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Original Research

Massive Pulmonary Embolism with Hemodynamic Compromise Successfully Treated with Veno-Arterial Extracorporeal Membrane Oxygenation

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Abbreviation List

CPR cardiopulmonary resuscitation
CT computed tomography
ECLS extracorporeal life support
ECMO extracorporeal membrane oxygenation
ICU intensive care unit
PA pulmonary artery
PE pulmonary embolism
RV right ventricle
tPA tissue plasminogen activator
VA ECMO veno-arterial extracorporeal membrane oxygenation

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Introduction

Cardiogenic shock that results from pulmonary embolus has a high mortality rate. Systemic thrombolysis is frequently used in submassive and massive pulmonary embolus and has been shown to restore circulation. However, in the event of impending or ongoing cardiac arrest, systemic thrombolysis or anticoagulation alone has not been always shown to be effective. Case reports have previously established that extracorporeal membrane oxygenation can effectively be used as an effective rescue strategy in cases of cardiac arrest as a result from massive pulmonary embolus. We report six cases of massive pulmonary embolism (PE), in which veno-arterial extracorporeal membrane oxygenation (VA ECMO) was utilized or used as a backup strategy with excellent outcomes. We highly recommend using this strategy at the bedside in a tertiary care facility where VA ECMO support is available.

Methods

This is a retrospective study of all patients that underwent VA ECMO or utilized VA ECMO at the bedside as a rescue strategy in the setting of massive PE. We abstracted relevant clinical information from patient charts for this review.

Results and analysis

Out of the 107 VA ECMO runs performed at our facility between 1 September 2013 and 31 December 2014, four patients utilized this strategy in the setting of massive PE with impending cardiac arrest; in two cases it was available to use as a backup strategy. All six patients (Table 1) had successful recovery with complete restoration of cognitive status, functional status, and without any clinical signs of right ventricular (RV) dysfunction on discharge.

Case 1

We report a case of a 75-year-old African American woman with previous history of hypertension that presented to our hospital six weeks prior to the current admission with symptoms of left sided weakness and was found to have a subdural hematoma. Patient underwent subdural hematoma evacuation and was found to have a mass in the right parietal area that was completely resected and was given the diagnosis of “Diffuse Large B Cell Lymphoma.” She was subsequently seen by neuro-oncology and was initiated on methotrexate, folinic acid, and rituximab. She had been doing well at home, was walking for two miles a day, and performing activities of daily living prior to the presentation. Two days after her second cycle of chemotherapy with methotrexate and rituximab, patient was noted to have dizziness and hypotension and was admitted to the intensive care unit (ICU) for further monitoring. In the ICU, patient was noted to have progressive hypotension and she underwent a computed tomography (CT) PE study that revealed filling defects within right and left pulmonary arteries (PAs).

An echocardiogram confirmed severe RV dysfunction. Given her recent craniotomy less than six weeks prior to the current presentation, systemic thrombolytics were not a viable option. Patient was emergently taken to the interventional suite for a catheter-directed thrombectomy with utilization of VA ECMO. In the interventional suite, patient emergently underwent cannulation because of severe hypotension, bradycardia and impending cardiac arrest. During this time, patient was given moderate sedation and a decision was made not to intubate given potential cardiovascular collapse with induction. Once stabilized on VA ECMO with a flow of two liters per minute at 2800 revolutions per minute, patient was able to talk and hemodynamics normalized. She subsequently underwent catheter-directed thrombectomy using AngioJet. Patient was then taken to the ICU and monitored for forty-eight hours on full anticoagulation with bivalirudin. On post-ECMO day 4, a repeat echocardiogram and CT Chest scan revealed decreased clot burden and RV strain. The ECMO was successfully decannulated and patient was monitored in ICU for twenty-four hours. She also underwent an inferior vena cava filter placement prior to transfer from the intensive care unit. She was subsequently discharged home one week later on warfarin. She was seen at one month, two month and six months follow-up and she reported excellent functional status. Her RV strain had significant improved from severe to mild at the time of the six-month visit.

