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Lung Ischemia Reperfusion Injury as a Complication of Pulmonary Thrombectomy

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Abstract

Pulmonary embolism (PE) leads to lung ischemia due to reduced blood flow which can be restored by thrombectomy to prevent infarction. However, this can lead to an under-recognized sequela called lung ischemia reperfusion injury (LIRI), such as in this case. An 86-year-old gentleman in rehabilitation after cervical laminectomy was found to have bilateral PE, right heart strain and newly reduced ejection fraction of 30-35%. He was started on heparin drip and since recent surgery precluded thrombolysis, he underwent emergent thrombectomy. Rapid improvement in perfusion of bilateral pulmonary arteries was noted. However, two hours later, he began to have hemoptysis with shock and hypoxia. He was intubated and bronchoscopy showed blood-tinged frothy secretions but no active bleeding. Despite a stable hemoglobin and improved ejection fraction, shock became progressively refractory to vasopressors. Repeat CTA showed improvement in clot burden but worsening bilateral ground-glass opacities (GGOs), predominant in previous areas of high clot burden. He improved over the next day with supportive care, and was extubated. Restoration of blood flow after thrombectomy to ischemic lung can cause aseptic inflammation and pulmonary edema, known as LIRI. In this, reactive oxygen species cause endothelial dysfunction and increased vascular permeability which presents as non-cardiogenic pulmonary edema in areas with previously obstructed blood flow which can progress to ARDS and death. Our patient's deterioration into refractory shock after thrombectomy and GGOs in previously ischemic areas can be best explained by LIRI. Therefore, it is imperative to be mindful of this catastrophic outcome when considering thrombectomy for PE.

Keywords: LIRI; Reperfusion Injury; Thrombectomy; Embolectomy; Pulmonary Embolism; Lung Ischemia

Introduction

Pulmonary embolism (PE) leads to lung ischemia as the metabolic needs of the lung cannot be met by reduced blood flow. A novel treatment option in intermediate-high, and high-risk PEs is thrombectomy which can promote rapid resolution of symptoms [1]. Even though this procedure can immediately restore blood flow and thereby, prevent progression of ischemia to infarction, more widespread availability and use of this modality is bringing our attention to a lesser-known physiological complication of this procedure-lung ischemia reperfusion injury (LIRI). LIRI, as the name suggests, is lung injury that occurs due to restoration of blood flow to previously ischemic lung. We present a case of LIRI after thrombectomy along with a review of literature on the topic.

Case Presentation

An 86-year-old African-American male, non-smoker, with hypertension, gastroesophageal reflux disease, arthritis, cervical stenosis, and a remote history of prostate cancer went to our inpatient rehabilitation unit after a C1-C2 and C5-C6 posterior cervical laminectomy. His outpatient medications were amlodipine, pregabalin, valsartan, terazosin, and aspirin.

On post-operative day six, he was noted to be hypoxic (SpO_2 79%) and hypotensive (BP 80/50). A stat CT angiogram of the chest showed bilateral pulmonary emboli with evidence of right heart strain. BNP had increased to 764 pg/mL from pre-admission

values of 51-83 pg/mL. Troponin (lab reference ≤0.03 ng/mL) increased to 0.23 ng/mL and peaked at 0.24 ng/mL. His pulmonary embolism severity index (PESI) score was 216 and he was upgraded to MICU. Echocardiogram demonstrated a hypokinetic right ventricular free wall (McConnell's sign) and a newly reduced left ventricular ejection fraction of 30-35%. Vascular surgery was consulted for mechanical thrombectomy as he was not a candidate for thrombolytic therapy for this high-risk PE [2] due to recent spinal surgery.

Patient underwent emergent mechanical thrombectomy and IVC filter placement. During clot evacuation, he was noted to have significant clot burden, right greater than left. He received a 5000-unit heparin bolus during the procedure and was continued on heparin drip after the procedure. The total clot removed from the right main pulmonary artery measured 3.6 cm x 3.1 cm x 0.6 cm. The total clot removed from the left main pulmonary artery measured 2.7 cm x 2.5 cm x 0.4 cm. After removal of these clots, excellent filling of both right and left main pulmonary arteries was confirmed intraoperatively. There was no evidence of dissection or extravasation.

