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Fat Embolism Syndrome

Renu Saigal*, M Mittal**, A Kansal**, Y Singh**, PR Kolar**, S Jain***

Abstract

Fat embolism syndrome is a rare complication occurring in 0.5 to 2% of patients following a long bone fracture. It is believed to be caused by the toxic effects of free fatty acids. Diagnosis is clinical, based on respiratory, cerebral and dermal manifestations. Treatment is only supportive, directed mainly at maintaining respiratory functions. ©

INTRODUCTION

The term 'fat embolism' indicates the presence of fat globules in the peripheral circulation and lung parenchyma after fracture of long bones, pelvis or other major trauma. It occurs in approximately all patients who sustain a long bone or a pelvic fracture. In 1861, Zenker described fat droplets in the lung capillaries of a railroad worker who sustained a fatal thoracoabdominal crush injury.¹

'Fat embolism syndrome' is a serious manifestation of fat embolism phenomenon characterized clinically by triad of dyspnoea, petechiae and mental confusion. In 1873, Bergmann was first to establish the clinical diagnosis of fat embolism syndrome.

Incidence

Fat Embolism Syndrome (FES) most commonly is associated with long bone and pelvic fractures, and is more frequent in closed, rather than open fractures. Patients with a single long bone fracture have a 1 to 3 percent chance of developing the syndrome, this increases in correlation with the number of fractures. FES has been noted in up to 33 percent of patients with bilateral femoral fractures.²

Incidence is also higher in young men as they are more prone to high velocity road traffic accidents. The syndrome occurs mostly in adults and rarely in children, as in children, the bone marrow contain more of hematopoietic tissue and less of fat.

Causes

FES is most common after skeletal injury and it is most likely to occur in patients with multiple long bone and pelvic fractures. Some non-traumatic conditions like diabetes, pancreatitis etc. have been found to be

associated with fat embolism syndrome.^{3,4} (See Table 1)

Table 1 : Conditions associated with fat embolism

Trauma related

- Long bone fractures
- Pelvic fractures
- Fractures of other marrow-containing bones
- Orthopaedic procedures
- Soft tissue injuries (e.g. chest compression with or without rib fractures)
- Burns
- Liposuction
- Bone marrow harvesting and transplant

Non-trauma related

- Pancreatitis
- Diabetes mellitus
- Osteomyelitis and panniculitis
- Bone tumour lysis
- Steroid therapy
- Sickle cell haemoglobinopathies
- Alcoholic (fatty) liver disease
- Lipid infusion
- Cyclosporine A solvent

PATHOPHYSIOLOGY

There is considerable controversy over both the source of fat emboli and their mode of action. Three major theories have been proposed.⁵

1. The Mechanical theory

According to this theory, proposed by Gauss in 1924, trauma to long bones releases fat droplets by disrupting fat cell in the fractured bone or in adipose tissue. These fat droplets enter the torn veins near long bone. This occurs when the intramedullary pressure is higher than the venous pressure. Fat droplets are then transported to pulmonary vascular bed where large fat globules result in mechanical obstruction and are trapped as emboli in the lung capillaries. Small fat droplets of 7 – 10 μ m size may pass through the lung and reaches systemic circulation causing embolisation to brain, skin, kidney

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or retina.

Another way in which these fat droplets pass to the systemic circulation is pulmonary precapillary shunts and existing pathological venous-arterial communication such as patent foramen ovale.^{6,7} However, this theory does not sufficiently explain the 24-72 hr delay in development after the acute injury.

2. Biochemical theory

This theory, given by Lehmann and Moore in 1927, states that there are a number of biochemical mechanisms potentially involved in the development of FES. The most widely held is that the embolized fat is degraded in plasma to free fatty acids. Although neutral fat, such as is found in bone marrow, does not cause an acute lung injury, it is hydrolysed over the course of hours to several products, including free fatty acids, which have been shown to cause ARDS in animal models. Free fatty acids have also been associated with cardiac contractile dysfunction, which can be a feature of FES. The plasma lipase concentration is increased in some patients.

Serum from acutely ill patients has been shown to have the capacity to agglutinate chylomicrons, low-density lipoproteins, and liposomes of nutritional fat emulsions. C-reactive protein, which is elevated in these patients, appears to be responsible for lipid agglutination and may also participate in the mechanism of non-traumatic FES.

The delay in development of symptoms could be explained by the time scale required to produce these toxic metabolites. The onset of symptoms may coincide with the agglutination and degradation of fat emboli. Levels of circulating free fatty acids are moderately elevated in fracture patients compared with controls. Nevertheless, evidence for these mechanisms of injury remains largely circumstantial.

