

Fat embolism syndrome

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ABSTRACT

Fat embolism syndrome is an often overlooked cause of breathlessness in trauma wards. Presenting in a wide range of clinical signs of varying severity, fat embolism is usually diagnosed by a physician who keeps a high degree of suspicion. The clinical background, chronology of symptoms and corroborative laboratory findings are instrumental in a diagnosis of fat embolism syndrome. There are a few diagnostic criteria which are helpful in making a diagnosis of fat embolism syndrome. Management is mainly prevention of fat embolism syndrome, and organ supportive care. Except in fulminant fat embolism syndrome, the prognosis is usually good.

KEY WORDS: Diagnosis, diagnostic criteria, fat embolism, fat embolism syndrome, management

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INTRODUCTION

Dyspnoea in the trauma wards is not a rare occurrence, and it is a usual practice for the respiratory physician to get a call for a patient in acute distress in the trauma wards. The causes of dyspnoea can vary in origin and in the gravity of situation it may lead to. The various causes of dyspnoea, secondary to trauma are pulmonary contusions, fat embolism syndrome, shock lung, thromboembolism etc. These conditions are to be differentiated from other causes of dyspnoea like metabolic causes and cardiovascular causes. Differentiating each clinical condition from the others, in optimistic terms is perplexing and in pessimist terms, almost impossible. Fat embolism syndrome is by far the most common cause, and also the most overlooked cause of dyspnoea. Affecting a diverse range of organs and organ system, fat embolism has always enjoyed a prominent picture in many controversies in autopsy meetings.

Two terms of interest are fat embolism and fat embolism syndrome. Often used in place of the other, these are not interchangeable. Whereas fat embolism refers to the

presence of circulating fat globules in circulation and pulmonary parenchyma, fat embolism syndrome (FES) is the clinical manifestation of fat embolism. It is associated with a complex alteration of hemostasis, usually presenting as a triad of respiratory insufficiency, altered sensorium, and petechiae.^[1]

The historical description of fat embolism dates back to 1861, when Zenker described fat droplets in the lung capillaries of a railroad worker who sustained fatal thoracoabdominal injuries.^[2] Two decades later, FES was first described by Bergmann in 1873, as a triad of confusion, dyspnoea, and petachiae, following fracture of long bones.^[3] Since then, there have been numerous reports on incidence of fat embolism.

Aetiology

FES is commonly seen in trauma wards and is usually associated with fractures of long bones or multiple fractures. It is estimated to occur in 3-4% of patients with long bone fracture.^[4] Apart from trauma surgical procedures such as intramedullary reaming, pelvic or knee arthroplasty are important causes of FES. Rarely, intra-osseous fluid administration, lipid soluble radio contrast, intravenous hyper alimentation, long term steroid administrations, liposuction, bone marrow harvesting and transplant are also implicated as iatrogenic causes for FES.^[5]

Non-iatrogenic causes of fat embolism are very rare, but have been related to sickling crisis, pancreatitis,

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fat necrosis of omentum, diabetes, hepatic steatosis, osteomyelitis, panniculitis and bone tumor lysis.^[1,5]

Incidence

The exact incidence of FE and FES are unknown. Fat embolism and milder forms of FES may go undetected clinically, and in obvious clinical situation, the diagnosis is overlooked. This is highlighted by the fact that incidence of clinically detected fat embolism was only <1% where as the incidence rose to up to 20% with the help of post mortem examinations.^[6]

Various studies report the incidence for fat embolism as 0.25% to up to 33%.^[7] A retrospective study by Bulger *et al.*^[8] reported incidence of <1% and while a prospective study by Fabien *et al.*^[9] reported a high incidence of 11-29%. A level I trauma center in India,^[10] after a retrospective analysis of case records of 1,692 patients reported an incidence of 0.7% of FES. The incidence of FES has been reported to be <1% in retrospective studies, while in prospective studies, it is usually higher. (Some as high as 35%).^[11] The exact reason for this varying incidence however is not clear, but may be due to difference in the diagnostic criteria used and possibly due to over-diagnosis in prospective studies and under diagnosis in retrospective studies.

