CASE REPORT

Successful treatment of massive pulmonary embolism with reteplase

Masif pulmoner embolinin reteplaz ile başarılı tedavisi

Ali Çoner, M.D.,[1] Davran Çiçek, M.D.,[1] Serhat Balcıoğlu, M.D.,[1] Sinan Akıncı, M.D.,[1] Haldun Müderrisoğlu, M.D.[2]

[1]Department of Cardiology, Başkent University Faculty of Medicine, Alanya, Turkey
[2]Department of Cardiology, Başkent University Faculty of Medicine, Ankara, Turkey

Summary– Unexpected and unexplained out-of-hospital cardiac arrests have a poor prognosis. Difficulties encountered during the differential diagnosis phase may delay the administration of specific treatment for treatable and reversible causes of cardiac arrest. Massive pulmonary embolism is a reversible cause of cardiac arrest, but without proper management it has a high mortality rate. Presently described is the case of a 53-year-old female patient with a massive pulmonary embolism.

Özet– Nedeni açıklanamayan ve beklenmeyen hastane dışı kalp durmasında prognoz kötüdür. Ayırıcı tanı aşamasında karşılaşılan güçlükler spesifik tedavi uygulanmasını kalp durmasına neden olan geri döndürülebilir faktörlere müdahale edilmesini geciktirmektedir. Yoğun pulmoner emboli kalp durmasının geri döndürülebilir bir nedenidir ancak spesifik tedavi uygulanmazsa yüksek mortaliteye sahiptir. Burada yoğun pulmoner emboli nedeniyle başvuran elli üç yaşındaki kadın hasta sunuldu.

A traumatic cardiac arrest in an adult previously known as healthy should be promptly evaluated with a differential diagnosis during ongoing cardiopulmonary resuscitation.[1] A massive pulmonary embolism may be the etiological factor behind cardiac arrest in these patients, and it is a treatable and potentially reversible process.[2] If there is a high suspicion of massive pulmonary embolism, thrombolytic treatment is strongly advised for short-term survival and the long-term prognosis. Reteplase is easy to use to treat a hemodynamically unstable, massive pulmonary embolism.

Described in this report is a case of massive pulmonary embolism presenting with cardiac arrest that was successfully treated with reteplase, a third generation thrombolytic agent.

CASE REPORT

A 53-year-old female patient was admitted to the emergency service with a loss of consciousness following respiratory distress. Her initial rhythm was pulseless electrical activity (PEA). While cardiopulmonary resuscitation was performed, her relatives relayed the information that she had arthroscopic knee surgery 5 days earlier and had been immobile since discharge. Bedside transthoracic echocardiography (TTE) revealed excess dilatation of the right heart chambers and a right ventricular wall motion abnormality. In light of the patient's personal history of immobility and the echocardiography findings, it was thought that a massive pulmonary embolism was the most probable diagnosis for circulatory collapse and cardiac arrest. Reteplase, a third-generation thrombolytic agent, and a weight-adjusted unfractionated heparin bolus were administered intravenously. Reteplase was given as 2 separate bolus injections of 10 IU 30 minutes apart. After administration of the first bolus of reteplase, recovery of spontaneous circulation (ROSC) was achieved in 6 minutes. Blood pressure was supported with intravenous fluid replacement

Abbreviations:

PEA	*Pulseless electrical activity*
TTE	*Transthoracic echocardiography*
ROSC	*Recovery of spontaneous circulation*

Received: May 20, 2017 *Accepted:* August 23, 2017
Correspondence: Dr. Ali Çoner. Doğanbahçe Sokak, No: 33/4, Demirlibahçe, 06340 Ankara, Turkey.
Tel: +90 242 - 510 25 25 e-mail: conerali@hotmail.com

