REVIEW ARTICLE

FAT EMBOLISM: A REVIEW FOR CURRENT ORTHOPAEDICS PRACTICE

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SUMMARY

Fat embolism (FE) is the occlusion of small blood vessels by fat droplets originated mainly from femur, tibia and pelvis fractures, as well as from knee and hip arthroplasty. It usually does not cause damage to the involved organs, unless when it is massive. In a few cases, FE evolves to the 'fat embolism syndrome' (FES), affecting most often the lungs and the brain, although any organ or structure of the body can be damaged.

Fat embolisms are hydrolyzed by lipase, forming free fatty acids (FFA), which cause a toxic effect to capillary endothelium, intensifying integrins activity, which, in turn, intensify neutrophils' adherence to endothelial cells, making easier the activity of the proteolytic enzymes of such neutrophils' lysosomes on the endothelium.

The result of those reactions is the capillary meshwork rupture, followed by hemorrhage and edema on affected organs. The FES presents many conditions, ranging from respiratory failure and variable neurological changes, to convulsions and deep coma. The diagnosis of FES is essentially made on clinical basis only, since there are no laboratory tests to validate it. Among imaging tests, only brain magnetic resonance clearly shows the perivascular edema and infarction areas.

FE treatment with uncountable drugs did not present positive results; however, the most required measure to FES is mechanical ventilation. Mortality rate is almost 100% in fulminant forms; approximately 20% in the sub acute forms, and there is no mortality in a sub clinical form.

In order to prevent FES is crucial to avoid shock and hypoxia from the accident scenery, and to proceed to the early fixation of fractures, which reduces the incidence of SARA and post-trauma mortality.

Keywords: Embolism, fat; Arthroplasty; Fractures.

INTRODUCTION

In this review of the "Fat Embolism" phenomenon, we could see that this subject not only still presents relevant obscure points, but also, for being multidisciplinary, has been causing controversies in virtually all specialties of medicine. This is due to the fact that fat emboli, although initially spread through venous flow, mostly affecting the lungs, in many cases may pass through pulmonary capillaries[1-3] or even through the inter-atrial septum[4-6] , and, through arterial path, potentially affecting any organ or structure of the body. Thus, we intend to synthesize here both basic and relevant knowledge and information revealed by the most recent clinical and laboratory researches. Also seemed to us as pertinent and useful, however, to not only reproduce those new pieces of information, but also to comment and discuss them upon previous evidences.

Firstly, we found interesting to highlight the definitions of the two nosologic entities that, although closely related, have completely different clinical and pathological meanings: the "Fat Embolism" (FE) and the "Fat Embolism Syndrome" (FES).

The "Fat Embolism" is defined as the occurrence of a mechanical blockage of vascular light caused by circulating droplets of fat with diameters exceeding 8 to 10u, usually getting trapped in the capillary meshwork. In addition to fat, those emboli also often carry hematopoietic cell of the bone marrow, which confirms its origin[7-11]. Because the FE is initially a venous phenomenon, it is natural and expected that lungs are not only their first target, but also the most affected organs. This, indeed, is what happens most of the time. However, there are some mechanisms by which fat emboli can damage other organs, as severely as the lungs, but via arterial flow: 1st) Through anatomical pulmonary arteriovenous micro fistulas. According to Goslling et al.[12,13], glass spheres with a diameter 20 to 40 times larger than pulmonary capillary reach the systemic flow after passing by those fistulas. 2nd) Through deformation of the fat droplet itself, which, by taking a more elongated form, would manage to pass through pulmonary capillaries[3]. 3rd) Through the inter-atrial septum, by the "Oval Foramen". Recent studies using the transesophageal echocardiography (TE-ECO), have demonstrated that in about 20 to 34% of adult individuals from a normal population, this foramen is patent[6,8,14-17]. It was also noticed that, even in individuals in whom this foramen was closed, it could be opened by the occurrence of acute pulmonary hypertension such as those that may occur in a massive FE[5,6,8]. In arterial-path FE, the mostly affected organs are the brain[1,2,5,6,18-21], skin (petechiae), and retina[13,19,20,22-25]. In thorough autopsies of car accident victims, however, fat emboli are also frequently found in kidneys, spleen, liver, adrenals, and myocardium[20,24-27]. Regarding this matter, it is necessary to emphasize that despite of the large number of patients affected by episodes of post-trauma per-operative massive fat embolism, only a little portion of them will develop clinical manifestations of major or minor severity (Table 1).

The "Fat Embolism Syndrome" (FES) is defined as the occurrence of injury and dysfunction of one or more organs, caused by fat emboli, that is, this is a complication or a non-typical evolution of FE. Organs compromised by FES are, thus, the same organs affected by FE. As lungs and brain are the visci mostly affected, the main clinical manifestations are the acute respiratory failure (with characteristics of the Adult Respiratory Distress Syndrome - ARDS) and cerebral damage, which may range from a simple anxiety to irreversible coma and death[28]. FES is a relatively rare, but extremely severe condition, with mortality rates ranging from 10 to 36%[18,29-32], most of the cases occurring in orthopaedic patients[8,16,20,22,24,32].

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ETIPATHOGENY

The main causes of FE and, consequently, of FES, are femoral, tibial, and pelvic metaphyseal fractures (Table 1). In current clinical practice, however, FE and FES cases are also often during or after knee and hip arthroplasties (Table 1), as well as in spinal procedures, moreover when pedicular screws are used[33]. More recently, a greater importance has been given also to the FE derived from severe traumas of the subcutaneous tissue, as can happen in extensive detaching injuries, as well as in soft parts closed traumas (falls and spanking), which can progress to FES, even resulting in life threat[2,8,35,36,44]. In an autopsy-based study, performed in 53 cases of death caused by spanking (only four of them had fractures), Hiss et al.[34] concluded that the cause of death was massive FE in 32 cases (60%) and only in 28% of them (15 cases, death was due to internal hemorrhage. By these findings, the authors not only called the attention to the frequency and severity of the FE in cases of spanking, but also emphasized the idea that the FE cannot be found only in post-trauma autopsy when death occurs at the accident site or within up to 4 hours later. The incidence of post-trauma FE, however, varies a lot among published experience, probably due to this "time factor", as well as to the appreciation made regarding the FE degree found in autopsies. According to Masson et al.[37], in 93% of the autopsies of soldiers who died in the War of Korea (1951-52), some degree of FE was found, although this was not necessarily the cause of death in all of those people. In the research by Mudd et al.[35], the occurrence of FE in autopsies performed after severe trauma was of 68%. Capan et al.[22], in their extensive and recent review, noticed that the FE had been detected in up to 95% of deaths caused by trauma with long-bone and/or hip fractures. Estébe[8], in another large and recent literature review, noticed that the FE finding in autopsies of trauma-related deaths ranged from 40 to 100% (average = 80%). On the other hand, Saldeen et al.[36] reported that FE was also found in about 30% of autopsies of non-traumatic deaths, although emboli here occurred in a lower amount and never massively as in FES cases. This issue will be discussed later in "Physiopathology" section, but we can advance that, in those cases, fat emboli are formed in the plasma itself due to hormonal changes that follow "stress situations", such as extensive surgeries, for instance. It is important to note here that FE detection upon autopsy not always means that this was the cause of death. In the vast majority of cases of "stress situations" mentioned above, the cause of death was well defined and the FE was only an incidental and little significant finding[8,22,26,32,34].

Although FES usually occurs, especially after long-bone and hip fractures in high-energy trauma[8,22,32,36,38], severe and even fatal FES cases have also been described, although rarely, after relatively mild trauma that caused humeral, ankle, vertebral body, ribs, and sternum fracture[8,38-40]. Indeed, it is worthy to emphasize that even external cardiac massage creates reasonable degrees of FE, which was detected in 40 to 85% of autopsied cases[8,35]. Other milder orthopaedic procedures, such as the manipulation of Wagner's stretcher, for example, have already caused fatal FES[13]. Similarly, here in our Service, we had the opportunity to see two cases of severe FES after a simple injection of medullary aspirate in a pseudoarthrosis focus. Recently, FES was described even after aesthetic procedures, such as liposuction[41,42] and perinasal autologous fat injection[43], but in a very limited number of cases. Despite of the extensive trauma caused by liposuction cannula, the resulting FE is almost always little when compared to that occurring after fractures. The reason for this difference is that, in the bone, venules and sinusoids, for having their walls attached to bone trabecules, tend to remain opened after being ruptured, while in subcutaneous tissue those vessels tend to collabate, which makes embolization difficult[8,44,45]. On the other hand, whereas in fractures and arthroplasties fat emboli are originated from medullary channel fat, in soft parts traumas they come, as expected, from subcutaneous fat itself. From the biochemical point of view, however, both medullary fat cells and subcutaneous tissue fat present the same kind of fat, the so-called "neutral" fat[5,6,8,16,22,46]. It would be still important to highlight that, in FE, fat emboli are not formed by macro- or microscopic fragments of adipose tissue, but by neutral fat droplets of numerous diameters, but still measured in microns, which remain in suspension in the blood until they occlude arterioles and capillaries of the lung and other organs. On the other hand, it is not rare that hematic thrombi are also formed, as it may occur after any severe trauma or major surgery. In case of femur, tibia, and hip fractures, mainly, the formation of combined thrombi is common, and they are composed by fat, platelet and red-blood cells. In cases of arthroplasties, embolizations of microfragments of bone, bone marrow, air, and acrylic cement were described[7,11]. However, none of those phenomena is related to FES development, which, as we will see, is triggered by the action of fatty acids following hydrolysis of embolic fat.

CLINICAL STATUS	FE	FES
FRACTURES (Femur, Tibia, Pelvis)		
-SINGLE	> 90%	0.05 to 3%[43,65,88]
-MULTIPLE	100%	0.25 to 30%[24,33,65]
ARTHROPLASTIES:		
- KNEE	100%	0.10 to 12%[28,85,86,91]
- HIP	100%	0.6 to 10%[28,85,86,91]
PEDICULAR SCREWS:	80%	- 0 -[102]

Table 1-: *Causes of FE and FES most commonly seen.*

Finally, we must explain that although FE and FES predominantly occur in orthopaedic patients[8,16,22,32], there is a wide range of clinical situations in which they may spontaneously manifest, that is, independently of external or surgical trauma. Although rare events, the following possibilities cannot be left out of mention: septicemia, intralipid infusion, falciform anemia crisis, pancreatitis, diabetes, hepatic steatosis, long-lasting corticoid therapy, extensive burns, sudden atmospheric decompression, massive blood transfusion, bone marrow transplant, kidney transplant, extra-body flow, intramedullary bone neoplasia rising pressure inside this channel[8,16,22,32].