Case 2

A 69-year-old Caucasian woman with past medical history of hypertension, hypothyroidism, and breast cancer status post bilateral mastectomy was doing well and presented after an accidental fall. She sustained multiple upper limb fractures and underwent serial surgeries over the course of a week. After the third surgery at an outside hospital, she was noted to be hypotensive, hypoxic and had a cardiac arrest. No thrombolytics were offered at the outside hospital given the recent surgery. During the resuscitation, our team was called and VA ECMO was emergently placed to stabilize the patient. Prior to the ECMO, she was on high dose levophed, vasopressin and dopamine. After the ECMO was placed, the pressors were weaned at our facility and CT PE protocol revealed extensive bilateral PE with an echocardiogram that revealed severe RV dysfunction. When patient's RV strain had not improved after systemic thrombolytics, the decision was made to proceed to surgical thrombectomy, and patient had a successful pulmonary endarectomy five days after presentation. During the procedure, she had a cardiopulmonary bypass time of sixty minutes. She was subsequently monitored in the ICU and was closely monitored for hemodynamic compromise. Explantation of the VA ECMO was done successfully within twenty-four hours of the pulmonary embolectomy. Patient remained hemodynamically stable and was weaned off sedation and subsequently extubated four days after the VA ECMO decannulation. She had an uneventful post-operative course and was discharged home. At nine-month follow-up, she had a normal echocardiogram and continues to live a healthy normal life.

Case 3

A 69-year-old gentleman with history of hypertension and diabetes mellitus was admitted to an outside hospital with generalized weakness and was found to have metabolic encephalopathy, diabetic ketoacidosis, and acute kidney injury. He was treated there appropriately for diabetic ketoacidosis and was discharged four days after admission. Prior to discharge, he had a right internal jugular central line removed. Patient notes that by the evening of the discharge, he had worsening dyspnea and presented to our emergency department with relative hypotension, tachycardia and dyspnea without hypoxia. He underwent imaging that revealed a saddle pulmonary embolus (Figure 1) and was admitted to the medical intensive care unit for further care. His laboratory investigations were unremarkable except for thrombocytopenia (75k). An echocardiogram revealed severe RV dysfunction with a thrombus in transit (Figure 2). Patient was subsequently noted to be hypotensive, but given the thrombocytopenia, thrombolytics were thought to be a relative contraindication. Additionally, interventional radiology refused the patient due to his unstable hemodynamic status. After discussion with the perfusion service, a VA ECMO was available in the interventional radiology suite in case of decompensation. Arterial and venous access was secured for potential ECMO prior to the initiation of catheter-directed embolectomy. Post extraction venography demonstrated no significant residual clot. Patient was subsequently transferred to the ICU and monitored for 24 hours. He was transitioned to warfarin and was discharged home once the INR achieved therapeutic range. He has followed up in our center for eight months without resulting hemodynamic consequences and displaying normal echocardiography.

Case 4

A 48-year-old man presented to an outside hospital with gradually worsening dyspnea on exertion over a period of three weeks. He was evaluated in the emergency center and was found to have dilated right heart chambers on bedside echocardiography. He was noted to be tachycardic with a heart rate at 120 beats per minute and normotensive on arrival, and a CT scan of the chest revealed bilateral occlusive thrombus in the right and left main PAs. He was planned to receive systemic thrombolysis, but suffered a cardiopulmonary arrest (pulseless electrical activity). He underwent about 45 minutes of cardiopulmonary resuscitation (CPR) in total, during which the thrombolytic (alteplase) was administered and endotracheal intubation was performed, with brief return of spontaneous circulation intermittently. Since he was neurologically intact between episodes of CPR, ECMO services were called in emergently for cardiopulmonary stabilization, and he was initiated on hypothermia protocol for neuroprotection after instituting VA ECMO (femoral to femoral). Following this, he was taken to the interventional radiology suite for concerning residual pulmonary embolus post-alteplase administration and for mechanical thrombectomy. Suction thrombectomy using an AngioJet was performed within the right PA and following multiple passes, the majority of the clot within the right main PA was successfully removed. There was markedly improved perfusion of the right lung

after this. Patient was monitored in the ICU and decannulated seventy-two hours after the VA ECMO cannulation. He was extubated within twenty-four hours after decannulation. Patient was followed up in clinic without any further issues from PE.

