

Refractory Hypoxemia in a Patient with Submassive Pulmonary Embolism and an Intracardiac Shunt: A Case Report and Review of the Literature

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Perm J 2018;22:17-061

E-pub: 03/02/2018

<https://doi.org/10.7812/TPP/17-061>

ABSTRACT

Introduction: Acute pulmonary embolism is the third leading cause of cardiovascular death. Management options include anticoagulation with or without thrombolysis. Concurrent persistent hypoxemia should be a clue to the existence of an intracardiac shunt.

Case Presentation: A 46-year-old man experienced acute hypoxemic respiratory failure requiring mechanical ventilation after anesthesia induction for elective hip arthroplasty. He was found to have submassive bilateral pulmonary emboli with acute right ventricular dysfunction and a coexisting patent foramen ovale with right-to-left shunt. He remained profoundly hypoxemic despite catheter-directed thrombolysis. He underwent surgical embolectomy with partial endarterectomy, resulting in clinical improvement.

Discussion: The management of acute submassive pulmonary embolism is undertaken on an individualized basis because of the wide spectrum of clinical presentations. In this report we review the literature and discuss the evidence behind the management of cases of acute pulmonary embolism complicated by hypoxemia from a patent foramen ovale. In a case of acute pulmonary embolism complicated by refractory hypoxemia from an intracardiac shunt, adjunctive therapies in addition to anticoagulation and thrombolysis must be considered.

his family history contained a Factor V Leiden mutation.

During induction of anesthesia, he remained hemodynamically stable but had progressively worsening hypoxemia demonstrated on serial arterial blood gas values. He was sedated with propofol, paralyzed initially with succinylcholine and maintained with rocuronium, and received mechanical ventilation with volume assist/control with a 100% fraction of inspired oxygen (FiO₂) and positive end-expiratory pressure (PEEP) of 10 cm H₂O. An arterial blood gas test on this setting showed a pH of 7.29, PCO₂ of 50 mmHg, and PO₂ of 65 mmHg. A transesophageal echocardiogram demonstrated right-sided heart dysfunction with a large right ventricle (RV) to left ventricle (LV) ratio and was positive for McConnell sign (contraction of the right ventricular apex with akinesis of the free wall).

INTRODUCTION

Acute pulmonary embolism (PE) is the third leading cause of cardiovascular death.¹ PE can be stratified by prognosis to guide treatment decisions. Submassive or intermediate-risk PE is diagnosed on the basis of normal blood pressure in conjunction with evidence of cardiac dysfunction, shown either on cardiothoracic imaging or with elevated serum cardiac biomarkers. Acute management options for PE include anticoagulation alone or in combination with systemic thrombolytic therapy or catheter-directed thrombolysis, although guideline recommendations reserve thrombolytic therapy for cases of PE associated with hypotension (massive or high-risk PE). Persistent hypoxemia in cases of acute PE should alert clinicians to the possibility of an intracardiac shunt, such as a patent foramen ovale (PFO).

CASE PRESENTATION

Presenting Concerns

Acute hypoxemic respiratory failure developed in a 46-year-old white man during anesthesia induction for elective left total hip arthroplasty. Four days before the surgery, the patient and his wife had noticed that he was having episodes of palpitations and dyspnea. He had been largely sedentary because of chronic hip pain. His medical history included morbid obesity, pseudotumor cerebri maintained on a regimen of acetazolamide, obstructive sleep apnea, and stable schizoaffective disorder. His prior cardiac workup, which was performed in the setting of chest pain and was ultimately deemed nonanginal, included a normal transthoracic echocardiogram and a coronary angiogram demonstrating non-obstructive coronary arterial disease. His social history was unremarkable, although

Therapeutic Intervention and Treatment

Acute PE was suspected, and an unfractionated heparin infusion was started. The patient's scheduled elective hip arthroplasty was aborted because of the degree of hypoxemia. The patient was transferred to the intensive care unit.

On arrival to the intensive care unit, he was afebrile, with a heart rate of 91 beats/min and blood pressure of 121/61 mmHg by arterial line. Laboratory findings included leukocytosis (15.2 × 10⁹/L) with 3% band forms. Lactate level was 1.39 mmol/L (within the normal range). Troponin I level was 0.05 ng/mL (normal range, 0-0.4 ng/mL) and did not change on serial testing.

