

Clinical Notes

Successful thrombolysis of submassive pulmonary embolism by tissue plasminogen activator

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A 45-year-old Sudanese male presented in June 2001 to the Accident and Emergency Department of Riyadh Medical Complex, Kingdom of Saudi Arabia, complaining of 3-days difficulty in breathing worsened by exertion, and now associated with chest pain and palpitation of one-day duration. The dyspnea had gradually increased over time and on the day of presentation became associated with orthopnea. The chest pain was dull deep and central non-radiating and moderate to severe and had no relieving factors. He was a former supervisor of an export and import company but had been jobless for the past 6 months, married with 6 children and a non-smoker. He denied any significant past medical or surgical history. There was no history of recent prolonged travel and no known allergies. On examination, he was in distress, dyspneic and tachypneic. The vital signs revealed a respiratory rate of 33 breaths per minute, pulse rate of 120 beats per minute, blood pressure 110/70 mm Hg and temperature of 37°C. Examination of the cardiovascular system showed a raised jugular venous pressure with a prominent, a wave, a fourth heart sound (S₄) gallop and loud pulmonic second sound (P₂), no murmurs were noted. The chest was clear on auscultation. Abdominal and central nervous system examinations were normal. No peripheral evidence of a deep venous thrombosis was noted. Urinalysis was normal. The complete blood count showed a white blood cell count of 5400, hemoglobin of 15.2 and a platelet count of 147. The erythrocyte sedimentation rate was 3 mm per hour. The urea and electrolytes, liver function tests, serum amylase and lipid profile were normal. The creatinine kinase level was normal but lactate dehydrogenase level was raised at 255 u/l. Prothrombin time was 18 seconds, the internationally normalized ratio was 1.15, and the activated partial thromboplastin time was 28.3 seconds, and D-dimer level was < 500. Arterial blood gases showed a pH 7.479, partial pressure of carbon dioxide (pCO₂) 22.1 mm Hg, partial pressure of oxygen (pO₂) 55 mm Hg, bicarbonate (HCO₃) 16.4 and a saturation of 70%. The electrocardiogram revealed a P pulmonale with a classical S1 Q3T3 pattern and later he developed a deep and symmetrical Twave inversion in the anterior leads v1-3 suggestive of a right ventricular strain. The chest radiograph showed radiolucency of the right lung "Westermark sign" with dilatation of the main pulmonary artery (PA).



Figure 1 - Spiral computed tomography scan with contrast showing complete obstruction of the right and partial obstruction of the left branch of the main pulmonary artery.

Based on the presentation and preliminary diagnostic work-up, a diagnosis of an acute submassive pulmonary embolism (PE) was made. A transthoracic echocardiogram (TTE) revealed a dilated right atrium, ventricle, and main PA as well as an inferior vena cava and hepatic vein with type 2 paradoxical septum. Left ventricular size and function was normal. Severe tricuspid regurgitation and a calculated pulmonary artery pressure of 95 mm Hg, no intracardiac clot was seen. Perfusion scan showed perfusion defects in the lower half of the right lung and patchy perfusion defects in the left lung compatible with a very high probability of pulmonary thromboembolism. Results of a computed tomography (CT) scan of the chest with contrast showed a filling defect within the lumen of the right PA and a filling defect and partial obstruction were noted in the left PA (Figure 1). The patient was treated with a standard protocol for tissue-type plasminogen activator (Actilyse: Registered trademark of Boehringer Ingelheim) with a 10 mg intravenous bolus over 2 minutes followed by a 90 mg intravenous infusion over 2 hours. He was then given a bolus of unfractionated heparin of 8800 units and continued on an intravenous infusion at 1400 units per hour adjusted to achieve an activated partial thromboplastin time of 1.5-2 times the normal. Warfarin 5 mg per os one dose was administered. Within 12 hours his dyspnea resolved, the pulse rate dropped to 76 beats per minute and an arterial blood gas exam showed a PO₂ of 86 mm Hg with a saturation of 90% on room air. A repeat TTE 5 days later revealed a dramatic improvement from the first one with a PA diameter of 2.7 cm, no more paradoxical inter-ventricular septal movement and only mild to moderate PA hypertension and tricuspid regurgitation, with mild right ventricular dilatation. The perfusion-scan showed small, and patchy residual perfusion defects over both lung fields indicating marked resolution of the pulmonary embolus. Anticoagulation with heparin was

