Thrombolysis in a mechanically ventilated patient with haemodynamically stable acute pulmonary embolism and a patent foramen ovale

JJ Arends¹, W Zondag², S Osanto³, MV Huisman²

¹ Department of Intensive Care, Albert Schweitzer Hospital, Dordrecht, The Netherlands.
² Section of Vascular Medicine, Department of General Internal Medicine-Endocrinology, Leids University Medical Center, Leiden, The Netherlands
³ Section of Medical Oncology, Department of General Internal Medicine-Endocrinology, Leids University Medical Center, Leiden, The Netherlands

Abstract - Systemic arterial hypotension is the only Food and Drug Administration approved indication for thrombolysis in patients with acute pulmonary embolism (PE). Recent guidelines suggest consideration of thrombolytic treatment in selected patients with haemodynamically stable PE, who have an intermediate risk for adverse outcome. Still, administration of thrombolytic therapy for hypoxia alone remains controversial. In this article we report a case of a patient with haemodynamically stable PE and a patent foramen ovale (PFO), requiring mechanical ventilation for hypoxaemic respiratory failure. We address the question whether the presence of a PFO in haemodynamically stable patients with acute PE could be an additional risk factor for an adverse outcome and an indication for thrombolysis.

Keywords - pulmonary embolism, thrombolysis, patent foramen ovale, hypoxaemia, respiratory failure, mechanical ventilation

Introduction
Systemic arterial hypotension is the most important risk factor for mortality and the only FDA (Food and Drug administration) approved indication for thrombolysis in patients with acute pulmonary embolism (PE) [1]. The indication for thrombolysis in patients with PE and a normal blood pressure, but with other indicators of poor outcome, is controversial. Generally, the bleeding risk was considered to outweigh the potential benefit of thrombolysis in these patients. Some of the most recent guidelines suggest consideration of thrombolytic treatment in selected patients with haemodynamically stable PE, who have an intermediate risk for adverse outcome [2,3]. The European Society of Cardiology guidelines state that “thrombolysis may be considered in selected intermediate risk patients with PE after thorough consideration of conditions increasing the risk of bleeding”[4]. In these guidelines, right ventricular dysfunction or positive markers of myocardial injury are considered to have an intermediate risk of short-term mortality in acute PE. However, their prognostic assessment is limited by the lack of universally accepted criteria [5]. The American College of Chest Physicians guidelines recommend administration of thrombolytic therapy in “selected high risk patients without hypotension, who are judged to have a low risk of bleeding (Grade 2B)”[6]. This guideline also suggests that “the decision to use thrombolytic therapy is based on the clinicians’ assessment of PE severity, prognosis and risk of bleeding”.

Tachypnoea and low arterial oxygen content are independent risk factors of an adverse outcome after acute PE [7,8]. The risk on short-term mortality in haemodynamically stable patients with acute PE and respiratory failure is unknown. Several randomized controlled trials on acute PE and thrombolytic therapy report on isolated parameters of hypoxia or respiratory failure, but the lack of universally accepted criteria currently makes risk assessment by analysis including meta-analysis impossible [9-14]. Therefore, administration of thrombolytic therapy for hypoxia alone remains controversial. Still, mortality due to respiratory failure in patients with haemodynamically stable acute PE might be as high as 12.9% [15].

In this article we report a case of a patient with haemodynamically stable PE and a patent foramen ovale (PFO), requiring mechanical ventilation for hypoxaemic respiratory failure. We address the question whether the presence of a PFO in haemodynamically stable patients with acute PE could be an additional risk factor for an adverse outcome and an indication for thrombolysis.

