Acute systemic inflammation in health and disease

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CHAPTER 3

FAT EMBOLISM AND PATENT FORAMEN OVALE

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INTRODUCTION
Fat is an integral constituent of the soft tissues and the bone marrow. After skeletal trauma, bone marrow emboli can rapidly enter the circulation. Especially long bone fractures are known to generate circulating, abnormally large fat globules that sometimes have diameters>10 µm, in contrast to the normal fat that circulates in the form of small lipoproteins [1].

Acute massive fat embolism
As forensic physicians know, a dead person with multiple fractures found three floors below an open window should have his lungs examined. If fat emboli are present in his lung he was still alive at the moment he hit the ground. However, if no fat emboli or marrow emboli are present he may have been dead before he fell, and thus may have been murdered [1]. The sometimes hyperacute nature of this embolization process is illustrated by a large post-mortem study done on aircraft accident victims. In 1979 a New Zealand jetliner crashed into Mount Erebus on Antarctica, killing all persons aboard. Detailed post-mortem analysis [2] in 205 of the 257 victims showed that despite an nearly instantaneous death, many had fat emboli (65%) and bone marrow emboli (29%) in their pulmonary capillary beds.
In a different study of 56 patients who died within 24 hours of blunt injury (including long bone fractures) 68% had significant pulmonary fat emboli upon post-mortem examination [3]. Acute massive fat embolism, as described above, should not be confused with classic fat embolism syndrome (FES) as defined below.

Classic fat embolism syndrome (FES)
Some trauma patients can develop the fat embolism syndrome (FES). The classical fat embolism syndrome is generally defined by three major symptoms that occur with a delayed onset of hours to days after the trauma [4]:
• A petechial rash on the anterior chest, face, axillae, conjunctivae and other non-dependent parts in general.
• Respiratory distress with diffuse bilateral abnormalities on the chest X-ray.
• Cerebral disturbances varying from mild to coma.
In addition to these three major criteria aspecific minor signs are usually observed, the most important being fever, tachycardia and thrombocytopenia.
Whereas acute massive fat embolism is often diagnosed post-mortem in very severely injured patients who rapidly succumb, patients with FES will usually survive. Apart from severity, the crucial difference between these two entities is the delayed onset that is seen in FES. In apparently similar patients with long bone fractures, only a minority will actually develop FES after the symptom-free period.
Two central problems in FES-research are:
• What is the precise origin and what are the effects of abnormal circulating fat that is observed in most patients after trauma?
Why does only a minority develop FES?

*Origin of circulating fat*

Two main theories on the genesis of circulating fat emboli exist: the mechanical and the chemical theory [1,4]. The mechanical theory explains the strong association between long bone fractures and FES through the entrance of bone marrow fat into the circulation. The chemical theory [5,6] is inspired by observations that fat emboli can occur in patients who have no trauma, such as patients treated by steroids or patients with sickle cell disease [7]. Also some biochemical changes can lead to the agglutination of fat and fat emboli, as has been observed in the early days of total parenteral nutrition [8]. The acute phase protein CRP can agglutinate fat - a property that has even been used for a new rapid bedside CRP-assay [9].

Although the mechanical theory is now the most popular, the mechanical and chemical models are not mutually exclusive and may act in concert. The mechanical theory may not only involve fat embolization from the bones, but also from the soft tissues, as confirmed in a recent study [3].

*Predisposing factors for FES*

It has proven very difficult to predict who will develop FES. Many investigators have wondered why FES only occurs in a minority of apparently similar patients. In a previous study we identified delayed stabilization of femoral fractures and early development of fever as a risk factors for the development of FES [10]. When venous fat particles reach the arterial circulation, the lungs must have been (by)passed somehow. In addition to exchanging oxygen and carbon dioxide with the surroundings, the lung has an important filtering function. The lungs continuously interact with and filter many particles that would otherwise enter the systemic arterial circulation. This includes thrombo-emboli, bone marrow emboli, air emboli and tumor emboli.

