Respiratory Medicine Case Reports 34 (2021) 101499

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Supportive care of right ventricular failure due to fat embolism syndrome

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ARTICLE INFO

Keywords:
Fat embolism
Right ventricle
Pulmonary hypertension
Hypoxemia

ABSTRACT

Pulmonary fat embolism is a common phenomenon in cases of traumatic long bone fractures, with only a minority developing the more catastrophic Fat Embolism Syndrome (FES). Diagnosis is clinical and requires a high index of suspicion. Treatment remains under-investigated, with common interventions having low quality level-of-evidence and no mortality benefit. In severe cases, focus should be on supporting the failing right ventricle through use of inotropes, pulmonary vasodilators, and mechanical circulatory support. This requires a thorough understanding of the unique physiology through the pulmonary circulation.

1. Introduction

Pulmonary fat embolism (PFE) is a common phenomenon following traumatic long bone fracture, with an estimated occurrence of 80–90% in all cases on autopsy series [1]. Of all patients with PFE, only a minority develop the more catastrophic fat embolism syndrome (FES), which carries a high rate of mortality [2]. FES is a diagnosis of exclusion with a syndrome classically characterized by hypoxemia, altered mentation, and petechiae. The pathophysiology of FES is thought to originate by mechanical embolization of fat from the bone marrow coupled with a dysregulated inflammatory response [1]. As a result, FES is associated with pulmonary hypertension which may lead to right ventricular (RV) failure. Treatment of FES remains relatively under-investigated, with current management based largely on case reports and case series. Interventions often used for treatment of FES have low quality level of evidence with no mortality benefit [1]. Thus, in severe cases, focus should be on supporting the failing right ventricle through use of inotropes, pulmonary vasodilators, and mechanical circulatory support. Here, we review current management strategies in a case of severe FES resulting in RV failure and *cor pulmonale*.

2. Case presentation

A 39-year-old African American male with no significant past medical history presented with a traumatic right sub-trochanteric fracture. Vital signs were normal and chest x-ray (CXR) was unremarkable. He underwent intramedullary nailing on day of admission. The following day, he had an acute decline in his respiratory status prompting admission to the ICU. At admission, temperature was 100.9F, pulse 150 bpm, mean arterial pressure 77 mmHg, and oxygen saturation 85% on ambient air. The patient was in respiratory distress, tachycardic with an S3 gallop, had clear lungs on auscultation, bilateral lower extremity edema, and jugular venous distention. No petechiae or conjunctival hemorrhages were noted. Neurologic exam was normal.

2.1. Differential diagnosis

- Pulmonary Embolism – blood, fat
- Pneumothorax
- Acute Decompensated Heart Failure
- Acute Coronary Syndrome
- Pulmonary Contusion
- Pneumonia

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https://doi.org/10.1016/j.rmcr.2021.101499
Received 8 June 2021; Received in revised form 11 August 2021; Accepted 24 August 2021
Available online 25 August 2021

- Hemothorax
- Cardiac Tamponade

2.2. Investigations

His PaO_2 was 70 mmHg on 45% FiO_2, corresponding to a PaO_2/FiO_2 of 155, and Alveolar-arterial gradient of 202 with an increased pulmonary shunt fraction. Complete blood counts showed a drop in platelets to 157,000 cells/mm3 from 283,000 cells/mm3 on admission, and a hemoglobin drop to 8.1 gm/dL from 14.1 gm/dL on admission. CMP results including renal and liver function were within normal limits. Troponin-I was 0.350 ng/mL (normal<0.04), B-type natriuretic peptide was 469 pg/mL (normal<100). A repeat CXR on hospital day 3 showed diffuse bilateral infiltrates (Fig. 1a and b). A CT angiogram demonstrated an enlarged RV and dilated pulmonary artery (PA) without evidence of thromboembolism (Fig. 1c and d). Transthoracic echocardiogram (TTE) showed a hyperdynamic left ventricle (LV), severely dilated RV with depressed systolic function, and an estimated RV systolic pressure of 75 mmHg (Fig. 2a and b). PA catheterization revealed pulmonary hypertension (mean pulmonary arterial pressure (mPAP) = 69 mmHg, pulmonary vascular resistance = 7.4 Wood units) in the setting of reduced cardiac index (1.72 L/min/m^2) but normal LV filling pressure (pulmonary capillary wedge pressure = 9 mmHg) (Table 1).

