**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 penuvascular 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.
ETIOPATHOGENY

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(39).

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(8,22,35-36,44). In an autopsy-based study, performed in 53 cases of death caused by spanking (only four of them had fractures), Hass et al.(54) 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 autopsies 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.(55), the occurrence of FE in autopsies performed after severe trauma was of 68%. Capan et al.(53), in their extensive and recent review, noticed that the FE had been detected in up to 90% of deaths caused by trauma with long-bone and/or hip fractures. Estébe(56), 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.(56) 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 FE 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(8,22,26,30,34).

Although FES usually occurs, especially after long-bone and hip fractures in high-energy trauma(8,22,35-36,56), 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(8,35). 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(8,50). 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 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 intramedullary bone 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. 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(8,19,22,32).

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.

<table>
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<tr>
<th>CLINICAL STATUS</th>
<th>FE</th>
<th>FES</th>
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<tbody>
<tr>
<td>SINGLE (Femur, Tibia, Pelvis)</td>
<td>90%</td>
<td>3%</td>
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<tr>
<td>MULTIPLEx</td>
<td>100%</td>
<td>25% to 30%</td>
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<td>ARTHROPLASTIES:</td>
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<tr>
<td>KNEE</td>
<td>100%</td>
<td>10 to 12%</td>
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<tr>
<td>HIP</td>
<td>100%</td>
<td>6 to 10%</td>
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<tr>
<td>PEDICULAR SCREWS:</td>
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<td></td>
<td>80%</td>
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Table 1: Causes of FE and FES most commonly seen.

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”(7,19,22,35,40,47).

“Mechanical Phase”:

This is the phase in which fat emboli (neutral fat droplets) enter the 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 capillaries meshworks(7,19,22,46,49). On the
other hand, if FE is massive enough to occlude about 80% of the pulmonary capillary meshwork, there will be a great increase of pulmonary artery pressure and, as a result, right ventricle acute failure (acute "cor-pulmonale"), with a rapid progression to death (12,15,49,50). 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 (12,14). Clinical end experimental studies widely demonstrated that fat emboli arise in pulmonary capillaries few seconds after a fracture or medullary channel manipulation (10,30). 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 (46,49,50). IMP measurements in human beings under anesthesia show normal values ranging from 30 to 50 mmHg, however, when IMP values just before fracture are 50 and 100 mmHg, FE may occur (59). 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 (46,15,38). 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 ventricle become totally opacified by fat emboli (46,15,38). 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 (59). The simple reaming of the medullary channel may cause great rises in IMP which can reach values up to 650 mmHg (59). Still in that study, the authors verified that with an IMP higher than 150 mmHg, the intensity of the FE was ten times stronger 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 (49,50,52,55). 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 (59). From the pulmonary function point of view (shunt and PaO2 measurements), however, this degree of FE did not manage to promote relevant changes (59,19,29). 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 (8,16,15,54,55). 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 (46). This fact, although already recognized, was also recently proved by ET-ECO (71). Thus, considering that in the rest of surgery (intradureal 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 impact on vessels. However, a less amount of emboli in this surgery phase (8,16,15,54,55). Indeed, intra-operative IMP measurements (9,48,55), as well as the use of ET-ECO (12,7,11,14,55,56) 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 (12,9,41,48,53,57). During prosthesis cementation, IMP can reach values of 650 to 1500 mmHg (7,9) and the embolization may last for more than 20 min (12,5,15,55). 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 (7,9,15,30,90). Those effects may last just for a few minutes, or may remain for many hours post-operatively (2,5,55). It is also interesting to note that those cardiopulmonary changes vary according to the intensity of embolism images showed by the ET-ECO (8,4,55). 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 (12,7,11,14,48,53,56). 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 (9,17,48,50,52). In a well-controlled clinical study, Ries et al. (46) observed that in their nine cases of cemented prosthesis, interluminal shunt increased up to 25% in average, while in 23 cases of non-cemented prosthesis, there were no significant changes on that parameter. In the experiment by Pitto et al. (51), shunt changes were 24% and 2%, respectively, for both kinds of prosthesis. Experimental studies in dogs (81), 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 (9,17,24,48,50,51). 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 (51). 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 (16,49,50), 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 (10,17,19,48,53). Woo et al. (46) 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%. Pittu et al. (51), 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 (46,48,53). Indeed, methyl-methacrylate is known to be able to play peripheral vasodilative and vasodepressor roles in the myocardium (46,50,53), but Homsey et al. (90) 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 (46,53,60,63).

