Corticosteroids in Experimental Fat Embolization

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FAT EMBOLI WERE FIRST described by Zenker in 1862 [24]. Since that time all aspects of the phenomenon have been the subject of controversy. Fat embolization refers to the finding of fat particles in tissues (especially lung, kidney, and brain). The fat emboli syndrome is a clinical picture thought to be produced by severe fat embolization. Fat embolization is associated with a diverse variety of clinical problems but most commonly occurs with trauma, associated with fracture of the long bones.

Fat emboli are a common finding at autopsy following trauma. Sevitt reports an incidence of 89% [19]. However, the incidence of the fat emboli syndrome is much less. The exact incidence in significant trauma is difficult to ascertain due to difficulties in making the diagnosis and a lack of precise criteria as to what constitutes significant trauma.

Fat embolization has been implicated as the cause of death in individuals dying after trauma in 5–25% of cases [18, 24]. Mortality is related to the severity of injury and the number of fat emboli per unit area of tissue examined at autopsy [7, 19]. The fat emboli syndrome is most common in young males paralleling the incidence of severe trauma in this group [15]. Recently, investigators have proposed the use of corticosteroids as an adjunct to ventilatory assistance and other supportive measures in the treatment of pulmonary fat embolization [3, 9, 21]. This study was undertaken to evaluate the effects of corticosteroids in an experimental model of fat embolization.

METHODS AND MATERIALS

Sixteen mongrel dogs were anesthetized with intravenous sodium pentobarbital (30 mg/kg) and maintained with 4 mg/kg/hr by continuous intravenous infusion. Animals were intubated and maintained on 20 cc/kg of room air at 16 respirations per minute on a fixed volume respirator. Catheters were placed in the femoral artery and vein for pressure measurements and blood sampling. A Swan–Ganz flow directed catheter was passed into the pulmonary artery from the femoral vein for pressure measurements [20]. The animals were divided into four groups (Table 1). Fourteen animals received Oleic acid USP 0.07 ml/kg intravenously at time zero. Seven of these animals (group 2) simultaneously received methylprednisolone 3 mg/kg intravenously. The other seven animals received an equivalent volume of normal saline (group 1). One animal received saline only (group 3), and one received only methylprednisolone (group 4).

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Table 1. Experimental and Control Groups

Group	Number of dogs	Insult	Treatment
1	7	Oleic Acid	Saline
2	7	Oleic Acid	Methylprednisolone
3	1	Saline	Saline
4	1	Saline	Methylprednisolone

Table 2. Mean Arterial pH Determinations in Experimental Fat Embolization

Group	Time (hours)					
	0	½	1	2	3	4
1	7.46(.04)	7.44(.02)	7.40(.03)	7.43(.03)	7.46(.03)	7.44(.02)
2	7.44(.05)	7.45(.06)	7.45(.06)	7.45(.06)	7.45(.04)	7.45(.03)
3	7.45	7.45	7.45	7.44	7.44	7.44
4	7.45	7.44	7.44	7.44	7.44	7.44

Table 3. Mean Arterial PCO_2 in Experimental Fat Embolization*

Group	Time (hours)					
	0	½	1	2	3	4
1	24(3)	25(3)	27(4)	25(4)	24(3)	25(4)
2	24(4)	24(4)	24(4)	24(4)	24(4)	23(4)
3	28	28	28	28	29	29
4	28	29	29	29	29	29

* Millimeters of mercury.

Table 4. Mean Pulmonary Artery Pressure in Experimental Fat Embolization*

Group	Time (hours)					
	0	½	1	2	3	4
1	20(0)	18(1)	18(1)	20(1)	22(1)	22(1)
2	20(0)	20(0)	20(2)	20(3)	24(4)	21(4)
3	20	20	18	18	24	22
4	20	20	20	24	24	22

* Centimeters of water.