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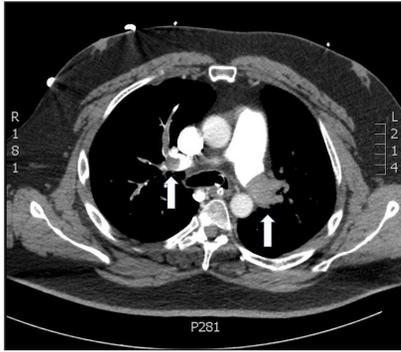


Figure 1. Computed tomography angiogram of the chest demonstrating bilateral large pulmonary emboli (arrows), nearly occluding the right and left pulmonary arteries.

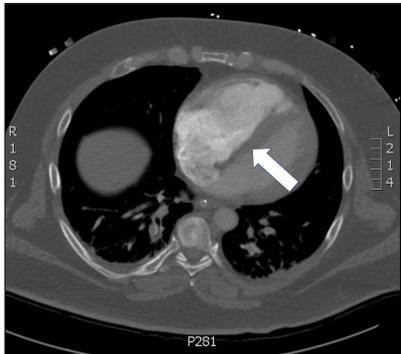


Figure 2. Computed tomography angiogram of the chest demonstrating dilation of the right ventricle (arrow).

A computed tomography angiogram of the chest showed bilateral large pulmonary emboli, nearly occluding the right and left pulmonary arteries, with extension into the upper and lower lobes as well as into the right middle lobe (Figures 1 and 2). Because of his hypoxemia while receiving an FiO_2 of 100%, we were concerned he had an intracardiac shunt. A transthoracic echocardiogram with agitated saline confirmed the presence of a PFO with right-to-left shunt. The estimated shunt fraction was approximately 40%. Because the patient had severe hypoxemia secondary to the acute PE, which was causing elevated RV pressures and right-to-left cardiac shunting, we performed catheter-directed thrombolysis with infusion of alteplase through bilateral femoral lysis catheters at 1 mg/h for 5 hours, and then 0.5 mg/h for 48 hours. The presence of a PFO was also confirmed during this procedure.

The patient continued to have intermittent desaturations despite oxygenation with 100% FiO_2 . The PEEP was lowered to 5 cm H_2O , and inhaled nitric oxide therapy was started in an attempt to reduce the shunt fraction. Cardiothoracic surgery was consulted for possible embolectomy in light of unsuccessful directed thrombolysis. However, our patient's hypoxemia stabilized with the administration of 100% FiO_2 and inhaled nitric oxide on 30 ppm, with arterial partial pressure of oxygen maintained above 60 mmHg. He was unable to wean off inhaled nitric oxide despite 48 hours of thrombolytic therapy, so we made the decision to pursue surgical intervention. Surgical embolectomy (Figure 3), partial endarterectomy, and closure of the PFO were performed on hospital day 4. The patient was successfully extubated on hospital day 6.

The hospital course was complicated by right-sided hemiparesis that was discovered on sedation hold that was performed a few hours before embolectomy. A noncontrast-enhanced computed tomography scan of the head demonstrated multiple small embolic strokes affecting the left premotor cortex. These were probably paradoxical emboli in the setting of the PFO, without evidence of hemorrhagic conversion. The patient was discharged to a skilled nursing facility on hospital day 11. Table 1 shows a timeline of the case.

Follow-up and Outcomes

On follow-up with his primary care physician four weeks after hospital discharge, our patient was noted to be

well-appearing and without residual deficits from his stroke. As of this writing, he remains on an anticoagulation regimen of rivaroxaban. He was evaluated for an underlying hypercoagulable state but did not have Factor V Leiden mutation or antiphospholipid antibodies.

Written informed consent was obtained from the patient. Institutional review board approval was waived by the Veterans Affairs Portland Health Care System in OR because the patient's demographic information was deidentified in this case report.

DISCUSSION

The all-cause mortality for patients in the US and Europe with acute PE ranges from 9% to 17%.¹ Acute PE is categorized into massive, submassive, and nonmassive types. Massive, or high-risk, PE occurs in the setting of persistent hypotension with systolic blood pressure less than 90 mmHg for 15 minutes or greater. Normotensive individuals with evidence of right-sided heart dysfunction, whether on imaging such as computed tomography or echocardiography, or by elevated cardiac biomarkers such as troponin or creatine kinase-myocardial band, are classified as having submassive, or intermediate-risk, PE.^{2,3} PE may also be stratified by the PE Severity Index, which is a validated scoring system based on independent predictors of mortality.³ We presented a case of a patient with a submassive PE and right ventricular dysfunction. He had an intermediate-risk PE Severity Index score (Class III), which gave him a 3% to 7% risk of 30-day mortality.



