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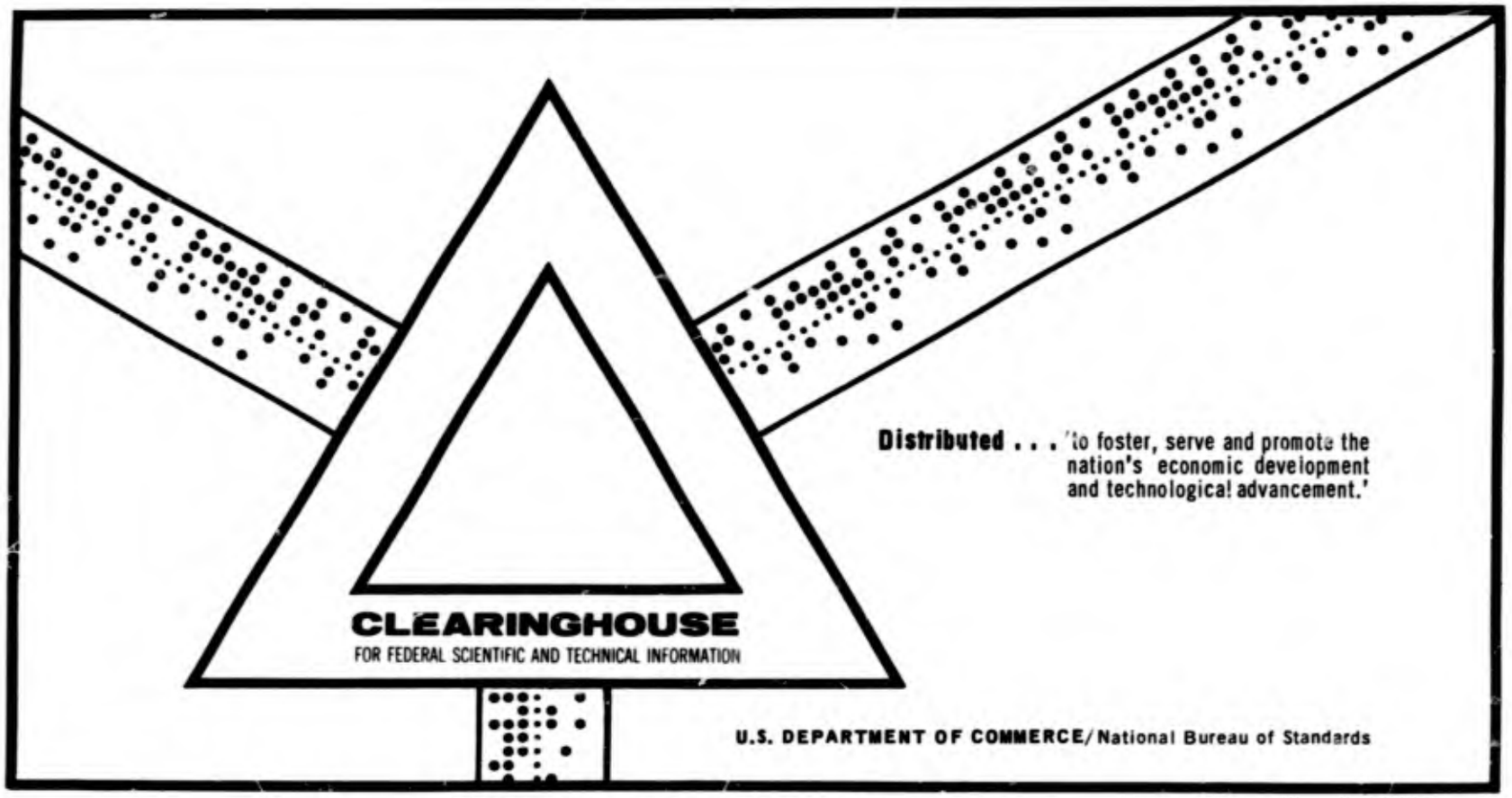
THE TREATMENT OF ACUTE RESPIRATORY FAILURE IN EXPERIMENTAL FAT EMBOLISM

David G. Ashbaugh

Colorado University
Denver, Colorado

15 November 1969



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Report #2

THE TREATMENT OF ACUTE RESPIRATORY FAILURE IN EXPERIMENTAL FAT EMBOLISM (U)

Annual Progress Report

David G. Ashbaugh, M.D.
University of Colorado Medical Center
4200 East Ninth Avenue
Denver, Colorado 80220

15 November 1969

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SUMMARY OF WORK

This work was undertaken to investigate clinical and experimental aspects of acute respiratory failure with particular emphasis on fat embolism. Experimental models using both neutral fat and free fatty acid (oleic acid) have been developed. The effects of continuous positive pressure breathing, intermittent positive pressure breathing, oxygen, and corticosteroids have been evaluated. Continuous positive pressure breathing is more effective than intermittent positive pressure breathing in improving oxygenation. The use of oxygen offers temporary benefit but the high percentage of physiologic shunt seen in these animals and the risk of oxygen toxicity make the use of oxygen alone of dubious value. Corticosteroids have been useful in clinical situations, however, they have not improved results in either of the experimental models. In both clinical and experimental illness associated with a high degree of physiologic shunting across the lung, large tidal volumes and continuous positive pressure breathing are effective in reducing the amount of shunt.

FOREWARD

This work was performed at the University of Colorado Medical Center under Contract Number DADA 17-68-C-8078 entitled Respiratory Failure Associated with Fat Embolism and supported by the U. S. Army Research and Development Command. M. Bartnik provided technical assistance.

In conducting the research described in this report, the investigator adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animals Resources, National Academy of Sciences-National Research Council.

The investigations encompassed by this application have been approved by the Committee of associates of the investigator in accordance with this institution's assurance on clinical research dated October 21, 1966.

I. THE PROBLEM

Respiratory failure following non-thoracic and thoracic trauma is a significant cause of mortality and morbidity in military and civilian casualties. Fat embolism is one of the causes of respiratory failure in this group of patients. Since no specific treatment is available for the prevention of fat embolism current efforts are mainly directed toward early diagnosis and treatment of the physiologic derangements seen in massive fat embolism. Shunting of blood across the lung appears to be largely responsible for the hypoxemia associated with pulmonary fat embolism and other forms of respiratory distress. Current evidence indicates that this shunt is secondary to ventilation/perfusion abnormalities and atelectasis and that anatomic shunts are of little importance. The investigations conducted under this contract have been directed towards the causes and treatment of respiratory failure associated with fat embolism and to the treatment of similar disease states associated with a high degree of physiologic shunting.

II. BACKGROUND

Respiratory failure associated with fat embolism is now well recognized as a major cause of morbidity and mortality.[1,2] Hypoxemia, probably secondary to atelectasis and physiologic shunting, is the primary and most serious derangement seen in both patients and in experimental models.[3] In Annual Report #1 of this contract and in several publications involving clinical and experimental data, the physiologic and pathologic changes associated with fat embolism were documented. The effectiveness of continuous positive pressure in overcoming hypoxemia and supporting respiration was also reported. In clinical fat embolism the use of corticosteroids has resulted in marked subjective and objective improvement of these patients. The use of corticosteroids in the oleic acid experimental model did not improve survival. This experimental model produces immediate and massive damage to the pulmonary capillary bed and therefore might not be a good model for the testing of corticosteroids. Although the use of neutral fat to produce experimental fat embolism has been tried with little success[4], we felt that a good model could be developed which might simulate more closely clinical fat embolism and provide a better model for testing corticosteroids.

