Part II: Respiratory Failure

Chapter 27: Fat Embolism

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Fat embolism is often a contributing cause of death in patients with multiple injuries. Although fat can be found in the lungs of almost all patients involved in major trauma, the clinical syndrome of fat embolism (FES) is found in approximately only 5% of such patients. In one report, 60% of major orthopaedic procedures have been associated with fat globules (of 7-14 microm diameter) passing to the lungs, but without development of the clinical syndrome. FES is more frequently seen in young adults, perhaps due to their predilection to motor trauma, and may be a contributing factor in the adult respiratory distress syndrome. It is less commonly seen in sporting injuries, children and elderly patients. FES may also be associated with systemic lupus erythematosus, pancreatitis, diabetes mellitus, rapid decompression, lymphography, poisoning, hepatic failure, hepatic trauma, sickle cell crisis (from marrow infarcts), extracorporeal circulation and intravenous lipid infusions; but in this group it is usually a post mortem histological finding rather than a clinical syndrome.

Aetiology

The aetiology of FES remains controversial, despite its recognition over 100 years ago and extensive research since. The temporal relationship with fractures is not in doubt. There is also no doubt that patients with FES have embolization of fat macroglobules into both the pulmonary and systemic circulations. However, many patients with long bone and pelvic fractures have embolization of fat, but without clinical evidence of the syndrome.

Source of Circulating Fat in Trauma

1. *Associated with bone fracture* (particularly pelvis or long bones of the leg), rupture of fragile medullary venous sinuses occurs, allowing intravasation of fat and marrow to join the venous return to the heart. Fracture haematoma may further increase intra-medullary pressure and facilitate the entry of fat into the sinusoids. Closed fractures have a higher incidence of FES than do open fractures. Tourniquets placed proximal to the fracture site may delay the passage of fat centrally.

2. *Massive trauma* may disrupt adiopose tissue (especially high velocity projectiles, explosion and extensive burns) causing the entry of large fat globules into the venous circulation. Liposuction has also been associated with fat embolism.

3. *Fat transported in the circulation* is usually emulsified and in the form of neutral triglycerides bound to albumin or low density lipoproteins. In the microscopic form of chylomicrons (of 1 microm in size), they are stable and a major calorie source. Following the stress of trauma, release of catecholamines and corticosteroids occurs, causing increased release of depot fat. Fat stores may be sufficiently mobilized for transport mechanisms to be overwhelmed, and the chylomicrons to become unstable and coalesce into larger (20 microm) particles which ultimately obstruct smaller capillaries. Calcium dependent C-reactive protein

may coalesce very-low-density lipoproteins (VLDL) and agglutinate chylomicrons into larger particles resulting in FES and pancreatitis.

Two main theories have been advanced as to the causative mechanism for fat embolisation.

1. Mechanical Theory

This proposes that there is simply a mechanical intraluminal obstruction of capillaries by blood-borne fat globules. It is postulated that not all fat globules are filtered out by the pulmonary circulation, but while in a semi-liquid state, pass through pulmonary capillaries, arteriovenous communications or a patent foramen ovale (present in up to 25% of population), eventually lodging in capillaries of the systemic circulation. Organs with high blood flow (i.e. brain, kidney and heart) often show histological evidence of capillary obstruction by fat.

2. Physiochemical Theory

It is proposed that there is a toxic effect of liberated free fatty acids (FFA) on body tissues. Patients with FES have been shown to have a lower albumin level and a higher lipoprotein lipase level in serum than patients who do not have the syndrome, suggesting the potential for endothelial tissue damage from a high level of free, non albumin-bound fatty acids. Pulmonary lipase can also break down neutral triglycerides into toxic unsaturated FFA.

Various reports have been submitted over the past 50 years supporting one or other theory. It seems likely that both mechanisms are involved to some degree. Experimentally, hypoxia and chemical pneumonitis can be produced by the injection of unemulsified fat (i.e. oleic acid). Radioactive carbon-labelled fat has been shown to pass from fracture sites through the pulmonary capillaries and into the systemic circulation.

Pathophysiology

Irrespective of the aetiology of FES, the main pathophysiological effects are due to blockage of pulmonary and systemic capillaries, either with fat alone, or with associated microaggregates of platelets, red cells and fibrin. It is likely that the pulmonary effects of FES occur in two phases, either of which may be sufficiently severe to result in patient death due to respiratory failure.

1. The firs phase is immediate in onset and associated with mechanical obstruction of pulmonary vessels (cf pulmonary thromboembolism). This may occur almost instantaneously, as in near instant death following aircraft disasters.