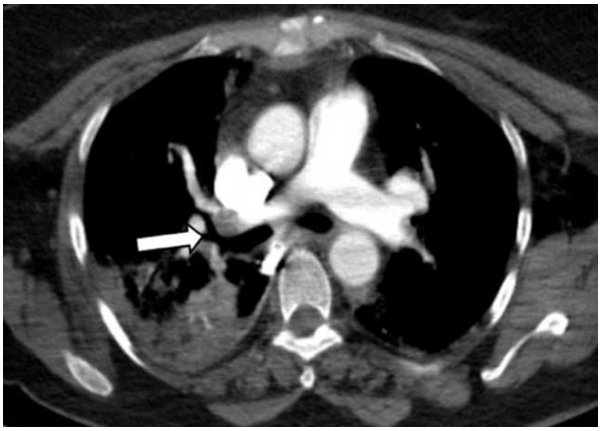

Figure 1. Thoracic computerized tomography with a contrast agent injection revealed a blood clot in the right pulmonary artery.

according to central venous pressure and the provision of positive inotropes was also required in the first few hours of hospitalization. Following hemodynamic stabilization, thoracic computerized tomography with a contrast agent injection was performed and a blood clot in the right pulmonary artery was documented (Fig. 1). Acute thrombosis in the right deep femoral vein was also detected with lower extremity duplex ultrasonography. The patient was extubated on the second day of hospitalization and there were no neurological complications. She was discharged without any medical problem after 1 week of hospitalization. Anticoagulation with warfarin was initiated, but due to unstable international normalized ratio values, rivaroxaban 20 mg per day was substituted as the anticoagulant 1 month later. Follow-up TTE examinations demonstrated that the right ventricular dilatation and dysfunction had receded and the mean pulmonary arterial pressure was under 15 mm Hg.

DISCUSSION

Pulmonary embolism is the third leading cause of death due to cardiovascular disease, following myocardial infarction and stroke. Only 4.2% of all pulmonary embolism patients present in a hemodynamically unstable condition or cardiac arrest, but the clinical prognosis is worse for these patients and the overall mortality is as high as 58.3%.[3] Treatable and reversible etiological causes of cardiac arrest should be considered during cardiopulmonary resuscitation. Massive pulmonary embolism is a potentially reversible process and is responsible for 13% of unexplained, unexpected cardiac arrests outside of the hospital.[4] Pulmonary circulatory restoration with the administration of a thrombolytic agent can be life-saving in these cases; however, difficulties in performing a differential diagnosis during ongoing cardiopulmonary resuscitation can delay the administration of a thrombolytic agent. A recently published paper evaluated out-of-hospital cardiac arrest patients managed with pre-hospital administration of reteplase.[5] Pre-hospital reteplase was not related to a greater rate of ROSC; however, only 3 (7%) of 43 patients had a proven pulmonary embolism as the cause of cardiac arrest. The majority of the study population comprised acute coronary syndrome patients. Clinicians have to decide on treatment based on a limited personal history, initial physical examination findings, and bedside diagnostic tools. The survival rate and long-term clinical outcomes are definitely better with the early administration of thrombolytics in massive pulmonary embolism patients presenting in cardiac arrest or periarrest condition. A retrospective study reported a 30% rate of thrombolytic agent usage among hemodynamically unstable pulmonary embolism patients.[6] On the other hand, there are few guideline proposals for the choice of thrombolytic agent type.[7]

There are some clues available for the differential diagnosis in these patients. For example, PEA is often associated with massive pulmonary embolism and PEA is the most commonly seen initial rhythm in massive pulmonary embolism patients presenting with circulatory collapse.[8] After ROSC, a harsh/loud systolic murmur and thrill can be heard, especially from an Erb's point focus, on auscultation. A parasternal lift can be felt with palpation. These physical examination findings are related to an abrupt increase in pulmonary arterial resistance and right ventricular workload. Courtney et al.[8] offered a triad to predict the possibility of massive pulmonary embolism as the cause of cardiac arrest. According to this triad, a massive pulmonary embolism may be the responsible factor for an atraumatic, witnessed cardiac arrest of a patient younger than 65 years of age with an initial rhythm of PEA. Some prearrest conditions that may be related to a massive pulmonary embolism were also defined in the same study: respiratory distress, a shock index (pulse/systolic blood pressure) greater than 0.8 and altered mental status. Despite the lack of diagnostic certainty, if the most probable differential diagnosis of cardiac arrest is massive pulmonary

embolism, thrombolytic treatment should be administered as soon as possible. Successful thrombolysis is associated with faster ROSC and better clinical outcomes in these patients.[9]