The first fact calling our attention in this table is that virtually all patients with long-bone or hip fractures, as well as in those submitted to knee or hip arthroplasties, fat embolisms occur. On the other hand, it is similarly notorious that in only a small percentage of them, FE evolves to FES. The reason for this, however, is still unclear, that is: "why so much FE and so little FES?" Another fact calling much attention in this table is the huge variation on the incidence of FES among different authors: 0.25 to 30% of FES in multiple fractures, for instance. As we will see later in this paper, it seems that the best explanation for those discrepancies is the use of different criteria for diagnosing this syndrome.

PHYSIOPATHOLOGY

Although FES genesis is an extremely complex phenomenon, its development can be considered as if two distinct phases occur, yet interconnected: the first would be the "Mechanical Phase", and the second would be the "Biochemical Phase" [1,2,8,22,25,46,47].

"Mechanical Phase":

This is the phase in which fat emboli (neutral fat droplets) enter in venous flow and become lodged in pulmonary capillaries. The amount of emboli is much variable, depending on trauma energy and extension, on the involved bone, on the kind of fracture (open fractures cause less FE) and on orthopaedic procedures used (reaming, screws and prosthesis). As mentioned before, the vast majority of patients subjected to FE do not present severe symptoms, despite the intense emboli, because in those patients, the effect is only mechanical, that is, the simple temporary occlusion of part of the pulmonary capillary meshwork[5-7,11,27,48,49]. On the

other hand, if FE is massive enough to occlude about 80% of the pulmonary capillary meshwork[13] there will be a great increase of pulmonary artery pressure and, as a result, right ventriculum acute failure (acute "cor-pulmonale"), with a rapid progression to death[1,2,5,10,15,49,50]. This may happen in a healthy young individual, while in an elderly patient and/or with a lower cardiopulmonary reserve, the "cor-pulmonale" probably arises after much less extensive embolisms[1,2,11,48]. Clinical end experimental studies widely demonstrated that fat emboli arise in pulmonary capillaries few seconds after a fracture or medullary channel manipulation[22,32]. Recently, with the use of the trans-operative ET-ECO, it was seen that even slight touches of hammer or chisel in a bone diaphysis are no longer enough to create low degrees of FE. The primary cause of all bone-sourced FE is the sudden increase seen in the pressure inside the medullary channel, that is, the intramedullary pressure (IMP). When an individual is submitted to a high-energy trauma, a great dynamic deformity of the bone, and, consequently, a great IMP rise occur just before fracture(18). At that moment, bone marrow vessels also disrupt, as well as their adipose cells, from which a great amount of fat droplets result and will be embolized through medullary channel's venules and sinusoids. Sinusoids seem to be more likely to receive the emboli because, as they have walls attached to bone trabecules, they remain always open and do not collapse as venules do[8,45,51]. IMP measurements in human beings under anesthesia show normal values ranging from 30 to 50 mmHg[16,51]. It is known, however, that with IMP values just between 50 and 100 mmHg, FE may occur[8,9]. Although long-bone and hip fractures are the main causes of FE and FES, recent studies using the trans-operative ET-ECO have demonstrated that any and all surgical manipulation of the medullary channel is followed by FE, of a major or minor degree, which can or cannot progress to FES[4-6,15,33]. The FE intensity depends on the surgical maneuver in concern: reaming, nailing, or the introduction of knee or hip prosthesis, with or without cementation. By the ET-ECO we can see that when there is no medullary channel manipulation, heart chambers appear filled only with blood. With the beginning of reaming, however, hyperechoic signs are shown, which causes an image comparable to a "snow storm", while during cementation, both atrium and right ventriculum become totally opacified by fat emboli[5,6,14,15,33]. Very recently, it was verified also by trans-operative ET-ECO, that even a simple insertion of pedicular screws on spine operations provoked FE of an intensity comparable to that seen during the insertion of knee and hip prosthesis, although in that pioneer study, effects as deleterious as those seen in arthroplasties had not occurred[33]. The simple reaming of the medullary channel may cause great rises in IMP, which can reach values up to 650 mmHg[9]. Still in that study, the authors verified that with an IMP higher than 150 mmHg, the intensity of the FE was ten times stronger than when IMP was lower than 150 mmHg. As a result, in all patients submitted to medullary channel reaming, FE occurs in this phase of the surgery[7,48,50,52,53]. In experimental conditions, they could also see that the degree of FE resulting from reaming was even higher than that caused by the fracture itself[52]. From the pulmonary function point of view (shunt and PaO2 measurements), however, this degree of FE did not manage to promote relevant changes[7,9,50]. If, from one side, fractures fixation with plates virtually do not cause FE, since it does not require medullary channel manipulation, fixations with intramedullary nails are an important cause of FE[8,9,16,51,54,55]. Although FE occurring during reaming is usually of low intensity, during the insertion of a medullary screw, however, strong FE occurs in up to 87% of the cases[16]. This fact, although already recognized, was also recently proved by ET-ECO[7]. Thus, considering that in the rest of surgery (intramedullary screw or prosthesis) an intense FE will certainly occur, the majority of authors have recommended the use of 'threaded' or 'grooved' reams ("fluted rods") that avoid significant increases of IMP, and, therefore, a less amount of emboli in this surgery phase[8,9,16,51,54,55].

Indeed, intra-operative IMP measurements(9,48,55), as well as the use of ET-ECO[1,2,7,11,14,15,56] have allowed the verification that massive and long-lasting episodes of fat embolism occur especially during insertion and cementation phase of knee or hips prosthesis in all cases studied[1,2,9-11,48,53,57]. During prosthesis cementation, IMP can reach values of 650 to 1500 mmHg[7-9] and the embolization may last for more than 20 min[5,6,15,33]. Although, fortunately, the vast majority of those patients do not really develop acute 'cor-pulmonale' during the most intense phase of the FE, they always present deep hemodynamic and respiratory changes during this period, such as: severe arterial hypertension, cardiac arrhythmia, increased pulmonary artery pressure and pulmonary vascular resistance, pulmonary arterial-venous shunt increase, and, consequently, a reduction on PaO2[6,7,9,15,17,30,99]. Those effects may last just for a few minutes, or may remain for many hours post-operatively[5-7,55,58]. It is also interesting to note that those cardiopulmonary changes vary according to the intensity of embolism images showed by the ET-ECO[5,6,14,59]. In terms of morbidity-mortality, there are many evidences that cemented prosthesis are those offering the highest risks of massive per-operative FE and severe FES post-operatively[1,2,7,11,17,46,48,53,58]. Nevertheless, non-cemented prosthesis, for causing a very little rise of IMP, are rarely accompanied by major FE and, consequently, they cause much less cardiorespiratory changes and FES[9,11,17,48,53,60]. In a well-controlled clinical study, Ries et al.[48] observed that in their nine cases of cemented prosthesis, interpulmonary shunt increased 28% in average, whereas in the 23 cases of non-cemented prosthesis, there were no significant changes on that parameter. In the experiment by Pitto et al.[11], shunt changes were 24% and 2%, respectively, for both kinds of prosthesis. Experimental studies in dogs(61), as well as the pre-operative monitoring with ET-ECO allowed to show that in the insertion of cemented hip prosthesis, FE is not only greater but also much longer-lasting that that seen with non-cemented prosthesis[7,11,27,48,49,53,61]. Experiments 'in vitro' allowed to observe that, in the insertion of cemented prosthesis, the 'IMP' could reach values of up to 3190 mmHg, while in the insertion of non-cemented nails, the 'IMP' reached, at most, 125 mmHg[11]. If we consider that the higher the IMP the stronger the intensity of the FE detected by ET-ECO, as well as the greater the amount of fat found in blood collected at the femoral vein on the operated side[16,27,39], we can expect that exactly during prosthesis cementation phase the most intense cardiorespiratory changes occur, which indeed happens. In referred literature, there are numerous reports of heart attacks and/or deaths secondary to FE in arthroplasties intra-operative period, noticing that patients' decompensation has always been initiated at the moment of prosthesis cementation[8,10,11,19,48,53]. Woo et al.[49] by reviewing cases of hip total arthroplasty (HTA) in many centers and by analyzing case series ranging from 400 to 2012 surgeries, found an incidence of intra-operative heart attack of 0.6 to 10%, and a mortality rate of 0.02 to 0.5%. Pitto et al.[11], in their review, noticed that, in a group of 14469 HTA cases with cement, 23 (0.16%) deaths occurred, while in the group of 15411 HTA surgeries without cement no deaths occurred. These same authors also noticed another aspect that was shown to be of great practice importance: 21 of the 23 patients who died, in the group of cemented prosthesis, had pre-existent heart and/or lung diseases. That is to say, although FE inevitably occurring in arthroplasties is usually well tolerated by patients with a good heart and lung function, it can be fatal for patients in whom these functions are severely compromised. Nevertheless, there are tactics and techniques that may lessen this risk, which will be discussed later, on the prevention section.

Still regarding prosthesis, another aspect that remained controversial for a long time was that of the potential role of the acrylic cement (methyl-methacrylate) on the genesis of severe hemodynamic and respiratory changes accompanying arthroplasties[10,48,49,53]. Indeed, methyl-methacrylate is known to be able to play peripheral vasodilative and vasodepressor roles in the myocardium[48,50,53], but Homsy et al.[63] demonstrated both in dogs and in their patients that, in the amounts usually used in

arthroplasties (2g/Kg of weight), the acrylic cement reach serum concentrations that are 40 to 50 times lower than required to trigger cardiovascular toxic effects. Other authors also report that in many of their patients in whom serum concentrations of methyl-methacrylate was intra-operatively probed in HTA or KTA the results were negative, that is, there was no detectable circulating methyl-methacrylate[3,48,53,60,63].

The occurrence of FE in re-surgeries of hip prosthesis is not well understood yet. Woo et al.[49] reported the case of a healthy patient who died during a re-operation of HTA in which cement removal was being performed by ultrasound. In this patient's autopsy, the presence of massive FE was confirmed in his lungs. As they did not find literature addressing the matter, those authors conducted an experimental study of HTA in dogs intending to test three different cement removal techniques: with an osteotome, with a high-speed drill, and with ultrasound. They did not find differences between the first two groups, but the use of ultrasound really promoted a great amount of FE, substantially stronger when compared to other methods. They also emphasized that the occurrence of FE is not exactly associated to cement composition (methyl-methacrylate), but to the IMP rise caused by it, since "the FE also occurs when medullary channel is filled by wax, plastilene or gum", sic[49].

