MICROEMBOLIZATION
IN THE
ADULT RESPIRATORY DISTRESS SYNDROME

MEDICAL GRAND ROUNDS

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June 26, 1980

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A. FAT EMBOLISM

1. *HISTORY*

a. *Recognition of fat embolism.* Zenker in 1862 first observed fat droplets in the pulmonary capillary bed in a railroad worker who died shortly after a crush injury to his chest and abdomen. Von Bergman, in 1873, is credited with the first clinical diagnosis of the condition. This feat was accomplished by Fenger and Salisbury 6 years later at Cooke County Hospital in the United States. (Peltier, 1971).

b. *Physiochemical vs mechanical theory.* Reports concerning the pathogenesis of fat embolism and the treatment of fat embolism have been confusing and at times, misleading. In 1927 Lehman and Moore reviewed available literature and summarized numerous medical conditions associated with pulmonary fat emboli that were not associated with trauma. They questioned the mechanical theory of fat embolism. They calculated on the basis of the lethal IV dose of cottonseed oil that release of fat from one human femur was inadequate to kill a man. They recognized that fat globules can be released from bone marrow after trauma but proposed that trauma also causes physiochemical changes in the blood which causes agglutination of circulating chylomicra and leads to fat globules in the blood. Subsequent studies by Glas in 1956 showed without question that there was enough fat in the marrow of one rabbit femur to kill a second rabbit. In 1968, Dr. Marvin Siperstein reviewed the subject of lipid embolization at Medical Grand Rounds at Parkland Hospital and concluded: "there is no real evidence to support the physiochemical theory of traumatic fat embolization. Traumatic fat embolization is best explained as being due to direct release of fat from bone marrow and/or soft tissue fat". In the following year, a series of animal experiments were reported by Kerstell and his associates, in a supplement to ACTA Medical Scandinavica that further laid to rest the physiochemical theory of fat embolism. They used the retrograde perfusion of the lungs to recover fat emboli in dogs after fractures. The emboli consisted mainly of triglyceride. The triglycerides and the emboli were similar to those from bone but differed from those in plasma in the fatty acid composition (Kerstell et al, 1969a). During fat embolization after the fractured femur, the serum lipoproteins did not change qualitatively or quantitatively suggesting that serum lipoproteins do not participate as a source or transport vehicle for fat emboli material (Gustafson and Kerstell, 1969). The animals were fed triglyceride with a fatty acid pattern different from post-absorptive plasma and bone marrow triglycerides. The dogs were then given trauma to produce a femoral fracture. Chylomicra appeared in the plasma with fatty acid patterns similar to the ingested fat but emboli and bone marrow triglyceride composition did not change.

(Hallgren et al, 1969a). Dogs that were fed alimentary fat labeled with 14c-tripalm tate and then traumatized did not have radioactivity in the pulmonary fat emboli (Kerstell 1969b). If the liver and the intestines were extirpated in the dogs before trauma, neither the amount of emboli or the composition of the emboli differ from those in earlier experiments in dogs having liver and intestines intact. These results indicated therefore that emboli are not formed from free fatty acid release by trauma and then reesterified in the liver and intestines (Kerstell, 1969c). Increasing free fatty acids secondary to norepinephrine or decreasing free fatty acids secondary to nicotinic acid prior to the trauma did not alter the number or amount of pulmonary fat emboli. When 14c-labeled fatty acids bound to albumin were infused during experiments where dogs received intravenous norepinephrine the fatty acids were not incorporated into fat emboli (Hallgren et al, 1969a). The conclusion of the whole series of experiments was that fat embolization after fractures in dogs is due to a mechanical liberation of marrow fat and is not due to the rise in the rate of fatty acid mobilization from adipose tissue induced by the trauma (Kerstell, 1971).

c. *Free fatty acid theory.* Peltier (1969) reviewed experiments of his own and others concerning the pathogenesis of the fat embolism syndrome. Largely through indirect evidence he concluded that the breakdown of neutral fats in the lung by lipoprotein lipase releases free fatty acids which serves as the focal point for (1) interfering with lung surfactant activity and causing atelectasis (2) damage to the alveolar wall causing fibrin deposition and (3) injury to the capillary endothelium causing first edema and then hemorrhage into alveolar spaces.

d. *Brain embolism theory.* Simon Sevitt wrote a book on fat embolism in 1962. He concluded that all clinically significant fat emboli are probably due to fractures but concluded that the pulmonary pathology and symptoms are not due primarily to pulmonary emboli but are secondary to cerebral embolization. However, in his review in 1977 he acknowledges the primary pulmonary role and the high incidence of inapparent hypoxemia after fractures.

e. *Hypoxemia in fat embolism.* Sproule et al, 1964 were the first to document, by blood gases, the hypoxemia of severe fat embolization. They pointed out that their 3 patients did not have clinical cyanosis probably due to coexistent anemia and high cardiac output. Collins and associates in 1968 during the Viet Nam war reported on the incidence of inapparent hypoxemia in casualities with wounded limbs. They included only patients with penetrating missile wounds with no other reasonable cause for hypoxemia. The most common condition associated with hypoxemia was high velocity missile wounds that resulted in a fracture of the femur and low velocity missile wounds never caused hypoxemia. Collins and associates proposed that pulmonary fat emboli were the likely etiology

for the hypoxemia. However, this hypothesis would be difficult to prove because of the lack of any reliable diagnostic test for the condition. Pulmonary fat embolism has always been and remains a clinical diagnosis that is fairly characteristic in its full blown picture, but very non-specific in less severe cases.

2. *PATHOGENESIS*

a. *Free fatty acids* Peltier demonstrated convincingly in 1956 that there was a very distinct difference between the behavior of those animals injected with neutral fat and those injected with free fatty acids. The free fatty acids were much more toxic. Unsaturated fatty acids were more toxic than saturated fatty acids. The LD 50 dose of human fat or triolein for rabbits was 900 mgm per kilogram intravenously. After injection of human fat or triolein the rabbits became dyspneic, the ear veins became engorged with blood and occasionally some white foam appeared at the nose and mouth. Sudden death, less than 1 minute after injection could not be produced by using larger doses than the LD 50. At the time of autopsy the striking findings were (1) the tremendous dilatation of the right heart and (2) the anemia or white appearance of the lung. The weight of the lungs was slightly increased above normal. Microscopically there was some congestion but the alveolar pattern appeared intact. There was little blood in the lungs and none in the alveoli. Occasionally some alveoli were noted to be filled with a clear transudate or edema fluid. The findings indicated that the animals died of acute right heart failure as a result of mechanical obstruction of the arterioles of the pulmonary vascular bed. On the other hand the LD 50 dose for oleic acid was only 250 mgms per kilogram. Following injection, dyspnea appeared more slowly and was accompanied by a profuse drainage from the nose and mouth of red bloody froth. In about 10% of the animals, death was immediately preceded by convulsion and marked opisthotnus By increasing the dosage above the LD 50 sudden death in less than 1 minute after injection could be produced. At autopsy the heart was not markedly dilated. The lungs were engorged with blood weighing 2 to 3 times their normal weight. The tracheabronchial tree was filled with bloody foam. Gross blood dripped from the pleural surfaces. Histologic examination showed alveoli filled with blood stained exudate and whole blood. The alveolar structure in many areas had completely disintegrated. These findings indicated that the animals died as a result of hemorrhaging to the lung due to the chemical action of fatty acids upon the capillary endothelium with resulting exudate and hemorrhage.

