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Modern approaches in experimental modeling of fat embolism (Literature review)

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A historical review on the experimental modeling of fat embolism syndrome is presented. Problems of diagnosis, prevention and prognosis, as well as the effectiveness of medication therapy and osteosynthesis at the stages of treatment in experimental animals are highlighted.

Keywords: fat embolism, lipid hyperglobulemia (LHG), experiment, diagnosis, prevention, treatment

Over the past decades, the concomitant trauma remains the object of close attention for researchers and practitioners. Scientific and technological progress, covering all spheres of human activity, has led to a steady increase in the general rates of injuries [1, 2].

Mortality rates from severe complications of traumatic disease range from 15 to 35 % in severe combined trauma [3, 4]. One of these complications is the syndrome of fat embolism (SFE). The most frequent conditions leading to the development of SFE are severe mechanical injuries resulting in fractures of lower limb long bones and pelvis, especially in the injured persons with unstable hemodynamic parameters on the first day and accompanied by massive blood loss. Despite fat embolism (FE) has been studied for more than a century, there is still no clear idea of its pathogenesis, clinical signs, prevention and treatment. Even the statistical data on the frequency and mortality presented by different researchers may differ significantly.

Embolism (*Greek* embole – insertion, intrusion) is a pathological process caused by various substrates (emboli) in the blood flow that are not found in the normal subjects and are capable of causing acute occlusion of the vessel resulting in an impaired blood flow to the tissue or organ. Fat embolism as a morphological phenomenon is a blockage of some of the blood vessels of small caliber, mostly in the lungs, by particles or drops of neutral fat.

In the pathogenetic sense, according to B.G. Apanasenko, a post-traumatic fat embolism is a complicated biodynamic process with formation and circulation of fat drops (emboli) in the large and small blood circle flow that block small and large blood vessels with further disruption of the organs. To denote fat emboli in blood with a diameter greater than 6 μm, Bschoor and Haash (1963) proposed the term *globules* (balls). Under normal conditions, only rare globules of fat (FG) with a diameter of 1 μm are observed in the healthy people blood stream. Post-injury, their number and dimensions increase. Fat embolism is possible only if a large number of large fat globules circulate in the blood.

However, the presence of FG does not mean the development of fat embolism syndrome. It was noted that lipid hyperglobuloma (LHG) occurs in 60-90 % of patients with skeletal trauma but clinical manifestations of fat embolism syndrome (SFE) develop only in 0.25–10 % of cases. The low frequency of clinically manifested cases of fat globulemia makes the research difficult. So, there is a need for continuing the research on this syndrome in the experiment. Mortality in this case reaches from 2.5 to 47–67 %. A large range in the rates can be explained by the lack of a unified view on the pathogenesis and diagnosis of this complication [5, 6].

The development of the SFE depends on the state of reactivity of the organism and its functional systems, the severity of damage, hemodynamic and metabolic shifts, the lack or insufficiency of immobilization during transportation of

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patients in the acute period of traumatic disease, frequent attempts to reduce fractures and invasive operations. Age, sex, overweight, osteopenia, and steroids therapy play a certain role in the development of FE [5, 7–10].

The first empirical attempt to study fat embolism in the experiment was undertaken by Richard Lower. In his *Tractatus* in 1669, he described the experiment with the injection of milk and fat into the venous flow of animals which led to their death, as it happens by the introduction of air into the vessels. This fact did not find an explanation for a long time. Only in 1841, F. Magendie demonstrated to his students his experiments on dogs. He injected olive oil into one of the veins of their necks, and opened its cause. The animals developed all the signs of pneumonia on the next day. When the dogs were sacrificed, F. Magendie discovered that the small vessels and capillaries of the lungs were blocked with fatty drops. On the basis of these pathoanatomical findings, he gave an explanation on the mechanism of animal deaths which approximated to the main provisions of the theory on fat embolism that were formulated much later [12–14].

The first purposeful experimental studies on fat embolism were performed by E. Bergmann (1863) who injected 6 ml of liquid pork fat heated to 37 °C into the superficial vein of the cats' thigh. The autopsy of animals that died immediately after the injection of fat revealed droplets of fat in the vessels of their lungs, areas of acute edema in the lung tissue alternating with foci of spotted and islet hemorrhages, and a pronounced expansion of the right heart. In the animals that remained alive for 6 to 24 hours, the author found fat in the urine and fat embolism of the vessels of the liver and kidneys at the autopsy.

F. Buch (1866) was the first to undertake a study to elucidate the pathogenesis of traumatic fat embolism. He injected a suspension of red cinnabar in the olive oil into the medullary canal of the rabbit's tibia and on the autopsy found fat drops containing traces of red cinnabar in the haversal canals, hip veins and lung vessels after producing a fracture of this bone.

Great attention was paid to the modeling of fat globulemia (FG) and fat embolism (FE) in the middle of the last century. The most common was the model with intravenous administration of non-esterified fatty acids that caused permanent morphological changes in the lungs, characteristic of a respiratory failure syndrome. For example, the dose of pure oleic acid causes acute diffuse lung damage. Its histological and morphological pattern is similar to the early stages of adult RDS. Olive oil which is close to the composition of the yellow bone marrow by the content of saturated and unsaturated fatty acids was used to develop adequate diagnostic tools and treatment in fat embolism modeling [5, 8, 10, 12, 15–17].

