REVIEW ARTICLE
Fat embolism

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Summary

Fat embolism syndrome is a collection of respiratory, haematological, neurological and cutaneous symptoms and signs associated with trauma and other disparate surgical and medical conditions. The incidence of the clinical syndrome is low ($< 1\%$ in retrospective reviews) whilst the embolisation of marrow fat appears to be an almost inevitable consequence of long bone fractures. There is debate over the pathogenesis of fat embolism syndrome and it seems a variety of factors interact to produce a spectrum of end organ damage. Many therapeutic interventions and prophylactic strategies have been tried with varying success. Current treatments are supportive and the condition is usually associated with a good outcome. The literature on fat embolism syndrome is extensive and this review aims to discuss the incidence, aetiology, pathophysiology, diagnosis and treatment of fat embolism.

Definition

Fat embolism describes both fat in the circulation and a clinical syndrome. As the former can occur without the latter, it is sensible to define each entity, acknowledging that there may be some overlap in clinical practice.

1 Fat embolism (FE) is fat within the circulation, which can produce embolic phenomena, with or without clinical sequelae.

2 Fat embolism syndrome (FES) is fat in the circulation associated with an identifiable clinical pattern of symptoms and signs.

Diagnosis of fat embolism syndrome

Clinical features

Fat embolism syndrome is a collection of symptoms and signs; as some of the manifestations are common to other critical illnesses, the diagnosis is often made by exclusion. The presentation may be fulminating with pulmonary and systemic embolisation of fat, right ventricular failure and cardiovascular collapse. This can occur intra-operatively [1]. More usually, the onset is gradual, with hypoxaemia, neurological symptoms, fever and a petechial rash, typically 12–36 h following injury [2]. Gurd suggested the use of 'major' and 'minor' clinical signs to make the diagnosis of FES (Table 1) [3].

The presence of any one major plus four minor criteria in addition to fat macroglobulaemia constitute FES. Using these criteria, the authors commented that it was important to examine blood daily as recent fat emboli, a change in fat quantity or a change in appearance of the globules may be associated with development of the clinical syndrome. Gurd's criteria have been criticised for being unreliable because fat droplets can frequently be found in the blood of healthy volunteers and trauma patients without any clinical evidence of FES [4]. Lindeque suggested that Gurd's criteria may underdiagnose the syndrome and proposed the following criteria based on respiratory parameters (Table 2) [5]. Any patient with a fractured femur and/or tibia showing one or more of these criteria was judged as having FES. These criteria lead to a diagnosis of FES in 29% of patients (in a series of 55) which is higher than other series, especially as this study excluded patients with chest injuries where some of Lindeque's clinical signs may occur without FE.

Table 1 Features of fat embolism syndrome

Major criteria	Petechial rash
	Respiratory symptoms – tachypnoea, dyspnoea, bilateral inspiratory crepitations, haemoptysis, bilateral diffuse patchy shadowing on chest X-ray
	Neurological signs – confusion, drowsiness, coma
Minor criteria	Tachycardia > 120 beat.min^{-1}
	Pyrexia > 39.4 °C
	Retinal changes – fat or petechiae
	Jaundice
	Renal changes – anuria or oliguria
Laboratory features	Thrombocytopenia $> 50\%$ decrease on admission value
	Sudden decrease in haemoglobin level $> 20\%$ of admission value
	High erythrocyte sedimentation rate > 71 mm.h^{-1}
	Fat macroglobulaemia

The most frequent presentation of FES is with respiratory symptoms and signs. Severity is variable but respiratory failure is relatively common. Bulger reported that 44% of the 27 patients diagnosed as having FES required a period of mechanical ventilation [6]. A 15-year study of trauma patients in the West Indies found 14 cases, four of whom required mechanical ventilation [7]. However, gas exchange deteriorates after long bone fractures with or without FE. In 16 of 28 patients with lower limb long bone fractures, the oxygen tension (P_aO_2) was reported to be less than 7.3 kPa [5] and, similarly, in another study of patients with multiple injuries, the P_aO_2 was reported to be less than 9.3 kPa in 90% of patients [8].