Case report
A 48-year old man presented to the emergency department of our hospital with a history of progressive dyspnoea for two days and abdominal pain. Six years ago he was treated for an idiopathic deep vein thrombosis with vitamin K antagonists for six months. Five months earlier he had been diagnosed with non-seminoma testis with para-aortal metastases, treated with a Bleomycin Etoposide cis-Platinum regimen, during which...
he used low molecular weight heparin (LMWH) as thrombosis prophylaxis (Nadroparin 2850 units of anti-Xa once daily). At his most recent outpatient evaluation he had no complaints and had a blood pressure of 110/65 mmHg and a pulse rate of 72/min. On examination in the emergency department he was tachypnoeic, breathing 36/min, with an oxygen saturation of 63% on room air. His blood pressure was 140/85 mmHg with a pulse of 115/min. Arterial blood gas analysis showed a pH 7.26, a PCO2 32.3 mmHg and a PO2 of 42.9 mmHg. He was immediately intubated and mechanically ventilated because of the hypoxaemic respiratory insufficiency and subsequently transported to the intensive care unit. A CT-scan of the thorax and abdomen prior to ICU admission, showed bilateral massive pulmonary embolism (figure 1) and infarction of both kidneys (figure 2) and the spleen (figure 3). During positive pressure ventilation, the patient's hypoxaemia worsened (PaO2 55 mmHg FiO2 95% PEEP 15 cm H2O), and required prone position mechanical ventilation. Because of the severe and progressive hypoxaemia, it was decided to give thrombolysis. He was treated with intravenous thrombolysis with alteplase (15 mg bolus, followed by 50 mg in 60 minutes and 35 mg in 30 minutes), followed by intravenous unfractionated heparin (UFH). Within seven hours of starting thrombolysis, patient-prone-position ventilation could be abandoned. Within 72 hours after the start of thrombolysis, mechanical ventilation was ceased. After removal of the ventilation tube an expressive aphasia was noted, suggestive for a paradoxical intracranial embolism developed during mechanical ventilation. Ceberal MRI showed a left subcortical parietal infarction (figure 4) and a left cerebellar infarction. Retrograde medical history revealed that the patient had had temporary pain in his left calf two weeks prior to admission. Doppler ultrasound showed a thrombus in his left popliteal and femoral vein. A transthoracic echocardiogram showed a right-to-left shunt, suggestive for a PFO or atrial septal defect. The patient was discharged in good condition with Nadroparine 7500 units of anti-Xa twice daily. He recovered quickly and the aphasia ceased during the following months. At the patient's request, further analysis and closing of the PFO was not performed until the completion of his chemotherapy sessions.

Discussion

The prevalence of PFO is high (20 – 35 %) through all decades of life [16]. In a study of 139 patients with PE, the presence of PFO was associated with a mortality rate more than twice as high as in patients without evidence of right-to-left shunt [18]. Patients with PFO also experienced five times more in-hospital complications, defined as death, ischaemic stroke, arterial embolism, major bleeding and the need for endotracheal intubation or cardiopulmonary resuscitation. Especially peripheral arterial embolism and endotracheal intubation were more common in patients with PE and PFO compared to patients with PE without intracardiac shunting. However, mechanical ventilation in these patients might not improve oxygenation and even increase the risk of paradoxical embolism by increasing the intracardiac shunt fraction [17-19].

Patients with PE and hypoxaemia caused by right ventricular shunting through a PFO could be considered as “selected intermediate risk patients”, as mentioned in the guidelines [20,21], who might benefit from thrombolysis. The extension of indication for thrombolysis in patients with PE and intracardial shunting has also been recently suggested by Konstantinides [22].

There are three major reasons, based on the pathophysiology, why patients with PE and intracardiac shunting could benefit from thrombolytic therapy, as stated below.

First, the elevated pressure in the right side of the heart, caused by the large thrombus in the pulmonary artery, increases the risk of paradoxical emboli in patients with acute PE and PFO. Elevated right ventricular pressure is a driving force for the

Figure 1. CT pulmonary angiogram of our patient, showing bilateral pulmonary embolisms.

Figure 2. CT abdomen of our patient, showing bilateral renal infarction.
Thrombolysis in a mechanically ventilated patient with haemodynamically stable acute pulmonary embolism and a patent foramen ovale

Migration of emboli to the left side of the heart. By reducing the volume of the thrombus by thrombolysis, the pressure in the right heart side declines and the risk of paradoxical emboli decreases.

One of the benefits of thrombolysis over standard treatment with UFH is that by resolving the clot, the right ventricular pressure improves impressively within 24 hours, in contrast to the normalisation with UFH treatment in which it takes three weeks [23-25]. Secondly, thrombolysis could prevent the need for mechanical ventilation, indirectly preventing a further increase in intracardiac shunt fraction by positive pressure ventilation, which could be considered an additive risk for the development of paradoxical emboli. Lastly, in patients with PFO and paradoxical emboli, thrombolysis could improve the outcome of the symptoms of arterial emboli. Most effect? paradoxical emboli in patients with PFO and PE affect the brain (40%) and limbs (15%)

Figure 3. CT abdomen of our patient, showing splenic infarction.

For ischaemic stroke, the administration of thrombolytic agents within 3-6 hours from the start of the symptoms effectively reduces the mortality and dependency in daily activities [27]. Also, for patients with arterial occlusion in a limb, thrombolysis could be beneficial [28].

Conclusion
Patients with PE and intracardiac shunting through a PFO are at high risk of mortality and other in-hospital adverse events. Haemodynamically stable patients with acute PE and a PFO could benefit from thrombolysis when they have a hypoxaemia that requires mechanical ventilation and a low bleeding risk. Additionally, thrombolysis could be favourable in the outcome of paradoxical emboli.

Figure 4. MRI brain (T2) of our patient, showing subacute infarction of the left parietal lobe.

References


