

## Case reports

# Life Threatening Massive Pulmonary Embolism Treated with Reteplase: A Case Report

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### ABSTRACT

*We describe a case of sudden and severe pulseless electrical activity in a 30 year old woman which was managed successfully with reteplase and heparin one day following an anterior cruciate ligament repair. The presentation of a sudden collapse with ECG findings of S<sub>1</sub>Q<sub>3</sub>T<sub>3</sub>, early precordial lead ST depression and partial right bundle branch block were indicative of an acute pulmonary embolus. The cardiopulmonary collapse necessitated rapid treatment in the absence of confirmatory investigations. Reteplase (10 U stat followed by 10 U at 30 minutes) led to a dramatic improvement in the cardiovascular status of the patient. One day following the cardiac arrest the patient was extubated and responding normally. A spiral CT performed later confirmed multiple small embolic defects in the lower pulmonary arteries of both lower lung zones.*

*This case highlights the utility of reteplase in the management of an acute pulmonary embolism and in an emergency, recent surgery is not necessarily a contraindication to its use. (Critical Care and Resuscitation 2000; 2: 278-281)*

**Key words:** Acute pulmonary embolism, reteplase, pulseless electrical activity, shock

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For more than 30 years thrombolytic agents have been used to dissolve or reduce thromboembolism and improve the circulation in patients with acute pulmonary embolism (PE).<sup>1</sup> Numerous studies have been conducted comparing different drugs and dosing regimes in haemodynamically stable patients<sup>2-8</sup>. All randomised controlled studies have been conducted on patients where the diagnosis had been firmly established and where patients with conditions contraindicating thrombolysis have been excluded. Reports of the use of thrombolysis in acute life threatening situations with cardiovascular collapse are rare<sup>6,13-16</sup>. In most cases the haemodynamic condition of the patient allowed sufficient time for pulmonary angiography to be performed. In the majority of recent cases the drug used was alteplase.

The hospital mortality rate in patients with massive PE and shock is high.<sup>6</sup> We report the successful use of reteplase in the management of a patient who suffered an acute cardiovascular collapse due to a massive PE.

### CASE REPORT

A 30 year old female had undergone an anterior cruciate ligament repair under general anaesthesia at a district hospital. She had been previously healthy and her only medication was an oral contraceptive consisting of levonorgestrel and ethinyloestradiol. A continuous femoral nerve block was used for post-operative pain relief. The nerve block was stopped and all intravenous lines were removed on the first post-operative morning.

At 0940 hours she felt faint and collapsed. On examination, she was pale and sweaty with a blood

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pressure of 99/54 mmHg and a heart rate of 39 beats per minute, which increased rapidly to 58 beats per minute. She regained consciousness within 15 seconds and had an oxygen saturation of 98% on O<sub>2</sub> at 10L/min via a facemask. She vomited but had no chest pain. Her blood pressure after a few minutes rose to 106/62 mmHg and her heart rate increased to 69 beats per minute. At this stage she was assumed to have suffered a vasovagal attack.

At 1310 hours she was found to be unrousable. Oxygen was again administered and she was transferred to the post anaesthetic care unit. Intravenous access was established but at 1330 hours she suffered a cardiorespiratory arrest with pulseless electrical activity. She was intubated and manually ventilated. While a thready pulse became palpable the blood pressure was unrecordable. A bolus of intravenous atropine (0.6 mg) and of adrenaline (1 mg) were administered with minimal effect. The ECG revealed a characteristic S<sub>1</sub>Q<sub>3</sub>T<sub>3</sub> pattern of pulmonary embolism and early precordial lead ST depression with partial right bundle branch block indicative of right ventricular hypertrophy or strain. She was transferred to a major hospital.

On arrival in the emergency department at 1400 hours she was unconscious, deeply cyanosed with no palpable pulses. She was intubated and ventilated with supplemental oxygen. An adrenaline infusion was in progress. Pulse oximetry was unable to record the oxygen saturation. Her core temperature was 35.0°C. Two further bolus doses of 1mg of adrenaline had no effect. On clinical and electrocardiographic grounds a diagnosis of PE was made and it was decided to institute thrombolysis.

At 1405 hours the patient was given unfractionated heparin 5000 U intravenously followed by reteplase 10 U intravenously. Within 60 seconds her colour improved noticeably and after 5 minutes the blood pressure was 112/90 mmHg, heart rate was 130 beats per minute and pulse oximetry revealed an oxygen saturation of 100%. The arterial blood gas taken at this stage (F<sub>i</sub>O<sub>2</sub> 100%) showed a pH 7.00, PCO<sub>2</sub> 57mmHg, PO<sub>2</sub> 303mmHg, bicarbonate 13.2mmol/L and base excess - 19.3 mmol/L. Blood biochemistry revealed a glucose 13.5 mmol/L and normal urea, creatinine and electrolyte concentrations.

She was transferred to the intensive care unit where a second dose of reteplase 10 U was administered 30 minutes after the first dose. The heparin was continued at 1000 U per hour and the infusion was adjusted to maintain the APTT at or above 2x normal. The arterial blood gas taken at 1630 hours (F<sub>i</sub>O<sub>2</sub> 50%) revealed a pH 7.1, PCO<sub>2</sub> 55 mmHg, PO<sub>2</sub> 251 mmHg, bicarbonate 16.8 mmol/L and BE - 13.2 mmol/L, and at 1845 hours (F<sub>i</sub>O<sub>2</sub> 40%) the blood gas revealed a pH 7.26, PCO<sub>2</sub> 36

mmHg, PO<sub>2</sub> 211 mmHg, bicarbonate 15.6 mmol/L and base excess - 10.3 mmol/L.

