Fat Embolism Syndrome

Ethan Kosova, MD, MPH; Brian Bergmark, MD; Gregory Piazza; MD, MS

Case Presentation

A 49-year-old man with a history of prostate cancer metastatic to bone suffered a pathological fracture to the left femur while hospitalized (Figure 1A). Eighteen hours after the fracture, he developed hypoxemia and hypotension followed by confusion and a petechial rash in the left axilla. Chest X-ray obtained after intubation demonstrated new diffuse bilateral patchy infiltrates (Figure 1B). Urgent transthoracic echocardiogram showed right ventricular dilation and free wall hypokinesis with preserved contractility of the right ventricular apex (McConnell's Sign; Figure 2, Movie I in the online-only Data Supplement). Based on the clinical presentation and supportive imaging, the patient was diagnosed with fat embolism syndrome. He was transferred to the intensive care unit for further management.

Overview

Although it was observed centuries ago that intravenous injection of oil resulted in mechanical obstruction of small vessels,[1] the exact pathophysiology of fat embolism syndrome (FES) remains uncertain. Fat embolism (FE) is defined by the presence of fat globules in the pulmonary microcirculation regardless of clinical significance. FES describes a characteristic pattern of clinical findings that follow an insult associated with the release of fat into the circulation.

FES is most commonly associated with orthopedic trauma, with highest incidence in closed, long bone fractures of the lower extremities, particularly the femur.[2] The risk of FES complicating orthopedic trauma is highest in ages 10 to 40 years and occurs in men more frequently than women.[3] Nonorthopedic causes of FES are exceedingly rare and include pancreatitis, sickle cell crisis, alcoholic liver disease, bone marrow harvest or transplant, and liposuction.[4]

In the orthopedic and trauma literature, the incidence of FES has ranged from <1% to >30% of cases. The wide range of incidence likely reflects the heterogeneity of diagnostic criteria. Recent population level data from the National Hospital Discharge Survey found an FES incidence of 0.17% in patients with isolated or multiple orthopedic fractures.[3] The incidence increased to 0.54% in isolated femoral fractures and 1.29% if multiple fractures including the femur were present.[3] Although FES remains a relatively rare entity, subclinical FE in the trauma population is highly prevalent, with an autopsy series finding fat emboli in the pulmonary circulation of 82% of trauma patients and 88% of patients who received cardiopulmonary resuscitation.[5]

Pathophysiology

The pathophysiologic mechanisms of FES have yet to be fully elucidated. End organ pathology is thought to be mediated by 2 main processes: mechanical obstruction and biochemical injury.

Mechanical Theory

The mechanical theory proposes that fat cells in the bone marrow gain access to the venous sinusoids after trauma. These fat cells have potent proinflammatory and prothrombotic potential. They trigger rapid aggregation of platelets and accelerated fibrin generation as they travel through the venous system, eventually lodging in the pulmonary arterial circulation.

From the Department of Medicine (E.K.) and Cardiovascular Division, Department of Medicine (B.B., G.P.), Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.114.010835/-/DC1.

Correspondence to Gregory Piazza, MD, MS, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115. E-mail: gpiazza@partners.org

(*Circulation.* 2015;131:317-320. DOI: 10.1161/CIRCULATIONAHA.114.010835.)

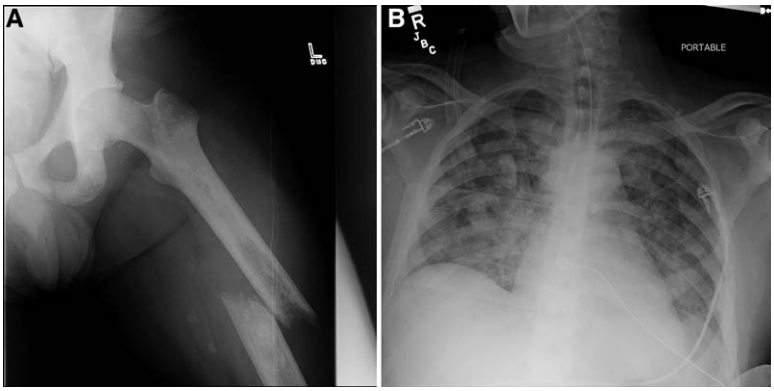

Figure 1. Initial imaging. X-ray of the left lower extremity demonstrating a closed, oblique fracture of the left femur with displacement of the distal femoral fragment (**A**). Chest X-ray obtained shortly after endotracheal intubation showing bilateral patchy infiltrates consistent with acute respiratory distress syndrome (ARDS; **B**).