Peltier's findings have been confirmed by others and there is little question that free fatty acids are more toxic to the lung than neutral fats. There is also little question that the lung has large quantities of lipoprotein lipase available on the surface of the endothelium which should be capable of hydrolyzing the triolein of neutral fats into glycerol and free fatty acids. (Dimant and Shafir, 1974). The question

is whether or not as the result of hydrolysis of the neutral fat, free fatty acids can reach high enough concentration to damage the capillary endothelium. Patients with fat embolism do not have unusually high free fatty acid levels, certainly not as high as patients with diabetic ketoacidosis. Some patients with diabetic ketoacidosis develop severe pulmonary edema during treatment, but this has been attributed to the high salt loads and the acidosis, similar to the sequence of events during treatment of cholera. Yet, small quantities of free fatty acids could conceivably result in rather high local concentrations, if pulmonary capillary blood flow is extremely slow in regions severely obstructed by fat globules. Szabo (1977) compared the intravenous injection of glycerol trioleate with mineral oil in rabbits. He found that the free fatty acid concentration in the lung increased after triolein but did not increase after mineral oil injection. The peak in the free fatty acid concentrations after triolein injection peaked at 24 hours but the increase in lung weight of these animals did not peak until 48 hours. Pathologic appearance of the lungs in rabbits receiving triolein injection began to improve by the 4th day but this did not happen after the mineral injection. The difference was attributed to the fact that mineral oil was inert and not metabolized whereas the triolein was metabolized. The metabolically inert mineral oil was not attacked by tissue enzymes and remained more permanently lodged in small vessels. This lead to stasis and hemorrhagic microinfarcts and a subsequent foreign body reaction around the oil droplets. The authors felt that their observation supports the assumption that pulmonary changes in fat embolism are due to the toxic effects of free fatty acids liberated from the particulate neutral fat emboli. In a separate study they found that if free fatty acids are given in small divided doses at 6 hour intervals the toxicity accumulated. The more fulminating acute symptoms were absent and small repeated doses of free fatty acid induced a syndrome quite similar to that observed after administration of sub-lethal doses of neutral fat. The lungs had interstitial and alveolar edema as opposed to the severe hemorrhagic alveolar damage induced by larger doses of oleic acid. Thus it is possible that free fatty acid release from embolic fat globules contributes to the lung injury. However, I doubt that free fatty acids carry the central focal importance given to them by Peltier.

b. *Surfactant* Hamilton (1964) utilized a Wilhelmy balance to investigate the surface tension lowering qualities of lung extracts both in vivo and in vitro experiments with cats. He compared mineral oil, triolein, and oleic acid. After IV injections in acute experiments good surfactant activity remained in 100% of the animals receiving mineral oil, 48% of the animals receiving triolein and only 7% of the animals receiving oleic acid. In more chronic experiments, 4 days after the injection, only 8% of the cat lungs had good surfactant activity following mineral oil. The reduction of surfactant activity was attributed to the obstruction of pulmonary arterioles which did not disappear because mineral oil is not metabolized. On the other hand by 4 days 55% of the

animals had good surfactant activity after triolein, similar to findings immediately after injection of triolein. Presumably the triolein was metabolized, reducing the degree of obstruction and allowing some improvement. In vitro experiments with normal cat lung extracts showed that mineral oil had no effect on the surfactant material whereas triolein and oleic acid both completely neutralized surface tension lowering qualities.

c. *Increased hydrostatic pressure* McKeen and associates (1978) infused 10% intralipid into unanesthetized chronically instrumented sheep. The infusion caused pulmonary hypertension, hypoxemia, increased lymph flow, and decreased lymph to plasma protein concentration ratio. These findings were similar to the findings when pulmonary vascular pressures are mechanically elevated with left atrial balloon and unlike increased permeability pulmonary edema (Fishman and Renkin, 1979). The response was not altered by heparin, which prevented triglyceride increase but not free fatty acid increase. The intralipid had high concentrations of oleic and linoleic acid. The response was blocked by endomethocin suggesting that the pulmonary hypertension was due to a prostaglandin that caused pulmonary vasocontriction or pulmonary venoconstriction.

d. *Coagulation* Intravenous fat emulsions used for parenteral hyperalimentation have been shown to increase the blood coagulability as measured by a thrombin generation test. Brockner and associates in 1965 used a thrombin generation test which measures excess thrombin over and above the amount needed to cause clotting. The excess thrombin generation could be shown both by adding the intravenous lipid preparations to plasma in vitro and by intravenous injection into patients. During the intravenous infusion of the lipids platelet count fell in 8 of 9 patients. Simultaneous treatment with a small dose of heparin, 5 units per ml of the intravenous lipid preparation prevented the excess thrombin generation.

Platelets Peltier (1969) injected small amounts of triolein into normotensive dogs and observed an immediate drop in circulating platelets. An even more dramatic drop followed intravenous oleic acid.

The thrombocytopenia could create a vicious circle making pulmonary edema worse. Lahnborg et al (1976) created thrombocytopenia with busulfan in rabbits who were given intravenous injections of hemologous retroperitoneal fat. There was twice as much increase in wet lung weight in the thrombocytopenia animals compared to increase in lung weight in animals with normal platelet counts.

Bradford et al (1970) reported on 23 patients who had acute traumatic injuries with one or more fractures to major long bones and frequent pelvic fractures. Serial platelet counts were available in 10 patients who became desaturated and 12 patients without desaturation. In the patients with desaturation, the lowest platelet count reached was 83,000 compared to 157,000 in patients without desaturation ($p < .02$). The

general pattern with other coagulation tests often showed an initial low fibrinogen followed by a sharp rebound in 3 to 5 days to levels above normal. An oscillatory pattern in the partial thromboplastin time and frequently prolonged prothrombin time and thrombin times were common and seemed related to the severity of the injury. The authors concluded that the findings probably reflected platelet aggregation and disseminated intravascular coagulation initiated by tissue thromboplastin release.