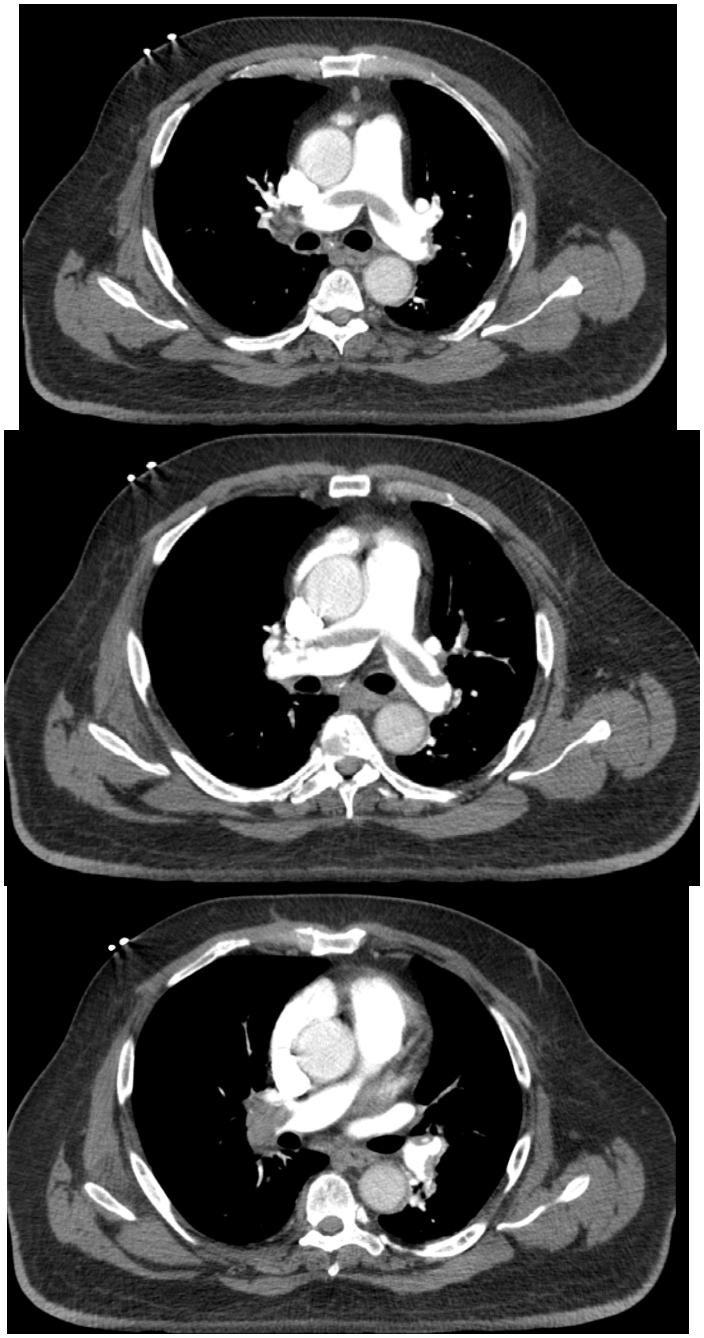

Figure 1: A representative computed tomography image of saddle pulmonary embolus and occlusive embolus in the right main pulmonary trunk.