Pulmonary capillary obstruction leads to interstitial hemorrhage and edema, alveolar collapse, and reactive hypoxemic vasoconstriction. Massive fat emboli may also lead to macrovascular obstruction and shock.[6] Fat cells may also enter the arterial circulation via a patent foramen ovale or directly through the pulmonary capillary bed, causing the characteristic neurological and dermatologic findings of FES (Figure 3).

Biochemical Theory

The biochemical theory suggests that the clinical manifestations of FES are attributable to a proinflammatory state. Bone marrow fat is broken down by tissue lipases, resulting in high concentrations of glycerol and toxic free fatty acids. These intermediate products lead to end-organ dysfunction. In the lung, toxic injury to pneumocytes and pulmonary endothelial cells causes vasogenic and cytotoxic edema as well as hemorrhage. The damaged pulmonary endothelium triggers a proinflammatory cytokine cascade, leading to the development of acute lung injury or acute respiratory distress syndrome.[6]

Biochemical studies on patients with confirmed FES support several aspects of this theory. Patients with FES have elevated levels of plasma phospholipase A2, proinflammatory cytokines (including tumor necrosis factor-alpha, interleukin-1, and interleukin-6), and free radicals.[7,8] These proinflammatory intermediates may explain FES in nontraumatic settings as well as the observed delay of hours to days from the traumatic insult until the onset of clinical findings in FES. Frequently elevated in patients with FES, C-reactive protein may result in further microvascular obstruction by promoting lipid agglutination.

The pathophysiology of most cases of FES combines these mechanical and biochemical processes (Figure 4). This interplay is exemplified by the manifestations of FES occurring in both the arterial and venous circulation. The petechial rash appears to be caused by postobstructive hemorrhage at the capillary level but in many patients may also result from a systemic inflammatory and prothrombotic state. Similarly, the varied central nervous system findings ranging from focal deficits to encephalopathy likely indicate a multifactorial pathophysiology.

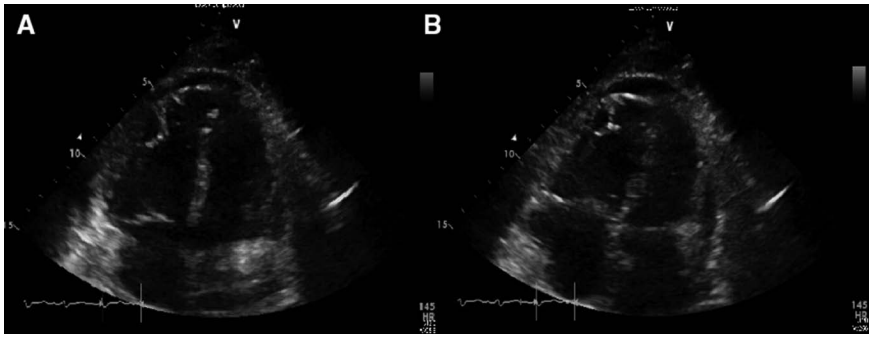

Figure 2. Transthoracic echocardiogram images obtained during diastole (**A**) and systole (**B**) demonstrating right ventricular dysfunction with hypokinesis of the mid right ventricular free wall and preservation of the apex.

Clinical Presentation

FES is characterized by multisystem dysfunction typically presenting 12 to 72 hours after the initial insult. The classic triad of FES includes hypoxemia, neurological abnormalities, and petechiae. Pulmonary manifestations are among the most common initial signs of FES and include dyspnea, tachypnea, hypoxemia, and respiratory failure. In 1 large series of patients with FES, hypoxemia was the most common finding, affecting 96% of patients.[9] Neurological defects are also common and typically manifest after the respiratory changes. Neurological abnormalities include focal deficits, confusion, lethargy, restlessness, and coma. The petechial rash is classically located in nondependent regions (conjunctivae, head, neck, anterior thorax, or axillae).[10] Other nonspecific findings include fever and retinopathy. Thrombocytopenia and unexplained anemia are common hematologic manifestations seen in 37% and 67% of cases, respectively.[9] Severe cases of FES can be complicated by disseminated intravascular coagulation, which is likely the result of excessive tissue factor expression after trauma. Fulminant cases of FES may present with right ventricular dysfunction, biventricular failure, acute respiratory distress syndrome, shock, and death.