III. EXPERIMENTAL APPROACH

A. DEVELOPMENT OF AN EXPERIMENTAL MODEL USING NEUTRAL FAT.

1. Preparation of neutral fat.

Obese dogs were sacrificed and subcutaneous adipose tissue harvested. This tissue was mixed in a blender with chloroform, heated, filtered, and the fat extracted, Analysis of this fat showed it to be largely triglycerides with traces of cholesterols, esters, fatty acid, and diglyceride.

2. Selection of dose of neutral fat.

Experimental animals were injected intravenously with 0.25 ml/Kg (1), 0.35 ml/Kg (1), 0.45 ml/Kg (2), 0.5 ml/Kg (1), 0.6 ml/Kg (1), 0.7 ml/Kg (1), 1.0 ml/Kg (2), 1.2 ml/Kg (2), 1.5 ml/Kg (4) respectively. Animals receiving less than 0.7 ml/Kg did not become ill or have significant drops in their arterial PO_2. Three of four animals receiving 1.5 ml/Kg died immediately from respiratory and hemodynamic failure. All animals at 1.0 and 1.2 ml/Kg survived more than 48 hours and developed significant hypoxemia. The dosage level of 1 ml/Kg was selected as the optimal dose for future experiments since it produced the desired physiological and pathological changes yet minimized the immediate hemodynamic and circulatory changes. Pathologic changes produced by neutral fat were documented by autopsy studies on dogs that died following neutral fat injections or were sacrificed. The physiologic and pathologic changes are identical to those seen in the oleic acid model, however, they develop more slowly and are not as severe in most instances. Untreated control animals were compared with animals treated with 1 mgm/Kg of methyl prednisolone intravenously at the time of injection and twice daily thereafter.

B. PHYSIOLOGIC SHUNTING.

The second experimental approach was the study of the effect of varying ventilation and perfusion on physiologic shunting. Perfusion and ventilation per gram of lung weight were varied in normal animals by progressively clamping segments of the pulmonary arterial and bronchial trees. Shunt was determined by the standard equation:

$$\frac{Qs}{Q} = \frac{C_c - C_a}{C_c - C_v}$$

Animals were ventilated with 100% oxygen to minimize the effect of diffusion abnormalities on the measurement of shunting. Two groups of animals were compared. Group I was ventilated using intermittent positive pressure and Group II was ventilated with continuous positive pressure. Shunt was calculated in a second series of animals with hemorrhagic edema secondary to oleic acid. These animals were divided into three groups: Group I animals breathed spontaneously; Group II animals were ventilated with intermittent positive pressure; and Group III animals were ventilated with continuous positive pressure.

IV. RESULTS AND DISCUSSION

A. CORTICOSTEROIDS IN NEUTRAL FAT EMBOLISM.

To test the efficacy of corticosteroids 10 animals were given 1 mg/Kg of methyl prednisolone immediately following the injection of neutral fat and twice daily thereafter. They were compared to a similar group of 10 control animals who did not receive steroids. Both groups were given penicillin and streptomycin daily.

1. Mortality

Eight of ten animals serving as controls survived longer than 24 hours and seven survived longer than one week. Seven of ten animals treated with corticosteroids survived longer than 24 hours and five survived longer than one week.

2. Physiologic parameters.

a. Systemic and pulmonary arterial pressures.

Mean systemic arterial pressure in the two groups varied but the differences were not significant at the 0.01 level. (Figure 1, appendix) Mean pulmonary artery pressures rose to comparable levels in both groups in the immediate post-injection period and declined slowly to control levels by the end of one week. (Figure 2, appendix)

b. P_aO_2 and S_aO_2

These values declined immediately post-injection. By one week values had returned towards the control values but had not yet reached this level. No significant differences were noted between control and treated animals. (Figures 3 and 4)

c. P_aCO_2

Values for P_aCO_2 were low in both groups and remained low throughout the testing period. Despite daily fluctuations the values for the two groups are not significantly different at the 0.01 level. (Figure 5)

d. pH

Arterial pH values did not change during the test period. (Figure 6)

e. Cardiac Index

An initial drop in cardiac index was noted in both groups. The control group had returned to near pre-injection levels by 24 hours whereas the steroid treated group did not rise until 48 hours. The differences between the groups are not significant at the 0.01 level. (Figure 7)

f. Hemoglobin

Arterial hemoglobin levels rose immediately following injection and at 24 hours. Thereafter they fell to below control levels. The differences between the two groups were not significant. It is unlikely that the fall in hemoglobin was due to blood drawn for testing since this was less than 10 cc per day. (Figure 8)

3. Pathology of the lung in neutral fat embolism.

Animals dying within the first week after the injection of neutral fat showed a characteristic picture of patchy areas of acute hemorrhagic edema. In some animals these areas remained relatively localized whereas in others the areas became confluent and involved the major portion of the lung. Microscopic sections demonstrated a characteristic picture of diffuse atelectasis, interstitial and intra-alveolar edema, and mild to moderate hemorrhage. There were occasional hyaline membranes. Numerous fat globules could be seen in arterioles. Despite the use of prophylactic antibiotics, several dogs exhibited evidence of inflammation and infection characterized by small micro abcesses and polymorpho-nuclear cell infiltrates.

Animals that survived were kept for periods up to two weeks at which time all blood gas and physiologic parameters had returned to normal. At autopsy these animals had grossly normal lungs. Microscopic sections demonstrated generally normal lung with patchy small areas of fibrosis and atelectasis.

The pathology in the steroid treated animals was indistinguishable from the non-treated controls with the exception that significant acute inflammatory lesions were seen in three steroid animals and in only two of the control group.

4. Surfactant activity.

Surfactant activity was measured on bronchial washings prior to injection and immediately following death or sacrifice. Washings were studied on a Greenfield-Kimray surfactometer. The surface area of the hysteresis loop was measured by a planimeter and used as the measurement of surfactant activity. Surface area of the hysteresis loop prior to injection averaged 8.4 $cm^2 \pm 2.5\ cm^2$ in the steroid treated animals and 8.3 $cm^2 \pm 1.6\ cm^2$ in the control group. Surfactant activity measured at time of death or autopsy averaged 5.8 $cm^2 \pm 2\ cm^2$ for the steroid group and 4.0 $cm^2 \pm 2\ cm^2$ for the control group. (Not significant at the 0.01 level.) Surfactant activity was depressed even in animals surviving up to 21 days.

Discussion:

The neutral fat model is in many ways a better model for longer term study of fat embolism and for the evaluation of various drug regiments. Most animals survive although they develop hypoxemia in a manner similar to that seen in clinical fat embolism. A certain number of animals, like certain humans, will develop acute hemorrhagic edema and hypoxemia severe enough to cause death. The pathologic changes in the animals that die are similar if not identical to those seen in the oleic acid model. Surviving animals, however, are able to repair this damage and make a complete clinical recovery, although the lungs in most of the surviving animals show residual changes up to 21 days. The findings of a drop in hemoglobin beginning at 48 hours is also comparable to the human situation. Corticosteroids have not, however, provided any protective effect in these animals nor have they improved significantly any of the physiologic indices measured. This is in marked contrast to clinical fat embolism where corticosteroids continue to be strikingly effective in reducing symptomatology and improving oxygenation. (See clinical studies section of this report.) The reasons behind these devergent observations are unclear. Since corticosteroids did not protect animals previously studied with oleic acid injections, we can assume that corticosteroids in both of these preparations are not beneficial. These results are directly opposite of those found by Wertzberger & Peltier[5] in rats injected with oleic acid. Sachdeva[6] et al injected rabbits with neutral fat and found a marked protective effect of ACTH and Phenergan^{R} and a lessor protective effect with atropine and papaverine. Differences in the experimental animals and man may explain these varied results, however, no definite statement can be made at this time.

