Online Case Report

Does Thrombolysis Have a Place in the Cardiopulmonary Resuscitation of Patients With Acute Pulmonary Embolism? A Case of Successful Thrombolysis During Pulmonary Embolism Induced Cardiopulmonary Arrest

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Objective: Pulmonary embolism often causes cardiac arrest. When this occurs, thrombolytic therapy is not routinely administered. There are multiple reasons for this, including difficulty with rapidly adequately diagnosing the embolus, the lack of good data supporting the use of thrombolytics during resuscitation, the belief that thrombolytic therapy is ineffective once a patient has already arrested, the difficulty of obtaining thrombolytics at the bedside rapidly enough to administer during a code, and the increased risks of bleeding, particularly with ongoing chest compressions. In this case report, we present a patient who was successfully treated with thrombolytic therapy during pulmonary embolism–induced cardiopulmonary arrest and discuss the role of thrombolytics in cardiopulmonary resuscitation.

Design: Case report.

Setting: Surgical ICU in a comprehensive cancer center.

Patient: A 56-year-old man who developed hypotension, dyspnea, hypoxia, and pulseless electrical activity 10 days after resection of a benign colon lesion with a right hemicolectomy and primary end-to-end anastomosis.

Interventions: After a rapid bedside echocardiogram suggesting pulmonary embolus, thrombolytic therapy was administered during cardiopulmonary resuscitative efforts.

Measurements and Main Results: The patient had a return of spontaneous circulation and showed improvement in repeat echocardiographic imaging. He had a prolonged course in the ICU and hospital, but eventually made an essentially complete clinical recovery.

Conclusion: As bedside echocardiographic technology becomes more rapidly and readily available, the rapid diagnosis of pulmonary embolism and use of thrombolytics during cardiopulmonary resuscitation may need to be more routinely considered a potential therapeutic adjunctive measure. (*Crit Care Med* 2016; 44:e300–e303)

Key Words: cardiac arrest; cardiopulmonary resuscitation; pulmonary embolism; thrombolysis; venous thromboembolism

Pulmonary embolism (PE) commonly causes cardiovascular collapse and is amenable to a variety of therapies, including thrombolysis in hemodynamically unstable patients. Currently, no treatment is offered in Advanced Cardiovascular Life Support (ACLS) protocols for this potentially deadly disease (1). This is likely due to several factors. First, diagnosing the PE needs certain tests and studies that are not often available during cardiopulmonary resuscitation (CPR). Second, no randomized study has proven the efficacy of thrombolysis in cardiovascular resuscitation (2). Third, it is often believed that by the time of diagnosing PE during an arrest, it is too late to start thrombolysis during resuscitation. Fourth, the risks of bleeding with thrombolysis are increased with chest compressions given during CPR, and fifth, obtaining thrombolytic therapy from the pharmacy may take too long to be effective in a code blue situation. Here, we present a case of successful treatment of PE during CPR, and we discuss the role of thrombolysis during cardiopulmonary arrest.

CASE REPORT

A 56-year-old African-American man was admitted to a tertiary cancer center for surgical resection of endoscopically

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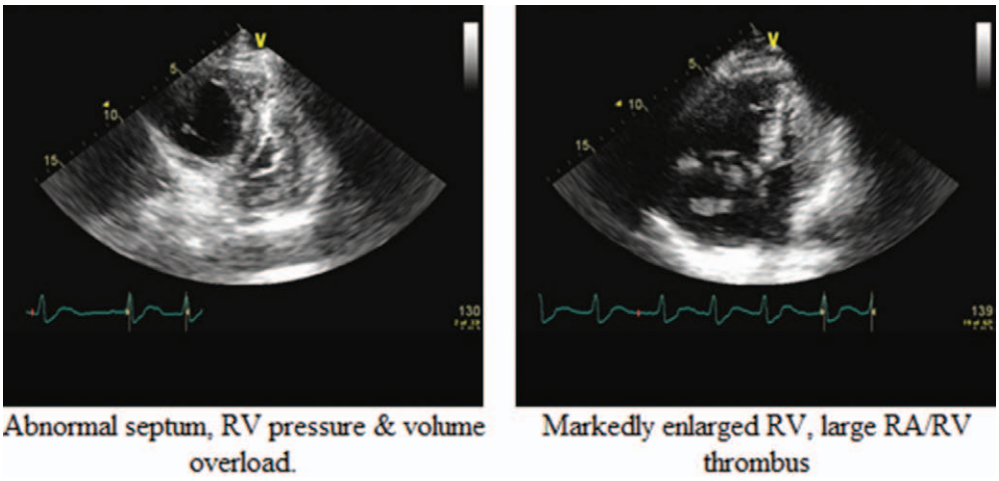

Figure 1. The bedside transthoracic echocardiogram showed the enlarged volume-overloaded RV and the thrombus on a standard short-axis parasternal view.

unresectable tubulovillous adenoma with high-grade dysplasia in the proximal ascending colon.