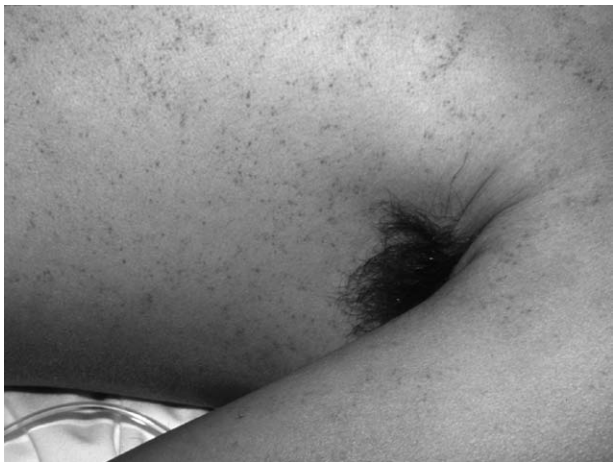

Figure 3. Characteristic petechial rash seen in the axilla of a patient with fat embolism syndrome. (Image used with permission from VisualDx. © Logical Images Inc.)

Diagnosis

There are no standardized, prospectively validated diagnostic criteria for FES. The diagnosis is made by recognizing the characteristic clinical syndrome in the context of supportive imaging and a predisposing insult. Chest X-Ray findings of bilateral patchy infiltrates consistent with acute respiratory distress syndrome may be difficult to differentiate from pulmonary edema or alveolar hemorrhage.[2] Frequently, the chest X-ray is interpreted as normal. MRI of the brain can reveal a star-field pattern of diffuse, punctate, hyperintense lesions on diffusion-weighted imaging.[11]

Directly sampling the pulmonary system for lipids has shown promise as a potential diagnostic tool. In one study, bronchoalveolar lavage samples with ≥30% of alveolar cells staining for neutral fat was strongly associated with a clinical diagnosis of FES.[12] Detection of fat in blood aspirated from a wedged pulmonary artery catheter lacks the sensitivity and specificity to add significant diagnostic certainty and is not typically used in clinical practice.

Given the absence of a gold standard diagnostic test or pathognomonic feature, a number of authors have proposed clinical diagnostic criteria. The most frequently cited are Gurd's Criteria (Table).[13]