Pathophysiology

Fat embolism syndrome is a disease affecting mainly capillaries and mainly on the venous side. Hence, the lung is the most common organ affected in FES. However, the fat globules and chylomicrons gain access to the systemic circulation and can also affect heart, brain, skin and retina. The various explanations offered for the systemic manifestations of FES are:

- Pulmonary A-V malformations.^[12]
- Passing of deformed fat globules through pulmonary capillaries.^[13]
- Bypassing pulmonary circulation via a patent foramen ovale.^[14,15]
- Re-opening of a closed foramen ovale due to an acute rise in pulmonary pressure.^[14,16]

The manifestations of fat embolism are varied and hence the exact pathophysiology of fat embolism is still a controversy. It is not exactly understood why some patients develop fat embolism while others do not. Avikainen *et al.*,^[17] proposed that it is the intrinsic metabolic changes in certain individuals, which turn them susceptible to FES after a fat embolism episode. The symptoms usually occur within 12 h to 72 h, but can occur over a wide range of time of 6 h to 10 days.^[18] Three major theories proposed as a mechanism for FES are:^[19]

Mechanical theory

Neutral fat droplets enter the venous blood and dislodge in pulmonary circulation. If the embolism is massive enough to occlude 80% of pulmonary capillary meshwork, it will lead to acute right heart failure. Pulmonary embolism by

fat globules lead to an increase in the perfusion pressure, engorgement of the pulmonary vessels rendering the lung more stiff, which in turn results in an increase in the workload of the right heart. As the work of breathing increases, the right side of the heart attempts to increase its output by dilatation, which requires an increased venous return. Electrocardiograms at this time will indicate right heart strain. The heart is most susceptible to the effects of hypovolemic shock with a decreased central venous return. Death at this stage is due to acute right heart failure.

Chemical theory

The lung responds to the presence of fat emboli by secreting lipase, which hydrolyses the fat into free fatty acids and glycerol. The free fatty acids acting locally to produce an increase in the permeability of the capillary bed, a destruction of the alveolar architecture, and damage to lung surfactant. The delay in onset of symptoms may be due to the time required for the production of toxic metabolites. Nevertheless the evidence for these mechanisms of injury is yet to be proven.

The other hypothesis proposed are combination of both mechanical and biochemical theories- initiation of symptoms by fat globules followed by the biochemical cascade responsible for the rest of the symptoms. Another theory – “coagulation theory” proposes tissue thromboplastin released with marrow elements to activate the complement system and extrinsic coagulation cascade via direct activation of factor VII which in turn leads to production of intravascular coagulation by fibrin and fibrin degradation products.

Risk factors

With the complexities of symptoms and intricacies in management, FES has always enjoyed the attention of physicians. It has not been possible to explain why only some people develop FES while others do not. The incidence is higher among trauma patients and with long bone fractures. Young children are more immune to this syndrome due to the relative preponderance of hematopoietic tissue.^[1] Gossling *et al.*,^[12] attributed the immune nature of children to FES due to a lower triolein concentration in medullary fat. Closed fractures, multiple fractures, and conservative therapy for long bone fractures have a higher association with FES.^[20] Reaming of medullary cavity, over-enthusiastic intra medullary nailing, increased velocity of reaming; also predispose a patient for FES.^[21] A study on the metabolic profile of patients who suffered from FES found that patients who developed FES had an increased glycemic status, lower alpha and beta lipoprotein ratio, abnormal capillary fragility test, higher number of platelets, and low cortisol levels.^[17] This study remained inconclusive regarding the significance of these findings but it can be safely presumed that the altered intrinsic metabolic changes in certain individuals predispose them to an episode of FES following FE. White *et al.*, conducted a prospective study, over a period of 8 years involving 7,192 patients in an attempt

to unravel the epidemiology of FES. They found that an injury severity score more than 16, the presence of femoral fracture, a combined abdominal and extremity injury, or abnormal vital signs at admission all were independently predictive of the later development of ARDS due to FES.^[4,22]

Clinical presentation

Fat embolism syndrome can present in a wide variety of severity and symptoms. Usually presenting with a delay of 12-72 h, the classical triad consists of respiratory distress, cerebral signs and petechiae. Fat embolism syndrome can go unnoticed clinically or may present as an acute fatal event within hours of the inciting injury. A non-fulminant fat embolism, which is clinically apparent and milder than the fulminant form has also been described by Sevitt.^[23]