2. The second phase develops as the onset of a chemical pneumonitis. Endothelial inflammation of small capillaries is caused by breakdown of embolic fat globules into toxic FFA, and due to the release of serotonin and histamine from embolism aggregated platelets. The ensuing increased capillary permeability results in the extravasation of proteinaceous fluid and even intra-alveolar haemorrhage.

From both mechanisms, hypoxia follows due to ventilation/perfusion mismatch, shunting, diffusion impairment, congestive atelectasis, decreased compliance and an increased dead space/tidal volume ratio. Type II pneumocytes are inactivated by FFA and surfactant production is diminished. Coagulation abnormalities may occur (i.e. disseminated intravascular coagulation), although infrequently. Cerebral effects often persist (at least temporarily) despite the correction of hypoxaemia and in the absence of direct cranial trauma. Renal function is rarely impaired. Hypovolaemic shock exacerbates right heart failure in FES.

Diagnosis

There is no pathognomonic sign or test during life, but a high index of suspicion is helpful in diagnosing FES in a patient who has respiratory and mental state changes 1-2 days following bone-trauma. One major and three minor/laboratory features in Table 1 may be highly suggestive of FES following trauma.

1. Clinical Features

There is usually a history of fracture of lower limb long bones, patient transport with insufficient fracture immobilization, or occasionally, arthroplasty and use of methylmethacrylate. A latent period of 24-48 hours frequently ensues before the onset of signs and symptoms, which may then progress rapidly. Dyspnoea and tachypnoea then develop, with cyanosis, cough and production of frothy bloodstained sputum less often seen. Initially, hypoxaemia is often present in FES with few respiratory signs. Petechial rash of the upper thoprax, axillae, neck, soft palate and conjunctiva occurs in 25-50% of cases. A mild to moderate fever of 38-39 °C is often present (in about 60%) during the acute phase, with an associated tachycardia. Mental changes are frequently seen in systemic embolization and may be the first clinical features observed. They include confusion, drowsiness, decerebrate signs, convulsions and coma. Expanding subdural/epidural collection after head injuries must be urgently excluded, usually by cranial CT scanning. Delirium tremens should also be considered.

Fat globules ("cotton wool spots") and petechiae are occasionally seen on retinal examination. A fall in cardiac output and increase in pulmonary vascular resistance has been shown to precede hypoxaemia in experimental fat embolism. Fulminant FES may have an onset in minutes to hours and is associated with hypotension, marked hypoxaemia, and often a poor prognosis.

2. Laboratory Tests

(a) *Arterial blood gases* - (with the patient breathing air) reveal a low PaO_2 (35-50 mmHg, 4.7-6.7 kPa), low $OaCO_2$ and respiratory alkalosis (from hyperventilation).

The appearance of a low PaO_2 usually precedes the onset of other clinical manifestations - the value of monitoring PaO_2 in patients at risk is thus obvious. There is an increase in the alveolar-arterial oxygen gradient and pulmonary shunt fraction.

(b) *Urine* - may contain fat globules (shown by the "sizzle" test using a platinum loop) as also may sputum (when stained with oil red O or Sudan III, IV), but neither test is reliable.

(c) *Coagulation/haematological* - Increased fibrin degradation products, thrombocytopenia and coagulation abnormalities (fat may release thromboplastin) may be detected during the acute phase of FES, but are not diagnostic. Bleeding problems are infrequently seen. A mild anaemia, sometimes with haemolytic features (detected by falling serum haptoglobin levels) is seen with FES. Intrapulmonary haemorrhage may be significant.

(d) *The cryostat test* - (in which clotted blood is frozen, sectioned and stained for fat) may be of assistance in detecting fat macroglobules microscopically (i.e. greater than 8 microm in diameter).

(e) *Blood chemistry* - Falling serial serum calcium levels may reflect the activity of circulating unbound FFA (forming soaps). Levels of both triglycerides and FFA are usually elevated in response to trauma and are not specific to FES.

(f) *Cerebrospinal fluid* - may stain positive for fat but is inconsistently seen in FES.

(g) *Chest radiography* - may often show diffuse "fluffy" opacification of lung fields bilaterally, peripherally and basally. Oedema may be sufficiently confluent to produce a "snowstorm" effect. Radiographic changes usually lag well behind deterioration of arterial oxygen tension. Effusions are not a feature of FES.

(h) *Electrocardiographic* - examination may reveal evidence of right heart strain in cases of fulminant FES.

(i) *Biopsy* - of kidneys and skin petechiae has revealed microinfarcts in association with fat macroglobules.

(j) *Enzyme tests* - have been used (i.e. serum tributyrinase, lipoprotein lipase, but not pancreatic lipase). Although levels may be elevated in FES after 5-8 days when the clinical signs are beginning to resolve, they do not aid in diagnosis.