A petechial rash is pathomnemonic of FES and in up to 60% of patients a rash may be present, usually on the conjunctiva, oral mucous membranes and skin folds of the neck and axillae. This curious distribution may be explained by fat droplets accumulating in the aortic arch prior to embolisation to nondependent skin via the subclavian and carotid vessels [9]. Factors contributing to the rash may be stasis, loss of clotting factors and platelets and endothelial damage from free fatty acids (FFAs) leading to rupture of thin-walled capillaries [10].

Neurological manifestations are also frequently seen [7, 11, 12] and signs range from drowsiness and confusion to coma. In one series, five of 14 patients were unconscious, four had decerebrate posturing and one suffered tonic-clonic seizures. Minor global dysfunction appears to be most common, but focal signs, such as hemipareis or

Table 2 Lindeque's criteria for FES

1. A sustained P_aO_2 of less than 8 kPa (F_iO_2 0.21)
2. A sustained P_aCO_2 of more than 7.3 kPa or pH of less than 7.3
3. A sustained respiratory rate of greater than 35 breaths.min^{-1} even after adequate sedation
4. Increased work of breathing judged by dyspnoea, use of accessory muscles, tachycardia and anxiety

partial seizures, are reported. Fortunately, the severe neurological symptoms of FES frequently resolve. Central nervous system involvement has been reported in the absence of pulmonary features but with a petechial rash, fever, tachycardia and hypotension [13].

Investigations

A wide range of investigations have been used to identify FES. However, none of these is 100% specific and this may reflect the multisystem pathology.

Thrombocytopaenia (platelet count $< 150 \times 10^9.l^{-1}$) and unexplained anaemia are common (37% and 67%, respectively) [6]. The mechanism causing thrombocytopaenia is unclear but both platelet activation by bone marrow emboli with thrombus formation and platelet consumption due to disseminated intravascular coagulation (DIC) have been postulated [14]. Plasma FFA levels rise following trauma and this may result in hypocalcaemia due to their affinity for calcium [15]. Accompanying hypoalbuminaemia has been suggested as a predisposing factor because FFAs bind to albumin and so are rendered innocuous [16].

Blood and urinary analysis may show fat globules, although both of these are non-specific signs. The chest X-ray classically shows multiple bilateral patchy areas of consolidation typically in the middle and upper zones giving rise to a 'snow storm appearance'.

Specific biochemical tests have been suggested to aid diagnosis. Serum lipase and phospholipase A_2 (PLA$_2$) rise in FE related lung injury [14, 17]. However, these increases are not specific to trauma victims in whom FES occurs [18, 19] and may merely reflect altered lipid metabolism following trauma [20].

A pulmonary artery catheter has been advocated for diagnosis of fat embolism either by detecting a rise in mean pulmonary arterial blood pressure [21] or by sampling pulmonary artery blood for fat. Bronchoscopy and bronchoalveolar lavage (BAL) have been used to provide samples containing macrophages. As macrophages act as lung scavengers, they might be expected to contain fat in FES. BAL in trauma patients has been proposed as a specific method for diagnosing FES within the first 24 h [22, 23]. However, there are difficulties in obtaining satisfactory samples, as shown in one study where only 67 out of 96 samples were adequate for analysis due to low yield of macrophages [24]. Also, the stain used in these investigations is a stain for neutral fat (oil red O) which does not produce lung injury [25]. Despite these reservations, the use of a threshold value (such as 30%) of macrophages staining positive might be useful in trauma patients. Regrettably, both pulmonary artery blood aspiration and BAL samples lack the sensitivity and specificity to detect subclinical FES but the absence of macrophages staining for fat on BAL should prompt the search for alternative reasons for hypoxaemia.

Radiology may be useful where neurological involvement is suspected. Computer tomography (CT) scanning may show generalised cerebral oedema or high-density spots but in general is non-specific and unhelpful. Magnetic resonance imaging (MRI) shows greater promise as it may detect lesions in the presence of a normal CT scan. Specific changes include both low-density areas on T1-weighted images and high-density regions on T2-weighted images [26]. The distribution of involvement seen on MRI may be characteristic (cerebral deep white matter, basal ganglia, corpus callosum and cerebellar hemispheres). Suzuki noted that there were multiple spotty lesions along the boundary zones of vascular territories suggestive of fat globules blocking capillaries [27]. The radiological abnormalities resolve as the clinical signs improve and so MRI may become a useful tool for quantifying FES injury [28].