2.3. Diagnosis

After excluding alternative etiologies, our patient was diagnosed with ***Fat Embolism Syndrome*** based on classic clinical signs and symptoms in the setting of recent orthopedic injury.

2.4. Management

The patient was transitioned to high-flow nasal cannula due to worsening hypoxemia. He subsequently developed hypotension and cool extremities concerning for cardiogenic shock. Intravenous methylprednisolone and milrinone were started. There was minimal improvement in mPAP with inhaled nitric oxide and intravenous epoprostenol. The patient continued to worsen, and he was canulated for venoarterial extracorporeal membrane oxygenation (VA-ECMO) via the left common femoral vein and artery. Oral sildenafil and ambrisentan were initiated and titrated. Inhaled and intravenous pulmonary vasodilators were weaned off and VA-ECMO was discontinued six days later (Table 1).

2.5. Follow up

The patient was discharged home on ambient air with only minor limitations in physical activity. Oral pulmonary vasodilators were tapered over the subsequent month. Follow-up TTE demonstrated normal RV size and function without evidence of pulmonary hypertension (Fig. 2c and d).

3. Discussion

3.1. Clinical discussion

Fat Embolism Syndrome (FES) is much less common than PFE, affecting an estimated 0.17–11% of trauma patients, but carries a mortality ranging from 5 to 15% [2]. Although most frequently the result of orthopedic trauma, FES has also been reported in severe burns, liposuction and bone marrow biopsy, in addition to non-traumatic etiologies such as pancreatitis, osteomyelitis, sickle cell crisis, and long-term steroid therapy [2]. Clinical manifestations typically occur between 12 and 72 hours from the inciting event [3]. The classic triad includes neurologic abnormalities, respiratory insufficiency, and petechial hemorrhages but are only present together in 2–4% of patients with FES, thus suspicion must remain high even in their absence [2]. Other less common manifestations include hematologic abnormalities such as anemia, thrombocytopenia and DIC, in addition to fever, tachycardia and retinopathy [4]. Diagnostic criteria have been proposed by different authors – Gurd, Schonfeld, Lindeque – but they are neither