Major trauma without FES can cause many of the above findings. Laboratory tests are often too insensitive and non specific to be clinically useful. *The diagnosis essentially remains a clinical one.* Differential diagnoses to be considered include pulmonary thromboembolism, cardiac or pulmonary contusion, septic shock, hypervolaemia, intracranial injury, aspiration pneumonitis, adult respiratory distress syndrome and transfusion reaction.

Repeated arterial blood gas analysis over 48 hours in these patients is the single most valuable guide to diagnosis and therapy.

Management

In the past, a number of different drugs and methods of treatment have been tried, some in large clinical trials, but with inconclusive results. These have included *ethyl alcohol* (a lipase inhibitor and emulsifying agent, used as an intravenous infusion or by nebulization to protect surfactant); *clofibrate* (to increase FFA metabolism); *dextran, heparin and aspirin* (to decrease platelet adhesiveness and promote microvascular blood flow); use of *increased*

fluids (to decrease stress-associated catecholamine secretion and lipolysis); *fluid and salt restriction* (to decrease pulmonary extravascular water); systemic *corticosteroids* (to decrease permeability of damaged pulmonary capillaries, stabilise lysosome membranes and increase surfactant production); and *glucose and insulin* (as a nonlipid caloric source to avoid lipolysis). Heparin is also a lipoprotein lipace inducing agent, which hastens metabolism of intravascular lipids, but at the cost of forming more FFA which may further damage pulmonary capillary endothelium. Its use is controversial and probably best avoided. Trasylol (aprotinin) has not been found useful.

FES is a self-limiting disease and therapy is mostly suportive, with an emphasis on the maintenance of oxygen delivery to peripheral tissues. Management at present follows these guidelines:

1. Oxygen by Facemask

The arterial PaO_2 is checked at least daily for 5 days in patients at risk of FES. This test is the most sensitive index of FES effects on the lung and is gauging therapeutic responses. The supplemental flow of oxygen is altered accordingly. Continuous positive airway pressure (CPAP) via a facemask may alleviate the hypoxaemia further. If the arterial PaO_2 cannot be maintained above 60 mmHg (8.0 kPa) or if there is evidence of respiratory distress, hypercarbia and exhaustion, then mechanical ventilatory support is instituted.

2. Mechanical Ventilatory Support

Mechanical ventilation, preferably volume controlled, is along the usual lines. The inspired oxygen concentration should, if possible, be kept below 60%. Positive end expiratory pressure (PEEP) is sometimes required to obtained a satisfactory arterial PaO_2.

3. Adequate Circulating Volume

Adequate circulating volume must be ensured during the acute phase of FES following trauma (i.e. with colloid or red cell replacement). Untreated shock is associated with a poorer prognosis in FES. Blood and fluid loss at the fracture site is often underestimated. If clinical signs of FES develop and cardiovascular stability can be maintained, if necessary with inotrope support, then the judicious use of (a) fluid restriction, (b) diuretics, may improve blood oxygenation by decreasing pulmonary extravascular water. Valuable guidance as to the adequacy of therapy may be gained by monitoring central venous pressure and pulmonary capillary wedged pressure.

4. Aspirin, Dextran, Mini-dose Heparin

There is some evidence that these agents may be of limited benefit in decreasing platelet adhesiveness and formation of fibrin-fat emboli aggregates, but they are not used routinely. Their use may exacerbate bleed from sites of recent trauma.

5. Steroids

The use of steroids remain controversial. However, evidence of the beneficial effect of large doses of steroids (i.e. methylprednisolone 30 mg/kg/8 h for 3 doses), and lower doses of steroids has been produced both in the clinical setting and in experimental situations. Following steroid therapy, hypoxaemia may often be diminished. It is probably more effective if given prior to onset of the features of FES. Large clinical trials of steroid usage in FES therapy are few as yet.

Most cases of fat embolism recover merely with salt and water restriction, diuretics and oxygen. Resolution of clinical features usually occurs over 2-3 weeks. An early, and if necessary, aggressive approach is required for treating marked hypoxaemia, with oxygen, CPAP and mechanical ventilation. Other complications such as coma, coagulation problems and cardiac failure must be treated supportively as required. Death is more likely to occur due to respiratory failure than cerebral, renal or cardiac sequelae. Other than for the most fulminant cases, the prognosis is very good with no residual respiratory or cerebral impairment.

Prophylaxis of Fat Embolism

There is convincing evidence that the incidence of FES can be markedly reduced by adequate immobilization of fractures prior to patient transport and the early operative fixation of long bone fractures. The severity of the clinical syndrome may be reduced by prophylactic use of oxygen and avoidance of hypoxaemia. Repeated arterial blood gas analysis over the first 48 hours in these patients is the single most valuable guide to diagnosis and therapy.