Subclinical FES

Seen in almost all long bone fractures,^[12] it manifests as a decreased PaO₂, minor hematological changes with no clinical signs or symptoms of respiratory insufficiency. It is often confused with postoperative symptoms such as pain, discomfort, or postoperative inflammatory process. Associated tachypnoea, tachycardia, and fever may be seen.^[24,25]

Non-fulminant (subacute) FES

Clinically, apparent form in which respiratory and cerebral changes, petechiae are seen.^[18] Petechiae are seen on anterior portion of upper chest, and areas adjacent to the axillae, shoulder, mucosa and mouth.^[26] Radiologic abnormalities on chest skiagram and other lab abnormalities may be seen. Neurologic signs such as coma, confusion or stupor are present in up to 86% cases.^[18] They are usually transient and non-lateralizing. Respiratory symptoms are usually benign and lung parenchyma tends to improve from third day. They may vary from minimal tachypnoea to development of ARDS. Changes similar to Purtscher's Retinopathy may be present.^[1]

Fulminant FES

This is a much rarer entity than the other two. Seen within hours of injury, it results in severe physiologic impairment including respiratory failure, and altered mental status. Cause of death, if occurs, is usually due to acute right heart failure.

Clinical symptoms

Respiratory symptoms

These are usually the first presenting features. Hypoxemia, tachypnoea, and dyspnoea are the initial findings. In some cases, the patients may progress to respiratory failure, requiring mechanical ventilation.^[18] In other cases, if no ongoing embolism or infection occurs, the lung usually recovers by the third day.

Neurological symptoms

The symptoms may appear within 10-120 h and are highly varying.^[27] Ranging from confusion, to seizures, these symptoms may even be the presenting symptoms of

FES.^[18] They are thought to be the direct result of cerebral hypoxia rather than embolization. The symptoms may include irritability, anxiety, agitation, confusion, delirium, and coma, which are described as progressive changes and as single manifestation in individual cases. These symptoms are usually non-lateralizing, transient and fully reversible.^[28] However, localising signs due to fat embolism have also been reported. Localizing signs, such as aphasia, anisocoria, apraxia in a patient with poly-trauma warrants a computerized tomography of brain to rule out hematoma, although in FES, a CT brain will be usually non-rewarding.

Cutaneous manifestations

Petechial rash may be the last component to develop in FES. Appearing within 36 h, this is believed to be pathognomic feature of FES.^[1] It is usually self limiting, and disappears within a week. It can be easily missed in dark skinned persons, and is to be actively sought on the upper portions of the chest and axillae. Other common sites of involvement are conjunctiva, oral cavity and shoulders. Petechiae are thought to develop due to extravasations of RBC's from over distended capillaries.^[5] The fat particles floating in aortic arch vessels are embolized to non dependant parts via aortic arch vessels and hence the site predilection.^[29]

Other manifestations

Fever, tachycardia are non-specific but seen in almost all cases of FES.^[30] The obstruction of retinal capillaries may lead to cotton wool spots, macular oedema and hemorrhage but these changes are usually reversible.^[31] Renal involvement is manifested as lipuria although oliguria and anuria have been reported. Hepatic involvement may manifest as jaundice.^[31]

Investigations

Blood investigations

Routine blood investigations will show a fall in hemoglobin, hematocrit, rise in ESR and thrombocytopenia.^[1] Hypofibrinogenemia and features of DIC such as prolonged prothrombin time may be seen.^[8] A transient elevation of lipase levels in blood is thought to be non-specific as high levels are seen in cases without fat embolism also. Hypocalcemia and hypoalbuminemia also have been reported to occur in patients with FES. The elevated serum lipase or FFA may cause a drop in calcium while it is postulated that the FFA binding to albumin is responsible for hypoalbuminemia.^[10] Presence of fat globules in blood and urine point to a diagnosis of fat embolism rather FES.^[5]