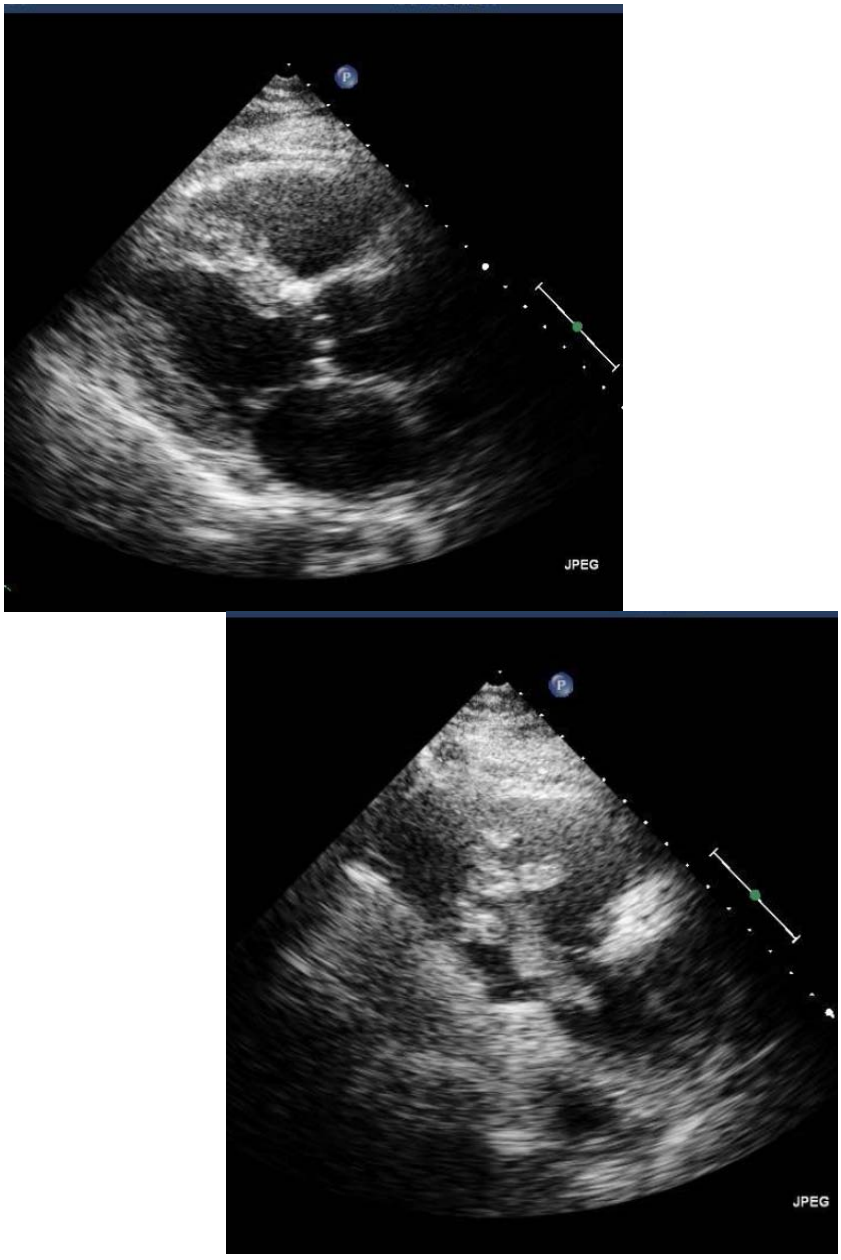

Figure 2: Two-dimensional echocardiogram displaying large echodensities within right-sided heart chambers consistent with thrombus in transit.

Case 5

A 50-year-old previously healthy female was brought to an outside hospital after sustaining cardiac arrest. She had a history of prolonged travel the week prior and was noted to be diaphoretic, pale, and pulseless on the airplane. She was resuscitated and brought to an outside hospital when our team was called to place an emergent VA ECMO. The CT angiogram showed extensive massive PE

and patient had forty-five minutes of CPR. An echocardiogram revealed severe RV dysfunction. She was air lifted to our facility after cannulation by our team with CPR in progress. She went to the operative suite for an emergent embolectomy. Upon return from the operative suite, we weaned all the pressors and the VA ECMO was removed on post-operative day three. She was extubated on post-operative day six. Patient was managed on bivalirudin and bridged to Coumadin. She was fully functional without any evidence of RV dysfunction upon discharge home. She is being followed up by the local pulmonologist at her hometown.