Evidence for DIC with fat embolism has been found by others. Curtis et al (1979) found that thrombocytopenia correlated better than anything else with the severity of pulmonary damage in the fat embolism syndrome. Risenborough and Herndon (1976) studied 118 patients with bone fractures from the pelvis to os calcis. Only 2 developed clinical finding of fat embolism syndrome but 58 patients had hypoxemia. Hypoxemic patients frequently had thrombocytopenia, increased platelet adhesiveness and elevated fibrin split products. These findings were generally absent in patients without hypoxemia.

They proposed that there is a subclinical form of the fat embolism syndrome. Herndon et al (1974) had already shown that macroscopic fat emboli can be found in large quantities in the femoral vein draining the region of a total hip replacement in all patients. Yet none of 34 patients with total hip replacement developed the fat embolism syndrome or enough hypoxemia to require oxygen therapy.

Others have shown that after fractures of the lower extremities macroscopic fat globules are increased in femoral vein blood samples but not in arterial or peripheral venous samples (Meek et al, 1972). Prompt immobilization is considered very important (Grossling and Donahue, 1979) for elevated pressure around the fracture site can increase fat embolism (Hamberger and Whitenach, 1972).

If fat embolism is so common why do so few patients develop the full blown syndrome with respiratory insufficiency, cerebral symptoms and petechiae? In animal models the quantity of fat emboli and the duration of embolization are important. Hypoxemia is worse following larger doses of intravenous depot fat in rabbits and repetitive small doses produce progressively more severe hypoxemia (Collins and Caldwell, 1970).

The general condition of the patient and the extent of trauma and ischemia elsewhere likely contribute to whether fat emboli induce much pulmonary damage. Experiments in rabbits show that an intravenous dose of homologous liquid fat of 0.45 ml/kg produces a mortality rate of 17% within 24 hours. (Hardman and Ragaz, 1950). Severe hind leg ischemia three hours before an injection of the same dose of fat leads to a mortality rate of 42% within 30 hours. The authors thought that shock

associated with the edematous hind limb was the factor that made mortality rates worse. However, subsequent studies have shown that regional ischemia produced by cross clamping the aorta of a dog leads to platelet microemboli and a typical ARDS picture (Goodman et al, 1968). The platelet microemboli can be prevented by pretreatment with heparin. In the hands of Hardman and Ragaz the ischemic hind limb alone did not lead to death of any animals within 30 hours. Creation of dehydration in the rabbits prior to injection of fat also increased mortality from 17% to 50%. Nevertheless some animals with marked hemoconcentration and extravascular dehydration survived,whereas others with little or no detectable change succumbed to fat injection. Obviously there are many factors involved that influence the response to fat emboli.

Traumatized patients who develop the fat embolism syndrome appear to be different constitutionally from those who do not (Avikainen et al, 1980). Ten patients who developed fat embolism syndrome were compared to 10 patients with similar degrees of trauma who did not develop the syndrome. Studies were performed at least a year following the trauma. Patients who developed fat embolism syndrome had significant abnormalities of carbohydrate and lipid metabolism, coagulation, capillary fragility, neurohumoral regulation and response to exercise stress that were different from traumatized patients without fat embolism syndrome, Table I. The diabetic heredity and the increase in beta lipoprotein is particularly interesting. Increased aggregation of platelets has been documented in diabetics, particularly those with retinopathy or nephropathy (Kwaan et al, 1972) but also even in latent diabetics or prediabetics (Sagel et al, 1975). Familial hyperbetalipoproteinemia (Type II hyperlipoproteinemia) is associated with increased in vitro aggregation of platelets to very low doses of stimulants such as epinephrine collagen or ADP. (Carvalho et al, 1974).

Table I

Following trauma patients who develop fat embolism syndrome differ from those who do not by having:

A. Disturbance of carbohydrate metabolism:
   - Blood glucose elevated in 3/10
   - Blood glucose rose after exercise in most
   - Beta lipoproteins were higher
   - Diabetes heredity in 5/10

B. Evidence of hypercoagulability
   - P & P values higher
   - Platelet counts higher, especially after exercise
   - ? increased fibrinolytic activity

C. Evidence of increased capillary fragility
   - More petechiae on Rumpel-Leede's Test

D. Abnormal neurohumoral regulation
   - Lower values for growth hormone
   - Urinary catechae amines ? higher
   - Cortisol did not fall after exercise
   - Total protein and albumin concentration did not fall after exercise

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Avikainen et al J. Trauma 20:148, 1980

Fibrin formation and lysis Saldeen has presented autopsy as well as clinical and animal experiments to support his contention that fat embolism induces coagulation of fibrin within the lungs and that break down products of the fibrin induce the increase in capillary permeability. In 1970 Saldeen reported on 325 autopsies with patients who had died more than 1 hour after severe trauma. Fat emboli were found in 79 or 26% of the patients at the time of autopsy. In 35 patients fat embolism was considered to have been the only cause of death. In these 35 patients, 14 (40%) had intravascular fibrin detected within the lungs. He used a Mallory PTAH and a PICRO-Mallory stain for detection of fibrin. In 44 patients fat emboli were found in the lungs but the fat embolism was considered only to be a contributing factor for the mortality. In these patients only 5% showed intravascular fibrin in the lungs. When there was no evidence of fat embolism intravascular), fibrin within the lungs was also detected in 4% of the patients. In 1969 Saldeen induced fat embolism in rats, either by heavy trauma to the thigh and lower leg with fracture or by intravenous injection of hemologous homogenized adipose tissue. When the rats were sacrificed at 24 hours after the intravenous fat, there was no fibrin found in the lungs. However, if 125-I fibrinogen was injected simultaneously with the intravenous fat, counts went up in the lungs between 5 and 15 minutes after injection, but disappeared by 60 minutes. He postulated that the rapid disappearance was due to rapid lysis of the fibrin that formed around the fat emboli. The increased counts of the 125-I fibrinogen in the lungs could be prevented by heparin or by pre-heating the fat to 100 degrees centigrade which is known to inactivate thromboplastic substances. In a subsequent similar experiment (1970b) Saldeen showed that premedication of the rats either with heparin or plasmin inhibited the deposition of fibrin in the pulmonary vessels and improved the tolerance of the animals to acute pulmonary fat embolism. (They could receive significantly more fat emboli before death). Also when he pretreated the rats with epsilon aminocaproic acid, a plasminogen activator inhibitor, there were more numerous and larger pulmonary changes after the same amount of intravenous hemologous adipose tissue (1969b) and intrapulmonary fibrin persisted longer (1970b).

The mechanism of the increased capillary permeability due to fibrin degradation products will be discussed under fibrin microembolization below.

There is evidence that following severe trauma there is an abnormal lipoprotein with increased affinity to fibrin which inhibits fibrinolysis (Kunz et al, J. Trauma 1978). Plasmatic lipids, particularly triglyceride, complexed with fibrins were elevated several fold in patients with adult respiratory distress and fat embolism syndromes when compared with multiple trauma patients without pulmonary complication. This was independent of plasma lipid levels which had all fallen. Plasmatic triglycerides complexed with fibrins were significantly higher in patients who died then in those who survived.