continued for 10 days and warfarin dosage was adjusted to yield an internationally normalized ratio of 2-3. Doppler ultrasound of the lower limbs as well as venography was negative for a deep venous thrombosis. Protein S activity was normal, however, protein C activity was reduced at 62.7% (normal range 70-140%). Protein C levels are often low in the acute stage of a thrombosis as in this case and were repeated off warfarin after 6 months of anticoagulation. The level was low, protein C activity was 45%, and anticoagulation therapy was aimed to be continued for 18 months. Sixteen months after, the patient remains well, symptoms free and maintained on warfarin anticoagulation, a repeat TTE showed normal right ventricular dimensions and an estimated pulmonary artery pressure of 23 mm Hg.

Primary therapy for PE is at present attracting much deserved attention. It comprises pharmacological thrombolysis (TLS) or mechanical removal of the obstructing embolus.¹⁻³ The return of vessel patency and the consequent avoidance of acute and chronic complications of PE are the aim of these therapeutic interventions.

Complications of these 2 modalities of treatment include major hemorrhagic complications, which may be fatal in the case of TLS, on one hand, and pulmonary infarction, wound hematoma and infection, myocardial infarction, ventricular perforation, and a reperfusion syndrome with hemorrhage and focal pulmonary edema in mechanical removal on the other.¹ Therefore, risk stratification of patients is needed to assign the optimal therapy in each individual case.

Pulmonary embolism is divided into 1) massive - systemic arterial hypotension present, 2) moderate to large (sub-massive) - right ventricular hypokinesis with normal systemic arterial pressure, and 3) small to moderate - normal right heart function and normal systemic arterial pressure.⁴ In massive PE the primary therapy with either TLS or embolectomy is undisputed and offers greatest chance of survival;⁴ in small to moderate PE the secondary therapy with anticoagulation or an inferior vena cava filter, or both, results in a good prognosis² and in cases of moderate to large (sub-massive) PE the optimal therapy is a matter of intense debate. These patients demonstrate right ventricular dysfunction (RVD) on echocardiogram, which occurs in approximately 40% of normotensive patients with acute PE.⁵ It is caused by pulmonary vascular obstruction, hypoxemia and a neuro-hormonal response releasing vaso-constricting compounds, which raise pulmonary vascular resistance.² This RVD entails an increased risk of recurrent PE despite adequate anticoagulation.⁴ Right ventricular dysfunction is defined as right ventricular enlargement combined with loss of inspiratory collapse of the inferior vena cava, without left ventricular or mitral valve disease.³ Apart from RVD patients with sub-massive PE, demonstrate pulmonary artery hypertension, which can readily be diagnosed by echocardiography and is defined by a tricuspid regurgitant jet velocity >2.8 m per second.⁴ The medical community generally favors non-invasive treatment