The occurrence of FE in re-surgeries of hip prostheses 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. Sami et al. (97) in 1979, in an effort 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 KTA (48,53,57,64,66). 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 ventricle function in patients receiving cemented prostheses, with those changes lasting for about 2 hours after cementation (67). 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 continues to be a potential problem (70). The 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 true for one of the most efficient ways to promote and reproduce an “ARDS” in laboratory animals is exactly through intravenous injection of oleic acid (16,19,27,68,69). 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 interstitium and alveoli. The role of the neutrophils in the genesis of those injuries, however, is essential, as it was later confirmed (25,13,19,27,47). Recent studies regarding this matter not only corroborated those events but also added histochemical data of great relevance. (34,67) noticed that the beta-2 integrins CD11b/CD18 (pulmonary adhesion molecule II) 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 based both on already known changes occurring in HTAs, and in case reports of hypotension, heart attack and death during KTA. 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 FET (52,65). 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. Koletis et al. (53) 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.

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 (53,65). 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 (13,19,65). 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 PO2 (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. Several authors have, indeed, caused serious controversies in their various aspects. In the case of 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 elaborated fat was really supplied by bone marrow(29,30). 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(6,7,9,15,30). 3) Experimentally, by medullary fat marking with radioactive isotopes, which are detected in the lungs seconds after any intramedullary manipulation(28, 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(30,32,52). In fact, it is not uncommon to find laboratory changes compatible to DIVC syndrome in some cases of FES(29,32,47). 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(30,74). For the great majority of researchers, therefore, DIVC is considered as an infrequent phenomenon, which can or cannot occur in conjunction with FES(32,14,36,92). Furthermore, the fact that DIVC is a common complication in polytraumatism patients is well known, regardless of the presence of absence of FES(30,70). 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 research 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 glyceric 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 normal 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(26,40,78). 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 polytraumatism or submitted to arthroplasties are affected by a huge load of FE large enough to determine the establishment of an acute 'coagulopathy', which usually results in death(9,10,15,34,45,47,49). 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(6,7,13). 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(5,6,30,22,28). 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(13,15,20,22,33,34,47,79). Typically, the onset of symptoms happens within 12 - 24 hours after trauma, although in 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(6,8,20,24). 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 opportune 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 46 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 areas 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(22,25). 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 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. The brain is the second organ mostly affected by FES, happening in 70 to 89% of the cases. Neurological changes, however, may appear within 10 to 120 h after trauma, and are extremely variable: irritability, anxiety, agitation, confusion, delirium, convulsions, coma, hypertension, 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. 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. 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 patients we should suspect and/or consider the Acute Fibrinous Embolic Syndrome (AFFES) and consider the request for differential diagnosis of intracranial hematoma. 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. But magnetic resonance has been shown as very useful due to its high sensitivity 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 and as soon as 4 hours after trauma. 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. Another important aspect of the BM is concerned to its high negative predictive value, that is, if the test is normal, the diagnostic hypothesis of FES can be dispelled. Skin petechiae represent the third most important sign for clinical diagnosis of FES. Those tiny lesions (1 - 2 mm) are, in fact, small hemorrhages caused by the rupture of skin capillaries. According to histological tests, the capillaries would be firstly stretched by fat emboli and then injured by the action of released fatty acids. 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. 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. In the majority of published studies, however, this incidence has been reported as between 40 and 60% of the cases. 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, although they are detected more typically within 36 and 72 h after trauma. The location of petechiae in FES also abides 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. Because petechiae are such tiny lesions, however, they can only be detected by means of a thorough and suspiscious clinical test performed in a well illuminated environment. Nevertheless, many times, the use of a magnifying glass is required to find them. Another important clinical datum regarding petechiae is that they don’t last long, usually being reabsorbed within about one week after the event. 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. In addition to lungs, brain, skin and conjunctivats, FES can severely affect many other organs or structures. The retina is involved in almost 50% of the cases. 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. Kidneys are often affected in FES, but the establishment of acute kidney failure is a very rare event. Gur and Wilson and Gur and Wilson and Gurd found in their vast case series of FE and FES detected oliguria in 17% of their patients, but anuria only in three of them, which required hemodialysis. Although typical, the three major clinical changes in FES are not pathognomonic of this syndrome, since they also often occur in polytraumatic patients not subjected to FES. In 1970, Gur and Wilson and Gur and Wilson and Gurd, 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” represent the Acute Fibrinous Embolic Syndrome (AFFES), and the “Minor Symptoms” would be: tachycardia, fever (38 - 39º C), retinal changes, urinary changes, sudden hematicrict and/or platelets drop, increase of hemosedimentation speed and positive fat on sputum. In a wider and later analysis of those cases, however, 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 Gur and Wilson and Gur and Wilson and Gurd were delayed by later experiences of other authors. In 1987, Lindeque et al. 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. evaluated especially post-trauma respiratory changes, considering FES as already established if at least one of the following signs was present: 1) PaCO2 < 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 those 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) 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. 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 conclusion, once the patient presents with a compromised respiratory and/or brain function, once the most evident causes for those symptoms are excluded.
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's (81)'s opinion, however, subclinical FES would, in fact, occur in 100% of those cases, but, due to its high level of benignity, 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 (27). 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 (20,22,24). 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 (26). As previously mentioned, the evolution of the subclinical form is extremely benign and its mortality rate is virtually zero (20).