Table 5. Mean Pulse Rate in Experimental Fat Embolization

Group	Time (hours)					
	0	½	1	2	3	4
1	167(10)	152(11)	144(12)	165(10)	170(10)	174(10)
2	160(11)	145(13)	148(8)	150(8)	149(10)	144(8)
3	170	170	160	160	160	160
4	175	175	170	170	160	160

Pulse and arterial pressure were measured and recorded with a Sanborn transducer and recorder. Pulmonary artery pressure (PAP) was monitored with a water manometer. Arterial blood samples were collected before injection and ½, 1, 2, 3, and 4 hr after injection and determinations of PaO_2, pH, and PCO_2 obtained with a Radiometer blood gas analyzer. Chest roentgenograms were obtained before injec-

Table 6. Mean Systemic Arterial Pressure in Experimental Fat Embolization*

Group	Time (hours)					
	0	½	1	2	3	4
1	130(4)	120(7)	120(5)	130(2)	130(3)	130(2)
2	135(10)	125(4)	126(6)	129(6)	131(3)	129(6)
3	120	120	120	120	120	120
4	125	120	125	125	120	125

* Millimeters of mercury.

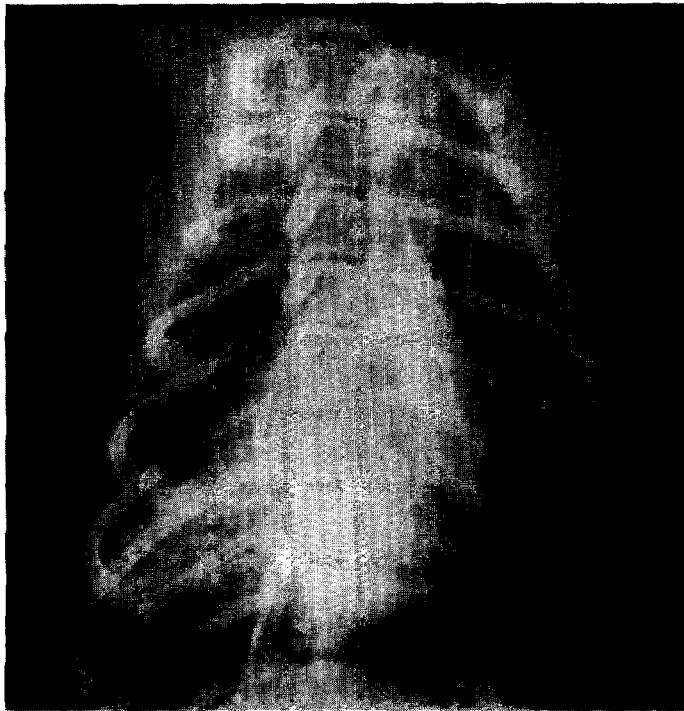Table 7. Mean Arterial PaO_2 in Experimental Fat Embolization*

Group	Time (hours)					
	0	½	1	2	3	4
1	89(4)	64(25)	52(15)	52(8)	49(10)	53(8)
2	89(4)	80(15)	71(15)	71(13)	74(10)	74(10)
3	87	87	87	86	89	88
4	86	89	88	90	88	89

* Millimeters of mercury.

Table 8. Graph of Mean PaO_2 ($\pm$ Standard Deviation) in Steroid Treated and Control Dogs Receiving Intravenous Oleic Acid