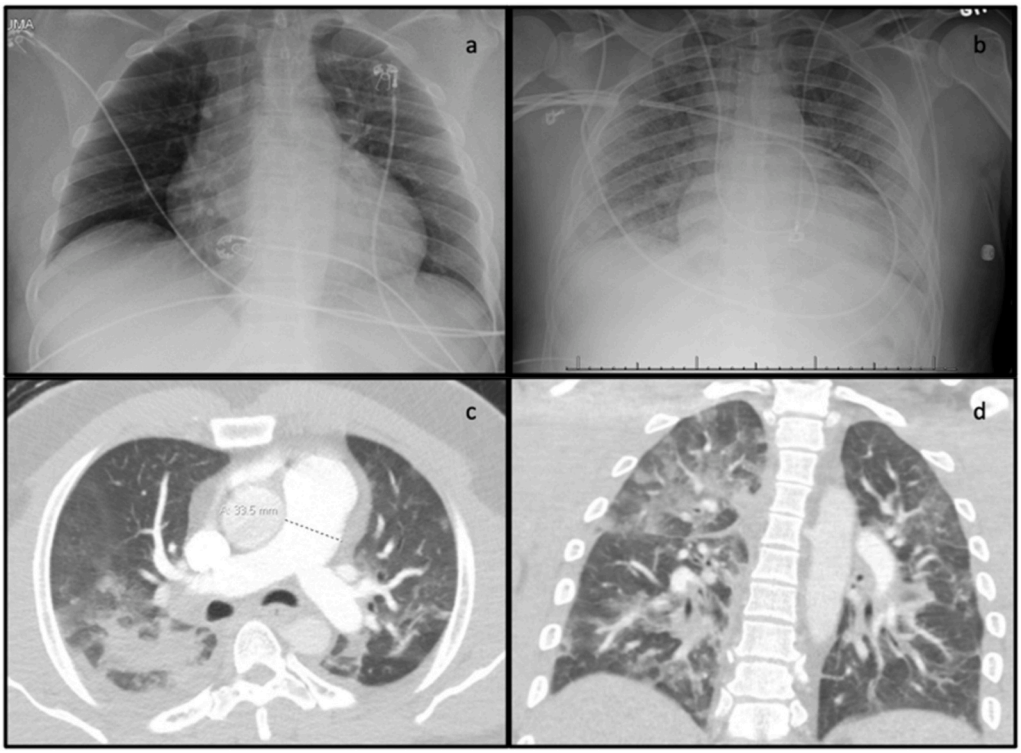

Fig. 1. Select chest imaging in FES. CXR on day of admission (a) and hospital day three (b) showing interval development of diffuse bilateral hazy opacities. CT Angiography of lungs at three days after initial injury in axial (c) and coronal (d) sections. Note dilated pulmonary trunk in (c) and presence of diffuse infiltrates and ground glass opacities, consistent with RV strain in the setting of hypoxic respiratory failure. CT = computer tomography; CXR = chest X-ray; FES = fat embolism syndrome; RV = right ventricle.

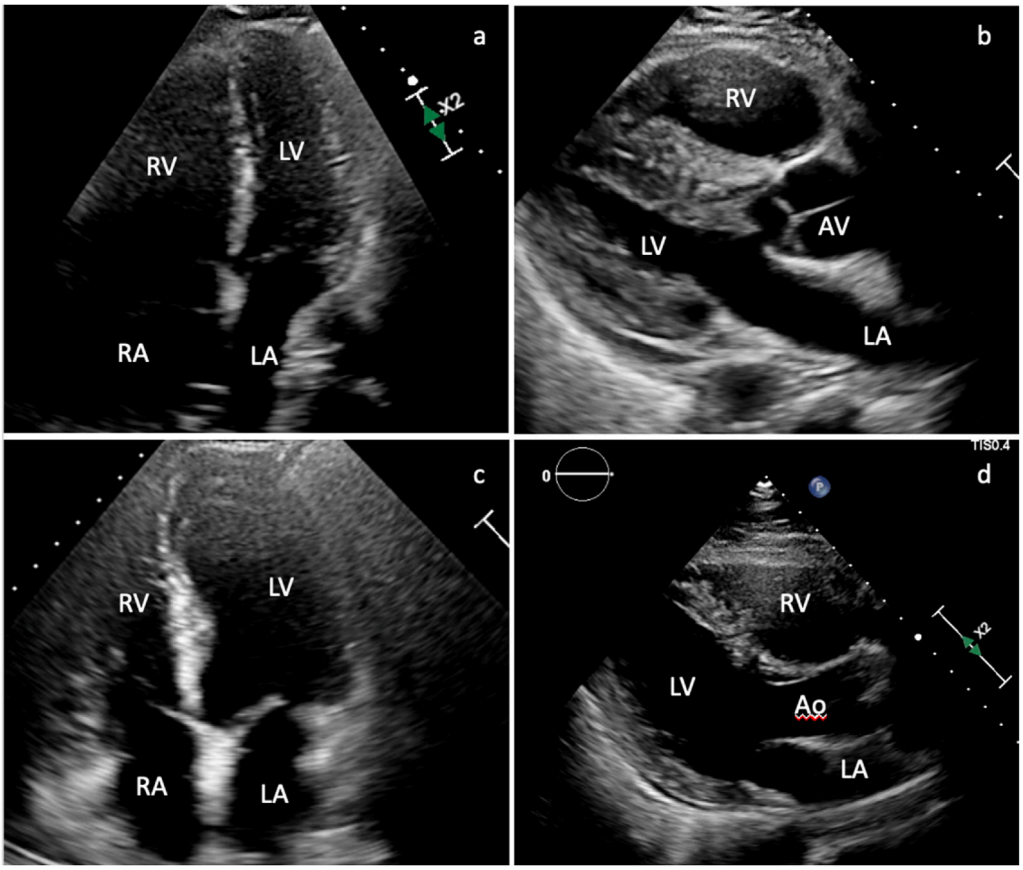

Fig. 2. TTE in FES.
TTE at presentation to ICU (a/b) and follow up 6 months later (c/d). Note bowing of RV into LV at presentation in apical four chamber view (a) indicating RV pressure overload which had resolved at follow up (c).
Ao = Aorta; AV = aortic valve; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Table 1
Hemodynamic measurements at select timepoints reflecting initiation of ECMO and titration of vasoactive medications.