Another issue to be addressed is related to the feasibility or not of having knee total arthroplasty (KTA) bilaterally, in a single surgical procedure. Samii et al.[57], in 1979, were the first to study hemodynamic and respiratory changes in this kind of procedure, based both on already known changes occurring in HTAs, and in case reports of hypotension, heart attack and death during KTAs[48,53,57,64,65]. In the ten cases in their study (five cemented prosthesis and five non-cemented prosthesis), the authors noticed the occurrence of an intense rise on the pulmonary artery pressure, and a significant reduction of the left ventriculum function in patients receiving cemented prosthesis, with those changes lasting for about 2 hours after cementation[57]. In addition, one of these five patients did develop an overt FES, predominantly cerebral (mental confusion and respiratory failure) 3 hours after surgery. Many clinical and experimental studies more recently conducted have confirmed that bilateral KTA causes more bleeding, more cardiac arrhythmia, and more FE than unilateral surgeries. The use of new surgical tactics, such as the practice of enlarging the entrance port of distal femur ("overdrill") associated to the fluted rods, however, have substantially reduced the FE severity in patients submitted to bilateral KTA, although this complication has not been completely eliminated yet[48,53,55,62]. It is still worthy to mention that even in patients submitted to condylar prosthesis insertion (that is, extramedullary) the risk of FE still exists, which, in these cases, is triggered by aligning nails insertion[66].

Considering that those nails are used for intramedullary manipulation, they also promote an increase of IMP, and, as a result, they can trigger FE[55,62,63]. Finally, it is worthy to mention the recommendation by these authors that the indication of KTA uni- or bilateral depends on the patient's ability to tolerate or not the effects of bleeding and the FE effects that are inevitable in those surgeries. In other words, the indication depends on each patient's cardiovascular and respiratory reserve. Kolettis et al.[55] reported that they managed to suspend the progression of a bilateral KTA after severe hemodynamic changes occurred during the insertion of a prosthesis in one of the knees. This intra-operative change of behavior was only possible because the patient was monitored with a Swan-Ganz catheter, which allowed for the continuous measurement of pulmonary artery pressure and cardiac output. Since then, this kind of monitoring became part of the routine of those authors when performing arthroplasty in all high-risk patients.

"BIOCHEMICAL PHASE"

Curiously, "as if FE was an expected physiological phenomenon", lungs alveolar cells were provided with the ability to produce lipase. Thus, as soon as fat droplets arrive and obstruct pulmonary capillaries, they begin to be hydrolyzed by pulmonary lipase that, in general, eliminates fat emboli within about three days[25,47]. The hydrolysis of the fat embolized in the lungs, however, releases fatty acids (palmytic, stearic and oleic), which are usually neutralized and carried by albumin. Maybe this neutralization by serum albumin contributes for the great majority of patients who suffered FE to not present symptoms, that is, to not develop FES. For reasons not yet clear, however, in a small percentage of patients with long-bone or pelvic fractures, as well as in those submitted to arthroplasties, the hydrolysis of fat trapped in pulmonary capillaries releases those same fatty acids that, unexpectedly, come to promote severe injuries in lungs alveoli and capillaries. This is so true that one of the most efficient ways to promote and reproduce an "ARDS" in laboratory animals is exactly through intravenous injection of oleic acid[8,16,32,67-69]. In 1956, Peltier[25] postulated that fatty acids played a direct injuring role on alveolar and endothelial cells. As a great concentration of calcium ions exists on intracellular joints, and as fatty acids have a great affinity to this element, Peltier[25] suggested that the acids would bond to Ca++ ions, from which intercellular joints rupture would result, and, consequently, the establishment of diffuse areas of hemorrhage and edema in pulmonary insterstitium and alveoli. The role of the neutrophils in the genesis of those injuries, however, is essential, as it was later confirmed[3,14,34,67]. Recent studies regarding this matter not only corroborated those events but also added histochemical data of great relevance: Mastrangelo et al.[70] observed that the beta-2 integrins CD11b/CD18 (proteins increasing adherence among cell membranes) of the pulmonary neutrophils had their 'expression' notably increased after intravenous injection of oleic acid. That is, in the presence of free fatty acids an enhanced adherence occurred between neutrophils and pulmonary capillary endothelium because of those integrins. Then, they observed that the neutrophils fixated to the endothelium released proteolytic enzymes from their lysosomes (especially the mieloperoxidase), which ended by 'digesting' endothelial and alveolar cells. Thus, here, we have an indirect injuring action of fatty acids, which closes what could be called as "current theory" of the pulmonary injury genesis in the FES[13,25,47,67,68,70].

The reduction of functioning alveolar volume becomes even more extensive due to the formation of atelectasis areas, since the injured pneumocytes stop producing the surfactant[25,68]. Still regarding pulmonary injuries, Gossling and Pellegrini[13] noticed that it is common the formation of combined thrombus, constituted by fat + platelets + leukocytes + fibrin, which also obstructed pulmonary capillaries. They suggested, then, that serotonin release by platelets would occur from these thrombi, which, for causing venoconstriction, would trigger pulmonary congestion. On the other hand, they reminded that, from mast cells, histamine would also be released, which would cause bronchoconstriction, increasingly worsening pulmonary ventilation[1,2,13]. The end result of all this complex cell and physicochemical changes chain is, therefore, the establishment of extensive lung areas in which alveoli are perfused but not ventilated ("shunt effect") and of other areas where the opposite occurs, that is, some alveoli are ventilated but not perfused ("dead space effect"). The direct consequence of the "shunt effect", as this is known, is the progressive reduction of the arterial POs (PaO2), while the "dead space effect" tends to progressively increase the PaCO2.

The physiopathology of the FES, however, is not limited to the changes described above. As this syndrome usually occurs due to external or surgical trauma, which alone is already accompanied by uncountable hormonal, cellular, hemodynamic, immunological, and blood-coagulation changes, many of the manifestations associated to FES may, in fact, be due to the trauma itself and not to FE per se[3,8,16,22,35,54]. Post-trauma metabolic changes, generically known as "Systemic Inflammatory Response"[69] or "Metabolic Response to Trauma"[71] have, indeed, caused serious controversies in their various aspects. In the comparison with the FE physiopathology, the first controversy regarding trauma comes from the fact that adrenaline, released in any stress situation, has,

among its actions, the ability to mobilize deposited fat and then release fatty acids in blood flow. Although this fact has already been used as a reason in favor of the "Serum Origin Theory" of FES, its was soon proved that not only the amount of fat mobilized by catecholamines was insufficient to cause FES[64,72,73] but it was also proved that the embolized fat was really supplied by bone marrow[23]. Evidences toward this are: 1) The medullary tissue often found among fat emboli[7-11], 2) The frequent observation of fat emboli in blood aspirated from right atrium or from the femoral vessel on the operated side[2,5-7,9,51]. 3) Experimentally, by medullary fat marking with radioactive isotopes, which are detected in the lungs seconds after any intramedullary manipulation[23], 4) The coincidence of intramedullary manipulations with trans-operative images of the ET-ECO, as previously mentioned.

Another major controversial area within FES physiopathology is regarding the changes on blood coagulation. Considering that fat has its own thromboplastic activity, that fat droplets are rapidly bonded to platelets, and that the fracture focus releases tissue thromboplastin, a hypothesis was raised that, in FE, a disseminated intravascular coagulation status (DIVC) would always exist, and that combined thrombi formed by Fat + Platelets + Red-Blood Cells + Fibrin + Leukocytes, would be responsible for the onset of FES[4,8,22,32].

In fact, it is not uncommon to find laboratorial changes compatible to DIVC syndrome in some cases of FES[22,27,45,74], yet the occurrence of the hemorrhagic syndrome secondary to this consuming coagulopathy is extremely rare[13]. On the other hand, there are well established FES case series, in which the authors did not manage to detect laboratory changes characterizing DIVC in none of the patients[30,75]. For the great majority of researchers, therefore, DIVC is considered as an infrequent phenomenon, which can or cannot occur in conjunction with FES[13,27,74,76]. Furthermore, the fact that DIVC is a common complication in polytraumatism patients is well known, regardless of the presence of absence of FE[22,75]. So, today, it is considered that DIVC and FES are two independent morbid conditions, but they may coexist in a same patient, which certainly compromises diagnosis.

Although much is already known about FES physiopathology, a long road of researches is still to be traveled before we can answer the following intriguing question: "If all patients with long-bone and pelvis fractures present with FE, why does only a minority of those patients develop FES?" In trying to answer this question, Avikainen et al.(77) extensively explored the metabolic profile of 20 young patients who had suffered femur fractures one year before, with 10 developing FES, but the other 10 did not develop it. Before and after a stress test in an ergometric bicycle, blood samples were collected for about 50 analyses, which included a thorough evaluation of blood coagulation systems, as well as a detailed study on the metabolism of hormones, glucose, lipids, proteins and minerals. Among all tests assessed, few significant differences were seen: 1) The glycemic status of patients with FES was likely to increase, but not reduce, as would be expected during effort. It was also noticed that, among the 10 patients with FES, five had diabetic parents; 2) Alfa and beta lipoproteins ratio was lower for FES cases; 3) the number of platelets was higher for FES cases, 4) the capillary fragility test was abnormal only for patients with FES; 5) cortisol levels were lower in non-FES cases. Although the study was not conclusive, we can suspect that intrinsic metabolic changes in certain individuals may turn them susceptible to FES development following a FE episode.

CLINICAL AND DIAGNOSTIC PICTURE

FES is a condition that may affect young adults, who are more susceptible to fractures resulting from car, labor and sports accidents, and the elderly, more susceptible to pathologic fractures and arthroplasties. Nevertheless, despite being rare, the occurrence of FES has also been described in 5-14 year-old children experiencing long-bone and pelvic fractures[35,40,78]. However, it is estimated that FES incidence in children is 100 times lower than in adults, and this could be due to the fact that their medullary fat presents a much lower triolein concentration than those of adults[13].