Two hours after the procedure, the patient started having active hemoptysis with worsening shock and hypoxia. The heparin drip was stopped, and PTT level was noted to be supratherapeutic. The patient was intubated for airway protection. His venous sheath, left in after the procedure, was assessed without evidence of bleeding or hematoma. No other bleeding source was identified.

His blood gas after intubation showed combined respiratory and metabolic acidosis with high alveolar-arterial (A-a) gradient (pH 7.28, $PaCO_2$ 50, PaO_2 291, HCO_3- 21 on 100% FiO_2). His post-intubation chest x-ray was notable for a left lower lobe opacification. Bedside bronchoscopy showed blood-tinged frothy secretions throughout the airways, more on the left compared to the right, but no focal source of active bleeding. He was started on nebulized tranexamic acid (TXA) every 8 hours. His chemistry panel was unremarkable with mild lactic acidosis of 2.2 mg/dL. His hemoglobin remained stable, however, his hemodynamics continued to worsen, and he went into refractory vasopressor dependent shock for the next twelve hours requiring significant doses of norepinephrine, epinephrine, and vasopressin (Table 1).

Date and Time	9/27 0600	9/27 0700	9/27 0915	9/27 1000	9/27 2300	9/28 1800	9/30 1200
HR	99	94	99	91	103	106	95
BP	94/63	66/54	92/50	50/33	107/64	125/61	149/52
MAP	73	58	65	37	79	78	78
SpO_2	93%	99%	95%	80%	100%	92%	91%
RR	28	30	25	21	18	23	18
O_2	HFNC 12L	HFNC 12L	HFNC 12L	100% FiO_2 (P-CMV)	50% FiO_2 (P-CMV)	HFNC 20L, 95%	HFNC 15L
Norepinephrine (mcg/min)	-	-	-	80	83	12	2
Epinephrine (mcg/min)	-	-	-	4	10	-	-
Vasopressin (mcg/min)	-	-	-	0.04	0.04	0.04	0.03
Event	Pre-embolectomy	Peri-embolectomy	Hemoptysis	Peri-Intubation	Post-intubation	Post-extubation	Immediately Prior to Comfort Care

Table 1: Vital Signs, Oxygen Support and Vasopressors.

Repeat echocardiogram showed improved ejection fraction of 40-45% with dilated IVC concerning for persistently elevated right sided pressures and a small to medium circumferential pericardial effusion. He had a repeat CT angiogram of his chest for hemoptysis and refractory shock which showed improvement in clot burden but residual clot in the segmental and distal subsegmental branches. Worsening patchy ground-glass opacities (GGOs) bilaterally but most severe in the left lower lobe were noted along with a small right pleural effusion and minimal ascites (Figures 1 and 2).

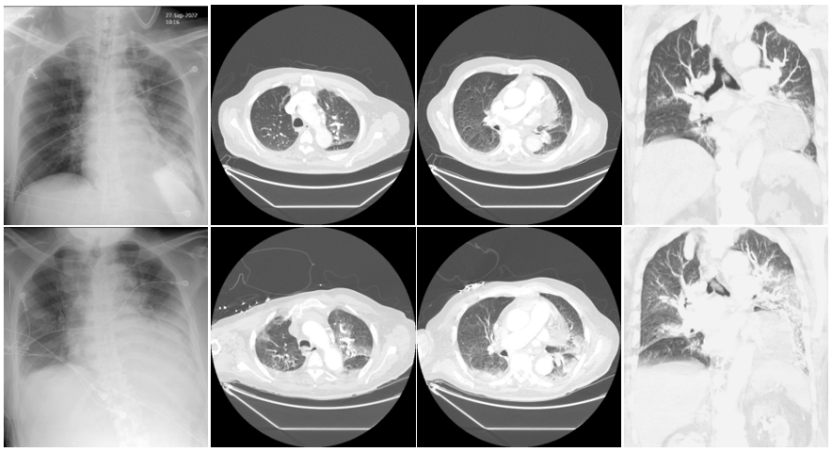

Figure 1: Chest X-ray and CT chest lung windows before (top row) and after (bottom row) thrombectomy.