B. EFFECT OF VARIOUS METHODS OF VENTILATION ON PHYSIOLOGIC SHUNTING IN ACUTE PULMONARY ARTERY OCCLUSION.

Of the 20 animals in this group 10 were ventilated with intermittent positive pressure breathing and 10 with continuous positive pressure breathing. In the IPPB group, an increase in perfusion/gram of lung weight was accompanied by an increase in shunt. (Figure 9) In the CPPB group no significant correlation was noted between perfusion and shunt. (Figure 10) In both the IPPB and CPPB groups, an increase in ventilation/gram of lung weight resulted in a decrease in shunt. (Figures 11 and 12) In both groups as the ventilation/perfusion ratio increased the percent of shunt decreased. (Figures 13 and 14) The most striking finding was the effect of CPPB in reducing shunt as compared to IPPB. When ventilation and perfusion/gram of lung weight were equal for both types of ventilation, the percent of shunt in the CPPB group was half that of the IPPB group. (Table 1)

C. EFFECT OF VENTILATION ON SHUNTING IN ACUTE HEMORRHAGIC EDEMA.

Using the oleic acid experimental model, physiologic shunt was calculated in three separate groups of dogs. In Group A, seven animals were allowed to ventilate spontaneously using 100% oxygen; Group B, eight animals received 100% oxygen with intermittent positive pressure breathing; Group C animals were ventilated with 100% oxygen but with continuous positive pressure breathing. This experiment again

demonstrated the CPPB animals had significantly less shunt at lower levels of ventilation than did the IPPB animals or animals allowed to ventilate spontaneously. (Figures 15, 16, and 17) This experiment demonstrates again the effectiveness of continuous positive pressure breathing as a means of decreasing the amount of physiologic shunt under conditions of acute hemorrhagic edema.

Discussion:

Physiologic shunting across the lung appears to be the primary cause of hypoxemia in patients with acute respiratory distress. These current experiments demonstrate the increased shunting that occurs following pulmonary artery occlusion and the resultant increased perfusion to the remaining lung. Studies by Ebert et al[7] using a similar experimental model demonstrated a progressive hypoxemia occuring with pulmonary artery occlusion. Increasing ventilation in their experiments did not improve the hypoxemia whereas oxygen breathing did. Our findings contradict theirs with respect to ventilation. In order for shunt to decrease, increased ventilation must equal or exceed the increased perfusion to a given segment of lung. Distribution of the increased ventilation is therefore vitally important. If ventilation is increased following pulmonary occlusion, much of the increased ventilation will be wasted in ventilating the non-perfused lung. Occlusion of the bronchus to the non-perfused lung insures that the ventilation will be distributed to the perfused areas thereby maintaining or increasing the ventilation/perfusion ratio. The conclusions to be drawn from this study are:

(1) That increased ventilation can reduce shunting and hypoxemia across the lung.

(2) CPPB is more effective than IPPB in accomplishing this.

(3) Very large increases in ventilation and tidal volumes are necessary to overcome the dead space effect created by pulmonary artery occlusion.

The effectiveness of CPPB in this particular experimental situation is probably secondary to the increased residual volume in the lung produced by CPPB. With more alveoli inflated and ventilated, the degree of shunting will be decreased. This effect of CPPB is probably enhanced by the bilateral thoracotomy which decreases the functional residual volume of the lung through the loss of the normal negative intra-thoracic pressure. CPPB was more effective than IPPB in reducing shunt in the closed chest oleic acid model indicating that it is probably an effective means of reducing shunting under a variety of conditions.

D. CLINICAL OBSERVATIONS.

During the past year four patients with clinical fat embolism received corticosteroids as treatment for fat embolism. Brief case histories are presented.

Case No. 1

A 55 year old white male was admitted to the hospital shortly following an automobile accident in which he suffered a fracture of the right femur, three fractured ribs on the right, and multiple contusions and abrasions. He was not in shock and remained alert and well oriented in the immediate post-injury period. Admission hematocrit was 45 and white blood count was 13,600. Twenty-four hours following injury mild confusion was noted and at 48 hours following injury this confusion deepened and he became semi-comatose. Petechia in the axillary folds and conjunctiva were noted at 48 hours. The diagnosis of fat embolism was made and he was immediately started on nasal oxygen receiving 10 liters/minute. Blood gases at this time showed a P_aO_2 of 105 mmHg, PCO_2 of 28.4 mmHg, pH of 7.484. This therapy was continued for the next 24 hours with very slight improvement in his cerebral status. Seventy-two hours following injury he was begun on intravenous hydrocortisone 100 mg four times daily. Over the next 24 hours he awoke and became rational. The oxygen flow was decreased to 2 liters/minute and the P_aO_2 was 83 mmHg. Thirty-six hours after the starting of steroids the P_aO_2 was 62 mmHg and the saturation 93% on no oxygen. Chest roentgenograms taken during the course remained essentially normal despite the need for rather high flows of oxygen. Comment: This patient represents a form of fat embolism in which the primary symptomatology was cerebral although the high flows of oxygen needed to maintain normal blood gases indicate some pulmonary involvement. The use of oxygen alone did not improve his mental status but within 24 hours of the onset of steroids his mental status had improved.

Case No. 2

A 21 year old male was admitted shortly after a motorcycle accident in which he received open fractures of the left tibia and fibula and closed fractures of the left third metacarpal and metatarsal bones. In addition, he had multiple lacerations. He was not in shock and remained conscious and oriented. On the evening of admission he was taken to the operating room for debridement. On the third hospital day his pulse rate rose to 140 and his temperature was 39.5° centigrade. He was noted to have petechia in the axillary folds and conjunctiva. His sensorium remained clear. On his fourth hospital day he was started on 100 mg of hydrocortisone intravenously twice a day. His temperature returned to normal within 24 hours after the onset of steroids; he went on to make a complete and rapid recovery. Chest x-rays showed typical bilateral alveolar infiltrates compatible with fat embolism. No blood gas analysis was performed. Comment: Although the diagnosis of fat embolism seems relatively certain in this patient, hypoxemia was not documented; therefore, the response to steroids rests entirely on clinical observations. We did not have the opportunity to study this patient as one of our study patients, however, he is included because he did receive steroids.

Case No. 3

An 18 year old negro female was admitted following an automobile

accident in which she received fractures of the left humerus, left radius, acetabulum and the third metacarpal. She was not unconscious or in shock in the immediate post-injury period. Forty-eight hours after injury she became somnolent, disoriented, and her temperature rose to 38° centigrade and pulse to 120. Petechia were noted in the conjunctiva. Blood gases drawn at this time showed a P_aO_2 of 30 mmHg, PCO_2 of 37 mmHg, and pH of 7.42. Chest x-rays showed a bilateral alveolar infiltrates. Clinical diagnosis of fat embolism was made. The patient was begun on nasal oxygen at 4 liters/minute and hydrocortisone 125 mg. I.V., Q6h. Temperature at the time of starting the corticosteroids was 39.7° centigrade, pulse was 160, and respirations were 40/minute. Within 24 hours of the administration of corticosteroids, her temperature had returned to normal and she was awake and oriented. Her cerebral symptoms cleared completely within 48 hours after administration of corticosteroids. Corticosteroids were discontinued after four days and the patient made an uneventful recovery. Comment: Again we did not have a chance to study this patient, however, initial blood gases demonstrated a severe hypoxemia. The response to corticosteroids was quite dramatic but was not documented by further gas studies.

