Fat embolism syndrome: history, definition, epidemiology

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Summary¹ The first clinical case of fat embolism was described over 100 years ago and significant progress has been made in the understanding of this condition since then. Gurd’s criteria, consisting of major and minor clinical features, is the most commonly used diagnostic tool in the literature. Due to the lack of a gold standard for diagnosis, clinical criteria cannot be validated. It is now recognized that although fat embolization occurs in the majority of patients with long bone fractures, clinical signs and symptoms occur only in 1–10% of patients with fractures.

History

The first animal model of fat embolism was described over 330 years ago by Lower who injected intravenous milk into dogs [1]. Magendie performed more elaborate studies in the early 19th century and observed that intravenous injection of oil led to mechanical obstruction of small vessels by fat globules [1]. Virchow reported that injection of intravenous oil produced pulmonary edema [1]. These experiments were undertaken without knowledge of human fat embolism syndrome (FES).

The first human case of posttraumatic fat embolism was described by Zenker in 1862 in a patient with a severe crush injury. Fat was observed in the pulmonary capillaries at autopsy [1]. Scuderi, who extensively reviewed the condition in 1934, stated at that time “the treatment of this condition is not very illuminating” [1]. However, in 1914 Tanton proposed that adequate fracture immobilization could help prevent the syndrome [2].

In the 1920s, the two theories of fat embolism that remain to this day were put forward. Gauss established the mechanical theory [3] in which he defined three conditions for fat embolism to occur: injury to adipose tissue, rupture of veins within the zone of injury, and “some mechanism that will cause the passage of free fat into the open ends of blood vessels”. Gauss thought that this mechanism was that blood vessels in bone were bound tightly to their bony channels thus remaining open, unlike veins elsewhere in the body that tend to collapse and thrombose. Lehman proposed a biochemical theory to explain FES, hypothesizing that plasma mediators can mobilize fat from body stores and cause it to form large droplets [4].

Following the emergence of intramedullary (IM) nailing in the 1940s, a number of surgeons were concerned about the potential complication of fat embolism [5, 6]. Peltier determined that solid nails
caused greater increases in intramedullary pressure than hollow nails [5]. Shortly after, he reported a case of fatal FES following IM nailing of a closed femur fracture [6]. He advised that prevention of FES should be based on preventing shock, using a hollow nail design, and “driving the nail in slowly with a pause between hammer blows” [6].

As with all traumatic conditions, a great deal has been learned about FES during armed conflict. In World War II, the incidence of FES was noted to be approximately 0.8% in a series of 1,000 combat wounds [7]. A study of 110 combat fatalities from the Korean War found that 93% had pulmonary fat at autopsy, but this was only moderate to severe in 19% of cases [8]. However, the authors were not convinced that pulmonary fat embolism could induce pulmonary dysfunction and stated that “serious pulmonary embarrassment may result from embolic fat in occasional cases, but such cases must be quite uncommon”. In Vietnam, technological advances made it possible to diagnose more subtle cases. Collins notes a high incidence of arterial hypoxemia in 69 wounded soldiers and attributed this to FES after carefully excluding thoracic injuries and hypoventilation as causes of hypoxemia [9]. He noted a strong association between hypoxemia and femur fractures from high velocity missiles. Cloutier was able to conduct a prospective study of 50 Vietnam battle casualties and found five classic cases of FES among them [10].

### Definition

There is no universally accepted definition of FES. The pathophysiological phenomenon of fat embolization (FE) must be differentiated from FES, which is defined by the presence of clinical signs and symptoms resulting from embolic showers.

Gurd proposed diagnostic criteria in 1970 that are still widely used today [11]. They are divided into major features and minor features (Table 1). Gurd stated that the diagnosis of FES could be made if one major feature plus four minor features plus fat macroglobulinemia were present. These criteria have been adapted by other authors who stated that one of the following combinations of major and minor features was needed to make the diagnosis: two major [12–15]; one major and three minor [16, 17]; two major and two minor [16]; or one major and two minor [18] features. Most authors have also dropped the requirement for presence of fat macroglobulinemia from the necessary criteria [12–19]. None of these authors, including Gurd, have provided justification for the number of features needed for the diagnosis.