3. *PATHOPHYSIOLOGY*

Ashbough and Uzatwa (1978) found that the dose of oleic acid of 0.06 mgms per kg intravenously produced death in all dogs within 5 hours. They investigated 10 dogs that survived long enough to study. The dogs developed progressive hypoxemia from a PO_2 of 80 to an arterial PO_2 of 33 along with decreased dynamic compliance. The pathologic exam of these dog lungs showed that they were collapsed and noncrepitant and that the pleural surfaces had blotchy areas of hemorrhage. Microscopic exam showed occasional thrombi and there was interstitial edema and congestion with variable amounts of atelectasis and intraalveolar hemorhage. There was a conspicious absence of acute inflammation which points out that the absence of acute inflammation cannot argue against free fatty acids as being the cause of lung injury. Baker et al, (1969) compared a similar dose of oleic acid as used by Ashboughwith triolein, 1 mgm per kg intravenously. The triolein had little or no effect on compliance, blood gases, chest x-ray or surfactant activity of extracts of autopsied lung. Oleic acid in dogs that were not treated with a respirator produced hypoxemia and a striking decrease in compliance along with thrombocytopenia. With the addition of a respirator the hypoxemia appeared to be about the same degree and significant decrease in compliance also occurred. However, in this experiment, positive end expiratory pressure was not used, and they did not state whether they periodically sighed the animals. The study of Baker would lead one to believe that triolein or neutral fat is relatively innocuous over a 24 hour period of time. However, in 1970 Collins and Caldwell injected depot fat intravenously into rabbits in doses varying from 0.1 ml to 0.4 of a ml/kg. There was a marked drop in arterial oxygen tension at 5 minutes with all but the smallest dose and with the larger doses, hypoxemia persisted for several days. With the larger doses there was somewhat of a biphasic curve to the hypoxemia that Collins felt was compatible with free fatty acids being released by lipoprotein lipase. If the rabbits were given a repetitive intravenous injection of 0.1 ml per/kg of depot fat over a 2 day period, the hypoxemia was progressive and severe. With the larger doses renal and cerebral fat emboli appeared.

Goodman and Silver (1978) showed that in the dog a femoral fracture alone produced through an open wound will not acutely produce the fat embolism syndrome. However, there is human data suggesting that a closed fracture of the femur is different (Perkoff and Collins, 1971). Goodman and Silver then reemed the medullary canal of the femur in order to free up bone marrow fat and particulate matter and allowed an arterial bleeder into the wound to mobilize the fat. An autotransfusion sucker was used to collect heparinized blood mixed with femoral marrow fat which was then re-infused intravenously into the dog. They showed without a question that there is enough fat in the femur of a dog to produce a full blown fat embolism syndrome. By use of selective filters they showed that fat globules between 20 and 125 microns in size are primarily responsible. With enough fat emboli of these sizes, brain fat emboli occur. With the acutely elevated pulmonary artery pressures associated with a lot of particulate fat emboli, some of the fat emboli probably

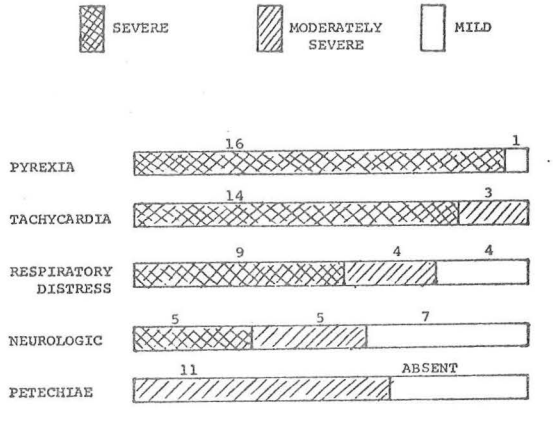
traverse arterio-venous connections that normally exist in the lungs. Tobin (1950) demonstrated that microspheres as large as 500 microns in diameter can pass through freshly atuopsied lungs that are having the pulmonary artery perfused with high pressures. Similar large pulmonary arterio-venous connections have been demonstrated by Prinzmetal (1948) in rabbits, dogs, and cats.

The Mechanism of Hypoxemia Sproule et al (1964) studied 3 patients with fat embolism syndrome with blood gases while inhaling different inspired oxygen tensions. In the early stages there appeared to be a diffusion defect suggested by a larger alveolar arterial oxygen tension gradient on room air than while breathing 40% oxygen. Later the oxygen deficit in arterial blood could not be corrected by breathing 100% oxygen and suggested intrapulmonic shunting. The multiple inert gas elimination method has been utilized in dogs with IV hemologous neutral fat to determine ventilation-perfusion relationships. (Tornabene et al, 1979). Immediately after embolism there was increased ventilation to regions with high V/Q in the range of 10 to 100 but there was no increase in regions with complete dead space ventilation. Also there was no increase of perfusion in regions with low V/Q or complete shunt. The high V/Q regions appeared immediately after ventilation and had disappeared by 2 hours. Even though the method of studying these dogs was sophistocated, the information is probably misleading because of the fact that the authors utilized 3 cms of water PEEP during the study. This may have opened up closed airways that would have appeared as shunting.

4. *CLINICAL MANIFESTATIONS* Herndon et al (1971) described the classic case as a patient within the first 3 days after a fracture being noted to have a tachycardia of 140 beats per minute, tachypnea of 30 to 40 respirations per minute, and a fever up to 103 degrees. Dyspnea may become prominent and the patient may become cyanotic but this is not a common finding. Rales may be heard, respiratory symptoms may reach such severity as to lead to eventual death. If systemic emboli have occurred, both the skin and the central nervous system are most commonly involved. Emboli to the brain lead to mild symptoms such as headache, restlessness or increasing irritability: and then go on to delerium, stupor, or coma. If the vital centers are involved shock or death occur. The frequency of clinical findings in 17 patients described by Herndon et al as shown in Table II.

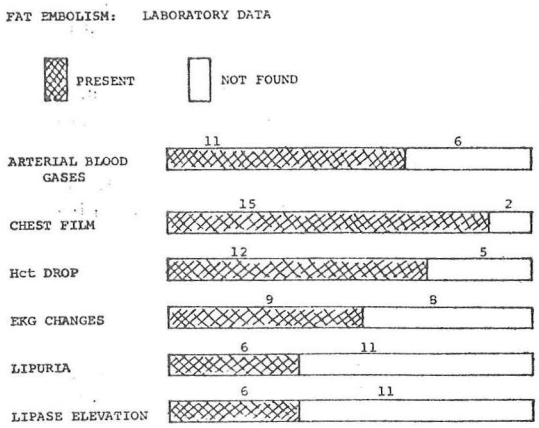
TABLE II

FAT EMBOLISM: CLINICAL MANIFESTATIONS



The frequency of laboratory findings are shown in Table III.