options, which make less or no harm, are readily available and offer patients the best prognosis. As early as 1964 it was demonstrated that streptokinase could be used in TLS of PE, and hence an alternative to heparin therapy, until then the proven standard for the treatment of PE,³ had materialized.¹ Three decades and 5 randomized clinical trials compare TLS and heparin therapy and Goldhaber et al⁶ raised the issue of RVD as an indication of TLS in submassive PE. Other studies, which followed, failed to confirm any benefit from TLS of hemodynamically stable patients with evidence of RVD.¹ Two recent studies are available that address this issue and warrant our scrutiny.⁴ The first study by Hamel et al⁵ a monocenter registry reported in July of 2001 on 128 patients divided into 2 groups of 64 each, to receive either TLS or heparin therapy showed no clinical efficacy results for TLS. The patients were categorized as massive PE with stable hemodynamics namely, submassive PE with RVD. Thrombolytic regimens were heterogenous and included alteplase, urokinase, and saruplase, and the only advantage found was one-week higher perfusion lung scan improvement in those treated with TLS. The in hospital mortality showed that recurrence rate of PE was the same in both groups and while all patients survived in the heparin treated group 4 died in the TLS group, 2 from intra-cerebral bleeding. While the authors claim that their patients were well matched as regard to baseline echocardiographic findings, which they base the power of their study to confirm the null hypothesis, they agree that all cerebral bleeding occurred in high-risk patients; namely elderly and hypertensive patients. They point out that the number of patients were relatively small, which is not surprising for a monocenter study in our opinion, and that it would take a prospective randomized trial with more than 1000 patients to compare the results of the 2 treatments with hard endpoints (death, severe bleedings and so forth). We believe that the study by Hamel et al⁵ did mainly address the efficacy and safety aspect of treatment with either heparin or TLS and did not take into consideration the possible long-term benefit of a return of RVD to normal since only in the hospital results of treatment were reported. Their patient population with a mean age of 72 ± 12 years was rather elderly, and complications of bleeding which occurred point to the necessity of avoidance of TLS in this group of patients. A follow-up study in this patient population is probably difficult and unyielding due to fallout. Konstantinides et al⁴ reported a prospective randomized double-blind placebo controlled trial of 256 enrolled patients with submassive PE and RVD, demonstrated a low risk of major hemorrhagic complications in the TLS (alteplase plus heparin) group and a 3 times the risk of death or treatment escalation in the heparin plus placebo group.⁴ For the first time they reported a short-term benefit (in-hospital) of TLS versus heparin in this particular patient group, their exclusion criteria were stringent and the patient population with a mean age of 62 ± 10 years somewhat younger than in the study by Hamel et al.⁵ Long term benefit results might be

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expected in the future. Our patient presented with the classical symptoms and signs of an acute submassive PE, but since thrombolysis carries the aforementioned significant risk of hemorrhage in individual patients, the diagnosis needs to be confirmed before TLS is initiated. This was accomplished by the clinical features, high probability ventilation-perfusion scan and spiral computed tomography of the chest which is known to have excellent correlation with pulmonary angiographic findings³ and the TTE confirming the presence of a submassive PE with RVD in a normotensive patient. Rapid diagnosis of the condition and expeditious use of appropriate imaging studies as mentioned in our report are important for the critical first hour since 70-80% of patients will need further therapy aside from heparin.² After considering the scientific background and publications prior to 2001 we opted to offer our patient thrombolytic therapy after ascertaining the absence of major contraindications as outlined by Al Moosa.¹ This therapy can be offered to patients presenting with PE up to 14 days after the onset of symptoms as has been previously documented.³ He improved dramatically. Investigations to identify the source of the PE were negative, as mentioned above, thrombophilia was suspected since our patient presented with a first unprovoked event and an age ≥ 45 years. The findings of protein C deficiency lead us to extend the treatment period to 18 months in accordance with recent recommendations. The relatively young age of our patient and the absence of major contraindications to TLS particularly hypertension lead in our opinion to a

smooth post TLS course in conjunction with the return of right ventricular function to normal. This benefit was maintained for now 16 months. Therefore, we eagerly await the long due large-scale clinical trial called for by Goldhaber.²

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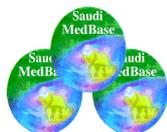
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Related Abstract

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Title: Deep venous thrombosis and thromboembolism
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Abstract

Venous thromboembolism continues to be a frequent cause of morbidity and mortality in medical and surgical practice. This paper describes the incidence and the identification of high-risk groups with special reference to orthopedic and congenital thrombophilia patients. The pathogenesis and natural history of deep vein thrombosis is described, based on Virchow's original triad, with a further discussion of the pharmacological and mechanical treatment options currently available. The original work showing the reduction of fatal pulmonary embolism with low dose heparin (UFH) is described, as well as a brief review of alternative methods of pharmacological thromboprophylaxis. The influence of thromboprophylaxis on venous thromboembolic disease has recently been brought into question. Data are presented showing a highly significant fall in the incidence of venous thromboembolism since the introduction of these pharmacological agents. The development of the low molecular weight heparins (LMWH) has provided an advance in thromboprophylaxis with their theoretical ability to be effective antithrombotic agents, with a lower bleeding tendency compared with UFH. Data are described from a recently completed 4000 patient double-blind trial comparing the safety and efficacy of LMWH with standard UFH. This shows an almost identical efficacy for the types of heparin; however, a significant reduction in the parameters of bleeding is seen with LMWH.