Depending on the time elapsed from the onset of symptoms to trauma, and of the severity of these, FES was categorized as "Fulminant Acute", Sub-acute", or "Subclinical"[22]. The "Fulminant Acute" is characterized by the picture described above in 'Physiopathology', which occurs when patients with polytraumatisms or submitted to arthroplasties are affected by a huge load of FE, large enough to determine the establishment of an acute 'cor-pulmonale', which usually results in death[2,9,10,15,34,35,47,49]. If those patients are monitored with a Swan-Ganz catheter, a sudden increase of the pulmonary artery pressure and of the pulmonary vascular resistance will be seen, and as a result of this, a reduction on cardiac output[5,6,7,9,12,15]. When a patent oval foramen exists, however, sudden death may result from massive brain FE, causing multiple infarctions in the white substance on encephalic basis, as well as on brain stem and cerebellum[2,5,6,20,22,28]

The "Sub-acute" type is the most commonly reported, because, besides being much more common than the 'Fulminant Acute', it usually presents with a highly suggestive clinical picture. The characteristic triad of symptoms is represented by progressive respiratory difficulty, changes on consciousness levels and/or on behavior, and skin petechiae[13,19,20,22,23,31,39,47,74,79].

Typically, the onset of symptoms happens within 12 - 24 hours after trauma, although some cases occurring after 36 - 72 hours are not rare[8,16,22,23]. Gurd et al.[20,24], however, in a detailed study of 100 cases of FES, observed that the latency time between trauma and symptoms ranged from 4 hours to 15 days (average = 46 hours). As expected, the lungs are usually the most affected organs, and only in rare cases this does not occur[5,6,8,20,22,24]. As previously mentioned, the lungs involvement is a result of the progressive number of alveoli being filled with blood and/or exsudates, or suffering atelectasis, from which a generalized hypoxia picture results. Typically, in the 'Sub-acute' type of FES, the clinical picture begins with tachypnea, which becomes a dyspnea, and if not opportunely treated, can rapidly lead to cyanosis and death within less than 24 hours. The thorax x-ray in those cases shows a diffuse bilateral infiltrate, predominant on basal and per-hilar regions, and usually appears only about 24 to 48 h after trauma. This radiological aspect, although 'typical' of FES, is found in only 30 to 50% of the cases[18,22] and cannot be considered as pathognomonic of this syndrome, because it can also occur in pulmonary congestion (due to CCF or hyperhydration), in pulmonary contusion, in tracheobronchial aspiration of gastric contents, and in ARDS. The differential diagnostic can be generally done by taking the immediate and previous history of each patient into account. The differentiation to pulmonary congestion is suggested when there is absence of cardiopathy history, when the patient is young, the cardiac area is small, and since a good control of the hydroelectrolytical balance has been achieved, whether it is a post-trauma resuscitation, or an arthroplasty, for example[8,16,22]. Infiltrates similar to FES' may occur in cases of pulmonary contusion, another common finding in polytraumatism patients. In the pulmonary contusion, however, radiological changes are usually present within the first six hours after trauma, almost always unilaterally, disregarding the scission between lobes and are usually located directly under the external area of the trauma. When the infiltrate of pulmonary contusion appears bilaterally, there is almost always a clear predominance of the contusion in one of the lungs[22,23]. The pulmonary infiltrate in FES should also be differentiated from that in ARDS, which is a common complication in polytraumatism patients, regardless of the occurrence or not of FE episodes. Nonetheless, ARDS tends to manifest later, usually arising within two or more days after trauma. There is, therefore, a period of coincidence, since the onset of FES may also occur within up to four days after trauma[74]. Thorax computed tomography (TCT) does not add much to regular x-ray in terms of diagnosis, although it shows minor and earlier infiltrates than ordinary x-ray.

Obviously, it better bounds compromised pulmonary areas and is very good in making a thorough inventory of intrathoracic visci and pleural cavities[19,20,22,23].

The brain is the second organ mostly affected by FES, happening in 70 to 89% of the cases[8,18,22,29,32]. Neurological changes, however, may appear within 10 to 120 h after trauma[18], and are extremely variable: irritability, anxiety, agitation, confusion, delirium, convulsions, coma, hypertonia, and decerebration have all already been described, whether in a progressive manner in a same patient, or alone among the different cases. Pathological changes responsible for those symptoms are diffuse capillary obstructions caused by fat emboli. From those obstructions, areas of hypoxia, ischemia and petechial hemorrhages result, the latter are due to rupture of capillaries submitted to fatty acids and neutrophils actions, similarly to lesions occurring in the lungs[8,21,22,51]. Those changes are always followed by brain edema, and the establishment of real cerebral infarctions can also occur in mostly affected regions, which are the white substance on the basis of the brain, brain stem and cerebellum. Although neurological manifestations usually denote diffuse aggression in about 12 to 25% of the cases, brain FES shows location signs such as: anisocoria, aphasia, apraxia, hemiplegia, paraplegia, tetraplegia, scotomas and eye conjugate deviation[8,80]. Considering that many of those patients are polytraumatic and that by finding location signs usually suggest cranioencephalic trauma (CET), it is obvious that in those cases a brain computed tomography (BCT) shall always be requested for differential diagnosis of intracranial hematoma[22]. As opposite to what happens in CET, however, for FES, BCT is useless for diagnostic purposes, because even in proven cases of brain FES, BCT is usually normal or shows only a non-specific cerebral edema[16,21,22,56,80]. But magnetic resonance has been shown as very useful due to its high sensitiveness and specificity in detecting encephalic lesions in FES. Characteristically, the BMR shows low-sign changes at T1 and high-sign changes at T2 in affected areas, and can detect lesions as small as 2mm in diameter[8,16,21] and as soon as 4 hours after trauma[8,16,21,76]. In BMR, the high-sign areas at T2 are considered as typical of FES and indicate the presence of perivascular edema secondary to ischemia and to hypoxia[21,80]. Another important aspect of the BMR is concerned to its high negative predictive value, that is, if the test is normal, the diagnostic hypothesis of FES can be dispelled[21].

Skin petechiae represent the third most important sign for clinical diagnosis of FES. These tiny lesions (1 - 2 mm) are, in fact, small hemorrhages caused by the rupture of skin capillaries[1,2,19,20,24,31,79]. According to histological tests, the capillaries would be firstly stretched by fat emboli and then injured by the action of released fatty acids[16,22,45]. Thus, as opposite to previous ideas, the occurrence of petechiae is not correlated to the occurrence of plateletopenia, which occurs in about 30% of FES cases[8,20,22,24,32]. Petechiae are much more common, but reports mentioning that they were found has been ranging from 25% to 95% of the cases, according to the extensive review by Estebe et al.[8]. In the majority of published studies, however, this incidence has been reported as between 40 and 60% of the cases[1,2,8,18-20,24,31,32,79]. Also, the time elapsed from trauma to petechiae onset varies a lot. Intervals of 12 to 96 hours are described after long-bone or pelvis fractures[22], although they are detected more typically within 36 and 72 h after trauma[8]. The location of petechiae in FES also demonstrates a typical pattern, because they are almost always found in axillary and high pre-sternal region, in lateral surfaces of the neck, and in eye conjunctiva[20,22,24,79]. Because petechiae are such tiny lesions, however, they can only be detected by means of a thorough and suspicious clinical test performed in a well illuminated environment. Nevertheless, many times, the use of a magnifying glass is required to find them[20]. Another important clinical datum regarding petechiae is that they don't last long, usually being reabsorbed within about one week after their onset[8,22]. Finally, it is important to remember that patients submitted to massive blood transfusions, or those subjected to long periods of hypoxia, may also present with petechiae, with this datum playing an important role on differential diagnostics of a polytraumatic patient[8].

In addition to lungs, brain, skin and conjunctivas, FES can severely affect many other organs or structures. The retina is involved in almost 50% of the cases[12,13,22]. The obstruction of retinal capillaries by fat emboli may lead to the occurrence of microinfarctions, hemorrhage and edema. Although in the great majority of cases those changes are reversible, when lesions occur in the peripapillary area, they usually leave permanent sequels, such as a reduction of visual acuity, and the presence of scotomas[8,22]. Kidneys are often affected in FE, but the establishment of acute kidney failure is a very rare event[8,22]. Gurd and Wilson[20] and Gurd[24] in their vast case series of FE and FES detected oliguria in 17% of their patients, but anuria in only three of them, which required hemodialysis.

Although typical, the three major clinical changes in FES (Respiratory Failure, Neurological Changes, and Petechiae) are not pathognomonic of this syndrome, since they also often occur in polytraumatic patients not subjected to FE. In 1970, Gurd and Wilson[20] and Gurd[24], based on the study of 100 FES cases treated within a period of four years, established a list of criteria for the clinical diagnosis of this syndrome. According to the analysis of their experience, they suggested that the FES diagnosis should only be made when at least one "Major" symptom exists associated to at least four "Minor" symptoms. The "Major Symptoms" would be the Acute Respiratory Failure, Neurological Changes, and Petechiae, while the "Minor Symptoms" would be: tachycardia, fever (38 - 39^{o} C), retinal changes, urinary changes, sudden hematocrit and/or platelets drop, increase of hemosedimentation speed and positive fat on sputum. In a wider and later analysis of those cases, in 1974[24], those authors confirmed their recommendations regarding those diagnostic criteria. Although they have brought important contributions in trying to rule diagnostic criteria of FES, the studies by Gurd and Wilson[20] and Gurd[24] were denied by later experiences of other authors. In 1987, Lindeque et al.[79] published their experience in the treatment of 55 polytraumatic patients with long-bone fractures, of which 16 developed FES. They could then verify that if they were based only on "Gurd's criteria" for giving a FES diagnosis, only seven of their 16 cases would be identified. Lindeque et al.[79] valuated especially post-trauma respiratory changes, considering FES as already established if at least one of the following signs was present: 1) $PaO2 < 60mmHg$, 2) $PaCO2 > 55mmHg$, 3) Intense dyspnea: breathing rate $> 35rpm$, labored respiration requiring the use of accessory muscles.