He had a medical history of hypertension, diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, coronary artery disease, sleep apnea, and a 45 pack-year history of smoking. He had a surgical history of wedge resection of the right upper lobe 6 years earlier for non–small-cell lung cancer, with no subsequent recurrence. He was a Jehovah's Witness and had emphasized repeatedly that he would not accept blood products even in the event of life-threatening emergencies. Additionally, he had an active lifestyle, working as a postal worker for 30 years.

Ten days after the surgical resection which involved a right hemicolectomy with primary end-to-end anastomosis, the patient was awaiting hospital discharge later in the day. He was ambulating around the floor and was not on deep vein thrombosis prophylaxis. He suddenly developed hypotension, dyspnea, and hypoxia, which rapidly progressed to pulseless electrical activity. He underwent CPR on the floor with successful return of spontaneous circulation and was subsequently admitted to the ICU within 10 minutes. The patient was hemodynamically unstable, requiring continuous infusions of norepinephrine and epinephrine. In the ICU, he arrested again within the hour and resuscitation per ACLS protocol was reinitiated along with implementation of a vasopressin infusion. Several minutes into the code, bedside echocardiography revealed a severely hypokinetic right ventricle (RV) and a large mass suggestive of a large mobile thrombus and likely PE (**Fig. 1**). The interventional radiology and cardiothoracic surgery services deemed that the patient was not a candidate for emergent embolectomy. Therefore, the risks and benefits of chemical thrombolysis were discussed with the family. The family agreed with thrombolytic therapy, despite the significant risk of bleeding, and reiterated the patient's wishes that he would not accept any blood transfusions.

IV alteplase at a dose of 100 mg IV over 2 hours was administered approximately 10 minutes into the code and circulated essentially with just chest compressions. CPR was continued for almost 20 more minutes, at which point the patient regained spontaneous circulation. The initial 10 mg of the alteplase was not administered as a bolus, as found in some studies in the literature (3), due to his significant bleeding risks from recent surgery, chest compressions, and religious desire to not accept blood transfusions.

Echocardiographic imaging at the moment of first arrest revealed a peak tricuspid regurgitation (TR) jet velocity of 3.36 m/s with an estimated maximum RV-right atrium (RA) gradient of 45 mm Hg. Repeat imaging 4 hours later showed that the peak TR jet velocity had decreased to 2.4 m/s and the RV-RA gradient had improved to 23 mm Hg. In addition, the heart rate had decreased from about 160 beats/min to about 115 beats/min (**Fig. 2**). We used a GE vivid e9 system (General Electric Medical Systems, Horten, Norway), and the bedside views were performed at intervals of "pulse-check" during the ACLS protocol in a specific attempt to avoid interruption of ACLS protocol. While at bedside we indeed were able to perform imaging during compressions from a displaced apical angle, admittedly these views were technically limited and not clinically helpful. However, the best views bedside in this particular case were from the parasternal and subcostal windows, respectively. We should clarify that once the patient was stabilized post-ACLS a more thorough, technically superior and complete echocardiographic examination was performed (using the same system).