CORTICOSTEROIDS IN FAT EMBOLI
PaO_2
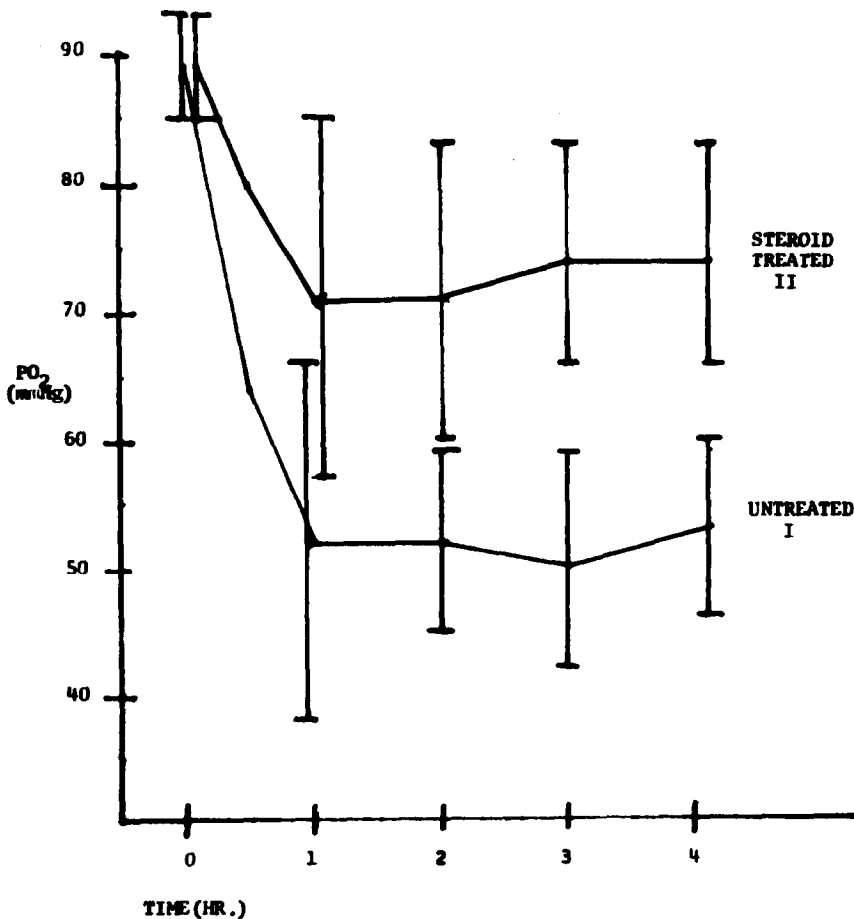
Fig. 1. Chest roentgenogram of untreated animal (group 1). Note diffuse patchy infiltrates.

Fig. 2. Chest roentgenogram of steroid treated animal (group 2). Note relatively normal appearance.

Fig. 3. Lung from untreated animal (group 1). There is marked congestion with focal hemorrhage.

tion and 3 hr later. Animals were sacrificed at 4 hr and sections of lung, brain, and kidney were subjected to gross and histologic examinations.

RESULTS

The arterial blood gas values, pulse, systemic arterial pressure and pulmonary artery pressures (PAP) are summarized in Tables 2–7. pH, PCO_2, PAP, pulse, and arterial pressure were stable in all groups. For the duration of the experiment PaO_2 (Table 8) showed a marked and sustained decrease in group 1 (oleic acid only). The decrease in PaO_2 was significantly less marked in group 2 (steroid treated ani-

mals). There was no change in group 3 and 4 animals.

In group 1 animals chest roentgenograms taken at 3 hr showed diffuse infiltration in both lung fields (Fig. 1). These changes were either very mild or absent in the steroid treated group 2 animals (Fig. 2). Chest roentgenograms were normal in group 3 and 4 animals.

Grossly, the lungs in group 1 animals were markedly congested with focal areas of hemorrhage (Fig. 3). The steroid treated animals (group 2) showed some passive congestion but to a much lesser degree than in the untreated animals (Fig. 4). Histologically, the nonsteroid treated animals

Fig. 4. Lung from treated animal (group 2) shows much less congestion.

(group 1) showed marked edema and congestion with focal areas of hemorrhage and inflammation (Fig. 5). The steroid treated animals (group 2) showed mild congestion and focal mild edema (Fig. 6). The lungs in group 3 and 4 animals were normal grossly and histologically. Brain and kidney sections were normal grossly and histologically in all groups.

DISCUSSION

Peltier has suggested the following course of events in the pathogenesis of fat emboli: emboli of neutral fat lodge in the pulmonary arterioles and capillaries; lung lipase hydrolyzes the neutral fat with the release of free fatty acids; the free fatty acids which are quite toxic cause local inflammation, congestion, and edema, which is responsible for the hypoxia always present in clinical fat embolism [14].

