

Case Report

Bivalirudin and Alteplase for Pulmonary Embolism Requiring Veno-Arterial Extracorporeal Membrane Oxygenation in an Adolescent

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Abstract: Saddle pulmonary embolism (PE) remains a challenge to diagnose and manage in pediatric patients. Current literature encourages early consideration of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in high-risk PE patients with impending right ventricular failure. We present a 17-year-old patient who was admitted to a pediatric cardiac intensive care unit with saddle PE requiring emergent VA-ECMO support because of cardiovascular collapse. Despite anticoagulation with bivalirudin and receiving systemic thrombolysis with alteplase, the clot burden was persistent with minimal improvement in right ventricular function. We proceeded to catheter thrombolysis while on VA-ECMO. This

ultimately led to a successful resolution of the PE and allowed for weaning off VA-ECMO. PE is rare in children compared with adults, and pediatricians may be unaware of therapies becoming increasingly used in adults such as the use of VA-ECMO, with systemic and local thrombolysis. The concurrent use of a direct thrombin inhibitor for ECMO anticoagulation alongside the thrombolysis is a novel combination in this condition and age-group. **Keywords:** pulmonary embolism, veno-arterial extracorporeal membrane oxygenation, bivalirudin, direct thrombin inhibitor, alteplase, thrombolysis, anticoagulation, children, pediatric. *J Extra Corpor Technol. 2020;52:327–31*

Pulmonary embolism (PE) was thought to be a rare pediatric diagnosis, but the incidence has been increasing as survival of children with critical illnesses and usage of indwelling catheters have increased. The diagnosis of PE remains challenging in children, and management guidelines are largely derived from adult protocols (1).

Massive PE presents mortality rates ranging from 15 to 80% (2) with 65% mortality described in PE requiring cardiopulmonary resuscitation (CPR) (3). Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has

been classically indicated when all other medical treatment modalities have failed leading to severe hemodynamic compromise or during CPR. These cases have been associated with higher morbidity and mortality rates (4,5). Systemic fibrinolysis is rarely used in patients on ECMO (3), and there are no reports of combination therapy with direct thrombin inhibitors (DTIs) with fibrinolytics (systemically or locally directed) on VA-ECMO, especially in pediatrics. DTIs act directly to inhibit not only circulating thrombin but also already clot-bound thrombin, independent of anti-thrombin III, providing a more consistent and predictable anticoagulation response. Bivalirudin, in comparison to its fellow DTI argatroban, has a short half-life of 25–35 minutes secondary to its intravascular proteolytic degradation and minimal renal clearance (~20%) (6). Bivalirudin and other DTIs increase fibrin gel permeability, facilitating fibrinolysis and also affect platelet aggregation (7).

Received for publication March 3, 2020; accepted September 3, 2020.
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The senior author has stated that the authors have reported no material, financial, or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.

We present our experience with a teenage patient who suffered a high-risk PE managed with VA-ECMO using bivalirudin as the primary anticoagulant. Repeated thrombolysis with alteplase (rTPA) was required and resulted in successful PE resolution.

CASE

Per institutional guidelines, case reports contribute to generalizable knowledge and are not considered research; therefore, no Institutional Review Board approval required.

Clinical Findings and Diagnostic Assessment

A 17-year-old boy presented to the emergency room with a 3-week history of progressive dyspnea, chest pain on exertion, and two syncopal episodes. These symptoms started after a 5-hour car journey. Previous medical and familial histories were unremarkable. He denied drug use, weight loss, or recent trauma. The patient was alert, tachycardic (147 bpm), with normal S1S2, normotensive, with no murmur, tachypneic (25 rpm), with symmetric pulses, and with <3-second capillary refill. He had no pain or swelling in his lower extremities. Oxygen saturation was 90% in room air. He spoke in short sentences because of precordial chest pain without radiation (8/10 intensity). The initial chest X-ray was unremarkable. The electrocardiogram showed sinus tachycardia and T wave inversion on leads III, aVF, V1, V3, and V4. Echocardiogram showed a dilated right ventricle (RV) and severely decreased RV systolic function with large mass near branch pulmonary artery (PA) concerning for saddle embolism. There was reduced flow through the pulmonary valve, main PA, and branch pulmonary arteries. Computed tomography angiography (CTA) of the chest was consistent with large volume PE involving the main, lobar, and segmental pulmonary arteries bilaterally and an area of pulmonary infarction in the left upper lobe (Figure 1, top). There was enlargement of the right chambers, ventricular