TABLE III



Peltier lists his criteria for the clinical diagnosis of fat embolism in Table IV.

TABLE IV

The Criteria for the Clinical Diagnosis of Fat Embolism

1. A history of skeletal injury, particularly multiple fractures of long bones, pelvis and ribs
2. A history of hypovolemic shock
3. Petechial hemorrhages
4. Tachypnea and dyspnea
5. Disturbances of consciousness: confusion, delirium, coma

However, not all of these features are present in any one patient. Another approach is the one suggested by Gard et al, (1970, 1974), as shown in Table V.

TABLE V

DIAGNOSIS OF THE FAT EMBOLISM SYNDROME

Injury	
Latent period	
Major features—	1) Respiratory insufficiency; 2) Cerebral involvement; 3) Petechial rash
Minor features—	1) Pyrexia; 2) Tachycardia; 3) Retinal changes; 4) Jaundice; 5) Renal changes
Laboratory features—	1) Anaemia; 2) Thrombocytopenia; 3) High erythrocyte sedimentation rate; 4) Fat macroglobulaemia

They divided the clinical features into major clinical features and minor clincal features. The clinical diagnosis was made in any case of injury in which at least one major feature plus 4 minor features of fat embolism were present along with fat macro globulinemia. Their method for detecting circulating fat globules will be described below. They did not have any independent means of validating their approach to diagnosis but at least it was standardized. They reported the findings in 100 patients with fat embolism syndrome diagnosed by their method. (Table VI and VII).

Table VI: Initial findings on admission

# of Patients	Findings
34	Cerebral-usually drowsiness or confusion
29	Tachycardia and pyrexia
20	Respiratory dysfunction-dyspnea, tachypnea or hemoptysis
17	Petechiae rash

Table VII: Findings during the total hospitalization

# of Patients	Findings
75	Respiratory involvement
80	Cerebral involvement
57	Petechiae
83	Temperature >39.4^{0} c and pulse >120
22	Renal impairment; 17 oliguric; 3 anuric
7	Retinae exudates
5	Jaundice

Recovery was full in 77 patients and partial in 7. Sixteen patients died--8 due to fat embolism syndrome.

The distribution of the skin petechiae in fat embolism is interesting. Tachakra in 1976 noticed a patient who had to recline on one side for comfort. The petechiae appeared only on the up side. When the patient was eliberately turned over and the old petechiae were marked, new petechiae appeared again only on the side that was up. The phenomenon was confirmed in other patients and he proposed that the distribution is consistent with skimming off floating fat emboli by the branches arising from the top of the aortic arch.

Fat embolism for years has been considered to have a latent period. Sevitt in 1962 reported that in 100 cases of fat embolism the appearance of symptoms occurred at less than 12 hours in 25%, less than 24 hours in 60% and then in less than 48 hours in 84%. More recent studies based on

early arterial blood gases have suggested that the latent period was an artifact of inaccurate clinical observation. The hypoxemia is there before the patients have overt symptoms.

In 1972 Sevitt reported on 854 cases of fractured hip and found that clinically important cases of fat embolism occurred in 16 patients. There were 8 deaths due to fat emboli. Fat emboli were more frequent with subcapital fractures than with trochanteric fractures. He also found that fat embolism was more common if the patient were treated without operation than if the fracture was immobilized with a pin, nail or plate operatively. One particular type of treatment had an unusually high frequency of fat embolism. This was found using Thompson's prosthesis which uses acrylic cement to hold it in place. He proposed that the acrylic cement sealed the bone while the prosthesis was being forced into place and high pressures were induced in the medullary canal. He suggested that more fat emboli occurred than if there had been a leak off valve. Another type of prosthesis, the Moore prosthesis, did not use acrylic cement, even though it required forcing into the medullary canal. The Moore prosthesis was not associated with any fat embolism syndrome. Collins, while discussing a CPC in the American J. Med. in 1971 commented that pulmonary fat embolism occurs in many patients with broken tibias, most patients with broken femurs. He also commented that in Viet Nam the incidence of fat embolism with open femoral fractures was about 2 per 100 patients, whereas with closed femoral fractures the syndrome of fat embolism occurred in about 5 out of 15 patients.

In Viet Nam,Collins and associates (1968) reported on inapparent hypoxemia in casualties with wounded limbs. He included 69 patients with penetrating and missile wounds of the limbs in patients who had no other reasonable cause for hypoxemia. Fourteen of the 69 had PaO_2 of less than 80 mm Hg on admission. This hypoxemia occurred in 6 of 13 patients with high velocity missile wounds that included a fracture of the femur but in only 2 of 21 high velocity wounds in the other regions. Also low velocity wounds did not have hypoxemia in any of 22 patients. Blast amputations of major limbs had hypoxemia in only 1 of 7 patients, but when there was a partial amputation of a foot as a result of stepping on a mine all 3 of those patients had hypoxemia. Pollak and Myers (1978) studied 100 consecutive patients with fractures of long bones of the lower limbs. Seventeen patients developed typical fat embolism syndrome and 16 additional patients had PaO_2 of less than 60 mm Hg without any other manifestations of fat embolism syndrome.

Three syndromes of fat embolism Curtis and associates (1979) described 3 distinct syndromes of fat embolism in patients collected from several institutions who all had classic triad of neurologic dysfunction respiratory insufficiency, and petechiae following major trauma.

The first response was the hyperacute response. Death occurred within 48 hours due to paradoxical embolization of the systemic circulation. One patient had an atrial septal defect that had been previously unrecognized and had multiple organ emboli including the brain. The second patient had coronary artery fat emboli with no anatomic shunt found.

The classic response was seen in 18 patients. The hypoxemia was mild in these patients and was corrected with 20 to 40% oxygen. Chest roentgenographic findings were variable with 3 showing normal patterns, 3 had localized patchy densities, 6 had bilateral linear densities spreading out from the hilar periphery consistent with interstitial edema and 6 had frank pulmonary edema. There were only 2 patients in the whole series who had pleural effusions and both of these patients died of multiple large pulmonary emboli shown at autopsy. Prothrombin time and APPT were about 75% of normal but the platelet counts were low in the 75,000 to 100,000 range with normal being 250,000 to 300,000. Lung biopsies showed fat droplets in scattered capillaries and arterioles. Edema fluid was present in the interstitium early and increased later. However, there was no extensive alveolar hemorrhage, hyaline membrane formation or interstitial fibrosis.