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 seen 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 (37). 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 after a sudden Ht drop after a 1 or 2 days of trauma (20,25,24,74,76). 2) PLATELETOPENIA: This is also a change that is classically considered as "typical" of FES, although many and recent studies have reported plateletopenia as occurring only in about 30% of the cases (8,22,30). 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. (21), in their series of 100 patients with femur or tibia fracture by direct trauma, noticed that in none of their 21 cases that evolved 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. (16) 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 DISC (disseminated intravascular coagulation), the hemorrhagic syndrome that sometimes follows this consuming coagulopathy would rarely occur in FES (18). Indeed, many authors have found laboratory changes suggesting DISC 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 thrombo- plastin, the release of FDPs (fibrin degradation products), and the reduction of circulating fibrinogen (8,16,17,20,24,27,39,74). 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 DISC shall be attributed mainly to coagulation changes that usually accompany a severe trauma than to a potential FES (24,75). 4) COMPLEMENT. In the past, "Complement" has even been suspected of being involved in FES genesis (16,20). 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 inexisten. This is, therefore, another non-specific laboratory change that is useless for FES diagnosis (27,84). 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 aterolamines, cortisol, growth hormone, prolatin, 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 of- fer to a severely injured body (23,39,73). 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 (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 (25,27,46). 6) LIPASE: Pelletier et al. (25,47,30) 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 (8,25,33,24,75). 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 ar- tery (27,37). 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 (2,3,29,16,22,87). 8. FAT DROPLETS IN THE URINE: According to the review by Capan et al. (20), 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 (23,34). It is, then, another laboratory finding that, alone, has no value for FES diagnosis (2,3,16,74,86). 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 phagocitized 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 mac- rophages with phagocizated 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 (16,23,20,20,91).
Alveolar macrophages with a phagocytosed 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. 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 intravascular 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.37,48,79