Hemodynamic Measurements at Select Timepoints				
	Pre-ECMO	ECMO		Post-ECMO
	ICU Admission	Mil + iPV	Mil + iPV + Oral PV	Oral PV
MAP (mmHg)	66	84	82	76
CO (L/min)	2.5	6.5	9.0	7.8
CI (L/min/m^2)	1.7	3.1	3.8	3.6
sPAP/dPAP (mPAP) (mmHg)	99/57 (69)	60/35 (44)	37/17 (25)	29/13 (20)
CVP (mmHg)	–	7	6	4
SvO2 (%)	38	60	61	64
	HD 3	HD 6	HD 9	HD 12

CI = cardiac index; CO = cardiac output; CVP = central venous pressure; dPAP = diastolic pulmonary arterial pressure; HD = hospital day; iPV = inhaled pulmonary vasodilators; MAP: mean arterial pressure; Mil = milrinone; mPAP = mean pulmonary artery pressure; PV = pulmonary vasodilators; sPAP = systolic pulmonary arterial pressure; SvO2 = mixed venous oxygen saturation.

sensitive nor specific and none have been prospectively validated [5]. Given the lack of a gold standard, the diagnosis is often made by exclusion in the right clinical setting as occurred in our case.

3.2. Imaging discussion

There are no imaging findings specific for FES. In severe cases, chest radiography may show diffuse bilateral patchy infiltrates as with our patient – however, it is often normal in milder forms or early in the course of disease, and if present must be differentiated from other common causes of hypoxic respiratory failure in the hospital [2,6]. Notably, a normal heart size and absence of other features of cardiogenic edema like septal lines, pleural effusions, and pulmonary venous congestion will assist in differentiation [6]. Unlike in pulmonary thromboembolism, fat globules are small and lodge within microcirculation, therefore will not appear on Chest CT as large perfusion defects. Rather, the most common findings on CT include ground glass opacities and, in severe cases, areas of consolidation [7]. If obtained, MRI of the brain may consist of diffuse hyperintense lesions in both white and gray matter on diffusion weighted images, known as a star-field pattern, and is more sensitive than CT Head which is oftentimes normal [1].

3.3. Brief literature review on treatment

As described, the pathophysiology of FES is thought to result from a mix of mechanical embolization of fat and a pro-inflammatory state. Vascular obstruction occurs that is similar to thrombotic emboli; however, the mechanism is related to fat globules causing endothelial injury with resultant platelet activation and fibrin deposition [1]. Obstruction of pulmonary vasculature causes an increase in right ventricular (RV) afterload which is further worsened by hypoxic vasoconstriction [8,9]. As afterload increases, the RV begins to dilate which then impairs left ventricular (LV) filling and affects coronary blood flow [9]. Ensuing acute RV failure and *cor pulmonale* carry the highest risk for mortality [10]. Biochemically, fat globules induce pro-inflammatory cytokines (TNF-α, IL-1β and IL-6), phospholipase A2 and free radicals [1]. Their activity may be mediators in an FES-induced Acute Respiratory Distress Syndrome (ARDS) and likely explain non-traumatic etiologies of FES [1].

Treatment of FES remains relatively under-investigated. Interventions often used for treatment of FES include heparin, aspirin, corticosteroids, and albumin but have low quality level of evidence. The

proinflammatory cascade associated with FES has prompted interest in using steroids for prophylaxis and treatment; however, results have been inconsistent and there is no mortality benefit [1]. Heparin has been proposed as treatment due both to its systemic anticoagulation effects and also its stimulatory effects on lipase activity. Despite a promising biological basis, heparin has had inconclusive results, and is often contraindicated in the setting of recent trauma [1]. Thus, current management focuses largely on supportive care with an emphasis on optimizing oxygenation, ventilation and stabilizing hemodynamics.