Figure 3. Thrombi removed from the pulmonary arteries during surgical embolectomy.

PA = pulmonary artery.

Table 1. Case timeline	
Milestone	Events/Interventions/Outcomes
Hospital day 1	Hypoxemia on anesthesia induction for elective hip repair
	Transthoracic echocardiogram: Increased RV to LV ratio; positive McConnell sign; PFO seen
	Computed tomography angiogram of the chest: Pulmonary emboli in both pulmonary arteries
	Catheter-directed thrombolysis administered
Hospital day 2	Persistent hypoxemia
	Inhaled nitric oxide administered
Hospital day 4	Computed tomography of the head: Left premotor cortex embolic strokes
	Surgical embolectomy with PFO closure
Hospital day 6	Extubation
Hospital day 11	Discharge to rehabilitation facility
4-week outpatient follow-up	No residual neurologic deficits or hypoxia

LV = left ventricle; PFO = patent foramen ovale; RV = right ventricle.

Acute PE is often considered when hypoxemia develops. However, PE alone rarely causes hypoxemia to the degree seen in our patient, and it may be useful in such cases to perform an evaluation for an intracardiac shunt. On the basis of autopsy studies, approximately 35% of the general population have a probe-patent PFO, and 5% to 10% have a flow-patent PFO, which is determined with the application and sudden removal of PEEP.⁴ In acute PE, the PFO acts as a “pop-off valve” such that the right atrial pressure increases, causing a right-to-left shunt. The shunt permits LV filling and near-normal cardiac output, thus preventing hypotension. However, hypoxemia ensues because of the intracardiac mixing of deoxygenated with oxygenated blood.⁴⁻⁸ The presence of PFO was associated with a significantly lower arterial partial pressure of oxygen among 85 patients with a hemodynamically significant PE, in whom there was a 39% prevalence of PFO.⁴ Unlike many other causes of severe hypoxemia, such as in acute respiratory distress syndrome, the administration of PEEP often worsens the hypoxemia, as it did in our case.^{9,10}

We conducted a PubMed search using the search terms [*pulmonary embolism* OR *embolus*] AND [*hypoxemia* OR *hypoxemic*] AND [*patent foramen ovale*] for articles published between 1990 and 2016. Individual cases, presented in either case reports or case series, were selected. Further relevant case reports were extracted

from the bibliography of articles gathered from the search. In total, there were 9 articles with 12 individual cases reported of acute PE occurring in the setting of PFO and resulting in persistent hypoxemia (Table 2).^{4,6-13} Submassive PE was present in 45% of patients, and of these, survival was 100%. In those with massive PE, survival was 20%. The overall survival was 45%. Two patients without hypotension received systemic thrombolytics, 27% of the total.^{7,8} In one case report describing a patient without hypotension who received thrombolysis, the authors advocated for systemic thrombolysis because of the size of the emboli and the impending risk of hemodynamic collapse.⁸ Surgical intervention was reported in 18% of patients. No patients received catheter-directed thrombolysis.

Among 1006 patients with submassive PE in the PEITHO (Pulmonary Embolism Thrombolysis) randomized controlled trial, systemic thrombolysis with tenecteplase resulted in significant improvement in the combined primary outcome of all-cause mortality or hemodynamic compromise within 7 days over the administration of unfractionated heparin alone (2.6% vs 5.6%, odds ratio [OR] = 0.44, 95% confidence interval [CI] = 0.23-0.87, $p = 0.02$). However, there was no overall mortality benefit, and there were more patients with major extracranial hemorrhages (6.3% vs 1.2%, OR = 5.55, 95% CI = 2.3-13.39, $p < 0.001$) and strokes (2.4% vs 0.2%, OR = 12.10,

95% CI = 1.57-93.39, $p = 0.003$) within 7 days.¹⁴

The ULTIMA (Ultrasound-Assisted, Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism) trial demonstrated that ultrasound-assisted, catheter-directed thrombolytic therapy in patients with submassive PE resulted in benefit in terms of change in RV-to-LV ratio from baseline to 24 hours, over unfractionated heparin alone (0.30 ± 0.20 vs 0.03 ± 0.16 , $p < 0.001$). There were no instances of major bleeding in this study. Patients with a right-to-left heart shunt, such as a PFO, were excluded from the study population.¹⁵