Case 6

A 61-year-old gentleman presented to outside hospital with past medical history of prostate cancer status post radiation, meningioma status post resection with craniotomy in 2000 and again eight months prior to current admission. He displayed exertional angina, and unilateral lower extremity edema in the right leg. On presentation, patient was hemodynamically unstable and was found to have a large saddle pulmonary embolism with bilateral thrombi, and patient was maintained on norepinephrine. An echocardiogram confirmed significant RV strain and patient was emergently transferred to our facility. After risks and benefits were discussed with the patient, with perfusion service as backup, patient underwent placement of EKOS catheter into the right and left main pulmonary arteries. A conservative dose of tissue plasminogen activator (tPA) was chosen because of meningioma surgery and a dose of 0.5 mg per hour were given for twenty-four hours along with fixed dose heparin at 500 units per hour. EKOS catheters were removed at the bedside on the second day and patient was switched to bivalirudin for increased clot burden detected on repeat CT angiogram. Six days later, patient was taken back to the cath lab for AngioJet 6-French system to lyse the clot further. He tolerated the successful debulking of the saddle embolus and was subsequently switched to warfarin and discharged home.

Table 1. Brief clinical summaries for each patient case

	Presentation	Treatment strategy	Outcome
Case 1	75-year-old African American woman admitted to ICU and noted to have progressive hypotension. CT PE and echocardiogram revealed RV dysfunction.	Cannulation of VA ECMO in interventional suite due to severe hypotension, bradycardia and impending cardiac arrest. Patient was not intubated given potential cardiovascular collapse. She underwent catheter-directed thrombectomy using AngioJet.	CT PE and echocardiogram on post-ECMO day 4 showed decreased clot burden and RV strain. Follow up visits show marked improvement in RV strain from severe to mild.
Case 2	69-year-old Caucasian lady was referred by outside hospital during resuscitation after surgery from accidental upper limb injury. CT PE and echocardiogram revealed extensive bilateral PE and RV dysfunction. Patient was on high dose norepinephrine, vasopressin, dopamine.	VA ECMO emergently placed and vasopressors weaned. Systemic thrombolytics did not work, so she underwent surgical thrombectomy (bypass time 60 min).	VA ECMO explanted within 24 hr of embolectomy. Patient weaned off sedation and subsequently extubated four days after decannulation. Nine-month follow-up visits showcase normal echocardiogram.
Case 3	69-year old gentleman admitted to emergency room with relative hypotension, tachycardia and dyspnea without hypoxia. He had been discharged the same day following treatment for diabetic ketoacidosis. Studies revealed a saddle pulmonary embolus and thrombocytopenia (75k). Echocardiogram revealed severe RV dysfunction with thrombus in transit.	Use of thrombolytics discarded due to thrombocytopenia. VA ECMO access was secured in interventional radiology suite in case of decompensation, but was not used.	Post-extraction venography demonstrated no significant residual clot. ICU monitoring for 24 hours and transitioned to Coumadin for INR stabilization. Eight months without resulting hemodynamic consequence and normal echocardiography.
Case 4	48-year-old normotensive male presented with tachycardia. CT Chest revealed bilateral occlusive thrombus in right and left main PAs.	Planned to receive systemic thrombolysis, but suffered cardiopulmonary arrest. He underwent CPR for 45 min, was administered thrombolytic alteplase, and intubated. Following neurological assessment, patient was put on VA ECMO and underwent successful mechanical	72 hr after VA ECMO cannulation, patient was explanted and in follow-up visits in clinic showed no issues from the PE.