In the experiments of D.A. Fonte and F.X. Hausberger (1991), 86 % of the lipids were concentrated in the lungs after intravenous administration of neutral fat in rats decapitated after 12, 24 and 48 hours. This model was used to study the effectiveness of artificial ventilation, regulation of respiration and pulmonary circulation in embolic pulmonary edema [10, 17–22].

To enhance the effect of pulmonary edema, a mixture of unsaturated fatty acids with olive oil was injected intravenously in the experiments. These experiments assessed the hydrostatic pressure, velocity of the blood flow in the lungs, and the systemic blood pressure [19, 22, 23].

Current foreign experimental studies on laboratory animals apply intravenous administration of 0.5 ml or 0.08 ml per kg of a solution of Triolein which contains free fatty acids. In this case, pulmonary pressure increases, the permeability of blood vessels augments, and the clinical signs of FE develop [6, 11, 24-26].

On the other hand, some researchers, in particular R.R. Jakobs et al. (1993, 1996), considered injection of fatty acids and oil in its pure formula for production of fat embolism as an inadequate experimental model. Modeling of SFE with intravenous administration of olive oil or its mixture with unsaturated fatty acids and Triolein solution, which are foreign bodies, causes reactive inflammation and inadequately reflects the FE pattern [6, 23, 27, 28].

An alternative approach to the method for FE modeling is the mechanical damage of large tubular bones. One such method is the simultaneous impact of a falling guillotine or of a lateral pendulum that may cause injury not only to soft tissues but also fracture bones, as well as a freely falling

weight of 8 kg from a certain height for this purpose [12, 29, 30].

Multiple damage model according to Noble and Collip uses 4 rotating drums in which small laboratory animals are placed tied. FE according to the method described above was obtained with polytrauma without hemothorax or fractures of long bones in 30-50 minutes in 100 % of cases but massive FE was present in only 30 % of laboratory animals [5, 8, 16, 30].

E.A. Reshetnikov et al. (1969) in their experimental studies used closed fractures of the forearm, tibia, femur and humerus bones on both sides under combined analgesia for a FG model. Histologically, in 80 % of cases a certain degree of FE was detected by application of this model but its description provided no indication of the severe FE portion in the lungs [30, 31].

The methods of FE modeling by mechanical skeleton bone injuries also have a number of shortcomings. The use of the Noble-Collip apparatus in addition to the bone damage may cause injuries of internal organs, bleeding with the development of hemorrhagic and traumatic shock. Closed fractures of long bones under combined analgesia can also cause hemorrhagic shock. Thereby, histological studies did not reveal the presence of FE in all the cases.

At present, the number of orthopedic surgeries has increased. Therefore, a lot of studies are aimed at optimizing surgical tactics. The medullary cavity in large laboratory animals was reamed and after the introduction of pressure sensors, the nail was inserted into the intact tibia and femur. This model established that only the combination of hypovolemia, reinfusion of blood and the introduction of the nail into the medullary canal contribute to the occurrence of significant FE and damage to the lungs [10, 21, 32].

Reaming of the femoral and tibial bones with hermetic sealing of the medullary cavity in combination with transverse osteotomy on the contralateral side with fixation of fragments was used to evaluate the effectiveness of various osteosynthesis types in the experiment and their safety in terms of the development of fat globulemia. It revealed that the urgently performed intramedullary osteosynthesis increases the FG intravasation more than plating, especially by hypovolemia. With delayed osteosynthesis, the fixation method did not have any influence on FG [10, 22].

P. Murphy et al. (1997) performed bilateral cemented arthroplasty in dogs. Also in the experiment, FE of animal lungs was obtained with unilateral hip arthroplasty. In revision arthroplasty after unilateral cemented single-pole hip arthroplasty, a significant increase in FG was revealed in dogs as a result of cement removal with ultrasonic tools. The shortcoming of these models is the complexity of reproduction and inability to take into account all factors of pathogenesis. In the description of the above-mentioned models, there is no histological data on the rates of severe FE [10, 17].

A model of intravenous injection of 10 % allogeneic homogenized bone marrow in a dose of 0.7 ml/kg or 100 mg/kg was used to study hemodynamic changes, changes in the biochemical composition and blood gases, the level of biologically active and vasoactive substances in the process of FG development and diagnostic methods. This method of modeling cannot be applied to small laboratory animals [5, 12, 17, 22, 25].

The literature presents data on the modeling of pulmonary embolism without bone fractures that is by forced immobilization for 5 hours. It results in lipoprotein lipase activity increase, rise of free fatty acid level in the blood, growth of glucacneum and the tendency to pulmonary surfactant insufficiency [10, 13].

All the described models of FE were reproduced in large laboratory animals (rabbits, cats, dogs, pigs).

Importance of studying fat globulemia and embolism

Thus, there is an opinion among clinicians that the FE is currently much less common than in the previous decades. There are no problems with this complication diagnosis and treatment. However, the study of world literature on this issue has revealed a significant number of publications, more than 2,000 over the past 50 years that confirm the existing problem.

Despite numerous clinical and experimental studies, there is no unambiguous understanding of the nature of fat embolism. The accumulated data are interpreted from various methodological positions. There are no methods of timely diagnosis,

prevention, treatment and prognosis of possible outcomes of FG and FE.

In fact, current FE studies have not one indisputable position either in theory or practical management of this syndrome. Mortality due to this terrible complication remains quite high, despite the improvement of medical technologies and wide exchange of the information.

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