3. Coagulation theory

This states that tissue thromboplastin is released with marrow elements following long bone fractures. This activates the complement system and extrinsic coagulation cascade via direct activation of factor VII that leads to the production of intravascular coagulation by products such as fibrin and fibrin degradation products. These products along with leukocytes, platelets and fat globules combine to increase pulmonary vascular permeability, both by their direct actions on the endothelial lining and through the release of numerous vasoactive substances. In addition, these same substances cause platelet activation.^{8,9}

CLINICAL FEATURES

The FES typically explain the delay presents 12-72 hrs after the initial injury. Rarely, cases occur as early as 12 hrs or as much as 2 weeks later.¹⁰ Patients present with a classic triad of : respiratory manifestations (95%),

cerebral effects (60%) and petechiae (33%).^{11,12}

Pulmonary manifestations: Respiratory changes are often the first clinical feature to present. Dyspnoea, tachypnoea and hypoxaemia are the most frequent early findings. The severity of these symptoms vary but a number of cases may progress to respiratory failure and a syndrome indistinguishable from acute respiratory distress syndrome (ARDS) may develop. Approximately one-half of the patients with FES caused by long bone fractures develop severe hypoxaemia and respiratory insufficiency and require mechanical ventilation.¹³

CNS manifestations: Neurological features resulting from cerebral embolism frequently present in the early stages and often occur after the development of respiratory distress. The changes range across a wide spectrum from mild confusion and drowsiness through to severe seizures. The more common presentation is with an acute confusional state but focal neurological signs including hemiplegia, aphasia, apraxia, visual field disturbances and anisocoria have been described. Seizures and decorticate posturing have also been seen. Fortunately, almost all neurological deficits are transient and fully reversible.¹⁴

Petechial rash: The characteristic petechial rash may be the last component of the triad to develop. It occurs in up to 60% of cases and is due to embolization of small dermal capillaries leading to extravasation of erythrocytes. This produces a petechial rash in the conjunctiva, oral mucous membrane and skin folds of the upper body especially the neck and axilla.¹⁵ It does not appear to be associated with any abnormalities in platelet function. This is believed to be the only pathognomic feature of fat embolism syndrome and usually appears within the first 36 hrs and is self-limiting, disappearing completely within 7 days.

Ocular manifestation: On fundoscopy, Purtscher's retinopathy may be seen consisting of cotton wool exudates, macular oedema and macular haemorrhage.

CVS involvement: Early persistent tachycardia, though nonspecific, is almost invariably present in all patients with fat embolism. Rarely, systemic fat emboli can affect the heart and lead to mottled myocardial necrosis and full blown right heart syndrome.

Systemic fever: A very common early sign of fat embolism syndrome is fever. It is often mild but may increase up to 39°C.

DIAGNOSIS

Diagnosis is usually made on the basis of clinical findings but biochemical changes may be of value. The most commonly used set of major and minor diagnostic criteria are those published by Gurd (See Table 2).

The diagnosis requires at least 1 major and 4 minor criteria.^{16,17} The reliability of these criteria have been questioned and other schemes based more on respiratory

Table 2 : Gurd's criteria

Major criteria
Axillary or subconjunctival petechiae
Hypoxaemia PaO ₂ <60 mm Hg, FI _{O₂} = 0.4
Central nervous system depression disproportionate to hypoxaemia
Pulmonary oedema
Minor criteria
Tachycardia <110 bpm
Pyrexia <38.5°C
Emboli present in the retina on fundoscopy
Fat globules present in urine
A sudden inexplicable drop in haematocrit or platelet values
Increasing ESR
Fat globules present in the sputum

Table 3 : Lindeque's criteria

Sustained Pa _{o₂} <8 kPa
Sustained PCO ₂ of >7.3 kPa or a pH <7.3
Sustained respiratory rate >35 breaths min ⁻¹ , despite sedation
Increased work of breathing: dyspnoea, accessory muscle use, tachycardia, and anxiety

features alone (See Table 3)have been proposed.¹⁸

More recently, a fat embolism index has been proposed as a semi-quantitative means of diagnosing FES, in which there are seven clinical features(SeeTable 4); each one is given a particular score.¹⁹ A score of >5 is required for a positive diagnosis.