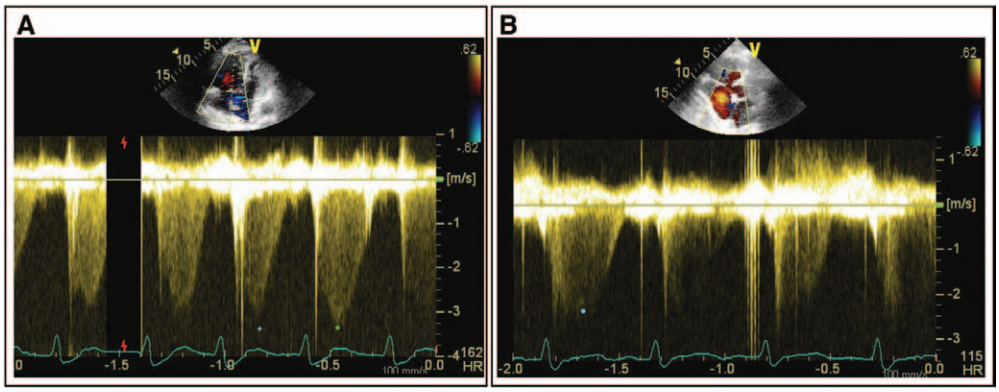

Figure 2. A, A standard apical RV-focused view during the ICU arrest. Peak TR jet velocity of 3.36 m/s, estimated Max RV-RA gradient 45 mm Hg. **B**, 4 hr later: Peak TR jet velocity down to 2.4 m/s, with RV-RA gradient improved to 23 mm Hg (heart rate also decreased from 160 to 115 beats/min).

About 40 minutes into the alteplase infusion, the patient developed bleeding from the oral and nasal mucosa and the thrombolytic infusion was stopped after administering 36 mg of alteplase. He stayed in the ICU for the next 18 days and was gradually weaned off vasopressor therapy and extubated. He received hemodialysis for acute renal failure. His hemoglobin concentration initially dropped to 4.0 mg/dL, but no blood was transfused to honor the patient's wishes. He was eventually discharged from the ICU without any significant neurocognitive dysfunction and was discharged from the hospital on postoperative day 41.

His surgical pathology revealed a tubulovillous adenoma of the right colon. No high-grade dysplasia or invasive carcinoma was identified. Fourteen lymph nodes were negative for tumor. The proximal ileal, distal colonic, and radial surgical margins were negative for tumor.

He was able to return to his day-to-day life, enjoying the company of his wife, children, and grandchildren, and also was able to walk into the ICU a few months later and met some of the staff who cared for him, much to their delight.

DISCUSSION

The use of thrombolysis is dictated by the balance of benefits versus risks. This case demonstrates the benefit of survival from a deadly PE that was not a candidate for other aggressive treatments. Some of the serious risks were bleeding from recently anastomosed bowel segments, intrathoracic bleeding in the setting of recent chest compressions, and intracranial bleeding. The patient's decision to forgo blood transfusion added further complexity to the picture.

PE is a potentially fatal disease. A significant number of cases of venous thromboembolism can be attributed to institutionalization, including hospitalization (4). In autopsy studies of patients who died in the ICU, PE is reported to be the most frequently missed diagnosis (5). Based on the facts that venous thromboembolism (VTE) is significantly associated with hospitalization and is the third most common cause of cardiovascular death in the United States (6), PE is one of the most likely causes of sudden cardiovascular collapse in an hospitalized patient. It is, therefore, reasonable to question whether thrombolysis has a place in the resuscitative efforts of hospitalized patients, as well as other patients at increased VTE risk, particularly in the event of a sudden cardiac arrest.

While many anecdotes in the literature support the efficacy of thrombolysis in cases of proven or highly suspicious PE (7–10), to the best of our knowledge, no randomized trial has proven the efficacy of thrombolysis in resuscitation. Performing randomized studies during acute resuscitation is challenging. In most studies evaluating thrombolysis in cardiac arrest, the sample populations were usually too small, and low prevalence of desired outcome made it difficult to achieve any statistical significance. The differences in baseline population and the diversity of health systems in the countries where studies were performed made reaching a conclusion even more difficult. The largest randomized double-blind trial is the Thrombolysis in Cardiac Arrest (TROICA) trial, which studied tenecteplase in 1,050 out-of-hospital cardiac arrests. In this study, patients receiving thrombolytic therapy had similar neurologic outcomes, as well as similar rates of return of spontaneous circulation, 24-hour survival, 30-day survival, and survival to hospital discharge compared with the placebo group. However, the thrombolysis group had more intracranial hemorrhages (2). It can be concluded that administering thrombolytic therapy to all patients with cardiac arrest is not currently advisable. Unfortunately, this study only had 37 patients with documented PE, making it difficult to draw any definitive conclusions about this particular subgroup.