Case No. 4

An 18 year old white male was admitted to the hospital following a motorcycle accident in which he sustained a closed transverse fracture of the left femur, a transverse fracture of the right metatarsal, and superficial lacerations over his scalp. He was not in shock and remained clearl mentally in the immediate post-injury period. Twenty-four hours after his injury he became markedly confused and bilateral axillary and conjunctival petechia were noticed. Arterial blood gases at that time showed a P_aO_2 of 34 mmHg and an oxygen saturation of 67%. He was begun on 10 liters of oxygen by face mask and his P_aO_2 rose to 50 mmHg. The patient was transfered to the intensive care unit where pulmonary and systemic arterial catheters were placed for measurement and recording of pressures. Cardiac output determinations were made using cardio-green dye solution. Initial cardiac index was 6 liters/minute, and his pulmonary artery pressure was 24 mmHg. Corticosteroids were given in the dosage of 100 mg of hydrocortisone intravenously every six hours. Two hours after the initiation of corticosteroids the cardiac index had dropped to 5.5 liters/minute, the pulmonary artery pressure had risen slightly to a mean of 26 mmHg. The P_aO_2 had risen to 54 mmHg. Twenty-four hours after the onset of steroids the pulmonary artery pressure dropped to 19 mmHg and the P_aO_2 had risen to 69 mmHg. P_aCO_2 remained relatively constant throughout. His sensorium completely cleared within 24 hours. Steroids were continued for five days and then stopped. He made an uneventful recovery. Comment: This patient represents both cerebral and pulmonary fat embolism with marked hypoxemia. He initially had a very high cardiac output and cardiac index. Within 24 hours of the administration of corticosteroids his mental symptoms had cleared and he showed marked improvement in his oxygenation.

These four patients demonstrate the effectiveness of corticosteroids in the treatment of fat embolism. In patients with cerebral signs, clearing of the mental confusion always occurred within 24 hours after the onset of corticosteroids and oxygenation of the blood was improved.

In addition to patients with fat embolism, we have seen in the past year, 20 patients with other forms of respiratory distress syndrome. The precipitating illness varied and included burns with secondary sepsis, influenzal pneumonia, trauma, drug injestion, renal and hepatic transplantation, carbon monoxide poisoning, and miscellaneous other causes. Of these patients, two with influenzal pneumonia died shortly after admission to the hospital and before resuscitative measures could be successfully instituted. Of the remaining 18, three survived and made complete recoveries, two other patients are surviving at the time of this report, however, they continue to have respiratory difficulties. Of the 13 remaining patients, 12 survived the initial episode of respiratory failure only to die of overwhelming sepsis. Pseudomonas aerogenes was the prime organism recovered. Failure to control secondary infections that develop represents the largest problem facing the treatment of patients with acute respiratory distress. Most of these patients were severely ill from their precipitating illness, and many were extremely debilitated. Despite antibiotic coverage, they went on to develop secondary pneumonias, septicemia and died. The use of continuous positive pressure breathing has continued to be encouraging in these patients. It has prolonged survival and prevented death from respiratory failure. In addition to CPPB, we have begun to use tidal volumes in the range of 15-20 cc/Kg., as a result of our experimental work in the laboratory. Despite these measures and despite the prevention of death from respiratory failure, our mortality has continued to run extremely high. This confirms our previous observations that the ventilatory aspects will prolong life but the control of the underlying disease process and prevention of sepsis are equally and possibly more important in ultimate survival.

V. MILITARY SIGNIFICANCE

Respiratory insufficiency following battle casualties and non-combat trauma are increasingly recognized as a source of morbidity and mortality. These studies have demonstrated that continuous positive pressure breathing and the use of large tidal volumes are safe and effective means of overcoming the hypoxemia of respiratory insufficiency. Although laboratory results with corticosteroids in the treatment of fat embolism are unencouraging, clinical results indicate that corticosteroids are highly effective in the treatment of mental confusion and hypoxemia.

VI. CONCLUSIONS

(1) Corticosteroids should be used in the treatment of clinical fat embolism. Dosage is 100 mgm hydrocortisone intravenously every six hours.

(2) Continuous positive pressure breathing is more effective in reducing physiologic shunting than intermittent positive pressure breathing.

CPPB is a useful technique in clinical and experimental conditions of acute hypoxemia secondary to shunting.

(3) Large tidal volumes are required to overcome the effect of increased dead space in pulmonary artery occlusion.

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13. ABSTRACT

An experimental model of fat embolism using neutral fat has been developed. This model is similar to a previously described oleic acid model but is less lethal and allows long term study of animals. (U)

Corticosteroids have been tested in two different experimental models of fat embolism and in patients with fat embolism. In experimental fat embolism caused by neutral fat or oleic acid, corticosteroids do not affect clinical course or survival when compared with control animals. Patients with clinical evidence of fat embolism have shown marked neurologic and respiratory improvement following administration of corticosteroids. (U)

Hypoxemia secondary to shunting of blood across the lung occurs in both acute pulmonary artery occlusion and respiratory distress. The effects of blood flow and ventilation on pulmonary shunt were studied in experimental animals with pulmonary artery occlusion and acute hemorrhagic edema. Ventilation is more important than flow in determining the amount of shunt. Large tidal volumes may be required to overcome the effect of increased dead space ventilation in animals with pulmonary artery occlusion. In the experimental situation, continuous positive pressure breathing is twice as effective as intermittent positive pressure breathing in reducing shunt. In patients with acute respiratory distress, large tidal volumes and continuous positive pressure breathing are useful in correcting hypoxemia secondary to shunting across the lung. (U)

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14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Fat Embolism						
Oleic Acid						
Neutral Fat						
Physiologic Shunting						
Pulmonary Artery Occlusion						
Continuous Positive Pressure Breathing						
Intermittent Positive Pressure Breathing						
Corticosteroids						
Ventilation/Perfusion Ratio						

