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


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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.
– 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 anti-diabetic 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 kg) 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 repulsion 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, yGT: 95U/L, total bilirubin: 0.43mg%, cholesterol: 272mg%, LDL: 163mg%, HDL: 67mg%, triglycerides: 209mg%. Blood gases: pH: 7.423, pO2: 49mmHg, pCO2: 30.3mmHg, HCO3: 20 Eq/l, O2SAT: 86.1%. Coagulation control: PT: 16sec, APTT: 25.5sec, INR: 1.20, FDP>20Ìg/ml (NV: <0.5Ìg/ml), D-Dimers>8Ìg/ml (NV: <0.5Ìg/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, V1, V2.

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 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
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% O₂ oxygen mask, 12lt/min: pH: 7.389, pO₂: 52.5mmHg, pCO₂: 38.2mmHg, HCO₃: 23 mEq/l, O₂SAT: 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 O₂ administration 3lt/min, pH: 7.397, pO₂: 80mmHg, pCO₂: 35.7mmHg, HCO₃: 21.9, O₂SAT: 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).
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, 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 immunoglobulins 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 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 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 b2-glycoprotein I and prothrombin or protein complexes with phospholipids.
The incidence of APA found in systemic lupus erythematosus and in the lupus-like syndrome ranges in various studies 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

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

<table>
<thead>
<tr>
<th>THROMBOTIC SYNDROMES</th>
<th>PATIENT RESULTS</th>
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<tbody>
<tr>
<td><strong>1. FAMILIAL (HEREDITARY)</strong></td>
<td></td>
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<tr>
<td>A. Insufficient inhibition of coagulation factors</td>
<td></td>
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<tr>
<td>i. Antithrombin III deficiency</td>
<td>antithrombin III:88% (n.v. 85-111)</td>
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<tr>
<td>ii. Protein C deficiency</td>
<td>protein C:103% (n.v. 78-134)</td>
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<tr>
<td>iii. Protein S deficiency</td>
<td>negative</td>
</tr>
<tr>
<td>iv. Leiden V factor</td>
<td></td>
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<tr>
<td>B. Fibrinolysis disorders</td>
<td>fibrinogen:268mg/dl (n.v. 146-380)</td>
</tr>
<tr>
<td>i. Fibrinogen disorder</td>
<td>plasminogen: 130% (n.v. 75-128)</td>
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<tr>
<td>ii. Plasminogen deficiency</td>
<td></td>
</tr>
<tr>
<td>C. Unclear mechanism</td>
<td>homocystein :14μmol/l (nv. 9.40-14)</td>
</tr>
<tr>
<td>i. Homocystinuria</td>
<td></td>
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<tr>
<td><strong>2. ACQUIRED</strong></td>
<td></td>
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<tr>
<td>A. SYNDROMES OR DISEASES</td>
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<tr>
<td>i. Cardiolipin syndromes</td>
<td>anti-Cardiolipin (ACA):</td>
</tr>
<tr>
<td></td>
<td>IgM:329 U/ml (n.v. 0-100)</td>
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<td></td>
<td>IgG:28 U/ml (n.v. 0-100)</td>
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<tr>
<td></td>
<td>B2-GPI:</td>
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<tr>
<td></td>
<td>IgM:55 U/ml (n.v. 0-100)</td>
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<tr>
<td></td>
<td>IgG:50 U/ml (n.v. 0-100)</td>
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<tr>
<td></td>
<td>DRVVT: Positive for LA (Lupus anticoagulant)</td>
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<tr>
<td>ii. Malignancies</td>
<td>– Thorax, lower / upper abdomen CT: negative tumor markers :negative</td>
</tr>
<tr>
<td>iii. Hyperlipidemia</td>
<td>hypercholesterolemia, hypertriglyceridemia</td>
</tr>
<tr>
<td>iv. Diabetes mellitus</td>
<td>yes</td>
</tr>
<tr>
<td>v. Collagenoses</td>
<td>– Antinucleic ANA, anti-n-DNA: negative</td>
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<tr>
<td></td>
<td>C3:1.664 g/l (n.v. 0.50-0.90)</td>
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<tr>
<td></td>
<td>C4:0.250 g/l (n.v. 0.10-0.40)</td>
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<tr>
<td></td>
<td>– Ra-test: &lt;9.6 IU/ml (n.v. 0-15)</td>
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<td></td>
<td>– CRP: 9.3 mg/l (n.v. 0.5)</td>
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<tr>
<td></td>
<td>– intravaginal ECHO: negative</td>
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<td></td>
<td>– progesteron: 4.7nmol/l (n.v. 0.85-8.3)</td>
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<tr>
<td></td>
<td>– FSH: 4.2 mIU/l (n.v. 4-13)</td>
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<td></td>
<td>– LH: 2.8 mIU/l (n.v. 1-18)</td>
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<tr>
<td></td>
<td>(hormonal measurements during the 1st phase of the menstrual cycle)</td>
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<tr>
<td>vi. Multicystic Ovaries syndrome</td>
<td></td>
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<tr>
<td>B. PHYSIOLOGICAL CONDITIONS</td>
<td>yes</td>
</tr>
<tr>
<td>i. Obesity</td>
<td>one month due to Achilles tendon rupture</td>
</tr>
<tr>
<td>ii. Immobilisation</td>
<td></td>
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</table>
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 per 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 (PGI₂) 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.

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 dipyriramole 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. 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.

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. 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% 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. 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.

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.

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.

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. 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. Several studies 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 the same with those of infarction. Their efficacy is almost the same when assessed angiographically and hemodynamically. However, the more expedient administration of rt-PA, as was observed in a comparative study 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. The angiographic, clinical and prognostic improvement of the patient can also be achieved with the administration of thrombolytics even 14 days after the episode, although in a retrospective study there seemed to be a benefit from the timely administration of treatment. 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, most of the authors agree that if there are no contraindications it is useful to administer thrombolytics. Goldhaber et al 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. 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