Two recent meta-analyses,^{16,17} both including PEITHO, found that systemic thrombolysis decreases overall mortality while increasing major bleeding for acute PEs of both high and intermediate risk. The meta-analysis by Marti et al¹⁶ found that 30-day mortality was significantly decreased with systemic thrombolysis (2.3% vs 3.9%; OR = 0.59, 95% CI = 0.36-0.96, $p = 0.034$) while there were significantly increased rates of major hemorrhage (9.9% vs 3.6%; OR = 2.91, 95% CI = 1.95-4.36, $p < 0.0001$) and fatal or intracranial hemorrhage (1.7% vs 0.3%; OR = 3.18, 95% CI = 1.25-8.11, $p = 0.008$). However, 30-day overall mortality was not significantly different when the analysis included only intermediate risk PE. The analysis also did not include ULTIMA.¹⁶ The meta-analysis by Chatterjee et al¹⁷ found a similar significant benefit in the 30-day all-cause mortality rate for all acute PEs with a number needed to treat of 59, which was counterbalanced by a significant increase in the rates of major bleeding (number needed to harm of 18) and intracranial hemorrhage (number needed to harm of 78). Additionally, a systematic review of 35 trials demonstrated a pooled survival of 87% among patients with massive PE treated with catheter-directed interventions; 60% to 67% of these individuals also had received systemic thrombolytics.¹⁸ We could not find analyses from these trials that separately reported outcomes for patients with significant intracardiac right-to-left shunts.

Table 2. Literature review of reported cases of acute pulmonary embolus in the setting of patent foramen ovale and intracardiac shunting

Source	Age, years/ sex	Presentation	Diagnostics	Hemodynamic classification	Mechanical ventilation	Management	Survival
Brydon et al, 1993 ⁴	64/M	Found unresponsive	RHC: PFO, bilateral PE	Submassive	Yes	Surgical closure of PFO; surgical embolectomy	Yes
Estagnasié et al, 1996 ⁶	74/F	Acute respiratory failure	TEE: PFO, atrial septal aneurysm; angiography: PE	Massive	Yes	Unfractionated heparin; inhaled nitric oxide	No
	68/F	Subacute dyspnea leading to respiratory failure and shock	TEE: PFO, atrial septal aneurysm	Massive	Yes	NR	No
	77/F	Respiratory failure	TEE: PFO, atrial septal aneurysm; angiography: Bilateral PE	Massive	Yes	NR	No
Mirarchi et al, 2000 ¹¹	74/M	Acute dyspnea and chest pain with hypotension and respiratory failure	TEE: PFO and right atrial thrombus	Massive	Yes	Unfractionated heparin alone	No
Slebos et al, 2000 ⁷	33/F	Respiratory failure	Angiography: PE; presumptive diagnosis of PFO	Submassive	No	Systemic thrombolytics	Yes
Rajan, 2007 ⁹	89/M	Intraoperative respiratory failure during open reduction and internal fixation of hip	CT: Multiple bilateral PEs; TTE: Dilated RV and PFO	Submassive	Yes; worsening oxygenation with increasing PEEP	NR	NR
Moua et al, 2008 ⁸	80/F	Acute dyspnea and presyncope	CT angiography: Bilateral PE; TTE: Dilated RV and PFO	Submassive	No	Systemic thrombolytics	Yes
	75/M	Acute dyspnea and dizziness	CT angiography: Bilateral PE; TTE: McConnell sign and PFO	Submassive	Yes	Unfractionated heparin, with addition of systemic thrombolytics	Yes
Weig et al, 2011 ¹²	34/F	Respiratory failure 4 weeks after biventricular assist device placement for postpartum dilated cardiomyopathy	TEE: PFO	Massive	Yes	Venovenous ECMO; surgical embolectomy; inhaled pulmonary vasodilator; percutaneous transcatheter closure of PFO with PFO occluder ^a	Yes
Vaid et al, 2011 ¹³	62/M	Respiratory failure 6 hours after vitrectomy to treat retinal detachment	CT angiography: Limited examination; TTE: McConnell sign; autopsy: PE, PFO present	NR	Yes; high PEEP and high FiO ₂ used	Systemic thrombolytics	No
Granati, 2016 ¹⁰	40/M	Acute dyspnea	CT angiography: PE with right-sided heart strain; TTE: PFO and atrial septal aneurysm; duplex ultrasonography: Left lower extremity DVT	NR	Yes; increasing PEEP caused worsening SaO ₂ ; improvement with switch to airway pressure release ventilation	NR	Yes

^a PFO occluder manufactured by Amplatzer, St Jude Medical, St Paul, MN.