		suction thrombectomy using AngioJet.	
Case 5	50-year-old female sustaining cardiac arrest referred by outside hospital where she was noted to be diaphoretic, pale, and pulseless. CT angiogram showed massive EP and underwent 45 min CPR. Her echocardiogram revealed severe RV dysfunction.	VA ECMO was placed on patient and she was air lifted with CPR in progress to our facility. Here, she underwent emergent surgical embolectomy.	Pressors were weaned and VA ECMO explanted three days after operation. She was fully functional without evidence of RV dysfunction upon discharge.
Case 6	61-year old man with history of prostate cancer. Saddle pulmonary embolism with bilateral thrombi maintained on norepinephrine Echocardiogram confirmed significant RV strain and emergently transferred to our facility.	Conservative tPA doses (0.5 mg/hr) and heparin drip (500 U/hr) were used due to past meningioma surgery. EKOS catheters placed into right and left main PAs. Bivalirudin was started on the second day due to increased clot burden revealed on CT angiogram. Six days later, patient underwent AngioJet intervention to lyse clot further.	Patient tolerated debulking of saddle embolus, switched from bivalirudin to warfarin, and discharged home.

Discussion

The manifestations of acute PE may range from being asymptomatic to sudden death. Current management practices mandate early diagnosis and risk stratification, which includes evaluation of hemodynamic parameters and of cardiac function/impairment with a 2D echocardiogram, and biomarkers of cardiac injury. Life threatening acute PE results from the interaction of clot burden and underlying cardiopulmonary status, resulting in hemodynamic instability.[5] Mortality from cardiogenic shock following massive PE approaches 75%.[2] Massive PE is defined as acute PE with sustained hypotension (systolic blood pressure < 90 mmHg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular dysfunction), pulselessness, or persistent profound bradycardia (heart rate < 40 bpm with signs or symptoms of shock).[6] The pathophysiology of massive PE consists of direct mechanical obstruction in the pulmonary arterial system, hypoxic vasoconstriction that increases pulmonary vascular resistance and RV afterload. Acute RV pressure overload may then result in RV hypokinesis and dilatation, tricuspid regurgitation, and ultimately RV failure. This presentation in extremis is not uncommon, and such patients are often too unstable to undergo definite management of the embolus, either successful thrombolysis and/or embolectomy. Thrombolysis in these patients should not be delayed because irreversible cardiogenic shock may ensue.[7] Management of massive PE

causing hemodynamic instability is challenging especially in the setting of contraindications to systemic thrombolysis, as in three of the patients described here. Even when patients with acute massive PE are prescreened for absolute contraindications, the rate of major hemorrhage from systemic thrombolytic administration is approximately 20%, including a 3% to 5% risk of hemorrhagic stroke.[8] Other modalities of treatment include catheter-directed or surgical embolectomy.

In a systematic review of available cohort data comprising a total of 348 patients, clinical success with percutaneous therapy alone for patients with acute massive PE was 81% (aspiration thrombectomy 81%; fragmentation 82%; rheolytic thrombectomy 75%) and was 95% when combined with local infusion of thrombolytic agents (aspiration thrombectomy 100%; fragmentation 90%; rheolytic thrombectomy 91%).[13]

Recommendations for Catheter-Based Treatment for Massive PE (adapted from reference 8)

1. Depending on local expertise, either catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE and contraindications to fibrinolysis (Class IIa; Level of evidence C).

2. Catheter embolectomy and fragmentation or surgical embolectomy is reasonable for patients with massive PE who remain unstable after receiving fibrinolysis (Class IIa; Level of Evidence C).

Surgical embolectomy has historically had a high mortality rate—between 20% to 30%.[14] Leacche et al.[15] reported a 6% mortality rate (3 out of 47 patients) in patients with massive PE who underwent a surgical embolectomy. However in this series, hemodynamic instability was noted only in 26% of the patients. A significantly higher mortality, up to 70%, has been reported in patients who undergo cardiopulmonary resuscitation.[16] The best surgical candidates are those patients with a large amount of clot limited to the central main PA. The decision to proceed with catheter-based versus surgical embolectomy requires coordinated teamwork involving the intensivist, interventional radiologist, and the thoracic surgeon.