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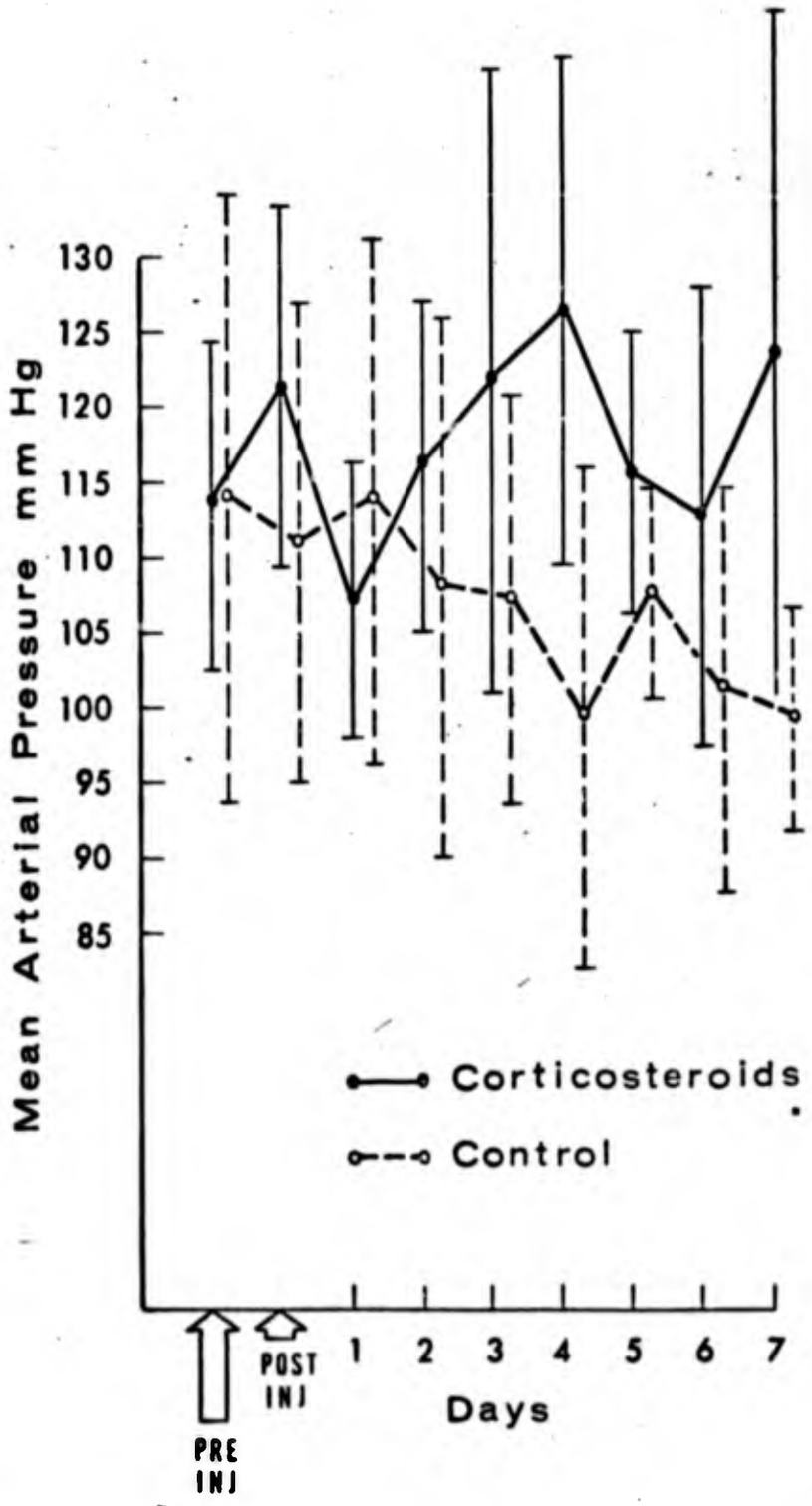

Figure 1 Mean systemic arterial pressures (± 1 SD) of control and treated animals following injection of neutral fat.

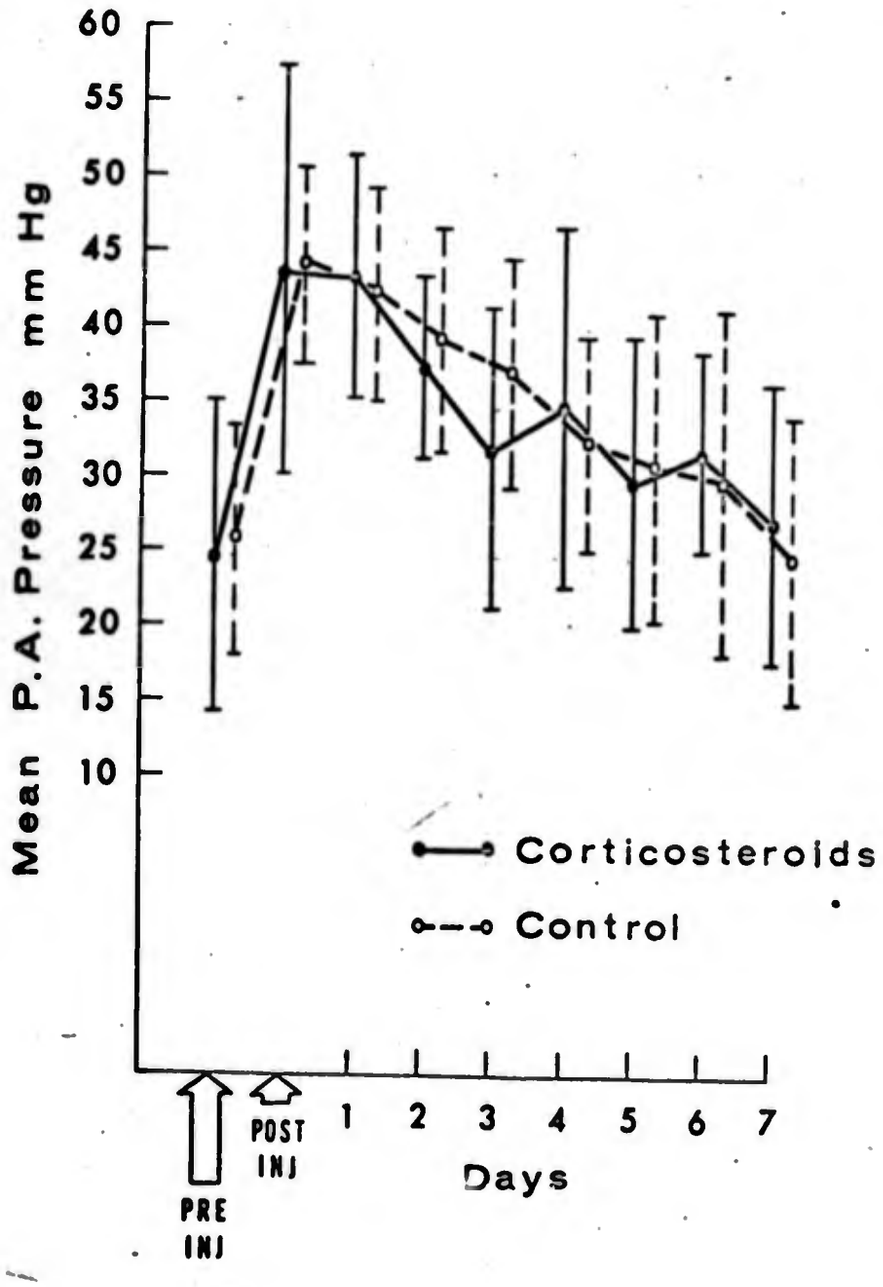

Figure 2 Mean pulmonary arterial pressures (± 1 SD) of control and treated animals following injection of neutral fat.