Incidence

Most large clinical series investigating FES involve elective orthopaedic or trauma surgery. The reported clinical incidence tends to be low (Table 3). These studies are striking because the incidence in retrospective long-term reviews is low (< 1%) while prospective studies state a far higher but consistent incidence (11–19%). The incidence of FE at post-mortem is several times that suspected clinically.

Incidence diagnosed by clinical criteria

In a 10-year review in an American level one trauma centre there was an incidence of FES of 0.9% using Gurd's diagnostic criteria [6]. There was no obvious correlation with severity, site or pattern of injury and FES. This contrasted with other studies which have shown an increase in incidence of FES with an increasing number of 'at-risk fractures' (a fracture involving femur, tibia or pelvis) [29, 38].

Incidence determined by physiological monitoring

When less subjective methods of evaluating the end organ effects of FE are used, the incidence rises. Using the alveolar–arterial oxygen tension difference as a marker for lung injury, one prospective study reported an incidence of 11% [12]. None of the patients had another cause for hypoxaemia other than FE and 40% of those with an increased alveolar–arterial oxygen tension difference had a petechial rash.

Incidence as identified by sophisticated imaging of emboli

Sophisticated measurement of emboli in the circulation with echocardiography has also been used to demonstrate a high incidence of embolic phenomena. In one study of 110 orthopaedic patients (111 procedures), transoesophageal echocardiography (TOE) detected embolic showers

Table 3 The incidence and mortality of fat embolism syndrome in recently reported series. TOE, transoesophageal echocardiography. FES, fat embolism syndrome

First author	Year	Study design	Incidence (*n*)	Mortality (*n*)
Incidence from clinical series				
Bulger [6]	1997	10 years review of trauma cases	0.9% (27)	7% (2)
Robert [29]	1993	25 years retrospective review	0.26% (20)	20% (4)
Data from prospective studies				
Fabian [12]	1990	96 consecutive long bone fractures	11% (10)	10% (1)
Kallenbach [30]	1987	Randomised trial of corticosteroids; 82 trauma patients overall	13% (11) overall	Nil
Lindeque [5]	1987	Randomised trial of corticosteroids; 55 trauma patients overall	13% (7) by Gurd criteria 29% (16) by revised criteria	Nil
Chan [8]	1984	80 consecutive trauma patients	8.75% (7) 35% of multiply injured patients	2.5% (2)
Schonfield [31]	1983	Randomised trial of corticosteroids; 62 trauma patients overall	15% (9) overall (No cases in treatment group *n* = 21)	Nil
Myers [32]	1977	100 consecutive trauma patients with long bone fractures	17% (17)	1% (1)
Incidence from TOE studies				
Christie [33]	1995	111 long bone fracture fixations	Emboli seen during 87% (97)	
Pell [34]	1993	24 tibial and femoral nailings	Significant emboli 41% (10), FES 12.5% (3)	4.1% (1)
Incidence from post-mortem data				
Behn [35]	1997	Consecutive post-mortem examinations following death from any cause		17% (92) of all cases
Hiss [36]	1996	Review of 53 blunt trauma deaths		60.4% (32)
Maxeiner [37]	1995	Retrospective analysis of deaths after total hip replacement		0.25% (9)

in 97 procedures [33]. Severe episodes were commonest during instrumentation of pathological fractures (59% of these procedures) and coincided with decreases in arterial oxygen saturation. TOE has demonstrated that embolic showers may continue postoperatively and tend to fragment causing pulmonary embolisation. The emboli may also coalesce forming thrombotic masses. Emboli of between 1 and 8 cm in diameter were seen and this was associated with patients developing FES [34]. In one patient, a large embolic load to the right heart was seen on TOE; ultimately, when the patient died, there was no evidence of fat macroemboli at post-mortem.