Ten patients had a frank adult respiratory distress syndrome. Hypoxemia was severe and inspired oxygen tensions of concentrations of 60 to 80% were required to correct hypoxemia. All had evidence of disseminated intravascular coagulation at some point with hematocrit less than 30, platelet count less than 100,000 prothrombin time more than 6 seconds above control, activated PTT more than 10 seconds above control, and fibrinogen less than 100 mgms per cent with a concomitant increase in fibrin split products. Six died as a result of pulmonary hemorrhage or fibrosis. Chest radiographs were all compatible with pulmonary edema. Wedge pressures when measured were normal. The histologic findings of lung biopsies showed occlusion of multiple pulmonary arteries with fat emboli in the pulmonary capillaries. Capillaries were surrounded by atelectasis, hemorrhage, macrophages and mononuclear cell inflammatory response. Electron microscopy showed platelet and fibrin aggregation within multiple capillaries and arterioles. In the whole study the thing that correlated better with the degree of pulmonary damage was thrombocytopenia and the eventual development of consumptive coagulopathy.

Total Hip Replacement

The lack of development of fat embolism syndrome following total hip replacement has always been perplexing, considering the degree of controlled trauma that is associated with this operation. Herndon, et al in 1974 carefully studied 34 patients who had total hip replacements. With 4 different methods they demonstrated that virtually all patients developed fat emboli although none developed the typical fat embolism

syndrome or required oxygen treatment for hypoxemia. An ultrasound probe was placed over the femoral vein on the side of the operation and it showed characteristic chirps for fat emboli at the time of surgery. Blood sample from the femoral vein compared to blood from a control site demonstrated considerable increase in fat globules by a cryostat test, a millipore filter test, and by demonstrating a decrease in tryglyceride measurement after filtering the plasma through an 8 micron filter. They also demonstrated that increased pressures with insertion of the prosthesis were related to the degree of fat embolization. The number of fat emboli could be significantly reduced by placing a catheter drain in the medullary canal and connecting it to a suction during the insertion of the cement.

5. *DIAGNOSTIC TESTS*

"Gold Standard" There is no definitive diagnostic test for fat embolism. It is obvious from studies such as that of Herndon following total hip replacement (1974) that fat emboli can occur in large numbers with great regularity without producing what we characteristically know as the fat embolism syndrome. Therefore, the syndrome will always likely be predominantly a clinical diagnosis. Even at the time of autopsy, cardiopulmonary resuscitation just before death can lead to pulmonary emboli making the autopsy diagnosis unreliable. Without a gold standard diagnostic test or even a reliable autopsy indication of the condition evaluation of any potential diagnostic test is of course very difficult.

Fat in sputum and urine Examination of the sputum for fat has been proposed but has been found to be very non-specific. Musselman et al, 1952, found that 80% of sick patients without injury had fat in the sputum. However, only 12% of these same sick patients had fat in the urine. 52% of his 109 patients with injuries had fat in the urine. 77% of the patients with hip fractures had fat in the urine. Glas and Grekin in 1953 re-evaluated the same 109 patients assuming that the presence of fat in the urine was diagnostic of fat embolism associated with injury. In 50 patients without injury to the chest, 1/3 of them had pulmonary symptoms. In 45 patients without head injury, 1/3 had cerebral symptoms. Petechiae were present in only 2 (4%) of the patients. In 17 patients with a full blown fat embolism syndrome only 6 had lypuria (Herndon, 1971).

Lipase Lipase elevations have also been proposed as a useful diagnostic test. However, in Herndon's 17 patients, only 6 had elevations of lipase (1971). A possible explanation for the lack of elevation of lipase in some patients can be seen in the animal experiments of Dimant and Shafir (1974). They infused rats with VLDL or triolein and found that the lipoprotein and lipase content of the lung decreased significantly while increasing markedly in the serum. However, when larger individual fat cells were infused intravenously, there was no reduction in lipo-protein lipase content of the lung or increase in lipase concentrations

in the serum. They proposed that triglycerides in the form of VLDL or triolein can interact with the surface bound enzyme and dislodge it, whereas the larger particle completely obstructs the lumen and does not dislidge the lipase.

Thrombocytopenia Bradford, et al (1970) found that all of the 10 patients who became desaturated after long bone fractures had thrombocytopenia at some point, whereas the 12 patients without desaturation did not develop thrombocytopenia. Curtis, et al (1979) also found that thrombocytopenia developed related to the severity of the fat embolism syndrome and occurred in all patients who developed the adult respiratory distress syndrome associated with fat embolism. Other findings typical of DIC and substantial drops in hemoglobin are not uncommon.

Hypocalcemia occurs at times (Sproule et al, 1964).

Biopsy of skin lesions show fat globules in the hands of some (Sevitt, 1962) but not others (Bradford, et al 1970).

Methods to detect fat globules in the serum Huaman in 1969 reported a method of obtaining a cryostat section of a retracted blood clot and then staining for neutral fat. In 1971 Huaman and his associates, reported on the results of the cryostat test in 120 patients with fractures likely to give rise to fat embolism. In patients who had typical fat embolism or mild respiratory symptoms, the cryostat test was positive in 26 and negative in 2. In asymptomatic patients the cryostat positive test was positive in 11 and negative in 81. 50 healthy normal persons all had negative tests.

Gurd (1970) reported a method of collecting serum and measuring triglycerides before and after filtering the serum by gravity through an 8 micron millipore filter. He made the diagnosis of fat embolism syndrome in patients who had one major symptom and 4 minor symptoms listed in Table V. In 30 patients with fat embolism syndrome the mean triglyceride level was 119 milligrams per 100 milliliters before the filter and 69 milligrams per 100 ml after the filter. In the 30 patients without the fat embolism syndrome tryglycerides were 113 milligrams per 100 ml before filtering and 104 mg per 100 ml after filtering. The differences in reduction of the tryglyceride level were significant with a $p < .02$. The average latent period after the fracture before the appearance of symptoms was 40 hours. In the patients with the fat embolism syndrome, in every case when symptoms were present circulating fat globules were found. In 70 patients without the clinical syndrome, 37 had circulating fat emboli immediately after injury, 10 had fat globules 24 hours later but none had fat emboli 48 hours later. Thus it appears that fat macro globules in serum rapidly disappear after major trauma. With delayed respiratory symptoms the presence of fat macroglobules gives support to the diagnosis of fat embolism syndrome.