The first clinical study investigating the effectiveness of thrombolytic treatment in massive pulmonary embolism patients with unstable hemodynamic status included a 1-hour infusion protocol of streptokinase. However, this relatively long infusion period is not suitable for patients presenting with cardiac arrest and ongoing cardiopulmonary resuscitation. In a retrospective study, Le Conte et al.[10] evaluated the result of alteplase treatment given as 0.6 mg/kg in a 15-minute bolus, and a shorter infusion time was found to be correlated with a lower mortality rate and did not cause an increase in bleeding complications. In the current pulmonary embolism guidelines of the European Society of Cardiology,[7] this shorter infusion protocol has been advised for hemodynamically unstable massive pulmonary embolism patients (0.6 mg/kg alteplase in a 15-minute infusion).

Reteplase is a third-generation, fibrin-specific thrombolytic agent, and is a recombinant form of alteplase. Reteplase binds to fibrin rich clots. There are case reports about the use of reteplase in massive pulmonary embolism patients presenting with cardiac arrest or a prearrest condition.[11] Tebbe et al.[12] compared reteplase and alteplase in hemodynamically stable massive pulmonary embolism patients and did not find any significant difference in the decrease of pulmonary vascular resistance. This study demonstrated that reteplase was at least as effective as alteplase in massive pulmonary embolism. However, we do not have any proposal in the current guidelines for the usage of reteplase in massive pulmonary embolism.[7] Reteplase can be a good candidate for massive pulmonary embolism patients presenting in a hemodynamically unstable condition, cardiac arrest, or with prearrest status since it is easy to administer as a bolus and there is no need for a dosing adjustment. Effective cardiopulmonary resuscitation with proper chest compressions and good ventilation is very important in these patients in order to provide sufficient time for reteplase activity to be visible. We have to emphasize the risk of major bleeding with thrombolytic therapy. The risk for major bleeding especially increases with advancing age. The individualized bleeding risk of a patient must be assessed before administering thrombolytic treatment. A previous study[13] compared reteplase and alteplase in terms of efficacy and safety in the treatment of acute myocardial infarction and found similar hemorrhagic stroke rates between the two. There was a slightly higher (2.5% vs. 1.7%) but statistically non-significant incidence of hemorrhagic stroke in patients over 75 years of age in the reteplase group. Tenecteplase is another third-generation thrombolytic agent. In the ASSENT-2 trial (Assessment of the Safety and Efficacy of a New Thrombolytic), its efficacy was similar to that of alteplase, with fewer bleeding complications.[14]

In addition to life-saving benefits, absolute and relative contraindications have been defined for the administration of thrombolytic treatment.[15] Absolute contraindications are prior intracranial hemorrhage, known structural cerebral vascular lesion, known malignant intracranial neoplasm, ischemic stroke within 3 months, active internal bleeding, and suspected aortic dissection. In situations where absolute contraindications apply, alternative, mechanical reperfusion strategies such as echosonic thrombolysis or rheolytic thrombectomy can be useful. Our patient had some relative contraindications: recent minor arthroscopic surgery and prolonged cardiopulmonary resuscitation. In cases with relative contraindications, the risk-benefit assessment depends on the physician's preference and the bedside evaluation. Although our patient had relative contraindications, he was considered to remarkably benefit from thrombolytic therapy, owing to circulatory collaps and a highly suspected pulmonary embolism as supported by bedside echocardiography.