Other diagnostic systems have been proposed. Schönfeld proposed a fat embolism index that gives points for different diagnostic criteria [20] (Table 2). A diagnosis of FES is made with a score of 5 or more. Schönfeld acknowledges that this system is not useful for patients with cerebral, thoracic, or abdominal injuries. Vedrinne developed a scoring system with the polytrauma patient in mind [21] that uses pulmonary infiltrates, neurological status, petechiae, platelet count, retinal changes, total blood lipids, and the presence of long bone fractures to assess patients. Finally, in a study of pediatric patients, Weisz made the diagnosis of FES when one of three signs was present: retinal embolism, positive skin, lung or kidney biopsy, or histological findings at autopsy [22].

<table>
<thead>
<tr>
<th>Major features</th>
<th>Minor features</th>
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<tr>
<td>Petechial rash</td>
<td>Tachycardia</td>
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<tr>
<td>Respiratory symptoms plus bilateral signs with positive radiographic changes</td>
<td>Pyrexia</td>
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<tr>
<td>Cerebral signs unrelated to head injury</td>
<td>Retinal fat or petechiae</td>
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FES = 1 major feature + 4 minor features + fat macroglobulinemia

Table 1: Gurd’s criteria.

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<tr>
<td>Diffuse petechiae</td>
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<tr>
<td>Alveolar infiltrates</td>
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<tr>
<td>Hypoxemia (&lt;70 mm Hg)</td>
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<td>Confusion</td>
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<tr>
<td>Fever &gt;38°C</td>
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<tr>
<td>Heart rate &gt;120/min</td>
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<tr>
<td>Respiratory rate &gt;30/min</td>
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<tr>
<td>FES = 5 or more points</td>
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Table 2: Fat embolism index.
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A number of investigators have sought a gold standard test for the diagnosis of FES but such a test remains elusive. The absence of a diagnostic gold standard makes it impossible to evaluate the value of these clinically-based evaluation systems. A correlation with autopsy findings would perhaps be feasible but fatal cases are rare events.

In the future, advances in diagnostic imaging and in laboratory tests may help with the diagnosis of FES. In polytrauma patients, it can be difficult to attribute pulmonary or brain dysfunction to fat emboli. A number of authors have described the MRI appearance of cerebral FES [19]. The appearance of pulmonary FES on high-resolution CT scans has also been described [23]. Another approach has been to evaluate cells staining positive for fat globules in bronchoalveolar lavage (BAL) fluid which, although it seemed promising at first [13], has conflicting data [14, 21, 24, 25]. These modalities are examples of tests that could help refine Gurd’s criteria. At this time, the diagnosis of FES remains clinical [26].

Epidemiology

The phenomenon of fat embolism is extremely common among trauma patients, especially those with long bone or pelvic fractures [27]. However, in the context of trauma, fat embolism is also common following extensive injury to subcutaneous fat, such as occurs in severe beatings [28, 29]. Fat emboli can be demonstrated in a number of ways. Gurd showed that 67% of trauma patients without evidence of FES had circulating fat globules [30]. Allardyce studied 43 cases of femoral shaft fractures and found that 95% of patients had circulating fat globules in blood draining from the fracture site [31]. Urinary fat droplets are also a frequent finding after trauma [16, 32, 33]. Mudd found pulmonary fat in 68% of patients dying from blunt trauma, most of whom had associated fractures [34].

The first study to use ultrasound to detect embolic particles was performed in 1972 [35]. This technology has since been used by many authors to study the phenomenon of fat embolism. Pell et al performed transoesophageal echocardiograms in 24 patients undergoing nailing of a lower extremity fracture [36]. In 41% of cases, embolic showers were detected, with 16% being graded as severe. The same group performed a second study that showed embolic phenomina in 94% of pathological femurs (59% severe), 62% of femur fractures (6% severe), and 94% of tibial fractures (none severe) undergoing IM nailing [37]. Blood sampling from the right atrium confirmed that fat was responsible for these echogenic masses. The severity of the embolic showers also correlated with the severity of decreased end-tidal CO₂ and hypoxemia.

