destructive antiphospholipid syndrome.* Patients present sudden shock, thrombocytopenia, jaundice, adult respiratory distress syndrome, multiple organs failure and eventually death.

The treatment of the Syndrome depends on the location of symptoms. We will discuss treatment of vascular thrombosis that was also observed in the specific case.

The acute treatment of venous or arterial thrombosis is no different to the treatment of thrombosis of any other etiology. In patients with this syndrome who present venous thrombosis we administer prophylactic anticoagulant treatment per os. In patients who present an episode of arterial thrombosis, we administer aspirin or combination of aspirin and dipyridamole or per os anticoagulants. A study suggested that in patients with this syndrome who had a thrombotic episode, long-term intensive warfarin treatment with or without a low dose of aspirin is efficient, as far as the prevention of further episodes is concerned[1]. In patients who have never had thrombotic episodes but have high levels of IgG anticardiolipin antibodies or positive lupus anticoagulant, prophylactic treatment with aspirin is indicated. In the case of destructive antiphospholipid syndrome, corticosteroids and anti-coagulant treatment are usually not enough and plasmapheresis is performed[11].

Regarding the prognosis, it has been shown that the presence of the IgM isotype of the anticardiolipin antibodies, as well as the history of thromboembolic episodes are strongly, negatively correlated with survival[5]. The recurrence rates for arterial or venous thrombotic episodes seem to be high in patients who are not under sufficient anticoagulant treatment and in one study, they reach 50%[(3)] in two years.

B) Pulmonary embolism (P.E.) may be characterized as massive either due to occlusion of high percentage of the pulmonary vascular network (usually more than 50% if there is no cardiopulmonary disease), or due to induction of hemodynamic instability. The use of the patient's hemodynamic condition is preferable in determining the severity of PE, because in case of previous pulmonary hypertension, even 20% occlusion of the pulmonary vascular network may cause hemodynamic instability of massive pulmonary embolism. The pathophysiology of this acute condition is due to the sudden and extensive occlusion of the pulmonary vascular network that leads to significant and abrupt increase of pulmonary arterial pressure and to right ventricle failure. Such patients present unstable hemodynamic condition, significant hypoxemia, despite oxygen administration and signs of reduced peripheral perfusion.

Mortality rates in massive pulmonary embolism are double to triple compared to total P.E. mortality rates. The main cause of death is the acute dilatation and failure of the right ventricle[12,13]. Hemodynamic and heart ultrasound studies in animals and humans have shown that the development of pulmonary hypertension leads to dilatation and right ventricle failure. The interventricular septum shifts to the left and this causes reduction of the pre-load of the left ventricle, of the pulse volume and of the cardiac output (syncopic episodes) and eventually of the coronary perfusion. Thus, the frequent identification of infarct in patients who died of P.E is explained[12.] But, even if the right ventricle dysfunction does not affect the left ventricle, the peripheral venous congestion that it causes may lead to the formation of new thrombi and P.E. recurrence as well as increase of mortality through this mechanism[14].

All these observations on the influence of the right ventricle dysfunction on the prognosis of P.E. led to the identification of a new group of patients with smaller degree of occlusion of the pulmonary vascular networks (at least >30%), stable hemodynamic condition and ultrasound-confirmed right ventricle dysfunction. This condition can be called severe or submassive pulmonary embolism and is associated with significant increase of mortality[15-18].

If our patient were assessed on the basis of the thorax CT scan, she suffered from massive pulmonary embolism. However, she was hemodynamically relatively stable upon admission (without forgetting of course the two syncopal episodes prior to admission that indicate significant hemodynamic instability). Her heart ultrasound though, presented a significant degree of right ventricle dysfunction and pulmonary hypertension, that significantly aggravates prognosis and indicates thrombolysis treatment.

Conservative treatment of pulmonary embolism with heparin administration initially and long-term coumarin anticoagulants later on is mainly secondary prevention against the formation of new thrombi and P.E. recurrence. Thrombolysis of thrombi that create the acute clinical condition is entrusted to the endogenous lytic system of the body that might not act on time or efficiently, thus leading to death. Thrombolysis presents the advantage of the more rapid resolution of thrombi, which is of fundamental importance in the prognosis of hemodynamically

unstable patients. Moreover, it seems to significantly reduce the rate of recurrence.