As previously mentioned, in a polytraumatic patient, both the respiratory symptoms and the neurological symptoms may have other sources than FES. Pulmonary contusion and cranioencephalic trauma, respectively, are the most common examples of these situations. Thus, at the moment of thinking about differential diagnosis, the time of the onset of signs and symptoms is a factor of great importance. In a typical FES case, both the respiratory symptoms (which occur in virtually 100% of the cases) and the neurological symptoms (which occur in about 80% of the cases)[8,22,29,32] have their onset within 12 to 48h after trauma. This time gap is attributed to the delay in the conversion of neutral fat triglycerides into free fatty acids[23]. The onset of the petechiae, 24 to 48 h after trauma, almost assures FES diagnostic, especially if we take into account that this whole clinical picture is being considered within very specific situations, such as long-bone or pelvis fractures, knee or hip arthroplasties, and extensive trauma of soft parts. Nevertheless, it must be always remembered that as the clinical picture of FES can overlay other post-traumatic conditions, and as no laboratory tests are available to assure or "close" this diagnosis, confirming a FES case becomes difficult, if not impossible. Currently, by considering a patient "at risk" of developing FES, most of the authors tend to make this diagnostic very soon since the patient presents with a compromised respiratory and/or brain function, once the most evident causes for those symptoms are excluded[19,21,29,51,56,79,81,82, 83].

Finally, within FES types categorization, there is the "Subclinical" form, which, according to the review by Estebe et al.[8], occurs in more than 60% of the long-bone fracture cases. In Hoffman[51]'s opinion, however, subclinical FES would, in fact, occur in 100% of those cases, but, due to its high level of benignancy, it is usually left unnoticed or unreported. The "Subclinical" term is due to the fact that patients present almost the same changes seen in the "Sub-acute form", but in such a lower intensity that usually do not manifest through signs and symptoms. The changes that are most commonly found are a slight to moderate increase on the respiratory rate and on temperature, a slight reduction on PaO2, which, in the "Sub-acute" form tends to increase above 50 mmHg, in the "Subclinical" form tends to drop up to about 30 mmHg, due to hyperventilation caused by tachypnea. Dyspnea, then, is not observed, and laboratory tests demonstrate few changes. Regarding the neurological part, there is usually a slight somnolence, confusion or irritability[74]. For those reasons, "Subclinical" FES diagnosis is considered as "difficult" to be made, unless persistently probed and observed in detail[20,22,24]. The "Subclinical" FES is also very common after osteosynthesis and arthroplasties, manifesting itself similarly to those found after fractures[9,56]. Similarly to the sub-acute form, the clinical picture of the subclinical form can be initiated within 12 to 72 hours after trauma(8), although the most commonly described interval is the 12 to 24 h[23]. As previously mentioned, the evolution of the subclinical form is extremely benign and its mortality rate is virtually zero[22].

LABORATORY CHANGES

The occurrence of FES, especially when secondary to severe trauma, is also accompanied by deep metabolic and hematologic changes that can usually be detected by laboratory tests. It must be soon emphasized that, however, although those changes are "typical" of FES, they are not unique or diagnostic of this syndrome: 1) ANEMIA: As it is essential and well known, the reduction of hematocrit (Ht) is one of the earliest and most expected findings after a severe trauma. In cases of FES without apparent hemorrhage, the Ht usually reaches levels of 30% in about 3/4 of the patients within the first or second day after trauma[22,83]. When an assisted patient with not much altered Hematocrit levels (Ht), but within 1 or 2 days after trauma it suffers a sudden drop, this drop may be due to pulmonary hemorrhages secondary to fatty acids toxicity, and to many other post-trauma complications, such as extensive thrombosis, or the very intracavity muscle and subcutaneous hemorrhages. Although these considerations seem obvious, they are mentioned here due to the likelihood of only thinking about FES soon after a sudden Ht drop after 1 or 2 days of trauma[20,25,34,74]. 2) PLATELETOPENIA: This is also a change that is classically considered as "typical" of FES, although many and recent studies had reported plateletopenia as occurring only in about 30% of the cases[8,22,32]. Riseborough et al.[74] reported a consistent and coincident reduction of platelets with PaO2 in their FES patients. On the other hand, they also noticed that many of their patients having a normal PaO2 also presented with plateletopenia. Ganong et al.[31], in their series of 100 patients with femur or tibia fracture by direct trauma, noticed that in none of their 21 cases that evolved to FES plateletopenia had occurred, nor a strong Ht drop. While anemia and plateletopenia were previously considered as FES "typical" findings[20,24] the studies mentioned above not only disagree with former concepts but also reinforce the idea that such changes more obviously result from trauma itself than from a potential FES. In our environment, Engel et al.[18] couldn't also detect the occurrence of plateletopenia in 61% of their 19 proven cases of FES. 3) COAGULOPATHIES: Although some FES cases may present laboratory changes compatible to DIVC (disseminated intravascular coagulation), the hemorrhagic syndrome that sometimes follows this consuming coagulopathy would rarely occur in FES[13]. Indeed, many authors have found laboratory changes suggesting DIVC in many of their FES patients. The changes most frequently described have been the reduction of kalcemia and platelets, the increase of platelet adherence, the prolonged times of activated partial prothrombin and thromboplastin, the release of FDPs (fibrin degradation products), and the reduction of circulating fibrinogen[8,16,17,20,22,24,27,39,74]. Those changes, however, do not occur in all FES cases[27,30,75] and, when they do, are usually subtle[27,76]. Thus, the majority of the recent authors think that laboratory changes suggesting DIVC shall be attributed mainly to coagulation changes that usually accompany a severe trauma than to a potential FES[22,74,75]. 4) COMPLEMENT: In the past, "Complement" has even been suspected of being involved in FES genesis[8,22].

Uncountable recent studies, however, have demonstrated that although there is an increase in the "Complement" activity after FE, this also occurs in the same way and intensity in other trauma situations in which fractures are inexistent. This is, therefore, another non-specific laboratory change that is useless for FES diagnosis[79,84]. 5) FREE FATTY ACIDS (FFA): A great portion of the hormonal metabolic response after a severe trauma or an extensive surgery consists of a great amount of released atecholamines, cortisol, growth hormone, prolactin, insulin, and glucagon(69). In parallel, an increase of serum levels of triglycerides and AGL also occurs, which here has the function of enhancing caloric offer to a seriously injured body[22,39,73]. When circulating, the AGLs are bonded to albumin molecules, therefore being inert. Despite all post-trauma metabolic changes, however, normal or reduced serum levels of AGL are often found in cases of FES[8,74]. Although the most typical pattern is the increase of circulating AGL after a trauma with severe fractures, serum levels of AGL have not been correlated to diagnosis or severity of FES[8,22,74,85]. 6) LIPASE: Peltier et al.[25,47,86] who studied this subject in detail, noticed that the levels of lipasemia increased between the 3rd and 5th day after trauma, reaching their peaks around the 8th day. These facts have recently been corroborated by Riseborough et al.[74]. The lipasemia dosage, however, lacks all and any diagnostic importance in FES, since it does not change much in many of the patients developing this syndrome, and also because it usually rises in cases of trauma, even when fractures are not present[8,16,22,27,46]. 7) FAT DROPLETS IN THE BLOOD: In cases of extensive trauma of soft parts, as well as after long-bone or pelvic fractures, fat droplets are commonly seen in central veins, right atrium or pulmonary artery[37,87]. As we saw at the beginning, this is the condition defining FE, but it does not close FES diagnosis, since the vast majority of patients progress with no signs of this syndrome[1,2,5-9,16,22,87]. 8. FAT DROPLETS IN THE URINE: According to the review by Capan et al.[22], the presence of fat droplets in the urine usually means the occurrence of a massive FE, but not necessarily accompanied by FES. In addition, in many patients developing FES, there is no detectable fat in the urine[22,84]. It is, then, another laboratory finding that, alone, has no value for FES diagnosis[1,2,8,16,74,83,88].

9. FAT IN BRONCHOALVEOLAR WASH (BAW): BAW is obtained by a bronchofibroscope located in a subsegmentar bronchium through which about 100 ml of saline solution are injected and aspirated soon after. The liquid obtained is then analyzed regarding its cellularity and chemical composition. In the first investigation on the role of BAW in FES, in which the authors assessed only 10 patients, Chastre et al.[89] concluded that it was a positively diagnostic test, because they noticed that 30 to 82% of macrophages of eight of those patients presented phagocytized neutral fat, while in cases without FES, this amount was lower than 2%. They then suggested that the diagnosis of FES could be made whenever at least 5% of alveolar macrophages with fat were present. Other studies on the matter, however, do not corroborate this idea, because the finding of high percentage of alveolar macrophages with phagocytized fat was shown to be very common (average of 40% - REIDER) in BAW of various clinical situations not related to fractures or trauma. These were ARDS of many other etiologies. In addition, in many cases with FES diagnosis, BAW not always showed the macrophages with fat[8,16,23,39,90,91].

Alveolar macrophages with a phagocytized fat only mean that fat droplets passed through pulmonary flow, whether there was trauma, FE or none of those intercurrences. Most recently, Aoki et al.[14] studied BAW in 20 patients with long-bone fractures, from which five developed FES. They also concluded that the positive result of macrophages with fat was a non-specific finding, since that finding was very similar both among the 15 patients that did not develop FES and in those five in which the syndrome has been established. On the other hand, they called the attention to the fact that the negative predictive value of this test is very high. Still in this study, the authors verified new facts that could come to be important if confirmed in the future. They noticed that in the five patients with FES, the number of intralveolar neutrophils was nine times higher and albumin concentration in BAW was 12 times higher than values correspondent to those 15 patients without FES. This shows that, according to these authors, for having FES after a FE, the participation of both humoral and cellular agents is required, especially neutrophils, as already mentioned by other authors[67,68,70]. 9) PaO2: Although there are many causes of PaO2 drop after a trauma, there are specific and very common clinical situations in which a PaO2 < 60 mmHg is found that can almost determine FES diagnosis. This is what happens, for example, after isolated long-bone (femur and tibia) and pelvic fractures[9,22,39,79]. In the historical series of Gurd et al.[20] the PaO2 measured in 50 cases showed the following results: it was lower than 50 mmHg in 24 cases, it was between 51 and 80 mmHg in 17 cases, and it was higher than 80 mmHg in 9 cases. Therefore, for newly-hospitalized and FES suspected cases, monitoring of arterial gases and/or of transcutaneous arterial saturation of hemoglobin are indispensable measures for following up the evolution of those patients[12,15,30,39,74].