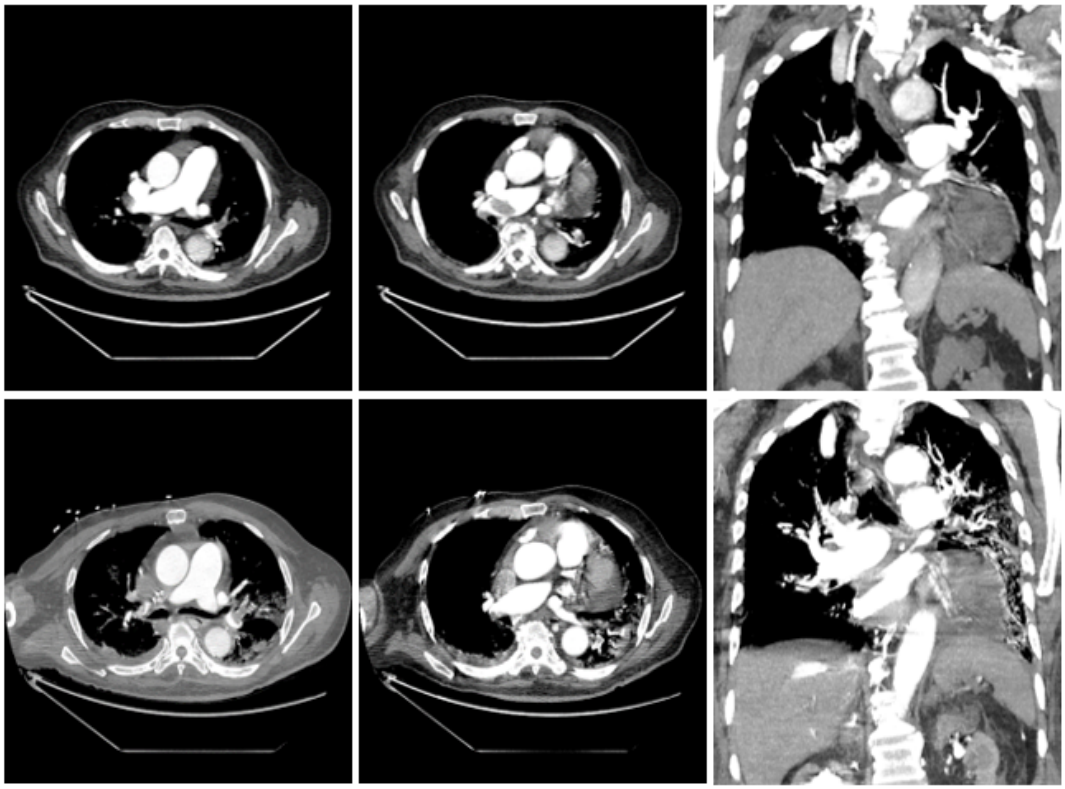

Figure 2: CTA chest before (top row) and after (bottom row) thrombectomy.

Given the elevated right heart pressures, he was started on inhaled epoprostenol 3-4 hours after intubation. Slowly but surely, his pressor requirements decreased over the next 24 hours, and he was successfully extubated to 20 L and 95% FiO_2 heated high flow nasal cannula (HHFNC). Over the next couple of days, his O_2 requirements came down to 15L. He continued to have low dose pressor requirements of norepinephrine 2mcg/min and vasopressin 0.03 units/min. Given his advanced age and his wishes to spend his last few moments with family, he requested transitioning to palliative care. He was transferred to the palliative care unit and passed away the next day.

Discussion

Lung ischemia reperfusion injury (LIRI) occurs because of restoration of blood flow to previously ischemic lung and remains a major cause of morbidity and mortality especially in lung transplant recipients [3]. The complex mechanism underlying LIRI is poorly understood but involves aseptic inflammation, alveolar damage, and pulmonary edema resulting in increased pulmonary vascular resistance and impaired oxygen exchange [4]. This rapidly escalating injury can result in acute respiratory distress syndrome, increased ventilator dependent days and even death. Similarly, in recent years, LIRI is being increasingly recognized as a major cause of mortality in post-thrombectomy patients [5]. On imaging, LIRI has a similar appearance to pulmonary edema but is more localized to the areas that have been reperfused after thrombectomy [6,7].