Since 1977, we have accepted (with the FDA approval) the use of thrombolysis for the treatment of massive P.E. that is associated with hemodynamic instability and hypoxia, despite oxygen administration[14]. Several studies[19,20-24] suggest treatment of massive P.E. with the administration of one of the approved thrombolytic preparations and regimes (streptokinase, urokinase and rt-PA) when there are no contraindications for thrombolysis that are the same with those of infarction. Their efficacy is almost the same when assessed angiographically and hemodynamically[20]. However, the more expedient administration of rt- PA, as was observed in a comparative study[25] between streptokinase (administered in 12 hrs) and rt-PA (administered in 2 hrs), leads to faster results, a fact that could be of significance for the patient's prognosis. As it has become obvious, there is no advantage in administering thrombolysis locally via catheter to the pulmonary artery compared to administration to a peripheral vein[26]. The angiographic, clinical and prognostic improvement of the patient can also be achieved with the administration of thrombolytics even 14 days after the episode[14,19,20] although in a retrospective study there seemed to be a benefit from the timely administration of treatment[27]. Nevertheless, in case of severe hemodynamic instability, thrombolysis must be immediate.

In submassive pulmonary embolism, as defined above, where there is an ultrasound picture with right ventricle dysfunction, despite limited disagreement[20,24,28], most of the authors agree that if there are no contraindications it is useful to administer thrombolytics. Goldhaber et al[29] first compared the treatment of submassive P.E. with heparin vs. rt-PA thrombolysis. Thrombolysis led to improvement of the right ventricle function, better pulmonary perfusion, reduction of relapses and reduced mortality (though not statistically significant). The results of this study were further verified by other studies, mainly the MAPPET study[16]. It is certain that larger studies are required for a definite answer to this question.

Our patient, upon admission, presented the following indications for thrombolysis: Recent episode of syncope (indication of hemodynamic instability), persisting hypoxemia with tachypnea and dyspnea, large occlusion of the pulmonary vascular network in thorax spiral CT (>50%) and right ventricular dysfunction affecting also the left ventricular function on echocardiogram. All the aforementioned classified her in the category of massive pulmonary embolism. The only indication that did not fit in that scheme was the normal arterial pressure but, aside from the fact that the patient had a history of hypertension, the two episodes of syncope proved that normal arterial pressure could not be taken for granted.

Following the first thrombolysis session, the patient did not present the expected clinical improvement. Although the second thorax CT scan indicated thrombolysis on the main branches of the pulmonary arteries bilaterally (complete on the right, partial on the left), large branches of the pulmonary arteries remained occluded, bilaterally. Furthermore, the heart ultrasound did not present any substantial improvement of the right ventricular function and there indications of pulmonary hypertension and hypoxemia still remained. Possibly, the patient's major disease (antiphospholipid syndrome) also affected the outcome of the first thrombolysis. We thus considered that the patient was in the category of submassive pulmonary embolism and due to lack of contraindications we proceeded to repeat thrombolysis. We did not in fact, find any similar reference in literature concerning repeat thrombolysis in case of non-satisfactory improvement of the patient. Given the lack of large and sufficient studies even on single thrombolysis, this was to be expected. However, the extent as well as the speed of clinical and imaging improvement of the patient justified our decision, at least for this specific case, without of course ignoring the fact that there was increased risk of hemorrhagic complications.

References

1. Khamastha MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR: The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl. J Med. 1995; 332: 993-997.
2. Rosove M, Brewer MC: Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. Ann Intern Med 1992; 117: 303-308.
3. Derksen RH, De Groot PG, Kater L, Nieuwenhuis HK: Patients with antiphospholipid antibodies and venous thrombosis should receive long-term anticoagulant treatment. Ann Rheum Dis 1993; 52: 689-692.
4. Levine SR, Brey RL, Kittner SJ: Antiphospholipid antibodies and recurrent thrombo-occlusive events. Lancet 1992; 340: 117-118.
5. Shah NM, Khamastha MA, Atsumi T, Hughes GRV: Outcome of patients with anticardiolipin antibodies (aCL): A ten year follow-up of 52 patients. Arthritis Rheum 1997; 40(Suppl): S300.