6. *TREATMENT*

Intravenous Alcohol Intravenous alcohol has been recommended since the late 1920s for the treatment of fat embolism. The rationale is that alcohol inhibits lipoprotein lipase which could conceivably present release of the free fatty acids that are toxic to the lungs. Her in 1932 presented experimental evidence in rabbits that intravenous alcohol made fat emboli disappear more rapidly. He injected 24 rabbits with 1 cc per kg of intravenous sterile fat warmed to 37°C. The rabbits were divided into groups that received none or increasing amounts of alcohol. They were atuopsied at 48 hours and examined histologically after sudan III staining for fat droplets. The number of fat droplets were graded from 1 to 4+. With no treatment the fat droplets were graded as 4+. With 1 dose of intravenous alcohol the amount of fat droplets were 3+. The dose of alcohol was 5 cc per kg of a mixture of 3 parts of 96% alcohol and 7 parts of 25% dextrose. Another group of animals received 2 doses at 12 hour intervals and the amount of fat at autopsy was graded as 2+. The animals that received 3 doses at 12 hour intervals had only 1+ fat at the time of autopsy. Intravenous alcohol has been used extensively since the time of this report and was still recommended in a review article by Peltier in 1971, despite equivocal results reported by his group (Adler et al, 1961) I can find no control trials of intravenous alcohol in humans with fat embolism.

Heparin Heparin has been recommended for exactly the opposite rationale as alcohol. Heparin activates lipoprotein lipase and some have theorized that this would help eliminate fat in the lungs. Saldeen (1979) has presented convincing evidence that coagulation and fibrin deposition on top of fat emboli contributes significantly to the pathogenesis of the pulmonary edema. However, even Saldeen admits that the problem is complex and because of the tendency for bleeding into the alveoli, he does not recommend treatment with heparin. In animals with fat embolism, heparin does not benefit survival (Mokkhavesa et al, 1969; Glas et al, 1956). I can find only one anecdotal report of the use of heparin in fat embolism that was associated with frank DIC. This patient recovered after being moribund (Keith et al, 1971). However, there are no control trials of the use of heparin in fat embolism in humans.

Oxygen Hardman and Ragaz (1950) demonstrated that a dose of intravenous fat of .55 mgs per kg in rabbits produced death within 24 hours in 50% of the rabbits. 80% oxygen treatment decreased the mortality rate to 0 at 30 hours. Autopsy at that time showed decreased pulmonary edema and absence of hepatic necrosis which was present in animals treated with oxygen. Since that time there is general agreement that the single most important aspect of treatment of fat embolism is adequate oxygen delivery to the tissues which usually requires an arterial PO_2 of over 50 mm Hg. As with other forms of ARDS if hypoxemia is severe enough to require an inspired oxygen tension above 50%, intubation and use of positive end expiratory pressure (PEEP) is commonly done to

avoid the problems of oxygen toxicity (Nash et al, 1967). There are no human studies comparing PEEP vs no PEEP in severe fat embolism syndrome.

In the oleic acid model of fat embolism PEEP prevented a 30% fall in compliance and a 40% drop in arterial PO_2 compared to control animals (Parker et al, 1974). The same group used the oleic acid model in dogs and compared the effect of PEEP on one lung to no PEEP on the other lung. (et al, 1975). In the lung that did not have PEEP there was a 30% shunt and this was reduced to 6.7% in the lung that did have PEEP.

Everyone agrees that PEEP increases functional residual capacity and opens up airways that are closed. Arterial oxygen content (CaO_2) is raised but delivery of oxygen to the tissues may not increase if cardiac output falls. Suter et al (1975) showed that the optimal PEEP which produced the greatest O_2 delivery to the tissues was the PEEP that resulted in the best effective lung compliance. The simplest way of determining optimal PEEP was to measure mixed venous oxygen (PvO_2) tension, which was higher when the product of C.O. and CaO_2 were maximal. Too much PEEP can lead to a drop in C.O. and a lower PvO_2 despite increased CaO_2. T he drop in cardiac output has been assumed in the past to be due to interference with venous return by positive intrathoracic pressure. However, in fact, the drop in C.O. is due to a reflex depression of left ventricular function (Cassidy et al, 1978, Prewitt and Wood, 1979). The reflex is induced by hyper-inflation of the lung and is mediated via the vagus nerve. (Cassidy et al, 1979).

The $P\bar{v}O_2$ is a sensitive metabolic index of the adequacy of tissue blood flow in animals with artificial hearts and patients during open heart surgery with cardio-pulmonary by pass. (Stanley and Isern-Amarl, 1974). Springer and Stevens (1979) reviewed the hospital course of 78 patients whose PaO_2 was < 70 mm Hg on a FIO_2 of 1.0. For the 22 patients that had $P\bar{v}O_2$ measured on FIO_2 of 1.0 all non-survivors had a $P\bar{v}O_2$ < 30 mm Hg and all survivors had a $P\bar{v}O_2$ > 30 mm Hg after PEEP on FIO_2 of 1.0. (Figure I.)

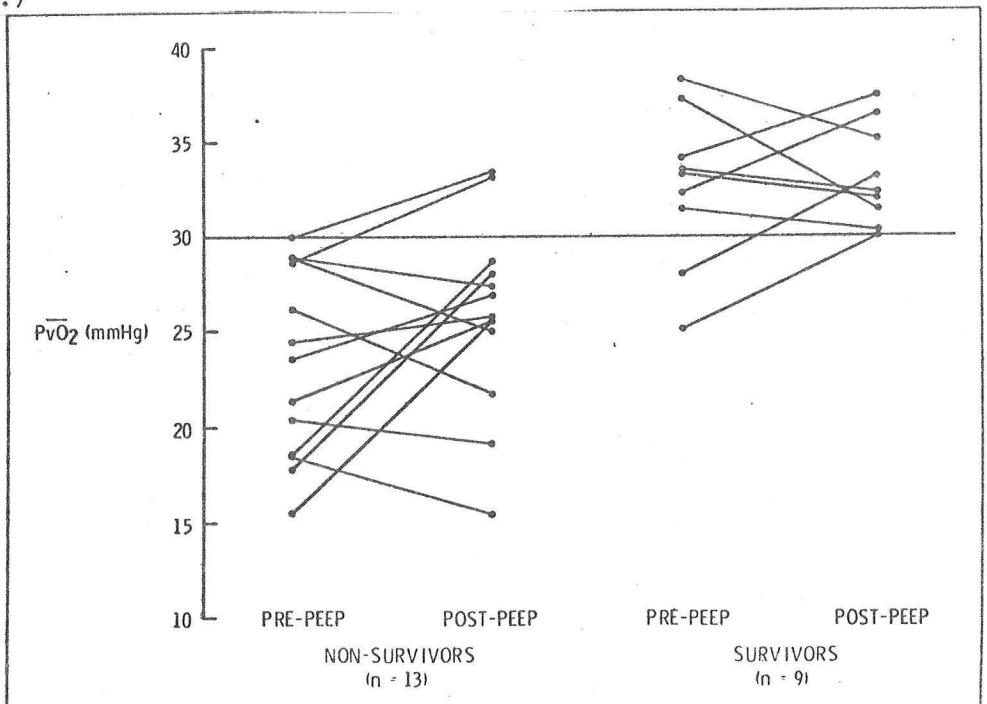


Figure I Mixed venous oxygen tension (PvO_2) before and after PEEP on FiO_2 1. PvO_2 was at least 30 mm Hg after PEEP in all survivors. In all patients who died, PvO_2 was 30 mm Hg or less prior to PEEP. There was no relationship between PEEP-induced changes in PvO_2 and