The use of corticosteroids in the treatment of respiratory distress associated with fat embolism was proposed by Ashbaugh and Petty in 1966 [3]. They felt that steroids might inhibit the local pulmonary inflammatory reaction, improve local blood flow and decrease the respiratory distress associated with clinical fat embolism. Recently Fischer *et al.* reported using large doses of corticosteroids in 13 patients with respiratory distress syndrome associated with fat emboli [9]. They noted that although PaO_2 improved soon after the administration of steroids, compliance did not improve until up to 72 hr later. They pro-
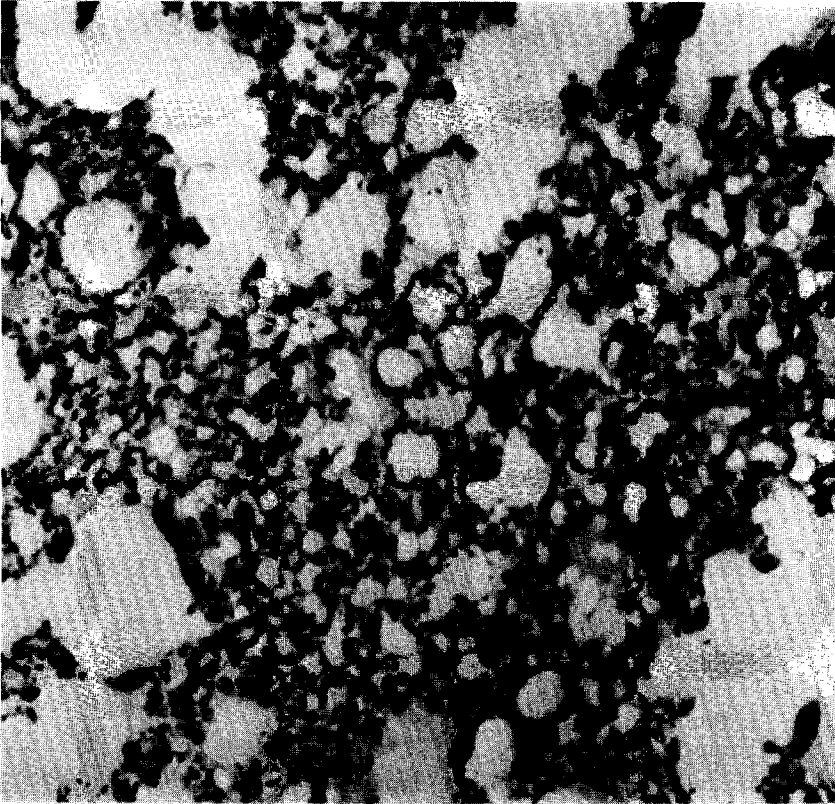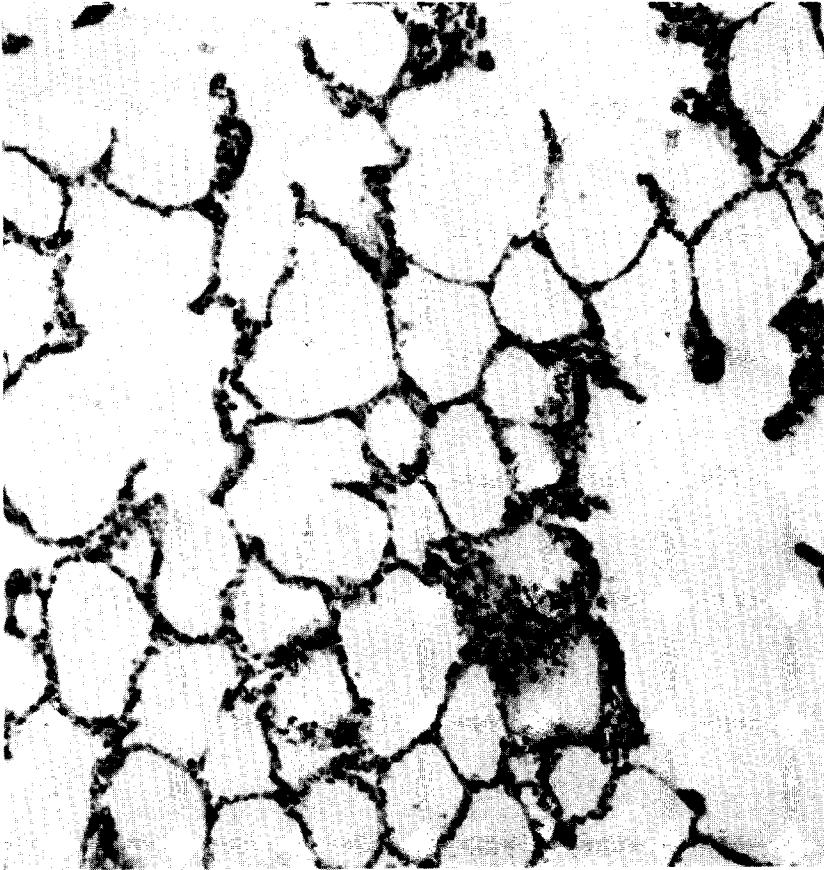
Fig. 5. Photomicrograph of lung tissue from untreated animal (group 1). There is marked edema congestion and leucocytic infiltrate. Hematoxylin and eosin. Original magnification ×200.