Blood gas analysis

Arterial Blood gas analysis initially reveals hypoxia with hypocarbia and respiratory alkalosis.^[1] Later on, as respiratory muscle fatigue develops, there may be carbon dioxide retention and respiratory acidosis. An increased alveolar-arterial shunt fraction, in the absence of ARDS, within 24-48 h of a potentially causative event is strongly suggestive of FES.^[1]

Pulse oximetry

Bulger *et al.*,^[8] found that patients who are hypoxemic are always at a higher risk of developing FES and its complications. Depending on ABG analysis for diagnosing hypoxia is a costly affair, which also causes discomfort to the patient owing to its invasive nature. Pulse oximetry is an equally reliable non-invasive testing method to diagnose hypoxic patients who are at risk for developing FES. It also helps in diagnosing sub-clinical cases more easily, where the only sign might be hypoxia.^[8,32]

Skiagram chest

Initially normal, the radiological abnormalities develop gradually as a diffuse fluffy bilateral infiltrates (Snow storm appearance), predominantly in bases and periphery.^[5] This classical snow storm appearance is seen only in 30-50 % of cases.^[33] This has to be differentiated from cardiogenic pulmonary oedema, pulmonary contusion, ARDS or aspiration pneumonia.

EKG

Usually non-specific. The abnormalities observed are tachycardia with non-specific ST-T changes, right axis deviation and RV strain.^[1]

Thoracic CT and Lung Scans

CT scan of chest may not be of much help other than in picking up small lesions in patients with apparently normal chest X-ray.^[34] Ventilation perfusion scanning detects areas of perfusion failures, but cannot differentiate between thromboembolism from FES.^[35]

Brain CT

CT of brain may be normal, or with minimal brain oedema, or diffuse white matter petachial hemorrhages. Though helpful in excluding traumatic causes of altered behavior, its use in FES is limited.^[5,36]

MRI brain

T₂ weighted images show areas of high intensity early in the course of FES.^[37] Many FES cases with normal brain CT have been found to have small cerebral infarctions on MRI. Fat embolism syndrome lesions are characteristically located deep in the white matter, brain stem and cerebellum ganglia.^[38] In cases where MRI of brain is totally normal, a diagnosis of brain FES can be safely excluded.^[37] MRI Brain can also be used in follow up of patients as an improvement in images is always associated to a clinical improvement.^[30]

Bronchoalveolar lavage (BAL)

There have been conflicting reports proposing BAL in the diagnosis of FES. Chastre *et al.*,^[39] suggested that the presence of fat globules in at least 5% of alveolar macrophages recovered on BAL helps in a rapid and specific diagnosis of FES. However, this has been challenged by Aoki *et al.*,^[40] who concluded it was a non-specific finding. Aoki *et al.* found similar results from BAL in trauma patients who did not develop FES and in those

who did develop FES. Fat globules in BAL may signify circulating fat globules of fat embolism and need not point on to FES. The absence of fat globules in BAL macrophages has a high negative predictive value and may help in ruling out fat embolism. Fat droplets in BAL have also been reported in patients with sepsis, hyperlipidemia, and patients on lipid infusions. Hence at present, the routine use of BAL in aiding to diagnosis of FES is controversial.^[41]

Transoesophageal Echocardiography (TEE)

Used in evaluating intra-operative release of marrow contents into blood stream during intramedullary reaming and nailing. This technique demonstrated a correlation between a reduction in oxygen saturation and fat emboli passing through right heart. It also demonstrated systemic embolization through patent foramen ovale. But the actual development of FES did not correlate with TEE.^[1]

Thus, in summary, it is apparent that FES presents in a myriad of clinical symptoms with varying severity. There is no pathognomonic and specific clinical sign, laboratory investigation or imaging modality that can accurately point out an early diagnosis of FES. Therefore, the diagnosis of FES depends largely on clinical features and ruling out other differential diagnoses. An early diagnosis can be made by close monitoring of pulse oximetry and ABG analysis in high risk patients. To aid in the diagnosis of FES, various scoring systems have been proposed for diagnosis of FES.

Diagnostic criteria for FES

Gurd and Wilson^[42,43] proposed a diagnostic criteria for fat embolism in suspected patients. One of the three major manifestations i.e., respiratory insufficiency, cerebral involvement or petachiae along with four of the five minor criteria (pyrexia, tachycardia, fall in hematocrit or platelet values, increasing ESR, retinal changes, and presence of fat globules in sputum or urine) are considered to be consistent with a diagnosis of FES. This criteria lacked lung pathology descriptions and arterial blood gas findings.