septal bowing, and reflux of contrast into the inferior vena cava and hepatic veins concerning for right heart strain (Figure 1, bottom). Ultrasound of lower extremities showed occlusive left popliteal vein thrombosis. The hypercoagulable investigation was performed after ECMO cannulation and is demonstrated on Table 1.

Therapeutic Intervention

The patient received enoxaparin 60 mg subcutaneous in the emergency department. With the aforementioned echocardiogram findings, the patient was taken for pulmonary angiography and planned catheter-directed thrombolysis. Because of high anesthetic risk, the procedure was planned awake with local anesthesia and ECMO standby. After accessing the right femoral vein and left femoral artery for eventual need for ECMO, an angiogram demonstrated near complete occlusion of the right and left main pulmonary arteries (Figure 2, top). The saturation decreased to 89% on 100% FiO₂ delivered through face mask, and the patient became suddenly bradycardic and hypotensive. Heparin 100 units/kg was administered, and the patient was cannulated to VA-ECMO with a 25-Fr Biomedicus cannula in the right femoral vein and a 17-Fr Biomedicus cannula in the left femoral artery supporting flow of 4.6 L/min using Cardiohelp (Maquet Cardiopulmonary, Hirrlingen, Germany). A 7-Fr distal perfusion cannula was inserted into the common femoral artery. The patient was then intubated, a right internal jugular (RIJ) vein central venous line was inserted, and the patient was transferred to the pediatric cardiac intensive care unit. Bivalirudin was started at .1 mg/kg/h as institutional practice once activated clotting time decreased below 300 seconds. Targeted activated partial thromboplastin time (aPTT) range was set between 60 and 80 seconds. The intravenous systemic rTPA dose was divided into two doses of .5 mg/kg with 8-hour intervals, given 6 hours post-cannulation.

On ECMO day 3, because of minimal RV improvement and persistent PE burden, the patient returned to interventional radiology suite for catheter-direct thrombolysis.

Figure 1. Pretreatment: Bilateral pulmonary embolus with significant enlargement of the main PA and area of pulmonary infarction (A, top). Significant enlargement of the RV with straightening of the ventricular septum and decreased left ventricle size (A, bottom). Initial pulmonary angiogram showing significant bilateral PE and right heart dysfunction (B, top). Persistent bilateral lobar and segmental pulmonary emboli on follow-up pulmonary angiogram (B, bottom). Initial posttreatment CT showing persistent but decreased clot burden (C, top). Three-month follow-up CT shows significant reduction in clot burden with minimal lobar and segmental emboli (C, bottom). PA, pulmonary artery; RV, right ventricle; PE, pulmonary embolism; CT, computed tomography.

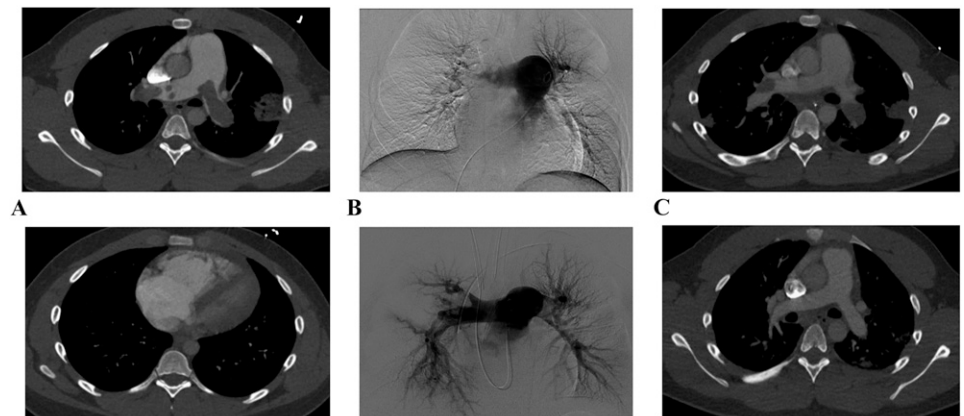


Table 1. Hypercoagulable investigation.