IMAGING TESTS

Considering that in FE the lungs are always the first organs affected and usually more severely[5,6,8,16,23,31,38], the investigation of a potential FES usually starts by thorax imaging. 1) THORAX RADIOGRAPHY (THORAX X-RAY): This is a mandatory test in any polytraumatism case, but not always constitutes a routine test after arthroplasties, for instance. When about 6 h after a trauma the patient present with a diffuse pulmonary infiltrate, almost certainly those images are resultant from pulmonary contusion or massive bronchial aspiration[23,32,84]. As lung lesion in FES is resultant from fatty acids and as those reactions take many hours to complete, x-ray images of the pulmonary lesion in FES usually appear only 12-24 h after trauma. As previously mentioned in section 'Clinical and Diagnostic Picture', later infiltrates (between 24h and 48h or more) may result either from post-trauma ARDS or from FES, or yet from both conditions. It was also referred that, in FES, the pulmonary infiltrate is usually bilateral and symmetric, affecting mainly the perihilar regions and lungs basis[23]. The classic image of "snow storm", considered as 'typical' of FES, however, occurs only in about 30 to 50% of those patients[2,16,22,30,31]. Histological tests of lungs, obtained from autopsies of patients who died during the Sub-acute phase of the disease, show, in addition to fat droplets obstruction, numerous capillaries and arterioles, alveoli hemorrhage and edema, which explains the intense hypoxia that led them to death[8,74]. 2) Thorax Computed Tomography (TCT): This test provides information similarly to x-ray, but much more detailed. Gurd and Wilson(20) noticed that among their 43 cases of FES with abnormal TCT there were seven patients with normal thorax x-ray. In those seven cases, however, the PaO2 was already lower than 80 mmHg, demonstrating that even if the patient presents with an apparently normal thorax x-ray, a significant pulmonary lesion may already exist. A similar observation was made by Fraser et al.[23], who classified as normal the thorax x-rays of patients with the Subclinical type of FES. In the TCT of patients with FES, it is common to find multiple sub-segmental infiltrates, also located in a larger amount in basal and perihilar regions[22,23]. 3) Pulmonary Perfusion Scintiscan: Due to its nature, in FE, this test enables the detection of lung areas with perfusion failure, even when the thorax x-ray is normal[22]. Nevertheless, here we have the same deadlock, that is, although perfusion failures may be due to FE, the test cannot close the diagnosis of FES, since the same kind of image may be found in pulmonary thromboembolism[22].

The brain, the second major organ that is mostly affected in FE, is usually evaluated by the following tests: 1) Brain Computed Tomography (BCT) - Although it represents a greatly valuable test in many neurological conditions, including cranial trauma, it does not add value to FES diagnosis. This is because, in those cases, the BCT shows only diffuse cerebral edema, which is non-specific, but it does not locate or bound ischemic lesions caused by fat emboli[16,21,22,56].

2) BRAIN MAGNETIC RESONANCE (BMR)- The BMR soon has shown to be superior to BCT for evaluating FES cases with cerebral involvement because it detects, in an early and specific manner, the damages caused by fat emboli. With this method, it is possible to demonstrate lesions as small as 2 mm in diameter, which generally correspond to perivascular edema[8,21,76]. As a result, many FES cases in which TCT was absolutely normal have been demonstrated, and the BMR showed the presence of small cerebral infarctions[21,80]. The typical findings of BMR in FES are the low-intensity signs at T1 and high-intensity signs at T2. When high-intensity signs at T1 appear, this means that a hemorrhagic infarction occurred, a very common injury in FES, since the emboli are small and thus rarely obstruct large-gauged vessels[21]. The most common lesion in cerebral FES is the perivascular edema, which imposes pressure to the capillaries, worsening local flow. This phenomenon may be indirectly evaluated through the transcranial Doppler, which has the ability to detect the slowness of cerebral blood flow secondary to the increase of vascular resistance[21]. The BMR may evidence FES lesions as soon as 3h to 4h after the occurrence of trauma. Characteristically, cerebral FES lesions are always located in the deep white substance of the basis, brain stem and cerebellum ganglia[76]. Another use for BMR may be seen in the very immediate and late follow-up of those patients, because the improvement in this test's images is always associated to clinical improvement of patients. On the other hand, it was also seen that, in cases where the BMR is normal, the diagnostic of brain FES can also be completely disregarded[21].

As we could see, as for what we have reviewed so far, there is no pathognomonic clinical picture, nor a laboratory or imaging test that could close a diagnostic of FES. In fact, petechiae are considered as a "specific" finding of FES in a patient with fractures or in arthroplasty post-operative period. However, as those lesions only appear within 48 to 72 hours after trauma or surgery, they obviously do not serve for the establishment of an early diagnosis[20,21,22,24,84]. FES diagnosis depends, therefore, on a whole data set, and history, signs and symptoms, and imaging tests should be always taken into account[18,19,21-23,51,54,81,82,84,91].

TREATMENT

"Disease with an undetermined physiopathology causes a non-specific treatment". With this sentence, Estebe et al.[8] described the current treatment status of FES. Indeed, as we will see next, uncountable treatments, very different from each other, have already been proposed for struggling against FES in the past decades, but none of them has shown to be effective.

1) Ethylic Alcohol:

In the decade of 1960, it was noticed that polytraumatism patients in a drunkenness status had generally a lower incidence of FES than the sober ones[8,22,38]. From this observation, it was confirmed, in laboratory, that the alcohol had the ability of reducing serum lipase activity and, consequently, of reducing the release of fatty acids. It was on that basis that ethylic alcohol was indicated for FES treatment, assuming that if the formation of free fatty acids was reduced, there would be fewer chances of pulmonary lesion occurrences. Although tested on clinical practice, experiences with alcohol were few, random and uncontrolled. And, as a prospective

and randomized study proving the usefulness or not of this kind of therapy has never been conducted, the use of ethylic alcohol was soon left aside[8,16,19,22]. Some authors were even more categorical when stated that the use of ethylic alcohol had no beneficial effect for FES[12,31].

2) Hypertonic Glucose (HG):

The infusion of 50g of glucose, oral or IV, reduces the concentration of circulating fatty acids within about 30 minutes[16]. It was never known, however, which effect this could have exerted on the release of fatty acids from the fat embolized in pulmonary capillaries. When the HG is administered along with insulin, the inhibition of post-trauma lipolysis is even higher[8,83]. Although some authors have noticed a lower incidence of FES in their patients receiving HG[46,83], in this case, there have never been controlled studies proving its use as well, so this therapy was soon left aside[8,18,22]. Freeman and Enneking[19], who tried this treatment, came to the conclusion that HG did not improve either the evolution or the survival rates of FES patients.

3) Human Albumin:

One of the albumin's properties is that of chelating free fatty acids and avoiding their toxicity[22]. Based on this evidence, the use of Albumin-IV was proposed and tested for FES treatment, but has never been adopted due to the lack of benefit evidences[8,16,22]. Even in excellent experimental conditions, that is, absolutely controlled conditions, Hoffman[54] wasn't able to reduce the degree of pulmonary lesion in dogs when he injected high doses of he substance immediately after the injection of oleic acid. When he injected both substances concomitantly, however, he reported noticing a less extensive pulmonary lesion. In this sense, maybe the infusion of albumin during arthroplasties might reduce the incidence and severity of FES occurring in those surgeries. However, as far as we could see, no prospective and randomized studies were found in literature recommending this approach. Such studies would be, therefore, very welcome.

4) Heparin:

Both experimentally and clinically, the use of heparin in FES cases was shown to be a completely inefficient measure, if not disastrous[19,25,42,45]. Theoretically, heparin functions in FES would be to reverse the DIVC picture and to stimulate lipase in order to reduce lipemia. Such effects, however, are highly undesirable, because, on one hand, it causes an undesirable increase of circulating fatty acids, and, on the other hand, it creates a high risk of hemorrhage in polytraumatic patients or in those in arthroplasty post-operative period[16]. Due to those potential and severe complications and, considering that the use of heparin considerably increased mortality in experimental animals, it became formally contraindicated for FES treatment[12,16,41,42,59].

5) Dextran-40:

This is a solution constituted of glucose polymers with molecular weight equal to 40,000, which considerably increase the osmosis ability of plasma. It was introduced for FES treatment because of the idea of, by promoting hemodillution, it would reduce the aggregation of platelets and erythrocytes[12]. Although its use was shown to be useful in maintaining or recovering volemia in polytraumatic patients, no benefit was shown regarding incidence reduction or patients' evolution, and its use for these purposes was soon left aside[8,16,18,19,22,32,83].

6) Aprotinin ("Trasylol"):

The actions of inhibiting platelets aggregation, reducing serotonin release, and blocking proteases actions, such as those present in neutrophils' liposomes are attributed to this drug. Although retrospective studies have indicated that patients receiving aprotinin evolved better than those not receiving it, no controlled study (prospective and randomized) was conducted to prove or disregard the value of this drug for FES treatment[8,20,22,32]. Sari et al.(58), who recently tested aprotinin, confirmed that the drug really reduced platelet aggregation, but did not avoid the PaO2 drop, which would be the most desirable effect. 7) Aspirin: According to reviews by Capan et al.[22] and by Mellor et al.[16], the use of this drug has never caused any benefits for FES treatment.

8) Corticosteroids:

Because of their recognized and proven anti-inflammatory actions, both local and systemic (inhibiting the release of proteolytic enzymes of neutrophils' lisosomes, complement activation, systemic inflammatory response, and platelet aggregation), corticoids have obviously been tested for FES treatment. Its efficiency, however, has never been proved by controlled studies and its use is not considered anymore[8,22,32,93]. On the other hand, as we will see later in "Prophylaxis", there are favorable signs showing that corticoids can really be efficient in preventing or reducing the severity and mortality of FES.

9) SUPPORT TREATMENT:

Considering that there is no specific treatment for FES, we must then directly address each of the organic consequences of this syndrome[1,2,8,18,22,51,84]. As SEG usually occurs after a severe trauma or extensive surgery, it is virtually certain that volemia (blood and byproducts, saline solution, Ringer-lactate, Dextran, etc) must be restored in order to maintain cardiac output, especially when signs of right ventriculum failure exist. Similarly, in case volemic restoring is not enough, vasoactive drugs must be used (Dopamine, Dobutamine, Noradrenaline) for the same purposes. As shock worsens the prognosis of FES, the same happens when hypoxia is present. Thus, it is recommended that a continuous monitoring of the O2 saturation is performed, aiming to keep it always above 95%. In some cases of slight subclinical or sub-acute FES, keeping this saturation level is possible only with a nasal O2 catheter (3-6 lpm)[38,79,94,95]. For patients in patent respiratory failure, however, mechanical ventilation is required[8,22,29,96]. Although pulmonary compromising is severe, for patients responding well to mechanical ventilation, the inflammatory process of FES is usually resolved within 3 - 7 days[16]. On the other hand, pulmonary hypertension that usually occurs in cases of FES, in general, does not respond to specific vasodilative drugs for minor circulation (Nitroglycerin, Isoproterenol, Prostaglandins). Those, besides not having presented any beneficial effect, many times were responsible for the onset or worsening of systemic arterial hypotension[8,16, 32].