Early thrombolytic treatment, even during ongoing cardiopulmonary resuscitation, can be life-saving and improve short- and long-term clinical outcomes. The patient's personal history, initial physical findings, and initial monitor rhythm and bedside TTE results are the only choices to make a proper differential diagnosis with a high clinical suspicion of massive pulmonary embolism presenting with cardiac arrest. Easy-to-use third-generation thrombolytic agents such as reteplase or tenecteplase can be good candidates for treatment.

Informed consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying image.

Peer-review: Externally peer-reviewed.

Conflict-of-interest: None declared.

Authorship contributions: Concept – A.Ç.; Design – A.Ç., D.Ç.; Supervision – H.M.; Materials – A.Ç., D.Ç., S.B., S.A.; Data collection &/or processing – A.Ç., S.B.; Analysis and/or interpretation – D.Ç., S.B.; Literature search – A.Ç.; Writing – A.Ç.

REFERENCES

1. Logan JK, Pantle H, Huiras P, Bessman E, Bright L. Evidence-based diagnosis and thrombolytic treatment of cardiac arrest or periarrest due to suspected pulmonary embolism. Am J Emerg Med 2014;32:789–96. [CrossRef]
2. Hess EP, Campbell RL, White RD. Epidemiology, trends, and outcome of out-of-hospital cardiac arrest of non-cardiac origin. Resuscitation 2007;72:200–6. [CrossRef]
3. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353:1386–9. [CrossRef]
4. Deasy C, Bray JE, Smith K, Harriss LR, Bernard SA, Cameron P. Out-of-hospital cardiac arrests in young adults in Melbourne, Australia-adding coronial data to a cardiac arrest registry. Resuscitation 2011;82:1302–6. [CrossRef]
5. Luiz T, Wilhelms A, Madler C, Pollach G, Haaff B, Grüttner J, et al. Outcome of out-of-hospital cardiac arrest after fibrinolysis with reteplase in comparison to the return of spontaneous circulation after cardiac arrest score in a geographic region without emergency coronary intervention. Exp Ther Med 2017;13:1598–603. [CrossRef]
6. Stein PD, Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused. Am J Med 2012;125:465–70. [CrossRef]
7. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35:3033–69. [CrossRef]
8. Courtney DM, Sasser HC, Pincus CL, Kline JA. Pulseless electrical activity with witnessed arrest as a predictor of sudden death from massive pulmonary embolism in outpatients. Resuscitation 2001;49:265–72. [CrossRef]
9. Er F, Nia AM, Gassanov N, Caglayan E, Erdmann E, Hoppe UC. Impact of rescue-thrombolysis during cardiopulmonary resuscitation in patients with pulmonary embolism. PLoS One 2009;4:e8323. [CrossRef]
10. Le Conte P, Huchet L, Trewick D, Longo C, Vial I, Batard E, et al. Efficacy of alteplase thrombolysis for ED treatment of pulmonary embolism with shock. Am J Emerg Med 2003;21:438–40. [CrossRef]
11. Kuisma M, Silfvast T, Voipio V, Malmström R. Prehospital thrombolytic treatment of massive pulmonary embolism with reteplase during cardiopulmonary resuscitation. Resuscitation 1998;38:47–50. [CrossRef]
12. Tebbe U, Graf A, Kamke W, Zahn R, Forycki F, Kratzsch G, Berg G. Hemodynamic effects of double bolus reteplase versus alteplase infusion in massive pulmonary embolism. Am Heart J 1999;138:39–44. [CrossRef]
13. Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. N Engl J Med 1997;337:1118–23. [CrossRef]
14. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators, Van De Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, Barbash G, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Lancet 1999;354:716–22. [CrossRef]
15. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e419S–96S.

Keywords: Cardiac arrest; pulmonary embolism; thrombolytic treatment.

Anahtar sözcükler: Kalp durması; pulmoner embolizm; trombolitik tedavi.