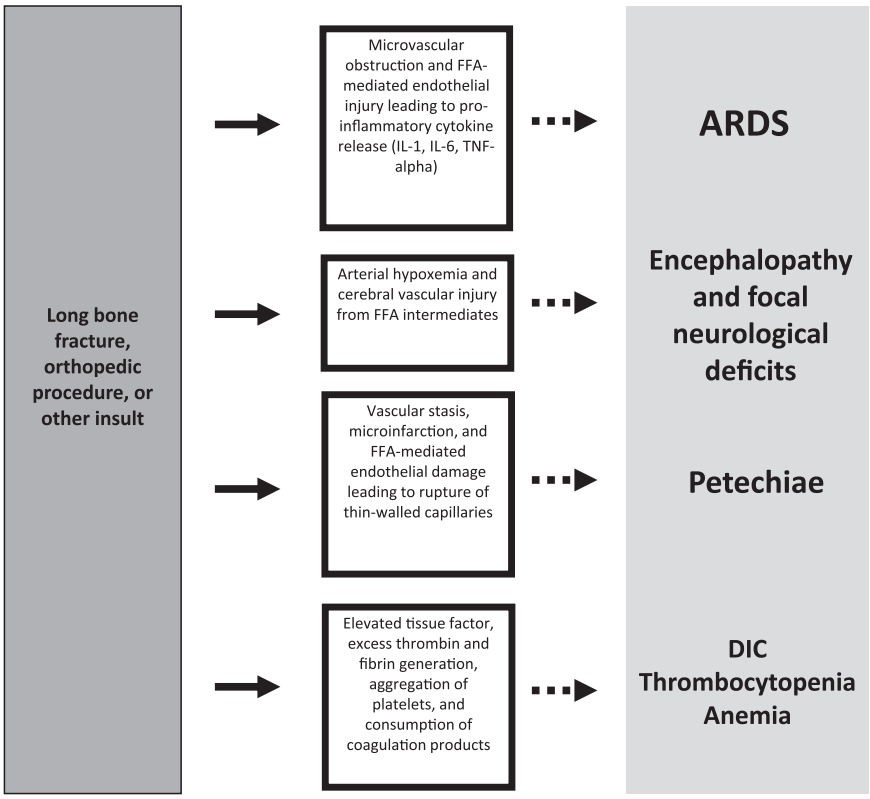

Figure 4. Proposed pathophysiologic mechanisms for the clinical findings observed in fat embolism syndrome. ARDS indicates acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; FFA, free fatty acid; IL-1, interleukin-1; IL-6, interleukin-6; and TNF-α, tumor necrosis factor-alpha.

Management

There are currently no disease-specific treatments for FES. Heparin and corticosteroids have been proposed as treatments but have not reliably demonstrated improved morbidity or mortality.[14] Systemic anticoagulation has been considered as a potential therapy for FES. Heparin stimulates lipase activity and therefore may accelerate the clearance of lipids from

Table. Gurd's Criteria

Major criteria
- Petechial rash
- Respiratory symptoms with radiographic changes
- Central nervous system signs unrelated to trauma or other condition

Minor criteria
- Tachycardia
- Pyrexia
- Retinal changes (fat or petechiae)
- Renal abnormalities (oliguria, anuria, or lipiduria)
- Acute thrombocytopenia
- Acute decrease in hemoglobin
- High erythrocyte sedimentation rate (ESR)
- Fat globules in sputum

Typically, the diagnosis of FES requires 1 major and 4 minor criteria.[13]

circulation, but the resultant increase in free fatty acids could exacerbate the underlying proinflammatory physiology.[4] Furthermore, anticoagulation in the setting of trauma and preexisting hematologic abnormalities may prove harmful.[4] No randomized, controlled trials or extensive retrospective data exist to support the routine use of heparin or other anticoagulants in FES. In cases of fulminant FES, corticosteroids may be considered. However, there is insufficient evidence to support routine administration of corticosteroids for the majority of patients with FES.

Supportive intensive care unit–level care is standard. Most patients are severely hypovolemic and require fluid resuscitation. Supportive correction of hypoxemia with supplemental oxygen or mechanical ventilation is often necessary while the patient recovers. If central nervous system dysfunction is present, frequent neurological examinations are required and intracranial pressure monitoring should be considered.[15] Vasopressors may be required. Case reports have suggested success with both mechanical support devices and extracorporeal membrane oxygenation as a bridge to recovery in patients with severe FES resulting in refractory systemic arterial hypotension and shock.[16,17]

Prevention

Current evidence suggests that prophylactic corticosteroids in patients with long bone fractures may reduce the incidence of FES. A recent meta-analysis of 7 small randomized, controlled trials found that prophylactic corticosteroids reduced the risk of FES by 78% with a number-needed-to-treat of 8 to prevent 1 case of FES.[18] Corticosteroids reduced hypoxemia without difference in mortality. A large, multi-center randomized trial is needed before the widespread administration of prophylactic corticosteroids in FES.

Surgical timing and technique have also been shown to play a role in FES. Early surgical fixation (within 24 hours of trauma) carries a lower risk of FES than delayed fixation.[19] In patients with prohibitive early surgical risk, a delayed approach or intermediate procedure, such as external fixation, may be attempted.[20]

Prognosis

The outcome of patients with FES is generally favorable. Mortality has decreased with advances in supportive care and is <10% currently. Pulmonary, neurological, and dermatologic manifestations of FES generally completely resolve.[1,4,14]

Case Follow-Up

Aggressive resuscitation with intravenous crystalloid and vasopressors was initiated in the intensive care unit. Mechanical ventilation was continued for hypoxemic respiratory failure. The patient's condition stabilized, and he was extubated two days later. His hypoxemia, altered mental status, hypotension, and petechiae resolved completely.

Disclosures

None.