CT = computed tomography; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; F = female; FiO₂ = fraction of inspired oxygen; M = male; NR = not reported; PE = pulmonary embolus; PEEP = positive end-expiratory pressure; PFO = patent foramen ovale; RHC = right-sided heart catheterization; RV = right ventricle; SaO₂ = arterial oxygen saturation; TEE = transesophageal echocardiogram; TTE = transthoracic echocardiogram.

The 2016 revision of the American College of Chest Physicians guidelines for venous thromboembolism,² as well as the 2014 European Society of Cardiology guidelines for acute PE,³ recommend systemic thrombolysis for acute massive PE (a Grade 1B recommendation in the American College of Chest Physicians guidelines). Both sets of guidelines recommend against routine systemic thrombolysis in individuals with PE but who do not have shock or hypotension, unless they have clinical deterioration (Grade 1B recommendation).^{2,3} We elected to treat our patient's submassive PE with thrombolysis because we did not expect his severe hypoxemia to improve otherwise.

Although there are no comparative trials of catheter-directed vs systemic thrombolytics,¹⁹ we pursued catheter-directed thrombolysis because of the possible lower risk of bleeding and our institutional experience with this procedure (Grade 2C recommendation per American College of Chest Physicians guidelines).² In one systematic review and meta-analysis, the risk of major bleeding from catheter-directed thrombolysis was about 10% from 24 studies performed in both massive and submassive PE²⁰; in another systematic review stratified by PE classification, the risk of major bleeding was 3.9 per 100 cases of catheter-directed thrombolysis in hemodynamically stable PE.²¹ In our literature review of similar patients, none of the reported cases used catheter-directed interventions; however, only 1 of these cases was published after ULTIMA.

Another negative consequence of PFO is the risk of paradoxical emboli resulting in strokes. Such patients may hypothetically be at increased risk of intracranial hemorrhage from hemorrhagic conversion of these paradoxical strokes after undergoing systemic or catheter-directed thrombolysis. The coexistence of a PFO was associated with the increased incidence of ischemic stroke among patients with acute PE in 1 observational study, with a 13% rate of stroke in 48 patients who were found to have a PFO, and 2.2% stroke rate among 91 patients who did not have a PFO. However, there was no between-group difference in the

proportion of patients receiving systemic thrombolysis.²² Although our patient was found to have strokes from paradoxical emboli, the use of catheter-directed thrombolysis in his case did not result in intracranial hemorrhage.

Other management considerations in patients with PE besides thrombolytics or anticoagulation therapy include mechanical or medical support of RV failure and surgical embolectomy. Pulmonary vasodilators may also be used to decrease pulmonary vascular resistance in situations of acute RV failure, such as acute PE. Inhaled nitric oxide has a rapid onset and short half-life, making it easily titratable.²³ Inhaled pulmonary vasodilators were used in 2 cases in our literature review.^{6,13} Extracorporeal membrane oxygenation (ECMO) can be used as another bridge to definitive therapy for persistent shock (venoarterial ECMO) or hypoxemia alone (venovenous). Venovenous ECMO was used in 1 case in our literature review as a bridge to surgery; that patient had concurrent cardiac failure and was reliant on a biventricular assist device.¹³ Surgical embolectomy is the definitive management for cases in which thrombolytics have failed or are contraindicated. The 1-year survival rate for surgical embolectomy in 1 series was 80% for submassive PE, compared with 66% for massive PE.²⁴ Surgical intervention was successful in resolving our patient's hypoxemia.

CONCLUSION

The management of acute submassive PE is undertaken on an individualized basis, given the spectrum of clinical presentations of such cases. The use of systemic thrombolysis should be weighed against the risk of severe bleeding. The outcomes of catheter-directed interventions compared with systemic thrombolysis are yet unknown. In acute PE with refractory hypoxemia in which an intracardiac shunt is the cause, there is even less evidence to guide decision making, because many of the large trials exclude patients with PFO or do not specifically identify these patients. When deciding between systemic or catheter-directed thrombolysis or anticoagulation therapy alone, the clinician should

consider individual patient factors and the potential increased risk of intracranial hemorrhage because of a PFO. Finally, if there is a failure of systemic thrombolysis to decrease pulmonary arterial pressure and the intracardiac shunt, then bridging therapies such as ECMO or surgical embolectomy must be considered. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgment

Kathleen Loudon, ELS, of Loudon Health Communications provided editorial assistance.

How to Cite this Article

Liew J, Stevens J, Slatore C. Refractory hypoxemia in a patient with submassive pulmonary embolism and an intracardiac shunt: A case report and review of the literature. *Perm J* 2018;22:17-061. DOI: <https://doi.org/10.7812/TPP/17-061>

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