Incidence using post-mortem evidence

Post-mortem studies show a markedly different and very high incidence of FE. A study of 527 autopsies found evidence of FE in 92 [35]. Maxeiner examined 130 deaths after hip fracture and found FE responsible for at least six deaths (three intra-operatively and three postoperatively), and contributory in nine other deaths [37]. A report of the examinations of 53 victims of fatal beatings found a high incidence [36]. These young men were murder victims and suffered severe blunt trauma within the 24 h preceding autopsy. Thirty-two cases showed FE to major organs with no other cause for death. The authors hypothesised that the source of the FE was mechanical disintegration of the subcutaneous adipose tissue.

The agreement between post-mortem and clinical findings is poor and this disparity has given rise to the concept of the 'iceberg effect of FE' [8]. The issue has been further complicated by the use of echocardiography and BAL that suggest a high incidence of FE in the circulation. FE may be common whilst FES relatively rare.

Predisposition

The incidence of FE is undoubtedly highest following trauma, particularly lower limb fractures; however, FES is reported in many other conditions (Table 4) and the difficulty in these cases is the lack of a consistent and reliable standard for diagnosis. Procedures such as liposuction which deliberately disrupt both fat and

blood vessels might result in FES; however, the reported incidence is very low [42–44]. FES occurs with hepatic necrosis and fatty liver [48, 49]. In these circumstances, protracted fat embolisation from damaged hepatocytes may be involved. Both lipid and propofol infusions have been reported to be associated with subsequent respiratory failure but not all the other features of FES [40, 46]. The mechanism may be different in that fat emulsions can produce exogenous fat overload leading to mechanical obstruction of the vascular tree and local damage.

FES is recognised as part of an acute sickle cell crisis [17, 23, 56]. Acute chest syndrome is the second most common reason for hospital admission and leading cause of death in sickle cell disease. This syndrome is characterised by cough, dyspnoea and chest pain and has been attributed to many causes including FE, pulmonary infarction, hypoventilation secondary to rib infarcts or pneumonitis. Bone marrow necrosis caused by hypoxia and stasis during an acute crisis may release bone marrow fat. In 60% of acute chest syndrome cases, the pulmonary macrophages stain for fat [23] and this is associated with bone marrow infarction as shown by either isotope scanning or magnetic resonance imaging. Biochemical markers such as PLA_2 may increase up to 100 times the usual value found in patients with quiescent sickle cell disease and more than five times greater than a similar control group ill with pneumonia [17].

Pathophysiological mechanisms

No single theory satisfactorily explains all the pathophysiological features of FES as it is associated with a wide range of conditions (including some with no obvious evidence of bone marrow trauma) and has a number of differing presentations.

Infloating theory

This traditional view of fat embolism suggests that fat is physically forced into the venous system following trauma [57]. The normal marrow pressure is 30–50 mmHg but can be increased up to 600 mmHg during intramedullary reaming [58]. Intramedullary devices are associated with

Table 4 Reported causes of fat embolism syndrome

Mechanical distruption to adipocytes	Mechanical disruption of bone marrow	Exogenous fat	Miscellaneous
Soft tissue injury [36]	Bone marrow harvest [39]	Total parenteral nutrition [40]	Burns [41]
Liposuction [42–44]	Bone marrow transplant [45]	Propofol infusion in intensive care [46]	Following extra-corporeal circulation [47]
Hepatic failure (fatty liver or necrosis) [48, 49]		Lymphography [50]	Acute sickle cell crisis [51–53]
			Acute pancreatitis [54]
			Altitude illness [55]

Anaesthesia, 2001, **56**, pages 145–154

A. Mellor and N. Soni • Fat embolism
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higher pressures within the marrow cavity and more FE than extramedullary fixation [59, 60]. Ultrasonographically, most emboli occur during opening and manipulation of the intramedullary cavity [61]. Intramedullary fat content is important and previously reamed femurs are associated with extremely low incidence of FES-type problems because of reduced intramedullary fat [62]. Cement is associated with a much higher incidence of FE, although the incidence is not zero in uncemented prostheses [63]. Bone marrow injection in animal models consistently produces cardiorespiratory signs [64, 65] and FE can be induced experimentally by reaming and pressurising the intramedullary space with polymethylmethacrylate cement [66]. Sampling of femoral vein blood has localised the origin of fat macroglobules to the injured extremity [67].