Although patients specifically with PE have not been evaluated in randomized controlled trials, one retrospective cohort study of thrombolytic therapy in patients with massive PE and prolonged CPR has been reported by Janata et al (11). In this study, a bolus of alteplase was shown to be associated with an increase in 24-hour survival, although with a nonsignificant increase in bleeding complications and no statistically significant change in survival to discharge (11). Another interesting case series by Ruiz-Bailén et al (12) used a 50 mg IV recombinant tissue plasminogen activator (rtPA) bolus followed by 50 mg as an infusion over 30 minutes during cardiac arrest for clinically suspected PE (12). Out of the six patients studied, four survived and remained symptom free. Clearly, further randomized controlled studies would be helpful to clarify the role of thrombolytics in cardiac arrest due to PE.

The dose and the rate of thrombolytic administration during cardiac arrest are also not entirely clear. Although the treatment of PE in a non–cardiac arrest situation is fairly agreed upon to be 100 mg of alteplase IV over 2 hours, the dosing during a code situation is not as well standardized. In attempted reperfusion for myocardial infarction, the optimal time of infusion is 90 minutes, since it provides better survival when compared with a longer (3 hr) infusion (13), and has fewer bleeding complications when compared with double-bolus administration (two divided boluses separated 30 min apart) (14). During CPR, however, time is of the essence and infusing alteplase over 2 hours or even 90 minutes is impractical, and therefore, a bolus is proposed in many studies. In the TROICA trial mentioned above, the tenecteplase was given as a bolus based on weight, and in the study by Janata et al (11), a bolus of 0.6–1.0 mg/kg (maximum 100 mg) of alteplase was given (2). Another study evaluated thrombolytic therapy after cardiac arrest, although due to myocardial infarction rather than pulmonary embolus. In this study, rtPA as a 100-mg front-loaded regimen was used and showed a nonsignificant trend toward improved neurologic outcome (15). Yet, another approach is to use part of the rtPA as a bolus and part as an infusion. This was the strategy used in the case series by Ruiz-Bailén et al (12) mentioned previously. Another dosing option involves an initial bolus dose of 15 mg of rtPA IV followed by an infusion of 50 mg over 30 minutes and then 35 mg more over 60 minutes. This protocol was studied in a retrospective review of patients with out-of-hospital cardiac arrest and found an improvement in return of spontaneous circulation, 24-hour survival,

and survival to discharge (16). Again, however, this study was not specific for patients with PE. In our case, we did not use a bolus in light of the concern for significant bleeding in the postoperative period, particularly in a patient who did not wish to receive transfusion of blood products. In the absence of any obvious significant propensity for bleeding or contraindication to transfusion, however, administering thrombolytic therapy either as a bolus or as a partial bolus with a subsequent shorter infusion time would certainly be a very appropriate therapeutic consideration.

Ultrasound imaging is becoming more readily available, and bedside echocardiography can often identify signs of PE, such as RV dilation, RV hypokinesia, paradoxical septal wall motion, and occasionally thrombus itself. Unfortunately, the sensitivity and specificity of these findings are low, and echocardiography cannot clearly rule out a PE. However, visualizing the mentioned signs with a bedside echocardiogram in a hemodynamically unstable patient or patient in cardiac arrest could guide further testing and treatment (17–19). The 2014 European Society of Cardiology Guidelines on the diagnosis and management of acute PE addresses a clinical situation similar to ours under the issue of a suspected high-risk PE and states that "the absence of echocardiographic signs of RV overload or dysfunction practically excludes PE as the cause of hemodynamic instability." It goes on to say—"Conversely, in a hemodynamically compromised patient with suspected PE, unequivocal signs of RV pressure overload and dysfunction justify emergency reperfusion treatment for PE if immediate CT angiography is not feasible." Additionally, mobile right heart thrombi are mentioned as reaching a prevalence of up to 18% in the intensive care setting. The guidelines express that "mobile right heart thrombi essentially confirm the diagnosis of PE and their presence is associated with RV dysfunction and high early mortality." These descriptions are consistent with the findings encountered in the case we present here (20).

Since PE is one of the likely causes of cardiovascular collapse in hospitalized patients, it may be reasonable to consider the use of emergent bedside echocardiography to help guide assessment and possible management with thrombolytic therapy in this group of patients. Indeed, all patients with cardiac arrest and any risk factor for thromboembolic disease may potentially benefit from this approach. In fact, as obtaining an echocardiogram quickly at the bedside becomes more common and readily available, changes in resuscitative guidelines could even potentially be considered.

That being said, it should be kept in mind that no treatment is better than prevention, and primary VTE prophylaxis, either pharmacologically or mechanically, has been proven to be beneficial in patients at risk for thromboembolic disease, including those who are hospitalized or critically ill (21, 22).

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