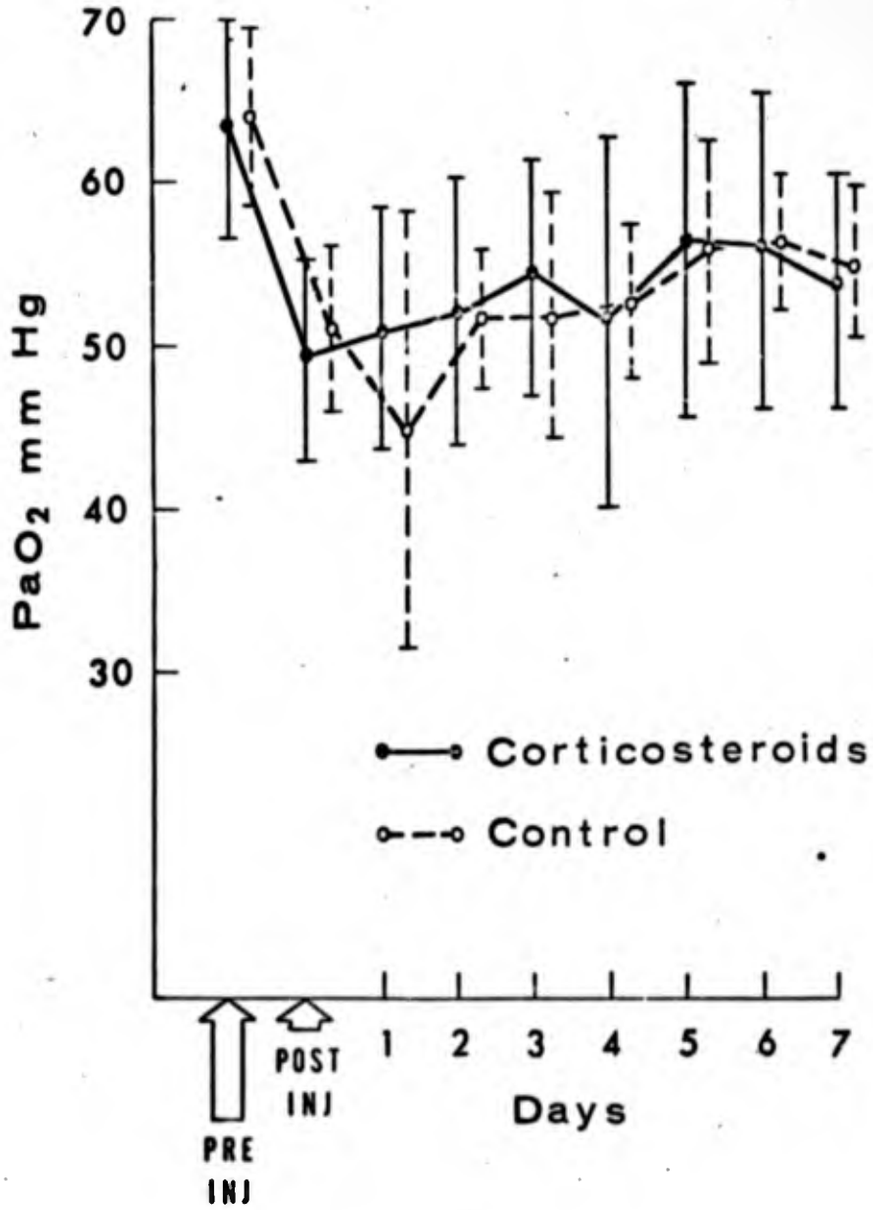

Figure 3 Mean values of arterial PO_2 ($\pm$ 1 SD) of control and treated animals following injection of neutral fat.

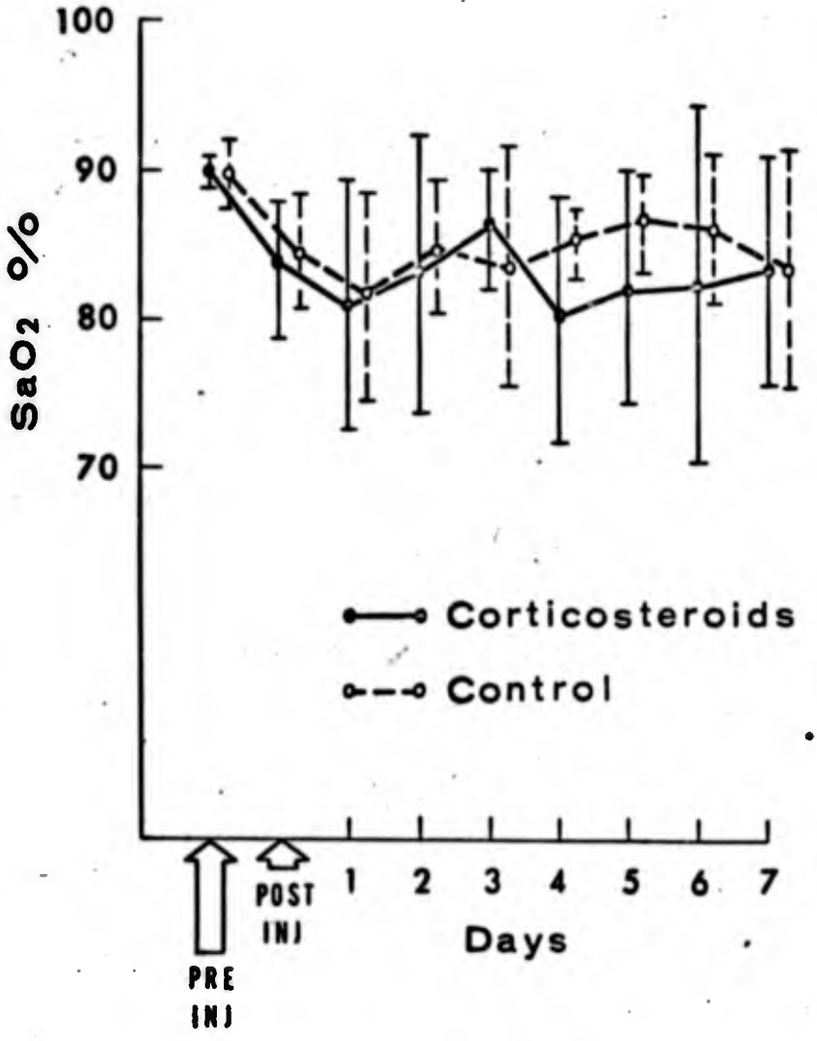

Figure 4 Mean values of arterial saturation S_aO_2 ($\pm$ 1 SD) of control and treated animals following injection of neutral fat.