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 fractures22,39,79. In the historical series of Gurd et al. the PaO2 measured in 50 cases of FES and 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.14,15,19,20,26,38,74

IMAGING TESTS

Considering that in FE the lungs are always the first organs affected and usually more severely, 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 aspiration20,23,26. As lung lesion in FES is resultant from fatty acids and as those reactions take many hours to complete, x-ray may register a pulmonary lesion in FES usually between 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.24. The classic image of “snow storm”, considered as ‘typical’ of FES, however, occurs only in about 30-50% of those patients.22,26,29,31. 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 death7,24. 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 normal TCT there were seven cases with normal thorax x-ray. In those two cases, however, the PaO2 was 51 and 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.25, 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.20,22. 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 normal20. 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.16,21,22,26. 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.21,86. 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 normal and thus rarely obstruct large-caliber 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 slowdown 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.26. 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 disregarded21.

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.20,21,22,25,26,54,58. FES diagnosis depends, therefore, on a whole data set, and history, signs and symptoms, and imaging tests should always be taken into account14,19,21,23,25,54,81,82,84,87.

TREATMENT

"Disease with an undetermined pathophysiology causes a non-specific treatment". With this sentence, Estebe et al. 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) Ethylc 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 ones22,26,38. 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 ethylc 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(8,16,20). 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(9,83). Although some authors have noticed a lower incidence of FES in their patients receiving HG(16,83), in this case, there have never been controlled studies proving its use as well, so this therapy was soon left aside(8,16,20). Freeman and Ennekking(16), 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 evidence(8,16,20). 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(18,25,42,45). Theoretically, heparin functions in FES would be, therefore, very welcome.

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 hemodilution, 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(8,16,18,19,20,22,32).

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). 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.(20) 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’ liposomes, 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(8,22,30,66). On the other hand, as we will see later in “Propylaxias”, 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(1,2,8,18,22,31,34). 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 ventricle 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)(38,79,80). For patients in patent respiratory failure, however, mechanical ventilation is required(8,20,29). 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 vasoactive drugs for minor circulation (Nitroglycerin, Isoprotenerol, Prostaglandins). Those, besides not having presented any beneficial effect, many times were responsible for the onset or worsening of systemic arterial hypotension.

As we could see regarding FES treatment, we can entirely agree with the observations by Murray et al.(83) 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(16,25). Fortunately, however, prognosis for those patients with brain involvement in FES is usually favorable(20,22,24,31,35) 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 sequelas, 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.(35) 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.(20), 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. (31), as well as Estebe et al. (30), on the other hand, in their respective reviews in 1990 and 1997, reported mortality rates between 14% and 87% in FES occurred in polytraumaism cases. In the review by Robsonson et al. (31) 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. (32) who reported a mortality rate of 33% (3/9 cases), and by Engal et al. (33) 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 polytraumaism patients and in those being submitted to surgery, it is crucial to avoid hypovolemia and hypoxia, because these are factors that much worsen a FES prognosis (34). This, 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 (35,36). Still concerning the prevention or reduction of FES effects on respiratory and cardiovascular systems intra-operatively, Orsini et al. (36) recommend the hyperoxygenation and volcano 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 with a Swan-Ganz catheter (37). 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 vasoconstiction is usually also present, an occlusion on capillary bed of about 20% is enough for pulmonary hyperten-

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 orthopaediatric 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 circumstances, over which no one has control, still remain. Thus, once upon a patient with a long bone and/or pelvic fracture, the orthopaedistic surgeon is responsible for making the most appropriate decisions in order to avoid FES (38,39). It is well known that unstable fractures allow friction between bone stumps and that this triggers the new fat emboli being spread, in addition to that already occurred at the moment of trauma (32). 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, reproducibly 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 (22,31,51,79,81-83,97,98). Although some of those studies are retrospective and uncontrolled, Robinson (22) and others published the potential benefits of the early fixation of fractures, even discussing 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 (22) could conclude that bone union did not increase the incidence of respi-

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 pre-
senting 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 reduc-
ing 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 of the kind
of rod to be used. It has long been proved that reaming causes
FE, because this maneuver significantly rises IMP (11,14,18,48,53)
potentially reaching up to 1500mmHg (103). Although this degree
of FE not always is translated into a PaO2 drop (56), 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-
arthritis and, therefore, to the number of secondary procedures
required for solving those cases (90,104). 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 (85,18,51,55,64,79).