Test	Result (Reference Range)
Homocysteine level	40.3 $\mu\text{mol/L}$ (4.7–40 $\mu\text{mol/L}$)
Protein C	73% (70–140%)
Protein S	125% (>50%)
Antithrombin III	94% (80–120%)
Antiphospholipid battery (anti-B2 glycoprotein IgG, IgM; anticardiolipin IgG, IgM)	Negative
Diluted Russell viper venom test time	Positive for lupus anticoagulant at the time of ECMO; follow-up was negative after 3 months
Factor V Leiden	Negative
Prothrombin (PT or factor II) G20210A mutation	Negative
Antinuclear antibodies	Negative
Anti-double-stranded DNA IgG	Negative
Plasminogen activity	54% (71–144%)
Methyl tetrahydrofolate reductase mutation	Homozygous A for c.665 C > T mutation

IgG, immunoglobulin G; IgM, immunoglobulin M.

There were persistent bilateral pulmonary emboli in the lobar and segmental pulmonary arteries (pressures: main pulmonary artery pressure 38/9 mmHg). A bilateral EkoSonic[®] endovascular system (EKOS) catheter was inserted via RIJ, and continuous rTPA was initiated at total 1 mg/h divided to both catheter lumens.

Clinical course was complicated by epistaxis and tongue oozing related to a bite blocker 18 hours post-rTPA initiation. Bleeding was controlled with packing of the airway, two units of fresh frozen plasma. The patient received only 2 units of packed red blood cells over a 3-day period for blood losses. During the second attempt of thrombolysis, the patient experienced bleeding from the arterial ECMO cannula site, and the aPTT goal was lowered 50–60 seconds together with local pressure dressing, leading to discontinuation of rTPA after 24 hours. Bivalirudin infusion was held for a total of 1.5 hours and then re-titrated according to the protocol. Repeated angiogram on ECMO day 7 (48 hours post-rTPA discontinuation) showed improved RV dysfunction, PA pressure decreased to 22/18 mmHg, and the EKOS catheter was then removed. The patient was started on milrinone .5 mcg/kg/min and epinephrine .02 mcg/kg/min and decannulated after a total of 9 days on VA-ECMO.

Follow-Up and Outcomes

Follow-up CTA chest showed significant improvement of central PA thrombus, PA enlargement, and right heart strain. Residual thrombus was noticed in the bilateral lobar and segmental arteries (Figure 3, top). CTA of the abdomen and pelvis ruled out malignancies and showed a small nonocclusive thrombus in the right external iliac vein.

Bivalirudin was transitioned to enoxaparin with target anti-Xa levels of .5–1 IU/mL. The patient was discharged home on enoxaparin, folic acid, and vitamin B12 after 22 days in hospital. A 3-month follow-up CTA showed significant reduction of clot burden with minimal lobar and segmental

pulmonary emboli and resolution of right heart strain (Figure 3, bottom).

DISCUSSION

PE has a broad clinical presentation and can be categorized into high, intermediate, and low risk PE. High-risk PE presents with cardiovascular collapse, hypotension, and bradycardia, and patients are at risk of sudden death (8). Categorizing PE by risk aids clinicians to guide management and anticipate interventions, especially in high-risk PE (4).

Hypercoagulable workup in the setting of ECMO and any active thrombotic process can be misleading, as follow-up levels of abnormal tests such as homocysteine and dilute Russell viper venom test time in this case normalized after 3 months. It is still somewhat unclear about the role of elevated homocysteine in thrombosis risk, especially in this patient's mildly elevated level. However, given the severity of his thrombus and the rather benign nature of first-line treatment of folic acid and B12, it was recommended to continue this regimen indefinitely alongside anticoagulation. It is also uncertain regarding the role of decreased plasminogen activity. Plasminogen is the precursor of plasmin, which degrades fibrin clots and fibrinogen. Plasminogen deficiency is not considered a risk factor for thrombosis, and hereditary deficiencies in plasminogen activity are extremely rare and do not seem to be associated with increased risk of thrombosis; moreover, they present with specific phenotype not present in our patient (9). The measurement of plasminogen activity in the setting of an active and dynamic thrombotic–fibrinolytic process can be misleading, as it lacks diagnostic specificity, with levels even below 50% (similar to that manifested in this case report). Acquired plasminogen deficiencies have been observed in patients with liver disease and sepsis, also not present in our patient. Genetically speaking, the polymorphisms (4G/4G and 4G/5G vs. 5G/5G)