In hemodynamically unstable patients, prompt surgical intervention with ECMO can be life-saving. In acute massive PE, use of extracorporeal life support (ECLS) was first reported in 1961.[3] VA ECMO support provides cardiac and respiratory support as it helps maintain blood flow with the help of centrifugal roller pumps and oxygenated venous blood through a membrane oxygenator. In addition, it corrects the resulting acidosis from respiratory failure. This hemodynamic stabilization restores organ perfusion and allows time to enable definitive management of PE—surgical or catheter-directed embolectomy. This is especially helpful in emergent situations in which the femoral vein and the artery can be easily cannulated, even in the presence of ongoing CPR. At our center, we believe that facilitated thrombolysis utilizing VA ECMO support offers “RV rest” and thereby rescues the patient in the setting of cardiac arrest. In these cases, utilizing thrombolytics without appropriate resuscitation of circulatory

arrest may not be fruitful, and utilizing VA ECMO will establish the circulatory support so that facilitated thrombolysis may be subsequently more effective. In all of the presented cases, we were able to decompress the acutely overloaded RV, allowing us time to undertake a definitive management choice.

When we were able to bypass the “obstruction” to the RV with ECLS, hemodynamic parameters improved and vasopressor requirements diminished resulting in improved end organ perfusion, as evidenced by lactate clearance. Following definitive treatment of the PE with the relief of the obstruction and restoring forward flow from the RV, all patients underwent successful decannulation of the ECMO circuit with subsequent improvement in RV function. Maggio et al.[4] reported a series of 21 patients with pulmonary embolism requiring ECLS, with a survival rate of 62%. The mean duration of ECLS was 4.7 days; however, 10 of the 13 survivors did not receive additional therapy other than anticoagulation. This was based on their observation that the clot typically undergoes significant autolysis in about 5 days. We add to this data and report one hundred percent survival utilizing this strategy.

We hereby report a series of six patients with massive PE out of which four who underwent initial stabilization with VA ECMO and subsequently underwent thrombectomy (3 catheter-directed and 1 surgical) with a 100% survival to discharge. The choice of therapy for massive PE—thrombolytics, clot fragmentation, catheter embolectomy or surgical embolectomy—depends on the expertise available at each institution. Currently, there are no randomized trials addressing superiority of one therapy over the other. Although ECMO appears as an attractive approach, potential drawbacks of using ECMO in this particular setting should be kept in mind. These may include vascular injury during cannulation, bleeding complications, and dislodging additional clots from the inferior vena cava, none of which were seen in our cases. In addition, there may be significant costs involved with instituting ECMO in patients who would have done well with systemic thrombolysis. ECLS should be considered in patients who are otherwise good candidates for systemic thrombolytics but who continue to be in persistent shock despite administration of thrombolytics. It should definitely be considered in patients with cardiopulmonary arrest due to a pulmonary embolus.

We also prefer using direct thrombin inhibitors (bivalirudin) in patients with significantly elevated clot burden. Bivalirudin, a direct thrombin inhibitor with short half-life, reliable anticoagulant response, and a capacity to reduce the thrombogenic potential of thrombin bound to clot is likely a better agent than heparin in patients with mechanical circulatory support devices. Previous studies utilizing bivalirudin in implantable ventricular assist devices as a first line agent have shown that there is no incidence of thromboembolic complications, which is similar to our experience. In one study, patients that have been on bivalirudin in the setting of post-cardiotomy shock, bivaliruidin has been found to have a less bleeding and less transfusion requirements, along with reduced costs. Large scale studies need to be done to show the cost benefit analysis of bivalirudin as a first line agent when compared to heparin.[17]

We also recommend management of these patients by a multidisciplinary team who are able to arrive to the bedside in a timely manner similar to the STEMI pager system utilized nationwide. We recommend an algorithm (Figure 3) to risk-stratify patients and suggest addition of the VA ECMO perfusion service, interventional cardiology/radiology, cardiothoracic service and an echocardiographer to the massive PE team in tertiary care centers where VA ECMO is a feasible option. We have found that the availability of this service at our institution has directly led to improved outcomes and excellent functional status at discharge.