Table 4 : Schonfeld's criteria

Petechiae	5
Chest X-ray changes (diffuse alveolar infiltrates)	4
Hypoxaemia (Pa _{o₂} < 9.3 kPa)	3
Fever (>38°C)	1
Tachycardia (>120 beats min ⁻¹)	1
Tachypnoea (>30 bpm)	1
Cumulative score >5 required for diagnosis	

INVESTIGATIONS

FES is a clinical diagnosis, no laboratory test is sufficiently sensitive or specific to be diagnostically useful. Investigations are usually performed to support the clinical diagnosis or to monitor therapy and include:

Hematology and Biochemistry : An unexplained anemia (70% of patients) and thrombocytopenia (platelet count <1,50,000 mm⁻³ in up to 50% of patients) are often found. Blood lipid concentration is not helpful for diagnosis because circulating fat concentrations do not correlate with the severity of the syndrome. Hypocalcemia (due to binding of free fatty acids to calcium) and elevated serum lipase have also been reported.¹⁴ Hypofibrinogenemia, raised ESR and prolongation of Prothrombin time may be seen.^{11,20}

Urine and Sputum examination : It is a common misconception that the presence of fat globules, either in sputum or urine is necessary to confirm the diagnosis.

However, the recovery of fat globules is of uncertain significance. In one study, the presence of fat globules was demonstrated in the serum of >50% of patients with fractures who had no symptoms suggestive of FES.¹⁶

Arterial blood gases : This reveals a low partial pressure of oxygen and a low partial pressure of CO₂ with respiratory alkalosis. An unexplained increase in pulmonary shunt fraction alveolar-to-arterial oxygen tension difference, especially within 24-48 hours of a potentially causative event is strongly suggestive of this syndrome.

Chest X-ray : The chest X-ray is often normal initially but in some patients bilateral fluffy shadows develop as respiratory insufficiency worsens. A minority has diffuse or patchy air space consolidation due to oedema or alveolar haemorrhage; this is most prominent in the periphery and bases. The classical chest X-ray of fat embolism syndrome shows multiple flocculent shadows ("snow storm appearance"). The radiological signs may remain for up to three weeks.²¹

CT Chest : Focal areas of ground glass opacification with interlobular septal thickening are generally seen on chest CT but ill-defined centrilobular and subpleural nodules representing alveolar oedema, micro-haemorrhage and inflammatory response secondary to ischaemia and cytotoxic emboli may be seen.²²

Lungs scan : It may show ventilation perfusion mismatch. In the initial phase the V/Q ratio is often high and this phase merges imperceptibly with the stage characterized by low V/Q and fulfilling Gurd's criteria.²³

ECG : ECG is usually normal except for nonspecific sinus tachycardia. However, non-specific ST-T changes, right axis deviation and RBBB may be seen in fulminant cases.

Transesophageal echocardiography : TEE may be of use in evaluating intraoperative release of marrow contents into the blood stream during intramedullary reaming and nailing. The density of the echogenic material passing through the right side of the heart correlates with the degree of reduction in arterial oxygen saturation. Repeated showers of emboli have been noted to increase right heart and pulmonary artery pressures. Embolization of marrow contents through patent foramen ovale also has been noted. However, evidence of embolization by means of TEE is not correlated with the actual development of FES.

Bronchoalveolar lavage : The use of bronchoscopy with bronchoalveolar lavage to detect fat droplets in alveolar macrophages as a means to diagnose fat embolism has been described in trauma patients and patients with the acute chest syndrome of sickle cell disease. However, diagnostic criteria vary and the sensitivity and specificity are unknown.

CT Brain : Findings from head CT performed because of alterations in mental status may be normal or may reveal diffuse white-matter petechial hemorrhages consistent with microvascular injury. It may show diffuse petechial hemorrhages in the white matter, or generalized cerebral edema or atrophy in patients with severe cerebral fat embolism.²⁴

MRI Brain : Spotty areas of high intensity may be seen on T2 weighted image. It may be useful in patients with neurological features of fat embolism and a normal CT scan.¹⁹ It has been shown to be useful in early diagnosis of FES.

TREATMENT

Medical Care : Medical care includes adequate oxygenation and ventilation, stable hemodynamics, blood products as clinically indicated, hydration, prophylaxis of deep venous thrombosis and stress related gastrointestinal bleeding and nutrition.

Various drugs have been tried but with inconclusive results. These include.

Corticosteroids : Corticosteroids have been extensively studied and recommended by some for the management of FES. The proposed mechanism of action is largely as an anti-inflammatory agent, reducing the perivascular haemorrhage and oedema. There are insufficient data to support initiating steroid therapy once FES is established. An experimental study showed no beneficial effect, and there have been no prospective, randomized and controlled clinical studies that have demonstrated a significant benefit with their use.¹⁴

Aspirin : A prospective study of 58 patients with uncomplicated fractures showed that the treatment of patients with aspirin resulted in significant normalization of blood gases, coagulation proteins, and platelet numbers when compared with controls.¹⁴

Heparin : Heparin is known to clear lipaemic serum by stimulating lipase activity and has been advocated for the treatment of FES. However, activation of lipase is potentially dangerous if increases in free fatty acids are an important part of the pathogenesis. There is also a possibility of increased risk of bleeding in patients with multiple trauma.¹⁴