Lipase theory

Trauma leads to an elevated plasma lipase titre which precedes any rise in FFAs [14]. This enzyme destabilises circulating fats by de-emulsification, saponification and mobilising lipid stores [68]. Kronke detected increases in serum lipase in 50–70% of patients with fractures and also a positive association between lipase titres and clinical manifestations of FE [69]. However, this rise was not found in another study [19].

Free fatty acid theory

A second biochemical theory invokes the histotoxic effects of FFAs which are known to cause severe vasculitis in animal models leading to haemorrhagic oedema and destruction of the pulmonary architecture within 6 h [70]. A flaw in this theory is that neutral fats are the major constituents of bone marrow and they do not display this effect [25]. However, it is highly likely that *in vivo* there is hydrolysis of neutral fats to FFAs and this may help explain the symptom-free interval before the onset of signs and symptoms during which hydrolysis occurs.

Shock and coagulation theory

This is based on the observation that many patients who develop FES are hypovolaemic secondary to multiple trauma or one of the other associated conditions. Hypovolaemia leads to a sluggish circulation with 'sludging' of blood components and microaggregate collection in the lungs. Trauma to the tissues exacerbates this by damage to the vascular intima leading to platelet activation. Bone marrow fat may then provide a surface on which activated platelets can adhere [71].

Systemic embolisation

A curious aspect of FES is the phenomenon of systemic embolisation without pulmonary effects [13, 28]. One suggestion is that this can occur via a patent foramen ovale, which has a prevalence of around 35% in the general population, and systemic embolisation via this route has been reported [1]. Alternatively, transpulmonary systemic fat embolisation has been demonstrated in dogs without a patent foramen ovale [72]. The deformability of the fat emboli coupled with the rise in pulmonary arterial blood pressure associated with FES may force the fat globules through the pulmonary capillary bed.

Relationship of fat embolism syndrome to multiple organ failure from other causes

Fat embolism syndrome shares many features characteristic of systemic inflammatory response syndrome and multiple organ failure from other causes. Bone marrow necrosis occurs in a wide variety of conditions such as bacterial infections and sepsis [73] and is associated with DIC [74]. Patients with the acute respiratory distress syndrome (ARDS) and sepsis often display fat in alveolar macrophages [24, 75]. PLA_2 levels increase in ARDS and sepsis and this increase precedes the development of hypoxia and shock but correlates with clinical severity [76, 77]. A 62-fold increase in PLA_2 has been recorded following trauma [78] and a 300-fold rise in sepsis with a significant correlation between decreasing P_aO_2/F_iO_2 ratio and increasing PLA_2 levels. PLA_2 may rise as part of a stress response to trauma and has an excess of substrate in cases of marrow fat release. C-reactive protein (CRP) rises dramatically in critical illness. It causes agglutination of chylomicrons and very low-density lipoproteins [79]. With a combination of bone marrow infarction, rising PLA_2 and CRP, FE may cause acute lung injury in some critically ill patients. This mechanism has been suggested in trauma patients (Fig. 1) [20, 71].

Treatment

Treatment is non-specific and supportive. Different approaches have been tried with varying success; however, the lack of universal diagnostic criteria and the small groups of patients studied make many of these trials difficult to interpret. Of paramount importance is the early resuscitation and stabilisation to minimise the stress response and hypovolaemia [71, 80].