References

1. Talbot M, Schemitsch EH. Fat embolism syndrome: history, definition, epidemiology. *Injury*. 2006;37 Suppl 4:S3–S7. doi: 10.1016/j.injury.2006.08.035.
2. Akhtar S. Fat embolism. *Anesthesiol Clin*. 2009;27:533–50, table of contents. doi: 10.1016/j.anclin.2009.07.018.
3. Stein PD, Yaekoub AY, Matta F, Kleerekoper M. Fat embolism syndrome. *Am J Med Sci*. 2008;336:472–477. doi: 10.1097/MAJ.0b013e318172f5d2.
4. Mellor A, Soni N. Fat embolism. *Anaesthesia*. 2001;56:145–154.
5. Eriksson EA, Pellegrini DC, Vanderkolk WE, Minshall CT, Fakhry SM, Cohle SD. Incidence of pulmonary fat embolism at autopsy: an undiagnosed epidemic. *J Trauma*. 2011;71:312–315. doi: 10.1097/TA.0b013e3182208280.
6. Husebye EE, Lyberg T, Røise O. Bone marrow fat in the circulation: clinical entities and pathophysiological mechanisms. *Injury*. 2006;37 Suppl 4:S8–18. doi: 10.1016/j.injury.2006.08.036.
7. Kao SJ, Yeh DY, Chen HI. Clinical and pathological features of fat embolism with acute respiratory distress syndrome. *Clin Sci (Lond)*. 2007;113:279–285. doi: 10.1042/CS20070011.
8. Prakash S, Sen RK, Tripathy SK, Sen IM, Sharma RR, Sharma S. Role of interleukin-6 as an early marker of fat embolism syndrome: a clinical study. *Clin Orthop Relat Res*. 2013;471:2340–2346. doi: 10.1007/s11999-013-2869-y.
9. Bulger EM, Smith DG, Maier RV, Jurkovich GJ. Fat embolism syndrome. A 10-year review. *Arch Surg*. 1997;132:435–439.
10. Georgopoulos D, Bouros D. Fat embolism syndrome: clinical examination is still the preferable diagnostic method. *Chest*. 2003;123:982–983.
11. Ryu CW, Lee DH, Kim TK, Kim SJ, Kim HS, Lee JH, Choi CG, Suh DC. Cerebral fat embolism: diffusion-weighted magnetic resonance imaging findings. *Acta Radiol*. 2005;46:528–533.
12. Mimoz O, Edouard A, Beydon L, Quillard J, Verra F, Fleury J, Bonnet F, Samii K. Contribution of bronchoalveolar lavage to the diagnosis of posttraumatic pulmonary fat embolism. *Intensive Care Med*. 1995;21:973–980.
13. Gurd AR. Fat embolism: an aid to diagnosis. *J Bone Joint Surg Br*. 1970;52:732–737.
14. Habashi NM, Andrews PL, Scalea TM. Therapeutic aspects of fat embolism syndrome. *Injury*. 2006;37 Suppl 4:S68–S73. doi: 10.1016/j.injury.2006.08.042.
15. Kellogg RG, Fontes RB, Lopes DK. Massive cerebral involvement in fat embolism syndrome and intracranial pressure management. *J Neurosurg*. 2013;119:1263–1270. doi: 10.3171/2013.7.JNS13363.
16. Sarkar S, Mandal K, Bhattacharya P. Successful management of massive intraoperative pulmonary fat embolism with percutaneous cardiopulmonary support. *Indian J Crit Care Med*. 2008;12:136–139. doi: 10.4103/0972-5229.43684.
17. Webb DP, McKamie WA, Pietsch JB. Resuscitation of fat embolism syndrome with extracorporeal membrane oxygenation. *J Extra Corpor Technol*. 2004;36:368–370.
18. Bederman SS, Bhandari M, McKee MD, Schemitsch EH. Do corticosteroids reduce the risk of fat embolism syndrome in patients with long-bone fractures? A meta-analysis. *Can J Surg*. 2009;52:386–393.
19. Bone LB, Johnson KD, Weigelt J, Scheinberg R. Early versus delayed stabilization of femoral fractures. A prospective randomized study. *J Bone Joint Surg Am*. 1989;71:336–340.
20. Pape HC. Effects of changing strategies of fracture fixation on immunologic changes and systemic complications after multiple trauma: damage control orthopedic surgery. *J Orthop Res*. 2008;26:1478–1484. doi: 10.1002/jor.20697.

Fat Embolism Syndrome

Ethan Kosova, Brian Bergmark and Gregory Piazza

Circulation. 2015;131:317-320
doi: 10.1161/CIRCULATIONAHA.114.010835
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539