As we could see regarding FES treatment, we can entirely agree with the observations by Murray et al.[95], when they say that "if until the end of the 1960 decade, FES therapy was oriented to the reduction of lipemia and coagulation changes, today, treatment targets the maintenance of oxygen levels and of the cardiac output".

PROGNOSIS

The major cause of death in FES patients is the progressive respiratory failure, meaning a pulmonary lesion that evolves to ARDS[22], although in cases with a prevalence of neurological symptoms death can also occur, either due to a massive cerebral infarction or to generalized cerebral edema[16,28]. Fortunately, however, prognosis for those patients with brain involvement in FES is usually favorable[20,22,24,31,32] and the evolution of clinical improvement can be accompanied or advanced by the disappearance of BMR changes[21,76,80]. In the cases where hemorrhagic infarction occurred, however, lesion evolves to irreversible cerebral atrophy, leaving the patient with localized sequels, or with disabilities, or even in a vegetative state[76].

Especially considering polytraumatic patients, many times is difficult, if not impossible, to precisely establish the cause of death in a victim that is finally affected by multiple and severe injuries, such as massive hemorrhage, shock, ARDS, and thorax, cranial and abdominal injuries[12,22,23,24,31]. Ganong et al.[31] reported that, in a study of autopsies of 5265 deaths caused by trauma, FES was considered as the cause of death in 16% of the cases. The mortality incidence in FES, however, varies a lot among the various authors, regardless of the time in which the studies have been conducted. Capan et al.[22], in their excellent review of 1993,

reported that FES mortality ranged from 10% to 20% until the end of the 1970 decade, but, due to a better and faster resuscitation and transport of accident victims, as well as to the use of an early fixation of fractures and to the modern care given in ICUs, deaths resulting from FES begin to occur in less than 10% of the cases. Takahashi et al.[76], as well as Estebe et al.[8], on the other hand, in their respective reviews in 1990 and 1997, reported mortality rates between 14% and 87% in FES occurred in polytraumatism cases. In the review by Robinson et al.[32] in 2001, the authors found mortality rates ranging from 5% to 15% in the majority of the studies, although they have also found higher rates, of up to 36%. Ganong et al.[31] verified that until the 1960 decade, the mortality mentioned in the different studies ranged from 10 to 35%, but, from 1970 decade on, those values had dropped, ranging from 0 to 20%. In our environment, we found recent reports by Araújo et al[29] who reported a mortality rate of 33% (3/9 cases), and by Engel et al.[18] who reported a mortality rate of 26% (5/19 cases).

For all we have reviewed so far, we believe that such a huge difference noticed among reported mortality rates by the different authors is due, in a great part, to the criteria used for diagnosing FES. That is to say, there is the "typical" FES, as well as there is a FES associated to other severe complications (Shock, TCE, for example), and there are those cases occasionally labeled as FES, but of other natures, such as post-trauma ARDS, for instance. Therefore, while no specific diagnostic method for FES exists, much of data and knowledge about physiopathology, clinical picture, diagnosis, therapy, prognosis and prophylaxis of this syndrome will remain, at a great extent, in an empirical level.

PREVENTION

General Measures:

Both in polytraumatism patients and in those being submitted to surgery, it is crucial to avoid hypovolemia and hypoxia, because these are factors that much worsen a FE prognosis[8,22,51,79,95]. Thus, in both situations, the close monitoring of the blood pressure and the PaO2 is recommended, as well as correcting their deviations as soon as they are detected[8,22,51,79,95]. Still concerning the prevention or reduction of FE effects on respiratory and cardiovascular systems intra-operatively, Orsini et al.[60] recommend the hyperoxygenation and volemia expansion before the beginning of prosthesis cementation. In severely injured patients, with debilitating cardiovascular and/or pulmonary disease (ASA 3 and 4), it is also recommended to intra-operatively monitor pulmonary artery pressure and cardiac output with a Swan-Ganz catheter[19,51]. One of the obstacles of these patients, especially for those with advanced pulmonary emphysema, is that their capillary bed is already much reduced. In normal experimental conditions, pulmonary artery pressure usually begins to rise only when more than 50% of capillary bed are obstructed. In FE, as pulmonary vasoconstriction is usually also present, an occlusion on capillary bed of about 20% is enough for pulmonary hypertension to occur[22].

Orthopaedic Measures:

Although diagnosis and support treatment for FES are usually in charge of the intensive care team, the most important part - prevention - is totally in charge of the orthopaedic surgeon. In terms of fractures, it is clear that modernization of vehicles accessories and traffic education campaigns are of great importance for reducing the incidence of such injuries. However, many other causes of fractures over which no one has control still remain. Thus, once upon a patient with a long-bone and/or pelvic fracture, the orthopaedist is responsible for making the most appropriate decisions in order to avoid FES[32]. It is well known that unstable fractures allow friction between bone stumps and that this triggers new fat emboli being spread, in addition to that already occurred at the moment of trauma[1,2,22]. These facts, among others, led to the concept of "early fixation" of fractures, intending to avoid FES and other complications, such as: infections, pseudoarthrosis, pain, and difficulties to handle the patient in bed. In the decade of 1990, many authors reported their experiences with early fracture fixation, reproductively proving its uncountable benefits. In general, those studies showed a considerable reduction in the incidence of respiratory failure (FES/ ARDS), mechanical ventilation and ICU stay time, a reduced occurrence of fever and bone or generalized infections, a lower mortality rate, a shorter hospitalization time, and, therefore, a lower treatment cost[1,2,8,22,31,32,78,81-83,97,98]. Although some of those studies are retrospective and uncontrolled, Robinson[32] recently published a meta-analysis of the "controlled studies" on the effects of early fracture fixation, which entirely confirmed the advantages mentioned above. This review also included a meta-analysis on the controversy in the indication of early bone union with intramedullary screws in patients with concomitant thorax fracture and trauma. According to this analysis, Robinson[32] could conclude that bone union did not increase the incidence of respiratory failure in those patients, since initial lung trauma was the real responsible for the changes that sometimes lead the patient to ARDS. Schemitsch et al.[3], in an elegant experimental study in dogs, came to the same conclusion, that is, that fracture fixation with intramedullary screw was not a decisively important factor in ARDS genesis, since FE occurring at the moment of trauma was much more intense than that seen during bone union. Bosse et al.[99], who recently published an extensive review on "21st Century Orthopaedics", came to similar conclusions, that is, the early fixation improved the prognosis of patients with severe fractures, even for those with concomitant thorax trauma. A similar controversy exists regarding the indication of early fixation in patients with fracture and CET. In a recently published series, comprising 119 cases with femur or tibia fracture associated to CET, Bhandari et al.[100] compared the results of cases of which fracture was treated with an intramedullary screw to those treated by fixation with plates. By the end of this study, which was a prospective and randomized one, they concluded that bone union with intramedullary screw did not jeopardize the neurological evolution in those patients, which only depended on the degree in Glasgow scale in which each patient was at the moment of enrollment.

Although the majority of the authors seem to consider that "early fixation" is the one performed within 24 hours after trauma, Behrman et al.[101] included, in their publication, cases that have been operated within up to 48 hours after trauma. Diamond, when discussing that article, expressed the opinion that "any fixation performed after 6 to 8h should be considered as late". As we can see, it seems that an absolute lack of consensus still exists about the definition of "early fixation". Another important issue concerning this subject is regarding the general status of the patient, that is, if he/she can really be submitted to a procedure. In the excellent history review by Bosse et al.[99], when referring to the introduction and acceptance of early fracture fixation, the author firstly reminds the discomfort, suffering and complications experienced by patients submitted to long-lasting traction in bed. Then, they present and discuss the benefits of early fixation, especially emphasizing the significant drop of the incidence of post-trauma respiratory failure, as well as of the overall mortality rate. In his opinion(99), which is currently shared by the majority of authors, every long-bone and/or pelvic fracture should, ideally, be fixated as early as possible. When the patient has multiple traumas, we should obviously wait for the clarification or resolution of occasional cranial, thoracic or abdominal traumas, as well as initial resuscitation. Once those problems are solved, however, fracture must be fixated as soon as possible, regardless if the patient has been submitted or not to an extensive surgery. Still according to Bosse et al.[99], the early fixation would only be formally contraindicated in extremely severe situations, such as in cases of deep shock and treatment resistance, or anoxia irresponsive to ventilation with O2 at 100%, or strong hypothermy and coagulopathy.

Another problem in this area is concerned to patients that, for one of those reasons, cannot be operated in the acute phase of trauma. Then, when would be the right time to operate him/her? General behavior is dictated by common sense, that is, surgery

is usually indicated when patients are "clinically stable" and presenting with no signs of organic dysfunction. Waydhas et al.[102] recently showed that the "Systemic Reaction To Trauma" has a deep influence in the progression of theses cases. In their group of 106 patients with multi-systemic trauma, in which all of them had to be submitted to bone union many days after trauma, 40 of them (38%) developed severe organic failure (respiratory, hepatic, or renal) after fracture fixation, while the other 60 cases (56%) progressed with no intercurrences. All of them were evaluated by the intensive care provider, by the anesthetist, and by the surgeon, who considered each patient "in stable conditions" and with no sign of any kind of organic failure. When reviewing the laboratory tests for those patients, however, they noticed that, in the group having complications, Reactive C-Protein and Elastase values were much higher, and that the number of platelets was much lower than the respective values for the group progressing with no complications. This fact called authors' attention to the fact that, at the time of bone union, patients in the first group were in a patent "post-trauma inflammatory state", that is, still subjected to metabolic, biochemical, and hormonal changes of the post-trauma or post-operative period of an extensive surgery[71,78,102]. The authors, then, started to recommend that a late fixation of a large fracture is not performed while the patient is showing signs of organic failure, or laboratory tests demonstrating that the post-trauma inflammatory status is still in course.