The most common manifestation of FES is pulmonary dysfunction and for this reason any patient at risk should be closely monitored. The routine use of pulse oximetry may detect early hypoxaemia and allows prompt correction with controlled humidified oxygen therapy [81].
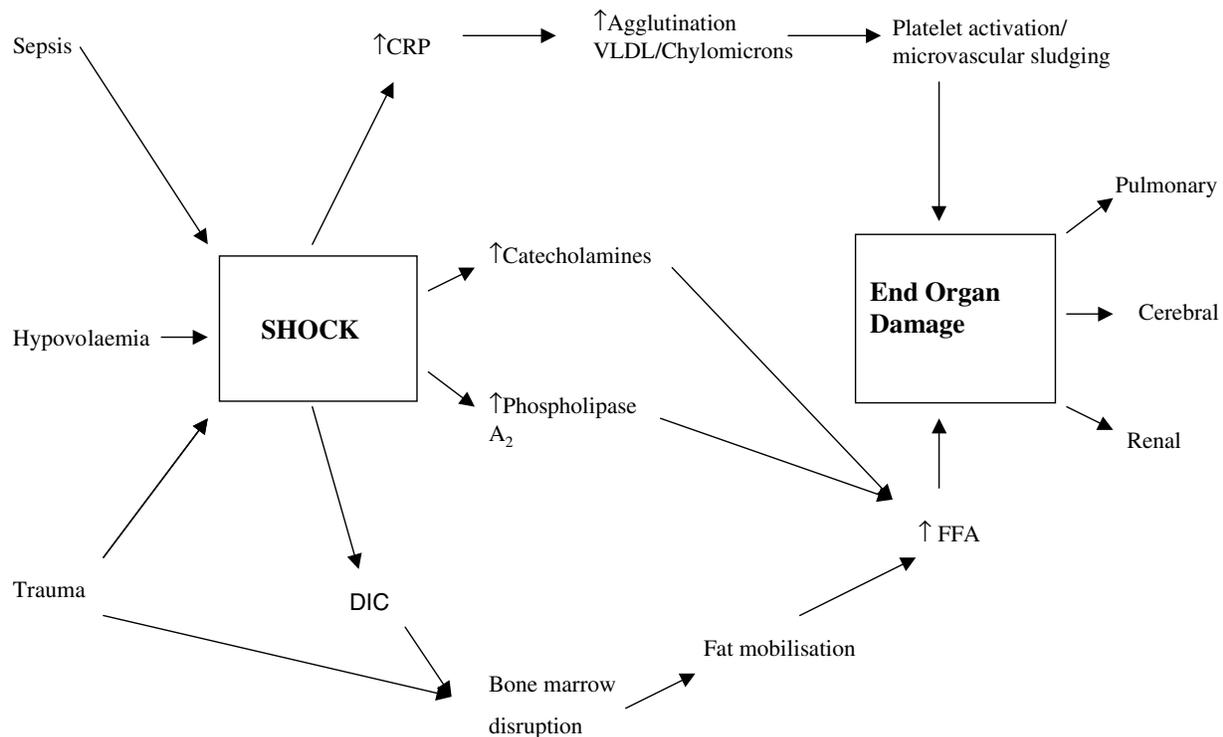
Figure 1 Proposed mechanisms of end organ damage in fat embolism. CRP, C-reactive protein; VLDL, very low-density lipoproteins; FFA, free fatty acids; DIC, disseminated intravascular coagulation.

Lindeque found that patients with a $P_aO_2 < 9.2$ kPa on admission were twice as likely to develop hypoxaemia [5]. Whether early administration of oxygen actually prevents the onset of the syndrome by preventing hypoxaemia, further catecholamine response and fat mobilisation remains unclear. Between 10 and 44% of patients require mechanical ventilation but the pulmonary dysfunction caused by FES usually resolves in 3–7 days [6, 7, 38].

Corticosteroids have been studied extensively in FE in both animal models and humans. In theory, there are many ways in which they could act to prevent the onset of FES. Possible beneficial effects include stabilisation of the pulmonary capillary membrane, thus reducing the leak that creates interstitial oedema, blunting the inflammatory response, stabilising complement system activation and retarding platelet aggregation [68]. Studies reporting beneficial effects [5, 31, 82, 83] used doses of methyl prednisolone between 9 mg.kg^{-1} and 90 mg.kg^{-1} (in divided doses). The results of these trials were impressive, with a 10-fold reduction of FES in one series; however, the only fatality reported in any of these trials was due to overwhelming sepsis in a patient receiving corticosteroids [30]. All these randomised controlled trials report significant decreases in FES, although only three [5, 30, 82] reported significantly improved gas exchange. The numbers of patients treated are small, ranging between 10

and 40 in the treatment groups, and factors including temperature and white cell count, which would be altered by corticosteroids themselves, were used as indicators of FES. On the contrary, other work suggests that methyl prednisolone does not modify pulmonary hypertension and prostenoid response [84]. Further work is required to elucidate the optimum timing of administration of corticosteroid therapy and most importantly its outcome.