The most prevalent occurring right-to-left shunt at the level of the heart is the patent foramen ovale. The presence of a patent foramen ovale (PFO) as detected by echocardiography is strongly increased in young patients who sustained ischaemic stroke [11,12] and divers who developed decompression sickness [13]. By analogy, it could be hypothesized that a patent foramen ovale might allow entry of fat globules into the systemic circulation. Might patients with a history of post-traumatic fat embolism have a patent foramen ovale? We investigated the presence of PFO by echocardiography in patients who developed FES after sustaining isolated skeletal trauma.
PATIENTS AND METHODS
We selected otherwise healthy patients with a history of fat embolism syndrome after isolated long-bone fractures. Of all trauma patients with isolated fractures of the long extremities that were seen at our hospital between 1968 and 1985, 12 met this condition. In a retrospective series of 172 patients with an isolated femoral fracture admitted to our hospital between 6 developed FES [10]. An additional 6 patients with FES were identified after screening patients with tibial, combined tibial and femoral or bilateral femoral fractures without significant additional injury [4]. To detect the presence of PFO, transesophageal color-coded Doppler echocardiography with a Toshiba 65A 3.75 MHz transducer was performed as an outpatient procedure. The Valsalva maneuver was performed during echocardiography to maximize the sensitivity for detecting a shunt across a patent foramen ovale.

Table 3.1.

| Patients who developed FES and were later investigated by trans-esophageal echocardiography. |
|---------------------------------|---------------------------------|
| Male/Female                     | 5/1                             |
| Mean Age (+/-SD)                | 24 +/- 11                       |
| Tibial fracture                 | 1                               |
| Isolated femoral fracture       | 4                               |
| Bilateral femoral fracture      | 1                               |

RESULTS
Of the total of 12 patients with diagnosed FES, 6 patients (Table 3.1) volunteered to undergo echocardiography. Echocardiography was performed without complications, and resulted in adequate imaging of the atria in all cases. In 5 patients no right-to-left shunt was present. 1 patient had a minute right-to-left shunt during the Valsalva maneuver. This short-lasting and barely detectable shunt was of no pathophysiological significance.

DISCUSSION
The fact that no patients in our series had relevant right-to-left shunting as measured with a sensitive technique [14], contrasts with the reported frequencies of PFO in patients who sustained idiopathic ischaemic stroke and serious air embolism (50% and 61% respectively) [11-13]. Whereas PFO obviously is of major importance in stroke and air embolism, the absence of a relevant foramen ovale in the patients we studied makes it unlikely that the presence PFO has a causal role in the development of FES. Although our series of FES patients is small, the observed incidence of 0 out of 6 makes PFO very unlikely as a necessary factor for the development of FES. It is no surprise that we found no relevant PFO in patients who had well-defined FES. In fact an important role of PFO in the pathogenesis of FES has long ago already been proposed and challenged [1]. In post-mortem investigations in seven patients who died with FES, Sevitt found no PFO in any of the patients [15]. With the availability of trans-esophageal echocardiography, assessing PFO after FES was a logical step. Our study is the first that confirms this observation in patients who are still alive (long) after recovering from FES.
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Another argument against a causal role of PFO in FES is the presence of circulating fat globules in the majority of trauma patients [16], while the population incidence of PFO is below 50% even when measured according to the most sensitive criteria. Thus systemically circulating fat is present regardless of a PFO. The fat emboli somehow (repeatedly) pass the lungs. Possibly the fat emboli deform to pass the lungs' capillaries (Fig 3.1). In the majority of patients with skeletal injury fat excretion in the urine can be shown according to some investigators [17], underscoring the ease with which fat globules reach the systemic circulation, and pass the glomerular filter as well.

Pell's case report in 1993
The discussion of the relevance of PFO would probably have been closed, had not a paper on this subject appeared in the New England Journal Medicine [18]. The editorial [19] accompanying this brief report was even optimistically titled "Unravelling the fat embolism syndrome". In their paper Pell and colleagues suggested a major role of PFO in the pathogenesis of FES on the basis of a report on a single patient who died shortly after intramedullary nailing of a femoral shaft fracture. Transesophageal echocardiography was performed during the operation. Showers of echogenic masses were seen passing through the right heart. Even a lump of 7 cm was seen. Material was seen passing through a PFO. The fatal outcome the authors vividly describe is one of acute cor pulmonale with secondary paradoxical embolism. The floating objects imaged by transesophageal echocardiography, must have been large thrombi or bone marrow fragments. Finally, the patient described was not previously healthy, and he did not display the characteristic symptom-free interval.