posed that platelets became adherent to fat particles that lodge in the lung vasculature and that serotonin and other amines are released from the platelets causing pulmonary arterial spasm and abnormal ventilation–perfusion ratios. They suggested that steroids counteract the affect of these amines and improve the ventilation–perfusion ratio and improve PaO$_2$. However, it is not until the edema fluid and cellular exudates are resorbed (over a period of a few days) that compliance returns to normal. This mechanism has also been advocated by Moritz *et al.* who have shown that reserpine pretreatment to deplete platelet (and other) stores of serotonin and other humoral agents results in a less severe response to experimental fat embolism [13].

Wertzberger and Peltier [21] showed a decrease in the mortality of rats undergoing experimental fat embolization when treated with large doses of steroids. They proposed that the steroids were beneficial for their anti-inflammatory properties and their ability to modify tissue response to injury in conditions associated with capillary permeability.

The period of time between the lodgment of neutral fat particles in the lung and the release of sufficient free fatty acids to cause the inflammatory changes necessary to result in respiratory symptoms may represent the symptom free interval seen between the external trauma and the respiratory distress associated with fat embolism [14]. The animal model used in this study avoids this interval by the direct administration of a free fatty acid. Oleic acid is the most abundant unsaturated free fatty acid in the bones and soft tissues [14, 16]. A number

Fig. 6. Photomicrograph of lung tissue from animal treated with corticosteroids (group 2). There is minimal edema and cellular infiltrate. Hematoxylin and eosin. Original magnification ×200.

of investigators have studied this particular model of pulmonary fat embolism and found that it results in a pathologic and clinical picture entirely similar to that seen in humans with respiratory insufficiency due to fat embolism (i.e., decreased PaO_2, roentgenographic changes, congestion, edema, and hemorrhage in the lung) [2, 4, 6, 12].

The diagnosis of clinical fat embolism is often difficult and the various diagnostic techniques utilized are not entirely satisfactory [8, 11, 15, 19, 22, 23]. PaO_2 reliably reflects the severity of respiratory distress and is of great value in following the progress of patients with pulmonary fat embolism [9, 22, 23]. Chest roentgenograms are less reliable but generally provide some measure of the severity of pulmonary fat

embolization and are a good means of following patients' clinical progress [1, 8, 9, 22, 23]. Pulmonary artery pressure has been reported to be elevated in experimental pulmonary fat embolism [4] but has not been adequately investigated clinically.

In this study animals treated with oleic acid showed a picture similar to the respiratory distress in patients with pulmonary fat embolism. There was a marked decrease in PaO_2, roentgenographic changes compatible with fat embolism were observed and inflammation, edema, congestion, and hemorrhage were present in the pulmonary parenchyma.

The animals treated with steroids showed significantly less marked changes in all of the above. The PaO_2 decreased less, the

roentgenograms showed mild or no changes, and tissue changes were less marked both grossly and histologically. These results suggest that massive corticosteroid therapy may be a valuable adjunct to ventilatory support in the treatment of the respiratory distress associated with fat emboli and support the clinical observations of the beneficial effect of corticosteroids.

SUMMARY

Adult mongrel dogs were given intravenous oleic acid in an experimental model of pulmonary fat embolism. The changes in PaO_2, chest roentgenograms, and pulmonary tissues were less marked when high doses of corticosteroids were administered.

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