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, pul-
monary hypertension, pulmonary shunt increase and the resultant
drop on arterial PaO2 (2,7,11,190), in addition to cerebral embolism that
occurs in about 80% of the cases (9,22,25,52,47,51). With the intention of
reducing the FE load during prosthetic 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 (9,10,111), 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 embolism (48).

3.3) VISCOSITY: The use of low-viscosity cements has also been
described as useful for avoiding incremental IMP rises (10,111).

3.4) PROXIMAL VACUUM: In an interesting prospective and
randomized study on HTA, Koessler et al. (113) applied a vacuum of
600mmHg through a metal cannula introduced at the intertrochan-
teric line in 60 patients during prosthetic 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. (113) 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 prosthetic cementation, those
authors considered using this maneuver even as a good alternative
to the indication of prosthesis without cement. Herdron 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. (49) 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 sever-
ity 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. (111), recently summarized
the topic with a high level of common sense and clinical experi-
cence. According to those authors, “The decision on the use of
a cemented prosthetism, 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 qual-
ity, 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 es-
tablished. Among the most important anti-inflammatory actions
of corticoids are: the complement activation blockage (C5α),
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.

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 immunodepressive association. The occurrence of opportunistic infections or super-infections, 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\(^8,12,13,16,22,32,96\).

### Table 2: *

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>METHOD</th>
<th>CORTICOSTEROID DOSAGE</th>
<th>RESULTS (% of FES)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOLTENBERG &amp; THURSTON &amp; ZARZAN (^{16})</td>
<td>G -1 = 20 patient</td>
<td>GLUCOSE 50% 2IV drip h 4</td>
<td>3 cases (14%)</td>
</tr>
<tr>
<td></td>
<td>G -2 = 20 patient</td>
<td>MP 50mg 1g IV at Adm, 7h and 24h</td>
<td>5 cases (25%)</td>
</tr>
<tr>
<td></td>
<td>G -3 = 20 patient</td>
<td>Placebo</td>
<td>2 cases (6%)</td>
</tr>
<tr>
<td>SCHOFIELD &amp; HENFIELD (^{16})</td>
<td>G -1 = 42 patient</td>
<td>Placebo</td>
<td>9 cases (21%)</td>
</tr>
<tr>
<td></td>
<td>G -2 = 24 patient</td>
<td>MP 50mg 7.5mg/Kg 6/8h, 3 days</td>
<td>6 cases (49%)</td>
</tr>
<tr>
<td></td>
<td>G -3 = 20 patient</td>
<td>Placebo</td>
<td>16 cases (49%)</td>
</tr>
<tr>
<td></td>
<td>G -4 = 20 patient</td>
<td>MP 50mg 30mg/Kg Adm and 4h</td>
<td>6 cases (30%)</td>
</tr>
<tr>
<td>KALLENBACH &amp; ALEXIO (^{16})</td>
<td>G -1 = 42 patient</td>
<td>Placebo</td>
<td>10 cases (24%)</td>
</tr>
<tr>
<td></td>
<td>G -2 = 42 patient</td>
<td>MP 50mg 1.5mg/Kg 12/12h, 2/2</td>
<td>1 case (2%)</td>
</tr>
</tbody>
</table>

\(\ast\) = Methyl-prednisolone, \(\ast\) = 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”.

### 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\(^85\). 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.
REFERENCES