She was sedated and ventilated overnight. The next morning she was noted to be awake and responding to commands. The sedation was stopped and later that morning she was extubated and appeared neurologically normal. Further recovery was complicated by extensive bleeding into the tissues around the operative and vascular puncture sites, necessitating a transfusion of 4 units of blood. After 4 days she was transferred to the general ward for initiation of warfarin therapy and further care. Her neuropsychiatric state appeared normal. A spiral CT showed extensive pulmonary emboli confined mostly to the peripheral pulmonary arteries of the lower lung zones. She was discharged from hospital 13 days after admission.

## DISCUSSION

In spite of improved prevention and treatment of pulmonary embolism, the mortality is still estimated to be between 20 - 30%. It is the third most common cardiovascular cause of death, with two thirds of the deaths occurring within the first few hours as a result of severe haemodynamic and respiratory disturbances.<sup>5,6,10</sup>

Thrombolytics are often used to dissolve or reduce the size of the thromboembolism and improve haemodynamic status and gas exchange. These agents are plasminogen activators which yield the fibrinolytic enzyme plasmin. Free plasmin is rapidly neutralised by the serine proteinase inhibitor alpha-antiplasmin. Fibrin bound plasmin is protected from this rapid neutralisation and clot lysis is promoted.

Thrombolytic drugs have been studied and used extensively in the treatment of acute myocardial infarction.<sup>8</sup> Streptokinase, urokinase and alteplase (tPA) have all been used in the treatment of pulmonary embolism and recently the newer drug, reteplase (rPA) has been studied.<sup>10</sup> Alteplase, as a two hour infusion, is approved in the United States of America by the Food and Drug Administration for use in the treatment of pulmonary embolism and has been used in several studies. Prior to the use of thrombolytic therapy it is recommended that the diagnosis should be confirmed and contraindications are excluded as the side-effect of haemorrhage can be severe and fatal.

Reteplase is the first clinically available modified tissue plasminogen activator produced by recombinant DNA technology. It has a longer half-life (e.g. 13 - 16 minutes) than alteplase, making it suitable for a more convenient, double bolus administration compared with an infusion.<sup>17</sup> Reteplase was developed for the treatment of acute myocardial infarction and the recommended dose is 10 U followed by a further 10 U after 30 minutes. Each injection must be given over a period of

no longer than 2 minutes.<sup>11,17</sup> Using this regimen, significantly higher coronary artery patency rates have been achieved in the treatment of acute myocardial infarction compared with other thrombolytic agents.<sup>8</sup> In pulmonary embolism there is no significant difference in effect when the thrombolytic drug is injected through a peripheral vein or directly into the pulmonary artery,<sup>12</sup> and there is a less severe systemic fibrinogen depletion (a significant problem with streptokinase and urokinase).<sup>11</sup> Reteplase is also not as antigenic as streptokinase or urokinase, although anaphylaxis has been reported.<sup>17</sup>

Contraindications to the use of thrombolytics include predisposition to haemorrhage, anticoagulant medication, brain tumours, vascular malformations, aneurysms, cerebrovascular incidents, prolonged cardiopulmonary resuscitation, severe hypertension, peptic ulcers, renal or hepatic failure or any of the following within the previous three months: major trauma or surgery, obstetric delivery, organ biopsy or puncture of noncompressible blood vessels. Major complications include cerebral haemorrhage and haemopericardium.

In the case we describe, the patient clinically appeared to have a large pulmonary embolus which had almost completely obstructed the pulmonary circulation. Her condition did not allow time for a spiral CT-scan or pulmonary angiography to confirm the diagnosis. The diagnosis was made on clinical and electrocardiographic evidence and confirmed retrospectively by spiral CT scan. Our institution does not have facilities for cardiothoracic surgery and so surgical embolectomy was not an option. We had no previous experience in the use of reteplase in pulmonary embolism but considerable experience in its use in acute myocardial infarction. The first dose of reteplase had an almost immediate effect on the patient's oxygenation and circulation with the deep cyanosis clearing within 1 – 2 minutes and the blood pressure returning to normal within 5 minutes. We postulate that the clot was sufficiently reduced to allow it to travel to peripheral pulmonary arterial vessels and improve pulmonary perfusion.<sup>18</sup> The arterial blood gas analysis performed 5 minutes after the first dose of reteplase revealed a severe metabolic and respiratory acidosis with a high partial pressure of oxygen, indicating a prolonged period of poor peripheral perfusion.

The knee surgery less than 24 hours previously is usually considered a contraindication to the use of reteplase but given the severity of the patient's condition, the risk of causing a severe haemorrhage was taken. The patient was also heparinised to prevent further clot formation or the extension of existing clot. The manufacturer recommends that a loading dose of heparin

be given concomitantly with the first dose of reteplase and that this is followed by a continuous infusion.<sup>17</sup> Our patient suffered bleeding complications due to therapy, with a large haematoma developing around the operative site and bleeding from all vascular puncture sites. The bleeding lesions slowly resolved in the days after discharge from the intensive care unit.

There is no evidence that thrombolytic therapy reduces the mortality or the rate of recurrent PE when compared with heparin therapy alone. Because of the high cost and serious bleeding complications that may arise with thrombolytic therapy, thrombolytic treatment should be reserved for patients with massive PE complicated by severe haemodynamic compromise. The high mortality in this group may be decreased, although this assumption has not been confirmed by a recent randomised clinical trial.<sup>6</sup> However, a trial to assess the therapeutic beneficial effects of thrombolysis in patients with a life-threatening PE may be impossible to conduct, due to the rarity of the condition and ethical limitations.

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