Lungs are in the unique position that they get oxygen delivery from two sources-alveolar oxygenation and bronchial arteries. When alveolar oxygenation is preserved but blood flow is impaired, it creates what is called ventilated ischemia. This kind of ischemia arises in pulmonary embolism, acute chest syndrome in sickle cell patients and in pulmonary arterial hypertension. When there is complete cessation of blood flow and alveolar oxygenation such as in a donor lung or during cardiopulmonary bypass, it gives rise to anoxic ischemia [8].

Unlike anoxic ischemia, ATP is preserved in ventilated ischemia and therefore, mechanisms not relying on ATP depletion are thought to be primarily responsible for the production of reactive oxygen species (ROS) in pulmonary embolism. One of these mechanisms demonstrated in animal models involves NADPH oxidase which is present in abundance in endothelial cells of pulmonary vessels. In the absence of blood flow, there is loss of shear stress on the vessel walls which in turn causes ATP-dependent activation of NADPH oxidase. This leads to the generation of superoxide anion which gives to ROS [9,10]. The amount of ROS generated overwhelms the body's natural capacity to control the damage, leading to activation of molecular signaling pathways such as NFkB and AP-1. This in turn leads to a rapid influx of inflammatory cytokines causing endothelial dysfunction which promotes adherence of inflammatory cells and vascular permeability. Moreover, bronchoalveolar lavage in patients suspected to have LIRI has shown an increased number of neutrophils which further proves this to be an inflammatory process6. Leakage of ROS and neutrophil sequestration due to above mechanisms can cause liver and myocardial injury [11]. This systemic inflammatory response, such as seen in our patient, can ultimately lead to profound, vasopressor non-responsive shock.

There are no well-defined criteria for diagnosis of LIRI and most literature describes it as a diagnosis of exclusion [12]. Clinically, LIRI usually presents as non-cardiogenic pulmonary edema leading to ventilation-perfusion (V/Q) mismatch. There is an increase in A-a gradient and reduction in lung compliance [13,14]. Moreover, pre-capillary vasoconstriction causes an increase in pulmonary vascular resistance which further contributes to hypoxia [15]. LIRI can appear as mild infiltrates to confluent opacities on imaging. There can be rapid worsening leading to ARDS and high risk of mortality.

There is no good evidence to suggest which treatment strategies work best in preventing and treating LIRI. While a small RCT showed benefit of using Cylexin (prevents endothelium adhesion of neutrophils) on the day of surgery [6], another RCT did not show any benefit with using methylprednisolone [16] which we know similarly promotes demargination of neutrophils from the endothelium. One study, albeit small, concluded that avoiding inotropes and vasodilators after a PEA arrest due to a PE; along with low tidal-volume ventilation was associated with low incidence of reperfusion edema [17]. Another center in the UK successfully employed veno-arterial ECMO post-PE to reduce mortality [18]. Unfortunately, this modality is limited to highly specialized and experienced centers. Ischemic conditioning, which involves application of brief, reversible, non-lethal ischemia and reperfusion, has been shown to be of benefit in avoiding reperfusion injury in transplant organs [19] but extrapolation of this technique to patients undergoing thrombectomy seems implausible.

We believe that our patient's rapid decompensation after thrombectomy can best be explained by LIRI. Soon after clot removal, he needed intubation and mechanical ventilation, and went into refractory shock requiring hemodynamic support with 4 vasopressors. This was despite improvement in right ventricular as well as left ventricular function- LVEF had improved to 40-45% from previous 30-35%. It is, therefore, unlikely that this rapid decompensation was due to cardiogenic shock. The time between the procedure and hemodynamic decompensation with negative microbiology data was improbable for septic shock. The patient did have brisk hemoptysis after the procedure, prompting bronchoscopy where no definite source of bleeding could be identified. Hemoglobin remained stable throughout the clinical

course making hypovolemic shock implausible.

Radiographic evidence supporting LIRI in our patient includes diffuse bilateral GGOs and persistent hypoxia despite immediate resolution of hemoptysis and correction of coagulopathy. Additionally, there was significant prominence of GGOs in areas of previously high clot burden (Figures 1 and 2) which signify reperfusion edema secondary to LIRI.

Conclusion

While mechanical thrombectomy is increasingly gaining traction as a safe alternative to thrombolysis for treating PE in intermediate-high, and high-risk PE patients, [20,21] it is imperative to be cognizant of this potentially catastrophic outcome. More research is needed to find out ways to prevent or at least, mitigate this complication.

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Conflicts of Interest: None.

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