that are thought to contribute to clotting risk through plasminogen activator inhibitor-1 occur too frequently; therefore, it is more likely to be a confounding factor, rather than a primary risk factor for clots. The elevated activity levels of the last one are also described as having increased clotting risk, primarily in adults and primarily in coronary artery disease and atherosclerotic disease, as are the polymorphisms (10). These are not the types of thrombotic disease that most pediatric patients get. It is difficult to find good evidence that it plays a role in venous thromboembolism/PE outside of case reports and as a primary risk factor. Although it remains unclear about the cause of massive PE, it is more likely, as it is in most cases, that multiple factors completed Virchow's triad.

Classical management of high-risk PE includes anticoagulation with unfractionated heparin combined with systemic or catheter-directed thrombolysis with rTPA. Unfractionated heparin remains the most common anticoagulation therapy used for PE and for ECMO overall likely because of historical familiarity of anticoagulation and the availability of protamine as an antidote. Mechanical thrombolysis and surgical embolectomy may be used for patients at high risk of bleeding, or for those with contraindications to anticoagulation, or if attempted thrombolysis has failed (8,11).

Despite historical use of ECMO in PE as a rescue strategy for low cardiac output or for cardiac arrest (3–5,12), a 20-year systematic review of case series of patients on ECMO with massive PE showed overall 70% survival (5). This improved survival has been attributed to advances in extracorporeal life support and intensive care, such as early ECMO deployment (as used by our patient), and protocolized approaches and potentially to designated PE response teams (13).

A protocolized approach of VA-ECMO described by Chetan Pasrija et al. (2) was shown to optimize the treatment of massive PE. After initiation of VA-ECMO with heparin anticoagulation, reassessment of the clot burden and RV function was performed with echocardiogram. If the thrombus burden resolved with 3–5 days of therapy, ECMO weaning was performed. Surgical embolectomy was performed if there is persistence of clot burden and RV strain. Non-surgical candidates were managed with catheter-based thrombolysis. In this author's series, 40% patients were treated with anticoagulation alone, 55% with surgical embolectomy, and 5% with catheter-based therapy with a 5% mortality. Interestingly, with incorporation of ECMO, this study demonstrated 95% survival with 80% survival in higher acuity patients who received CPR before cannulation.

None of the VA-ECMO protocols for massive PE describe the use of a combination of fibrinolytic and DTIs. Most of the studies discuss heparin as an anticoagulant for high-risk PE on VA-ECMO (2,3). In this particular case, a DTI also is of great benefit as per its fibrinolytic properties

by binding to the catalytic site of circulating and clot-bound thrombin, further enhancing PE management (14). Although the risk of bleeding is taken in consideration especially with the combined use of rTPA, the short acting characteristic of bivalirudin makes titration to different ranges to aPTT easily applicable. Although the use of DTI is increasing in the ECMO population, there is a paucity of formal studies on pharmacological profile, laboratory monitoring adequacy, and risks and benefits (14,15).

Our case demonstrates the successful use of bivalirudin on VA-ECMO with systemic followed by catheter-directed thrombolysis in a patient with high-risk PE. As the amount of data of use of DTIs for pediatric ECMO remains dearth, knowledge sharing of challenging anticoagulation cases should be promoted. This case also highlights the importance of extracorporeal support in pediatric patients with high-risk PE: thoughtful consideration of early mechanical circulatory support may prevent rapid end-organ dysfunction and hemodynamic collapse and may allow for rapid initiation of further interventions in a more controlled manner. Early recognition of high-risk PE, strategic planning, and allocation of resources are key factors for a good outcome.

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