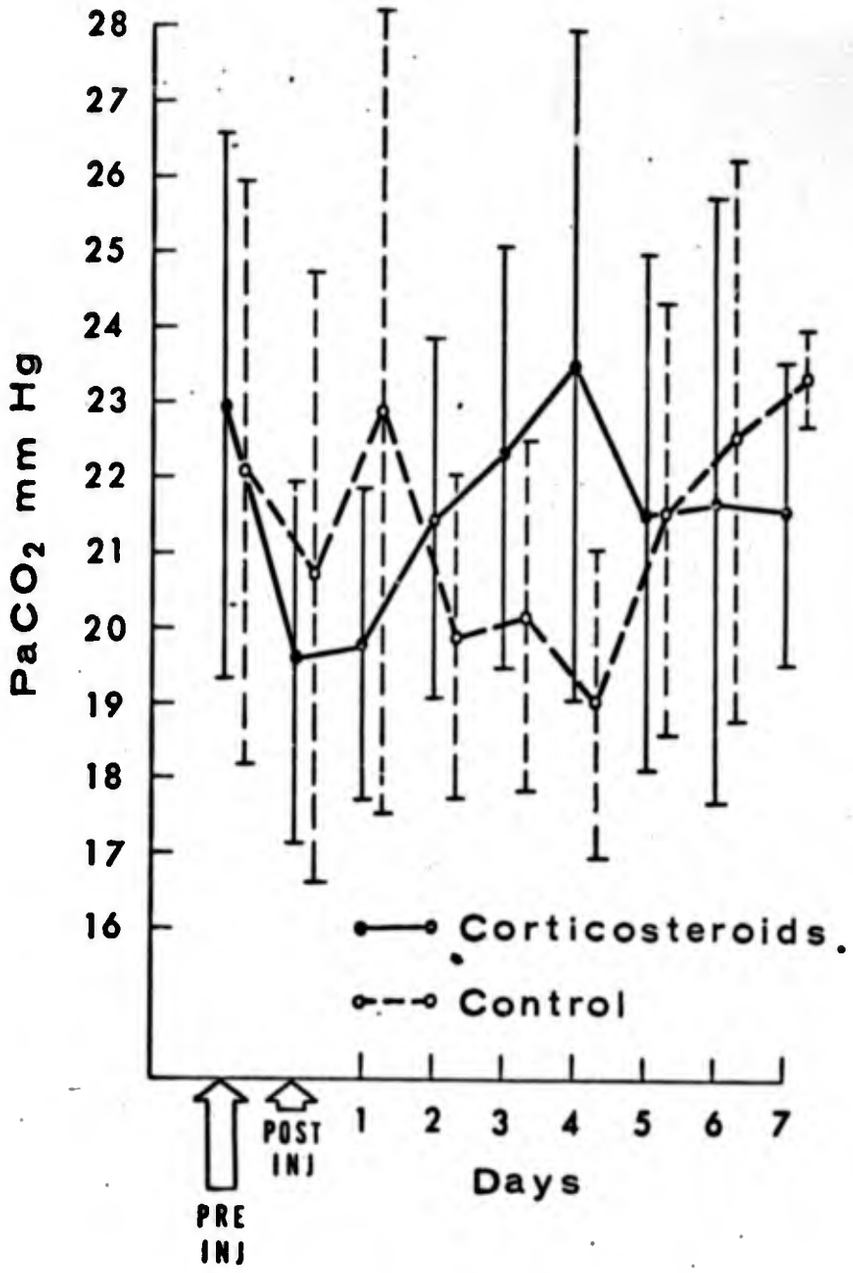

Figure 5 Mean values of arterial PCO_2 ($\pm$ 1 SD) of control and treated animals following injection of neutral fat.

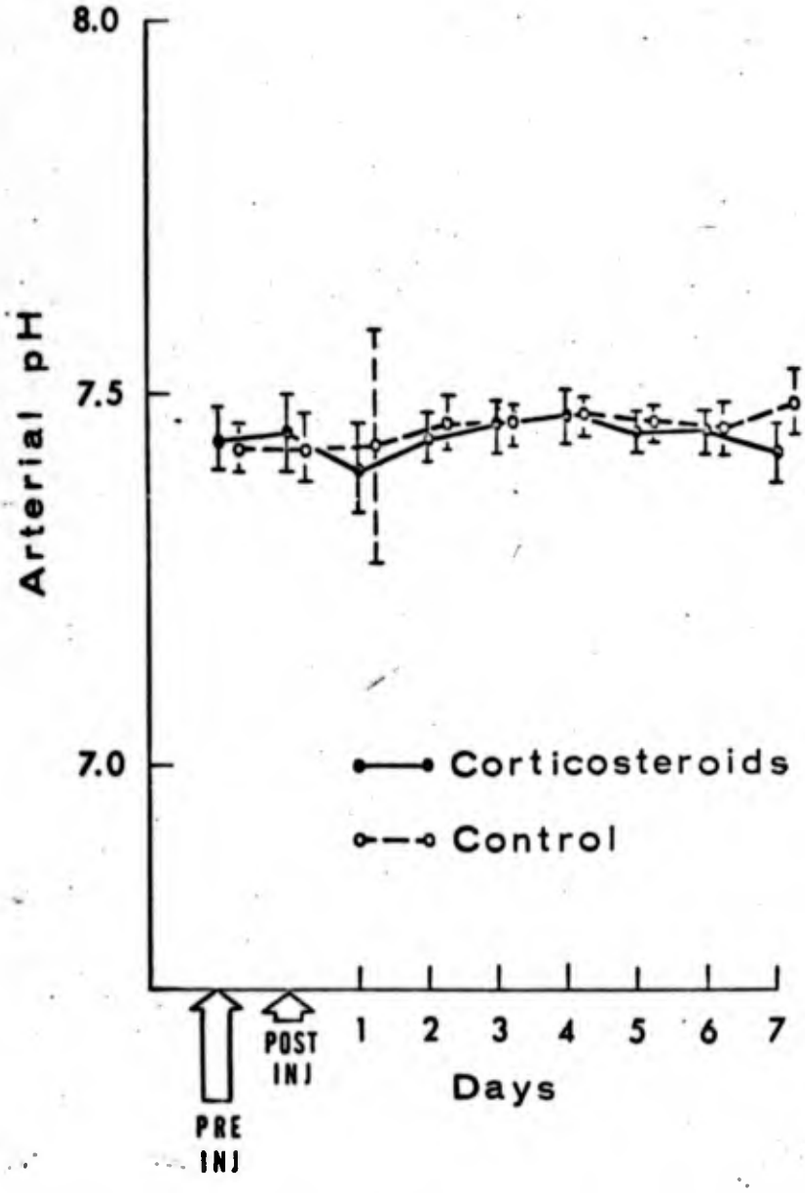

Figure 6 Mean arterial pH values (± 1 SD) of control and treated animals following injection of neutral fat.

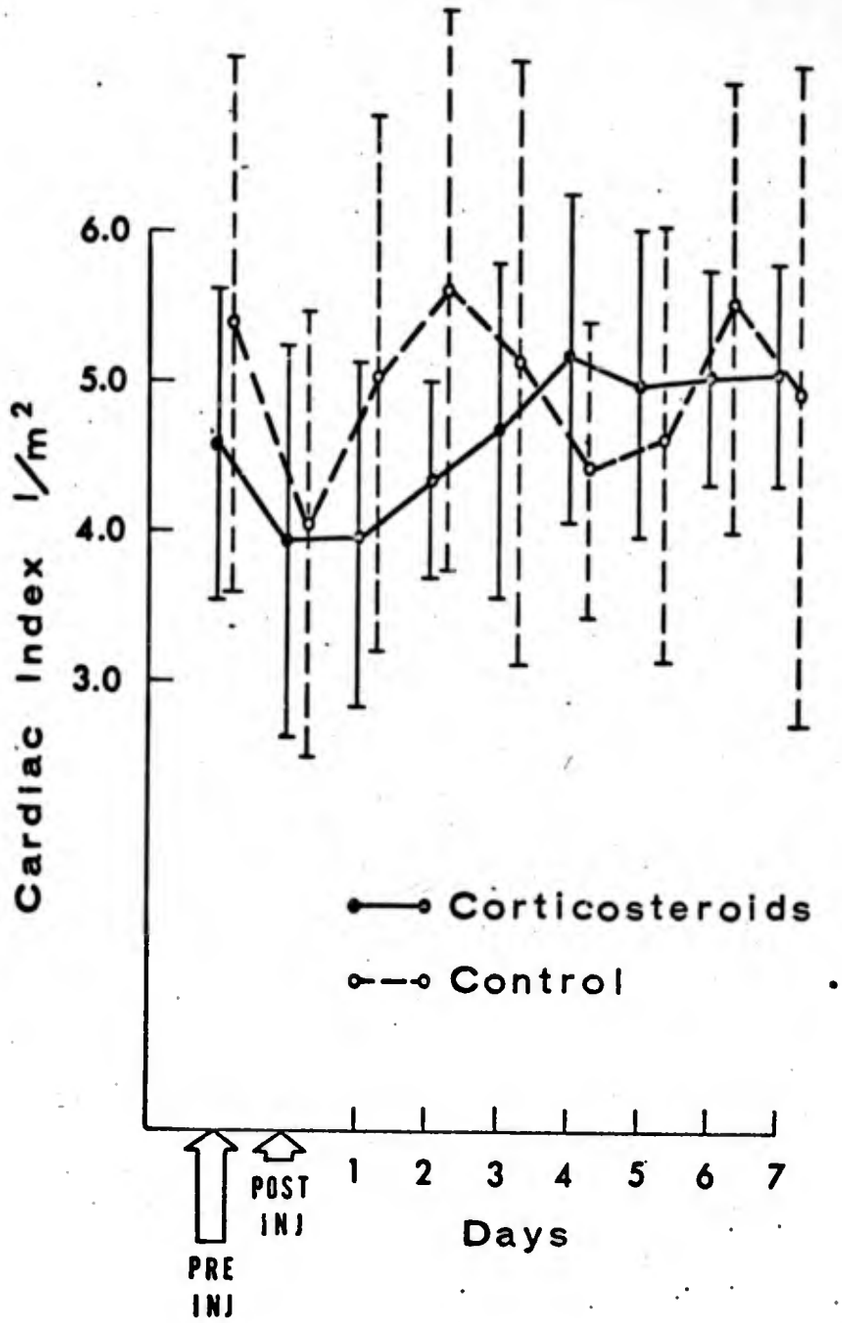

Figure 7 Mean cardiac index (± 1 SD) of control and treated animals following injection of neutral fat.