Hypoxemia after long bone fractures is a frequent occurrence, which in many cases could be represented by mild pulmonary dysfunction induced by intravasated fat without full blown FES developing. Moed et al found arterial hypoxemia in 35% of patients with fractures of the femur, tibia, or pelvis using intermittent pulse oxymetry [38]. The use of continuous pulse oxymetry has shown that these events occur in nearly all patients with these injuries [17]. McCarthy found hypoxemia (PaO₂ < 80 mmHg) in 74% and an elevated alveolar-arterial O₂ gradient (> 20 mmHg) in 100% of patients with uncomplicated extremity fractures [32]. Whether this incidence truly represents subclinical FES remains to be determined with certainty.

Despite the high frequency of embolic fat globules entering the circulation, the incidence of FES (ie, patients who develop signs and symptoms from the emboli) is much lower. In 1974, Gurd reported that the syndrome occurred in 19% of major trauma cases admitted to a Belfast hospital [30]. Riska reported an incidence of severe FES (ie, in need of respiratory support) of 22% in a group of 384 multiply injured patients with long bone fractures treated nonoperatively between 1967 and 1974. In subsequent years (1975–1978), internal fixation was instituted as a standard treatment and the incidence fell to 1.4% in a similar group of 211 patients [39]. However, 9% had milder forms of the syndrome not requiring respiratory support, making a total incidence of 10.4%. In Pell’s echocardiographic study, 12.5% of patients were diagnosed with FES [36]; all of whom were in the group in which embolization was graded as severe. Allardyce reports an incidence of 11% [31].

Bulger and Fabian provide the best modern data on the incidence of FES. Both conducted studies at level 1 trauma centers. Bulger retrospectively studied all cases of FES over a 10-year period at Harborview medical center [16]. They found 27 cases out of 3,026 patients with long bone fractures admitted during that time period, which gives an incidence of 0.9%. Fabian conducted a prospective study over a 12-month period of patients with femoral, tibial, and pelvic fractures [40]. In this population, the incidence of FES was thought to be at least 11%. They based the diagnosis on increased pulmonary shunt fraction as inferred from an increased alveolar-arterial oxygen tension difference. The authors emphasize that this is the minimum incidence of FES given that many cases with concomitant chest injuries may have gone undetected.

The timing of the fracture fixation also appears to impact on the incidence of FES. Pinney reported on
a series of 274 consecutive femoral shaft fractures [18]. The overall incidence of FES was 4%, but all cases occurred in the group that had IM nailing performed more than 10 hours after surgery. Ten Duis studied 172 consecutive patients with isolated femoral shaft fractures over an 18-year period [15]. Overall, 3.5% of patients were diagnosed with FES. Their data also suggest that early surgery might prevent FES as all cases occurred in patients that underwent fixation after 24 hours. Talucci did a retrospective study of 100 patients undergoing IM nailing of the femur [41]. They found that the incidence of FES was 11% in the group that had delayed fixation compared to 0% in the early fixation group. These findings were also confirmed by Bone in a prospective randomized study of early versus delayed stabilization of femoral shaft fractures [42]. The influence of the method of fracture fixation on FES has not been directly studied in humans, although one study showed no difference in the rate of adult respiratory distress syndrome (ARDS) when comparing plating versus nailing of femoral shaft fractures [43].

The incidence of FES in children is said by some authors to be up to 100 times lower than in adults [27, 44], but the incidence might be higher when signs and symptoms are carefully sought [22].

Mortality directly attributable to FES is relatively low with modern ICU care. Fabian reports a mortality rate of 10% [40], while Bulger reports a death rate of 7% [16]. This compares favourably to the 10–20% mortality rate reported by a panel of experts from four different institutions in 1974 [45]. That same year, Moreau also reported a mortality rate of 15% in a series of 100 patients [44].

Summary

Fat embolism is a frequent occurrence in trauma patients. Despite technological advances in diagnostic imaging and numerous attempts to find a confirmatory laboratory test, the diagnosis remains a clinical one. Diagnostic criteria have remained essentially unchanged over the past 30 years. Early fracture fixation and modern critical care should help minimize the impact of fat embolism.

Bibliography