Murry and Racz^[44] proposed the presence of tachycardia, tachypnoea, pyrexia, and cerebral involvement with a decreased arterial oxygenation as a diagnostic criterion for FES.

Lindague *et al.*,^[45] proposed a diagnostic algorithm based on respiratory status alone. Presence of any one of the following was considered diagnostic of FES in post-trauma patients - A sustained hypoxia of <60 mm of Hg, sustained hypercarbia of >55 mm of Hg, pH <7.3, respiratory rate >35 despite adequate sedation and an increased work of breathing manifested as accessory muscles use, tachycardia, anxiety.

More recently a quantitative means of diagnosis of FES was proposed by Schonfeld.^[46] He assigned scores to seven clinical signs - [Table 1], and a cumulative score >5 is required for a diagnosis of FES.

Table 1: Clinical scoring as suggested by Schonfeld *et al.*

Symptoms	Score
Petechiae	5
Diffuse alveolar infiltrates	4
Hypoxemia – PaO ₂ <9.3 kPa (70 mm of Hg)	3
Confusion	1
Pyrexia >38°C	1
Tachycardia >120 / min	1
Tachypnoea >30 / min	1

Differential diagnosis for FES

The list of differential diagnosis in a patient with signs and symptoms of FES is exhaustive. The clinical symptoms are vague and non-specific and hence require detailed evaluation for ruling out each. However, the time of presentation and associated laboratory findings may be helpful in clinching the diagnosis.

Apart from intra vascular volume loss, respiratory distress may be due to pulmonary contusion, thromboembolism, pneumonia, ARDS. The classical Chest skiagram features of FES (Snow storm Lung) appear only about 24-48 h of trauma. The presence of clinico-radiologic and lab findings of pneumonic consolidation is usually not missed. Pulmonary contusion presents with radiologic findings within 6 h of injury and are not confined to lobar anatomy. Rapid evolution of cavity and its resolution suggests a diagnosis of post traumatic pulmonary pseudo cyst. The radiologic findings in contusion will always correspond anatomically to the external area of trauma.

The appearance of petechial rash in patients of poly-trauma is considered by many to be diagnostic of FES. They appear after an interval of 12-96 h of the inciting trauma and are usually seen around the axillae, neck and over the sternum. Though reported to have a frequency of 25-95%,^[47] these should not be confused with DIC, prolonged hypoxia and repeated blood transfusion.

Cerebral changes in a poly-trauma patient usually warrant a CT head to rule out parenchymal injuries and also hematomas inside the brain. Although not specific for FES, gross abnormalities such as hematomas may be picked up on routine CT study of brain.

Thus, in a patient with high risk for FES, development of hypoxia and altered sensorium in the absence of other evident causes virtually diagnoses FES.

Management

There is no specific treatment for FES. The main line of treatment is supportive. Prevention of FES and early diagnosis with prompt management of complications is the cornerstone in managing this condition.

Preventive measures

Fat embolism syndrome is associated with multiple long bone fractures and unstable fractures. Hence, an

early fixation of long bone fractures within 24 h is a key step.^[48] Various surgical techniques are suggested to reduce intra operative embolization of fat globules, whose description will be beyond the scope of this paper. Prophylactic corticosteroids have been advocated by many authors, though there is no consensus about the dose. A prophylactic dose of Methylprednisolone for 2-3 days in a dose ranging from 9-90 mg/kg was not associated with any opportunistic or super infections. Schonfeld *et al*, in a double blind randomized study, diagnosed FES in 9 out of 41 placebo treated cases while none of the 21 patients treated with steroids developed FES ($P < 0.05$). There has also been other studies also demonstrating a lung protective effect of corticosteroids, in patients with high risk for FES.^[46] The PaO₂ measured in patient group receiving corticosteroids was always higher ($P < 0.03$) than the placebo group. There were no reports of opportunistic infections or delayed bone healing after prophylactic doses for 2-3 days. However, all the studies recruited a patient group of size 20-40, differed in criteria of patient selection and administered different doses of Methylprednisolone. Hence, these findings need validation with a large number of patients and uniform criteria of patient selection and management.^[27,49]