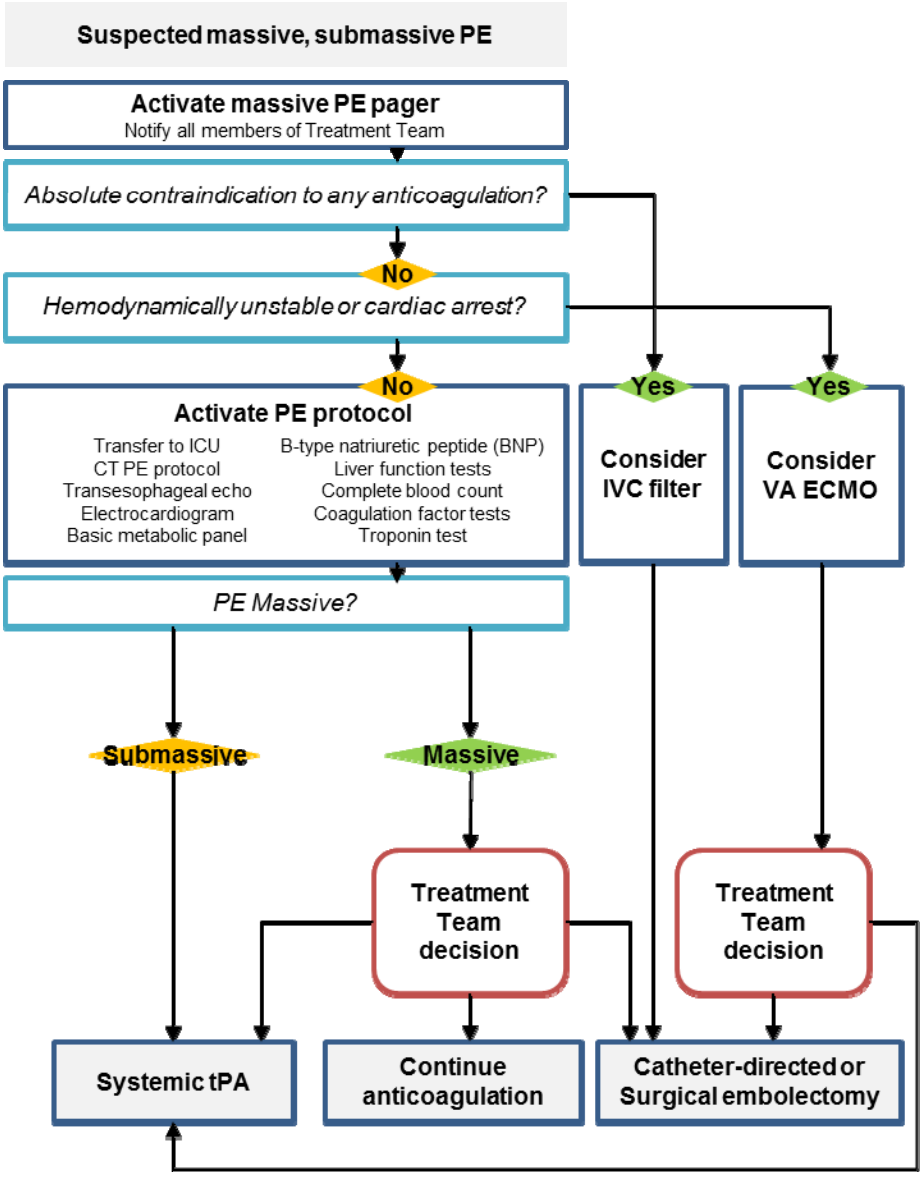

Figure 3: A proposed algorithm to manage massive or submassive pulmonary embolus

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