Heparin is known to clear lipaemic serum by stimulating lipase activity and has been advocated for treatment of FES. However, the evidence for heparin treatment in FES is contradictory [85, 86]. If increases in FFAs are an important part of the pathogenesis of FES, then activation of lipase is a potentially dangerous therapeutic intervention. Furthermore, the risk of bleeding, even with low-dose heparin, cannot be ignored in patients with multiple injuries. Prevention of FFA mobilisation by providing adequate glucose has been used as a prophylactic strategy [87]. Alcohol decreases serum lipase activity. FES has been found to be less common in accident victims whose blood alcohol levels were greater than 0.03 g.dl^{-1} compared with those with blood levels < 0.02 g.dl^{-1} [32]. However, the relationship between blood alcohol levels, FFA levels and the development of FES may not be casual [88]. Aspirin has been recommended as a prophylactic agent as it prevents

gas exchange abnormalities [82]. Aspirin blocks the production of thromboxane which occurs in animal models of FE [64, 89]. Dextran has been rejected because of problems with coagulation and renal function. Aspirin, heparin and dextrans reduce the platelet adhesiveness and thus reduce the formation of microaggregates [74].

Surgical strategies for preventing FES

Surgical fixation of fractures increases intramedullary pressure and causes mobilisation of marrow fat [60]. The relationship between intramedullary pressure and FE has led to the development of specific strategies in trauma surgery [90]. External fixation or fixation with a plate produces less lung injury than intramedullary fixation [66]. After reaming, the pressure generated during nail insertion is similar to that produced by an unreamed nail but the incidence of FE has been shown to be lower when unreamed nails are used. The tools themselves may play a role as blunt reamers produce much higher pressures than sharp reamers [91] and hollow nails produce far lower pressures than solid ones [92]. Repeatedly pushing and pulling the reamer may also result in high-pressure peaks [93]. Ultrasonic reamers used in revision arthroplasty significantly increase the showers of emboli seen by TOE [94]. Venting the medullary canal reduces the emboli during the insertion of the femoral component of hip arthroplasty [95]. Intramedullary lavage has been shown to reduce the incidence of hypotension, pulmonary fat deposition and arachidonic acid metabolites if used prior to cement and prosthesis insertion [96]. Timing of the operative procedure appears to be important. Pulmonary complications are increased and hospital stay lengthened in patients with multiple injuries in whom fixation is delayed for more than 24 h [97–99]. However, early nailing may not be advantageous in patients with thoracic trauma as there may be increased lung injury with this approach [100].

Summary

Fat embolism is frequently found when actively sought but seldom produces all the classical clinical signs of respiratory failure, petechial rash and pyrexia. Additional factors such as hypoxaemia and catecholamine release may be required to produce FES, and fatty acid release resulting from bone marrow damage are only one aspect of an exaggerated inflammatory response. Despite the many therapeutic interventions tried, the only one proven in randomised controlled trials is corticosteroids but the currently available literature is inadequate to recommend corticosteroids for either treatment or prophylaxis. The cornerstone of treatment is preventing the stress response,

hypovolaemia and hypoxia and then operative stabilisation of fractures within 24 h in the absence of chest trauma. It may well be that with current advanced trauma life support guidelines on the early use of intravenous fluids, high-flow oxygen and analgesia, the incidence of FES has decreased. There are few prospective studies in the literature and more recent results from centres providing appropriate early resuscitative and surgical intervention are needed. Further studies are required to elucidate the role of FE in the genesis of acute lung injury and multiple organ failure in critical illness.

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