N-Acetylcysteine : Introduction of fat micelles into isolated perfused rat lungs caused fat embolism as evidenced by the lung weight changes, increases in exhaled nitric oxide and protein concentration in bronchoalveolar lavage, pulmonary hypertension, increased capillary filtration coefficient, and lung pathology. The insult also increased nitrate/nitrite, methylguanidine, tumor necrosis factor- α , and interleukin-1 β in lung perfusate, increased neutrophil elastase and myeloperoxidase levels, and upregulated inducible nitric oxide synthase expression. Posttreatment with N-Acetylcysteine abrogated these changes induced

by fat embolism.²⁵

So, There is no specific therapy for fat embolism syndrome; prevention, early diagnosis, and adequate symptomatic treatment are of paramount importance. It is a self-limiting disease and treatment is mainly supportive which includes:

1. Spontaneous ventilation

The initial management of hypoxia associated with pulmonary fat embolism should be spontaneous ventilation. Oxygen inhalation using facemask and high flow gas delivery system can be used to deliver FIO₂ (inspired O₂ concentration) of 50 – 80%.

2. CPAP and noninvasive ventilation

CPAP (continuous positive airway pressure) may be added to improve PaO₂ without increasing FIO₂. Mechanical ventilation may also be applied via CPAP mask and has been used successfully in patients.

3. Mechanical ventilation and PEEP

If a FIO₂ of >60% and CPAP of > 10 cm are required to achieve a PaO₂ > 60mm Hg, then endotracheal intubation, mechanical ventilation with PEEP (positive end expiratory pressure) should be considered.¹²⁶ Neither PEEP nor mechanical ventilation has intrinsic beneficial value on the process of pulmonary embolism, and they may even promote acute lung injury. Therefore, the principle objective of PEEP and mechanical ventilation is to accomplish adequate gas exchange without inflicting further lung damage.

While PEEP may be associated with an increase in PaO₂, occasionally it can decrease the PaO₂ by increasing right atrial pressure and decreasing cardiac output. Therefore, close monitoring of arterial blood gas and haemodynamic status is required when PEEP and mechanical ventilation are used.

SURGICAL CARE

Early immobilization of fractures reduces the incidence of FES and the risk is further reduced by operative correction rather than conservative management. Another strategy to prevent FES is to limit the elevation in intraosseous pressure during orthopaedic procedures, in order to reduce the intravasation of intramedullary fat and other debris.¹⁸ In a randomised trial of 40 patients, half were randomized to receive a venting hole for drainage of the medullary cavity between the greater and the lesser trochanter in order to limit intraoperative rises in intraosseous pressure. Significantly fewer major embolic events were detected by transoesophageal echocardiography in the venting group (20% vs 85%). Other operative refinements may also serve to limit intraosseous pressure including the use of cementless fixation of hip prostheses and undreamed intramedullary femoral shaft stabilization.¹⁸

PROPHYLACTIC TREATMENT

Albumin : Albumin has been recommended for volume resuscitation, especially in cases of hypoproteinemia, because it not only restores blood volume but also binds fatty acids and may decrease the extent of lung injury.⁵

Corticosteroid : The use of corticosteroid prophylaxis is controversial, largely because it is difficult to definitively prove efficacy in a condition with a low incidence, unclear risk factors, low mortality, and a good outcome with conservative management. Nevertheless, a number of studies report decreased incidence and severity of fat embolism syndrome when corticosteroids are given prophylactically.^{27,19} In a double-blind randomized study, 64 consecutive patients with lower-extremity long-bone fractures received either placebo or methylprednisolone, 7.5 mg kg⁻¹ every 6 h for 12 doses.¹⁹ FES was diagnosed in 9 of 41 placebo-treated patients and 0 of 21 steroid-treated patients ($P < 0.05$). No complications related to steroid treatment were observed.

One rational, conservative approach would be to give prophylactic steroid therapy only to those patients at high risk for FES, for example, those with long bone or pelvic fractures, especially closed fractures. Methylprednisolone 1.5mg kg⁻¹ i.v. can be administered every 8 h for six doses.

Although numerous studies have shown beneficial effects of prophylactic steroid use because of anti-inflammatory effects, there were no significant changes in mortality.^[19,28] Another experimental study concerning steroid use showed no beneficial effects.²⁹ Currently, corticosteroids use is not recommended for prophylaxis or treatment.

Prognosis

The duration of FES is difficult to predict. Prognosis is good except in fulminant cases. Residual neurologic deficits and residual diffusion capacity deficits may persist. Mortality is estimated to be 5-15% overall, but most patients will recover fully.^{2,30}

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