In this retrospective study 60% of the patients were treated with PEEP. PEEP increased the duration of survival from 4.2 to 9.2 days ($p < .05$). However, survival with PEEP (31%) was similar to survival without PEEP (26%) Weigelt et al (1979) performed a prospective study in the SICU at Parkland Hospital comparing early PEEP of 5 cm H_2O to later PEEP only if severe hypoxemia developed. Patients that met criteria for high probability for developing ARDS were assigned to early PEEP or late PEEP according to day of admission. Fifty-six of 135 patients were excluded from the final analysis because insufficient qualifying data and physicians choice not to adhere to the protocol. The 79 patients that were included had significantly lower incidence of ARDS (20% vs 53%; $p < .002$) and pulmonary death (11% vs 29%; $p = .02$) Crude mortality with early PEEP was 16/45 (35%) compared to 17/34 (50%) with late PEEP ($p = .06$). The ABC's of Respiratory Care in fat embolism syndrome (or ARDS in general) have recently been outlined and discussed (Murray and Galver, 1974; Gossling et al, 1974). I like to use the approach of Dr Alan Morris (1979) as a mental check list for doing everything possible to improve oxygen delivery to tissues with the minimum FIO_2 possible. The Fick equation,

$$C.O. = \frac{\dot{V}O_2}{CaO_2 - C\bar{v}O_2}$$

can be rearranged as follows:

$$C\bar{v}O_2 = CaO_2 - \frac{VO_2}{C.O.}$$

Mixed venous oxygen content (and $P\bar{v}O_2$) can be raised by the following maneuvers:

Increase CaO_2

Increase FIO_2
PEEP
Diuresis
Increase hemoglobin by blood transfusion
Correct alkalosis
Correct hypophosphatemia

Decrease $\dot{V}O_2$

Cooling blanket if febrile
Sedation with valium
Paralysis with Pavalon

Increase Cardiac Output

Digitalis
Dopamine
Dobutamine
Unload with nitroprusside drip

Corticosteroids Ashbough and Petty (1966) reported their anecdotal experience of beneficial results with corticosteroid treatment of fat embolism in 3 patients. One patient appeared moribund on the 6th day and rapidly improved within 12 hours after starting cortisone. Fisher et al, reported similar anecdotal experience in 1971. They claimed that high doses of solumedrol in fat embolism makes the arterial PO_2 increase in 6 to 8 hours, the pulse improve in 12 to 24 hours and the pulmonary compliance improve in 60 to 72 hours. Animal studies with the oleic acid model of fat embolism show that steroids given before and after the oleic acid markedly reduced mortality (Wertzberger and Peltier, 1968). This study was in rats. Parker et al, (1974), studied the oleic acid model in dogs that had catheters placed completely surrounding the pulmonary capillary bed including the pulmonary wedge position and the pulmonary venous wedge position. They studied 11 control dogs and 6 dogs given methylprednisolone sodium succinate in a dose of 30 mgs per kg intravenously after the dogs had received oleic acid injection. The steroids did not prevent a 30% fall in compliance or a 40% fall in arterial PO_2. Steroids did prevent a 400% (3.6 mm Hg) increase in the gradient from the pulmonary artery wedge position to the left atrium.

Many object to the oleic acid model of fat embolism. Nylén and Sylvén in 1976, studied radiolabeled fat globules given intravenously in rabbits. The fat globules produced significant increase in net weight of the lung by 22 hours. Treatment with Dextran 70 caused significant increase in edema. Dextran 40 had no benefit. Solumedrol given before and after fat emboli significantly reduced lung weight and microscopic interstitial edema. However, they did not study any animals given solumedrol only after the emboli.

Prophylaxis Shirer et al (1977) studied 48 patients with uncomplicated fractures without head or chest injury. The patients were randomly assigned to 5 prophylactic treatment groups: (1) control, (2) increased fluids, (3) hypertonic glucose infusion, (4) aspirin 650 mgms with meals, (5) methylprednisolone sodium succinate 30 mgms per kg intravenously for 2 doses at 6 hour intervals. They studied coagulation parameters and arterial blood gases on 5 consecutive days. The methylprednisolone group had significant differences compared to the control on the majority of days. With steroid treatment there was less increase in fibrinogen, more lowering of factor V, more lowering of platelets, and a higher arterial oxygen tension. With aspirin the platelet counts were stable and consistently higher than the controls but not significantly different. The arterial PO_2 was significantly higher on days 2, 3, and 4 with aspirin.

In another study evaluating prophylaxis of fat embolism syndrome Stolenberg and Gustilo (1979) studied 64 patients with isolated tibial and/or femoral fractures. They were randomly assigned to receive: (a) hypotonic glucose consisting of 50 mls of 50% dextrose in water every

4 hours for 4 days, (b) methylprednisolone 1 gm IV every 8 hours for 3 doses and (c) no prophylaxis (control). Three of 21 patients in the glucose group and 2 of 23 patients in the control group developed the fat embolism syndrome. None of the patients in the steroid group developed fat embolism syndrome. The mean arterial PO_2 in the steroid group of 81.9 was significantly higher than the control group where the PO_2 was 75.6 mm Hg. ($p < .03$). The difference in PO_2 was slightly more impressive when femoral fractures alone were evaluated. Also, when femoral fractures were evaluated, platelet count was significantly lower in the control group than in the steroid treatment group. ($p < .01$) Although it is not certain that the fall in platelet count and fall in arterial oxygen tension in these two studies reflected fat embolism, such an assumption is likely. Thus it seems that steroids can probably prevent undesired pathophysiologic consequences of fat embolism if treatment is started early enough. I could make no better recommendations for the treatment of fat embolism than the recommendations of Dr Watts Webb's group. (1974). They reported that they had no death in their last 13 cases of severe fat embolism treated as follows: (1) increased inspired oxygen tension (2) PEEP (3) steroids (4) judicious use of diuretics (5) volume expanders with albumin and plasma. With regard to the last recommendation there is no question that in a situation with increased pulmonary capillary permeability that the albumin leaks out into the interstitial space of the lungs. However, it is also clear that diuresis will diminish pulmonary edema in situations with the increased pulmonary capillary permeability. The limiting factor in the use of diuretics is fall in systemic blood pressure and development of low output renal failure. Whether the use of albumin and/or plasma would allow more diuresis without drop in blood pressure and without significant damage to the lungs needs further study.

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