Albumin for volume resuscitation is recommended because it helps in restoring euvolemia and also binds to free fatty acids and reduces further injury of lungs.^[19]

Careful vigilance with a high degree of suspicion in high risk patients is vital in early detection of FES. These patients should be monitored continuously for a fall in oxygen saturation. Analgesia, if provided should not be a hindrance to a periodic neurological assessment. The patient should not be over sedated. Careful monitoring of vitals and temperature is also mandatory in such patients.^[18] An early initiation of oxygen (and steroids) in desaturating patients might help in reducing the hypoxic insult and sequela of a full blown FES.

Treatment

Once diagnosed of FES, the patient should be transferred to an intensive care unit, preferably with CVP monitoring. If clinical evidence of right heart failure is evident, along with acute pulmonary hypertension, CVP measuring will be useful to guide the treatment. Albumin, having an additional lipophilic action, is preferred for restoring intra vascular volume.^[18,19] Hypovolemic due to inciting trauma or surgery should be corrected with normal saline, Ringer lactate, Dextrin, etc, especially in a setting of right heart failure. Dobutamine is a more potent inotropic agent and hence is advocated over norepinephrine, if the patient remains in shock, in spite of judicious administration of plasma expanders.^[27,50]

Hypoxia occurring with FES is initially managed by oxygen inhalation using face mask or high flow gas delivery systems like venture masks, non-rebreather reservoir masks.^[51] The oxygen content of blood and required FiO₂

should be calculated. The aperture of masks should be adjusted so as to deliver the required FiO_2 . The flow rate of oxygen is also to be taken care of and should be matching with the FiO_2 requirement. PaO_2 may also be improved by Continuous positive pressure ventilation (CPAP) without increasing FiO_2 . If a FiO_2 of $>60\%$ and CPAP >10 cm are required to achieve a PaO_2 , then mechanical ventilation with Positive end-expiratory pressure (PEEP) should be considered.^[1] Vigilance should be maintained against ventilator induced lung injury, and a decrease in cardiac output by increase in right ventricular pressure. Recent data suggests that PEEP may protect and at times even delay the onset of ventilator associated lung injury.^[52] Close monitoring of arterial blood gases and hemodynamic status is recommended when PEEP and mechanical ventilation are used.^[1] Prone positioning, extra corporeal membrane oxygenation may also be tried in patients with severe pulmonary dysfunction.^[53]

Corticosteroids have been extensively used as an anti-inflammatory agent. However, there is insufficient data to support its use once FES is established.^[28] Aprotinin, a trypsin inhibitor has been tried in FES because of its inhibition of platelet aggregation.^[54] However, this drug has been associated with increased renal dysfunction, anaphylaxis and hence has been withdrawn from market. Alcoholic patients in a state of drunkenness had less incidence of FES than sober ones.^[5,55] It was thought to be the result of alcohol's action on serum lipase, thereby reducing the level of free fatty acids. However, there have been no prospective randomised studies and the idea of alcohol as a drug for FES has been disregarded by many.^[7,56] Heparin also has been used with caution in the prevention and management of venous thrombosis that may occur in post-operative cases. But the regular use of heparin for FES has been contraindicated because of undue risks of bleeding in poly trauma patients.^[1,28]

Prognosis

Mortality incidence due to FES varies among varied studies, probably because of its underdiagnosis.^[27] Acute fulminant FES may lead to death due to right heart failure, while majority of deaths are usually due to respiratory failure. Though prognosis for neurological defects is good, deaths have also been reported. Incidents of acute coronary syndrome, probably due to circulating fat globules have also been reported.^[57] Overall, the mortality is estimated to be 5-15%.

CONCLUSION

There is no specific diagnostic method for FES. A high degree of suspicion, combined with continuous monitoring of vitals including pulse oximetry and supportive lab investigations such as unexplained fall in platelet count and hematocrit, MRI brain etc will enable an early diagnosis of FES. Initiation of prompt supportive management will help in reducing the morbidity and mortality among such patients.

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