Management of RV failure in the setting of FES remains a challenge. The RV normally operates in the low-pressure system of the pulmonary circulation. As such it has an overall smaller mass and lesser contractile force as compared to the LV but is also more compliant allowing for higher end-diastolic volumes and thus similar CO [10]. This difference means the RV is especially sensitive to acute changes in afterload. The mechanical obstruction and inflammatory cascade in FES results in an acute rise in pulmonary vascular resistance (PVR), leading to a vicious cycle of RV dilation, compromised cardiac output (CO), and hypoxemia with resultant pulmonary hypoxic vasoconstriction, further increasing afterload and worsening RV dysfunction [9]. To overcome this, efforts must be made to either increase contractility through preload optimization and inotropes, or to decrease afterload. Due to similar pathophysiology, decisions for RV failure in FES are often extrapolated from algorithms treating massive pulmonary embolism with *cor pulmonale* [11].

Volume management in RV failure depends in part on the status of PVR. In patients with normal PVR but impaired RV contractility (as may occur in right sided MI), CO can be augmented via fluid boluses to increase preload. However, implementing such a strategy in a patient with elevated PVR, such as those with FES, could lead to cardiovascular collapse due to displacement of the interventricular septum into LV and impairment of diastolic filling and output [9,10]. Conservative fluids to keep the CVP near high normal values (e.g. 8–12 mmHg) has been suggested by some experts [10,11]. This is one population where continuous monitoring of hemodynamics via use of pulmonary artery catheter may be beneficial, although caution should be used as CVP may not always be a reliable indicator of fluid responsiveness in RV failure [12,13]. Given this delicate balance of preload, early consideration should be given to initiate pressors [9]. Inotropes such as dobutamine and milrinone can be used to increase contractility, though their use must be weighed against the risk of systemic hypotension and tachyarrhythmias. If hypotension is observed, the addition of a vasopressor such as norepinephrine is often warranted [11].

In RV failure, vasodilators improve CO by reducing PVR [14]. Inhaled pulmonary vasodilators such as nitric oxide and epoprostenol also have the theoretic advantage of acting preferentially in well aerated lungs, thus improving ventilation/perfusion (V/Q) matching. In contrast, oral pulmonary vasodilators should be used with caution as these medications blunt hypoxic pulmonary vasoconstriction and may impair V/Q matching [14]. As our clinical understanding of these medications expands, they are increasingly being considered in refractory RV failure, though data is sparse in the acute setting [14]. Nevertheless, after correcting of hypoxemia, acidemia and hypercapnia, administration of pulmonary vasodilators in FES may be appropriate.

When patients remain refractory to inotropes, vasopressors and pulmonary vasodilators, ECMO is indicated. ECMO has been shown to reduce PA pressures, improve CO and reduce CVP independent of other medical management such as vasodilators or mechanical ventilation [14]. In RV failure due to hypoxemic respiratory failure Veno-venous (VV) ECMO is recommended as the initial strategy due to lower rates of bleeding and ischemic complications as compared to VA-ECMO [15]. However, as VV-ECMO provides no direct circulatory support, VA-ECMO is the method of choice in severe cardiogenic shock [15]. New data is promising for use of protocolized system of ECMO utilization in thrombotic embolism [13]. Although ECMO use has been reported in FES, there have been no prospective trials, and current studies have not shown a reduction in mortality for this particular indication [13].

4. Conclusion

4.1. Learning objectives

- To identify and manage pulmonary fat embolism and its more severe counterpart fat embolism syndrome.
- To understand the unique physiology of the right ventricle and how to support RV failure during times of critical illness.

Author contribution credit roles

Kevin T. Schwalbach: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Roles/Writing - original draft, review & editing. R. Chad Wade: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Roles/Writing - original draft, review & editing. Takudzwa Mkorombindo: Conceptualization; Formal analysis; Investigation; Methodology; Roles/Writing - review & editing. Sam M. McElwee: Conceptualization, Investigation, Resources, Supervision; Validation, Writing - review & editing. J. Michael Wells: Conceptualization, Investigation, Resources, Supervision; Validation, Writing - review & editing. Keith M. Wille: Conceptualization, Investigation, Resources, Supervision; Validation, Writing - review & editing.

Declaration of competing interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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