Regarding the FES that may occur after arthroplasties or bone union, today, many surgical maneuvers or tactics exist for reducing this risk. As expected, all of them aim to avoid pressure rise inside medullary channel (IMP) during surgery. Surgical techniques currently used for this purpose are:

1) MEDULLARY CHANNEL DEPLETION: It is obvious that, the little the amount of intramedullary fat, the lower the chance of occurring FE. Among currently available techniques, the ones that seem to provide the best results are the medullary channel cleaning, with 1 liter of saline solution, in high-pressure pulsed streams, followed by the aspiration of the medullary content[11,15,16,48,53,101,103].

2) FLUTED RODS: In literature, much was discussed and is still being discussed about the use of reaming, and also about the kind of rod to be used. It has long been proved that reaming causes FE, because this maneuver significantly rises IMP[7,11,14,18,48,53] potentially reaching up to 1500mmHg[8,18]. Although this degree of FE not always is translated into a PaO2 drop[50], the FE caused by reaming can and should be minimized, because larger loads of fat emboli will always occur in subsequent surgical times. The attempt to use narrower intramedullary screws with the intention of avoiding reaming has not conquered many adepts, since those screws have been implied in an increased time for fracture union, in addition of being associated to a higher incidence of pseudo-arthrosis and, therefore, to the number of secondary procedures required for solving those cases[99,104]. Regarding the two most common kinds of rods - cylindrical and fluted - uncountable evidences exist, both clinical and experimental, showing that the cylindrical type causes a much higher increase of IMP, and, thus, cause much more FE than fluted rods[8,9,18,51,55,64,73].

3) CEMENTATION: As previously discussed in Physiopathology section, this is the arthroplasty phase in which the largest load of fat emboli occurs, which may result in systemic hypotension, pulmonary hypertension, pulmonary shunt increase and the resultant drop on arterial PaO2[1,2,7,11,60], in addition to cerebral embolism that occurs in about 80% of the cases[8,22,25,32,47,51]. With the intention of reducing the FE load during prosthesis cementation, many surgical tactics were introduced:

3.1) VENTING: The simple performance of a 4 - 6 mm-diameter hole in the diaphysis portion located at few centimeters from the prosthesis end does not help much on the reduction of IMP during cementation[9,10,11], but, when combined to other measures, such as the use of fluted rods, overdrill (entrance port of 12 mm), and proximal vacuum (see below) this has been considered as useful for reducing IMP and, therefore, FE[11,51,55].

3.2) RETROGRADE FILLING: Filling the medullary channel with cement, from the distal end of the prosthesis, not only helps on lessening IMP rise, but also on avoiding gas embolisms[48].

3.3) VISCOSITY: The use of low-viscosity cements has also been described as useful for avoiding incremental IMP rises[10,11].

3.4) PROXIMAL VACUUM: In an interesting prospective and randomized study on HTA, Koessler et al.[15] applied a vacuum of 600mmHg through a metal cannula introduced at the intertrochanteric line in 60 patients during prosthesis cementation, whereas in other 60 cases vacuum was not used. All patients were monitored by ET-ECO and arterial gasometries. They could then see that in the group without vacuum, the incidence of FE "degree 2" was 93% while the "degree 3" was 51%, and for the group receiving vacuum, the FE "degree 2" was 13%, while the "degree 3" was only 8% ($p < 0.5$). They also noticed that, at the moment FE occurred, as detected by ET-ECO, there were arterial hypotension, shunt increase, and PaO2 drops. Similar results were then reproduced by Pitto et al.[11] in the group without vacuum, with FE occurring in 85% of the cases, whereas in the group with vacuum the incidence was only 5%. Due to the strong protective effect of the vacuum, applied in proximal femur during prosthesis cementation, those authors considered using this maneuver even as a good alternative to the indication of prosthesis without cement. Herndron et al.[27] also noticed a significant reduction on intensity and severity of FE with the use of vacuum, but instead of using an intertrochanteric metal cannula, they used an intramedullary catheter.

3.5) DISTAL OVERDRILL: In a detailed study on KTA, Fahmy et al.[9] tried five different techniques designed to avoid the inevitable increase in IMP occurring in those surgeries. Among the various combinations of maneuvers used, they noticed that the lowest IMP changes occurred when the entrance port at the distal femur was enlarged from the usual 8 mm to 12.7 mm, which they called "overdrill". They also noticed that with the use of fluted rods, the increase in IMP was much lower. From the five tested groups, it was verified that the association of the fluted rod with the overdrill allowed the maintenance of IMP levels close to its normal values (40 - 50 mmHg), whereas with other techniques, those values ranged from 180 mmHg to 650 mmHg.

3.6) PROSTHESIS WITHOUT CEMENT: These were introduced due to severe and frequent complications seen with the increasingly use of cemented prosthesis, especially the occurrence of massive and long-lasting FE. By clinical and experimental observations, it was verified that, indeed, their use considerably reduced FE severity during arthroplasties[7,9,11,48,53,57,60]. On the other hand, prosthesis without cement also present disadvantages, which makes this an extremely controversial topic. Pitto et al.[11], recently summarized the topic with a high level of common sense and clinical experience. According to those authors, "The decision on the use of a cemented prosthesis, or a not cemented one, should take into account a surgeon's experience and the following patient's characteristics: age, gender, weight, physical activity, bone quality, and proximal femur anatomy". Despite all the techniques and maneuvers discussed so far, however, to be able to completely avoid the occurrence of FE, either traumatic or per-operative, is still an impossible objective[48, 53].

4) CORTICOSTEROIDS: Although they have not been shown as useful for treating an already established FES, there are many studies suggesting that corticosteroids may play an important protection role when administered before FES is completely established. Among the most important anti-inflammatory actions of corticoids are: the complement activation blockage (C5a), platelet aggregation, and, most of all, lisosomes membranes stabilization, thereby avoiding the release of proteolytic enzymes

over endothelial and alveolar cells[8,16,22,32,105]. Although presenting relatively small case series, there are at least four prospective and randomized studies demonstrating the efficiency of corticoids in reducing the incidence of FES in patients with femur and/or tibia fracture, when administered for prophylactic purposes, that is, soon after the patient is admitted in hospital. The most relevant data in those studies are summarized in Table 2.

AUTHORS – year	METHOD	CORTICOSTEROID DOSAGE or Placebo or other drugs	RESULTS (% of FES)
1- STOLTEMBERG -'79 [99]	G-1 = 21pat	GLUCOSE-50% IV 4/4 h 4 days	3 cases (14%)
	G-2 = 20pat	MPred* 1g IV at Adm, 8h and 16h	0 cases (**)
	G-3 = 23pat	None	2 cases (8%)
2- SCHONFELD-'83 [96]	G1 = 42pat	Placebo	9 cases (21%)
	G2 = 21pat	MPred* 7.5mg/Kg 6/6h, 3 days	0 cases (p<.02)
3- LINDEQUE -'87 [57]	G1 = 35pat	Placebo	16 cases (46%)
	G2 = 20pat	MPred* 30mg/Kg Adm and 4h	6 cases (p<.02)
4- KALLENBACH-'87 [48]	G1 = 42pat	Placebo	10 cases (24%)
	G2 = 41pat	MPred* 1,5mg/Kg 12/12h, 2d	1 case (p<.01)

TABLE 2: ** = Methyl-prednisolone, ** = There was no statistically significant difference regarding the incidence of FES among the three groups, but a 'trend' towards the benefits of the corticosteroid. In the other three studies, this difference existed, and was indicated here by the corresponding "p".*

In the study # 1[46], although there wasn't a statistically significant difference regarding FES incidence among the three patient groups, in the group receiving corticoids, the incidence of FES was zero. Besides, there was indeed a very significant difference among the values of PsO2 measurements for patients from the different groups, where we could notice that those receiving corticoids had always a higher PaO2 than the other groups ($p<0,03$). The interpretation of this fact, according to the authors, was that PaO2 measurements were higher in that group probably because the corticoid would have protected the lungs of those patients against further damages. Another interesting factor that can be noticed from the data comprised in that Table is that the administered dose of Methyl-prednisolone strongly varied among the different authors. Respectively to the order and its mention in the Table, those doses were 40mg/Kg, 90mg/kg, 60mg/kg, and 9mg/Kg.

Except for the study # 1, all other studies indicated an important prophylactic action of the corticoids regarding the occurrence of FES after femoral and tibial fractures, although doses ranged from 9mg/Kg to 90mg/Kg. One of the surgeon's major concerns regarding the use of corticoids is its recognized imunnodepressive association. The occurrence of opportunistic infections or superinfections, however, usually occur only in cases of prolonged use of this kind of drug, a very different situation when compared to "prophylactic use", which is carried out for only one, two, or three days[84,106]. Despite some good evidences[79,84,106] and suggestions[46] saying that the methyl-prednisolone, when administered soon after patients' admission could avoid or reduce the incidence of FES after long-bone and pelvic fractures, this approach is still not accepted or adopted routinely. According to the authors who reviewed and discussed this subject, this is due to the fact that all studies conducted so far present small case series, different criteria for patients selection and different dosages of the corticoid used, making the analysis of the results not so reliable. They also highlight the need of conducting further prospective and randomized studies with a large number of patients before we can assume a definitive conclusion regarding this matter[8,12,13,16,22,32,96].

FINAL CONCLUSIONS

To perform a thorough review on "Fat Embolism" is a virtually unfeasible task to a small number of investigators, if we consider that only in current MEDLINE files (1950 to 2004) there are 2622 articles on this subject. We also do not believe that the review of all those articles should explain the uncountable obscure points in this syndrome. According to what was demonstrated in the text, there are many controversial or little explained issues about the phenomena involved in the FE and FES. So, it seemed to us that, more importantly than obtaining a thorough review of the subject would be the conduction of different prospective and randomized studies, with representative case series, specifically designed to explain the doubts and controversies imposed here[92]. The potential diagnostic role of the bronchoalveolar wash, the potential prophylactic effect of corticoids, the real benefit of each of the different techniques used in arthroplasties aiming to reduce FE, would be some examples of this proposition. There is no doubt that such studies would certainly bring more reliable information, and thus, a higher utility to orthopaedics practice. The crucial question, however, would not be solved yet. That is, 'why only a small portion of patients suffering FE develop FES?' Considering that, in almost all medical centers, the number of FES cases is not high, and that the progression of lesion must be studied from its very beginning, experimental studies seem here to be the best way for trying to elucidate the whole physiopathology of FES.

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