6. Gharavi AE, Harris EN, Asherson RA, Hughes GRV: Isotype distribution and phospholipid specificity in the antiphospholipid syndrome. Ann Rheum Dis 1987; 46: 1-6.
7. Hughes GRV, Harris EN, Gharavi AE: The anticardiolipin syndrome. J Rheumatol 1986; 13: 486-489.
8. McNeil HP, Simpson RJ, Chesterman CN, Krilis SA: Antiphospholipid antibodies are directed against a complex antigen that includes a lipid-binding inhibitor of coagulation: β_2-glycoprotein I (apolipoprotein H). Proc Natl Acad Sci USA 1990; 87: 4120-4124.
9. Arvieux J, Darnige L, Caron C, Reber G, Bensa JC, Colomb MG: Development of an ELISA for autoantibodies to prothrombin showing their prevalence in patients with lupus anticoagulants. Thromb Haemost 1995; 74: 1120-1125.
10. Gharavi AE, Wilson AE: Antiphospholipid antibodies. In: Wallace DJ, Hahn BH(eds) Dubois lupus erythematosus. Williams & Wilkins, Baltimore, 1997: 471-491.
11. Asherson RA: The catastrophic antiphospholipid syndrome. J Rheumatol 1992; 19: 508-512.
12. Coma-Canella I, Gamello C, Martinez-Onsurbe P, et al: Acute right ventricular infarction secondary to massive pulmonary embolism. Eur Heart J 1988; 9: 534-540.
13. Lualdi JC, Goldhaber SZ: Right ventricular dysfunction after acute pulmonary embolism: pathophysiologic factors, detection and therapeutic implications. Am Heart J 1995; 130: 1276-1282.
14. Goldhaber SZ: Thrombolytic therapy in venous thromboembolism: clinical trials and current indications. Clin Chest Med 1995; 16: 307-320.
15. Goldhaber SZ, De Rosa M, Visani L: International Cooperative Pulmonary Embolism Registry detects high mortality rate (abstract). Circulation 1997; 96 (Suppl I): I-159.
16. Konstantinides S, Geibel A, Olschewski M, et al: Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: results of a multicenter registry. Circulation 1997; 96: 882-888.
17. Ribeiro A, Lindmaker P, Juhlin-Dannfelt A, et al: Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate. Am Heart J 1997; 134: 479-487.
18. Kasper W, Konstantinides S, Geibel A, et al: Prognostic significance of right ventricular afterload stress detected by echocardiography in patients with clinically suspected pulmonary embolism. Heart 1997; 77: 346-349.
19. Goldhaber SZ: Pulmonary embolism. N Engl. J Med. 1998; 339: 93-104.
20. Arcasoy SM, Kreit JW: Thrombolytic therapy of pulmonary embolism: a comprehensive review of current evidence. Chest 1999; 115: 1695-1707.
21. Tapson VF, Witty LA: Massive pulmonary embolism: diagnostic and therapeutic strategies. Clin Chest Med. 1995; 16: 329-340.
22. Hyers TM: Venous thromboembolism. Am J Respir Crit Care Med 1999; 159: 1-14.
23. Jerjes-Sanchez C, Ramirez-Rivera A, Garcia M de L, et al: Streptokinase and heparin versus heparin alone in massive pulmonary embolism:a randomized controlled trial. J Thromb Thrombolysis 1995; 2: 227-229.
24. Ginsberg JS: Management of venous thromboembolism. N Engl J Med 1996; 335: 1816-1828.
25. Meneveau N, Schiele F, Vuillemenot A, et al: Streptokinase vs alteplase in massive pulmonary embolism: a randomized trial assessing right ventricular hemodynamics and pulmonary vascular obstruction. Eur Heart J 1997; 18: 1141-1148.
26. Vestraete M, Miller GAH, Bounameaux H, et al: Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. Circulation 1988; 77: 353-360.
27. Daniels LB, Parker A, Patel SR, et al: Relation of duration of symptoms with response of thrombolytic therapy in pulmonary embolism. Am J Cardiol 1997; 80: 184-188.
28. ACCP Consensus Committee on Pulmonary Embolism: Opinions regarding the diagnosis and management of venous thromboembolic disease. Chest 1996; 109: 233-237.
29. Goldhaber SZ, Haire WD, Feldstein ML, et al: Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993; 341: 507-511.