The case report by Pell illustrates the devastating consequences of acute cor pulmonale in patients who often are already in a compromised cardiopulmonary condition. Unfortunately, the patient described in the case report in the New England Journal of Medicine did not have typical FES. Contrary to what might be inferred from the report's title, this patient did in all likelihood not die from FES or from PFO, and he certainly did not show the classic picture of FES. Whereas the genesis of FES is not understood, acute right heart failure in patients where embolic material is dislodged during operative procedures is well-known and well-understood. In fact today more patients may die from this form of acute pulmonary embolism than patients who die from the classical FES.

Pell later published a series of 24 patients who were monitored with TEE per-operatively [20]: small emboli were observed in 14 patients; in 6 patients moderately large emboli (up to 10 mm) and in 4 patients large emboli >10mm were observed. The dimensions of the observed emboli underscore that 70mm is very large indeed for an embolic 'lump' as was described in the case report [17].

Animal models of FES
One of the difficulties in investigating FES is finding an appropriate animal model. A correct animal model should include a trauma or at least a simulation of the effects of trauma, a subsequent interval that is relatively free of signs that is later followed by organ manifestations of fat emboli in affected organs. Despite the fact that many animal experiments designed to model
Fat embolism and patent foramen ovale

Fat embolism have been carried out, no model reproduces the events observed in humans. Either the animals rapidly succumbed from traumatic shock [21], or immediate pulmonary edema was induced by fatty acid injury [22,23], or unrealistically massive neutral fat infusions resulted in obstructive shock [24]. None of the models reproduce the intriguing 'incubation period' that is observed in classical FES.

Decreasing incidence of FES

Although FES undoubtedly remains a real entity [25], the incidence of clinically manifest FES has decreased to such extent that many clinicians have never seen a patient with the classical FES. Probably a combination of changes in modern management of trauma patients has contributed to this decrease [26]. Except for the more rapid stabilization of fractures [27] it is not clear which other changes have been decisive in reducing the incidence of FES. Potential factors are: more aggressive fluid infusions, early application of positive end-expiratory pressure (PEEP) or the routine early administration of low-molecular weight heparins. Although this decreased incidence of manifest FES may be good news, observational studies into the causes of FES are hampered by the low incidence of the syndrome. Thus it may be wise to direct research efforts to detect subclinical FES, for example with modern imaging tools.

Imaging in FES

In a further advance in real-time monitoring of embolic events, Edmonds recently reported on the use of transcranial Doppler to detect fat or air emboli during total hip arthroplasty [28]. Embolic signals in the middle cerebral artery were found in 8 of the 20 patients that were monitored. The number of embolic signals in these patients varied from 1 to 200 - in all cases coinciding with the impaction of a cemented component or after hip relocation. Another useful application of real-time imaging is the use of peroperative TEE to compare two different techniques of artificial hip fixation for their potential to generate emboli.

Whereas conventional cementing generated emboli in 95% of the patients, a new 'bone vacuum' technique resulted in only 5% emboli [30]. Such studies have also shown that patients with pre-existing disease are especially prone for complications from iatrogenic emboli. CT-scans of the lungs have shown that the radiological picture of FES [31] differs from acute pulmonary edema or ARDS. CT-scanning and magnetic resonance imaging of the brain has shown lesions caused by cerebral FES [32], indicating that although patients survive FES, it is may leave permanent defects.
CONCLUSION
The pathogenesis of FES is still not understood, but patent foramen ovale is unlikely to be relevant in FES. Early inflammatory responses and especially timing of the operation are probably important in FES, although the mechanisms are not clear. Investigating FES in its isolated form in patients with solitary long bone injuries has become more difficult due to the decreased incidence of FES.

Figure 3.1 Illustration from Zenker [29] showing a fat droplet deformed into sausage shape at the upper right of the capillary bed.

Nowadays, it may be more relevant and fruitful to study subclinical fat embolism or fat embolism in patients with multiple injuries where the classical manifestations of FES will be overshadowed by the effects of the injuries. Such an approach will probably benefit from new sensitive techniques that can determine the behavior of fat emboli.
REFERENCES