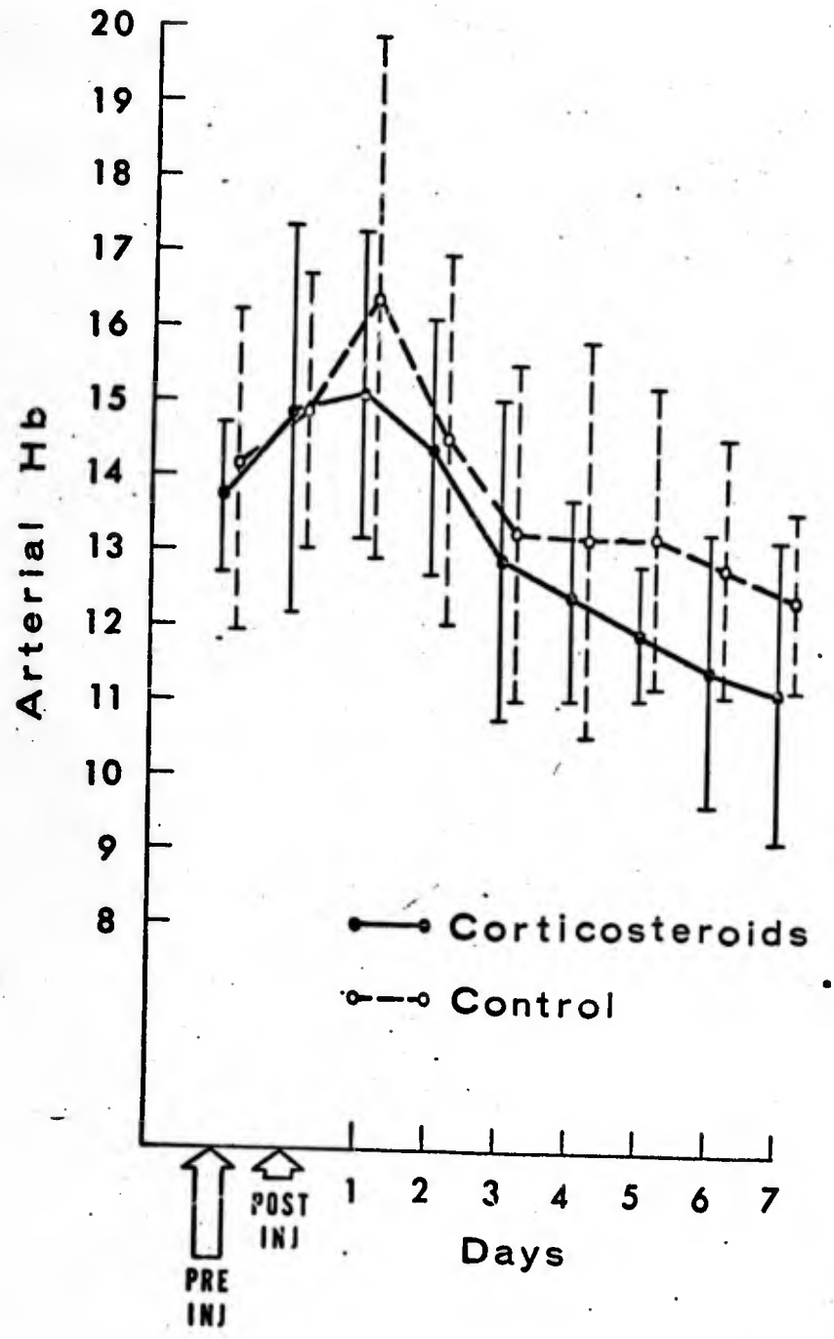

Figure 8 Mean Hgb values (± 1 SD) of control and treated animals following injection of neutral fat.

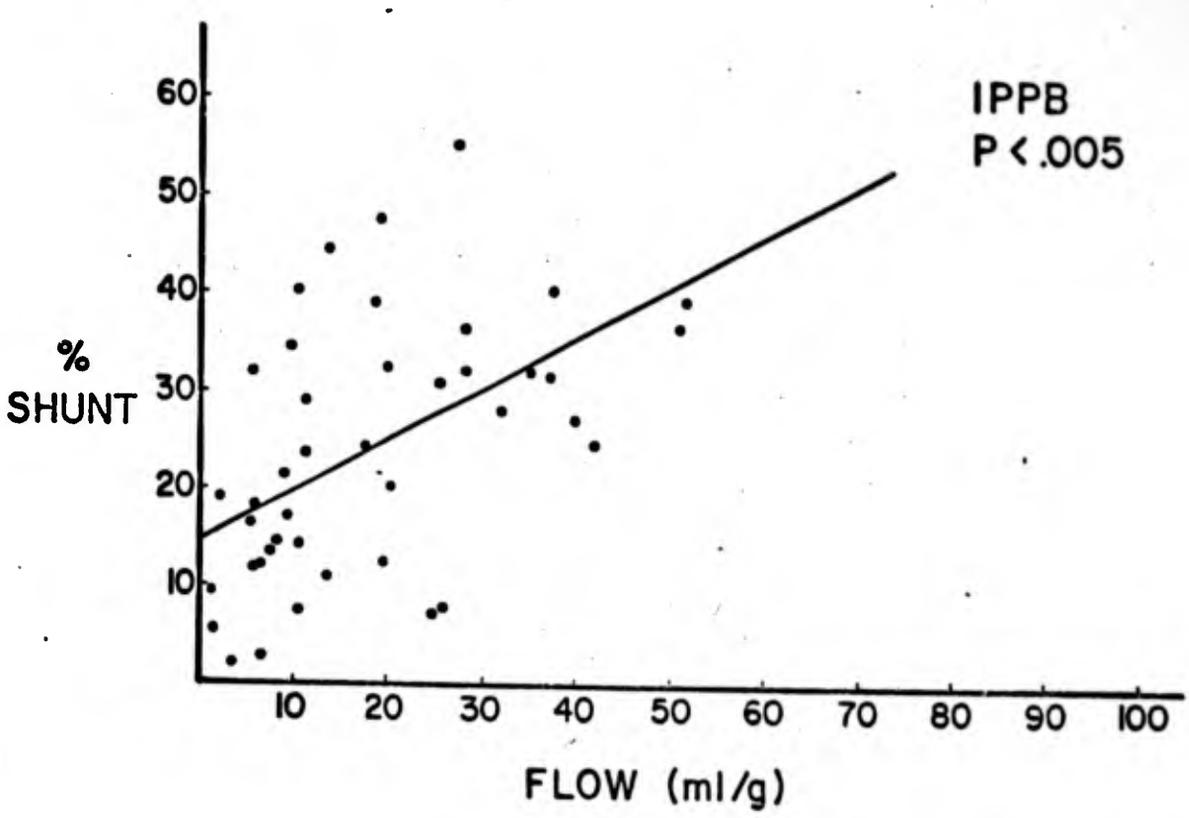

Figure 9 Correlation is shown between shunt and flow/gram of lung weight with CPPB (calculated linear regression line).

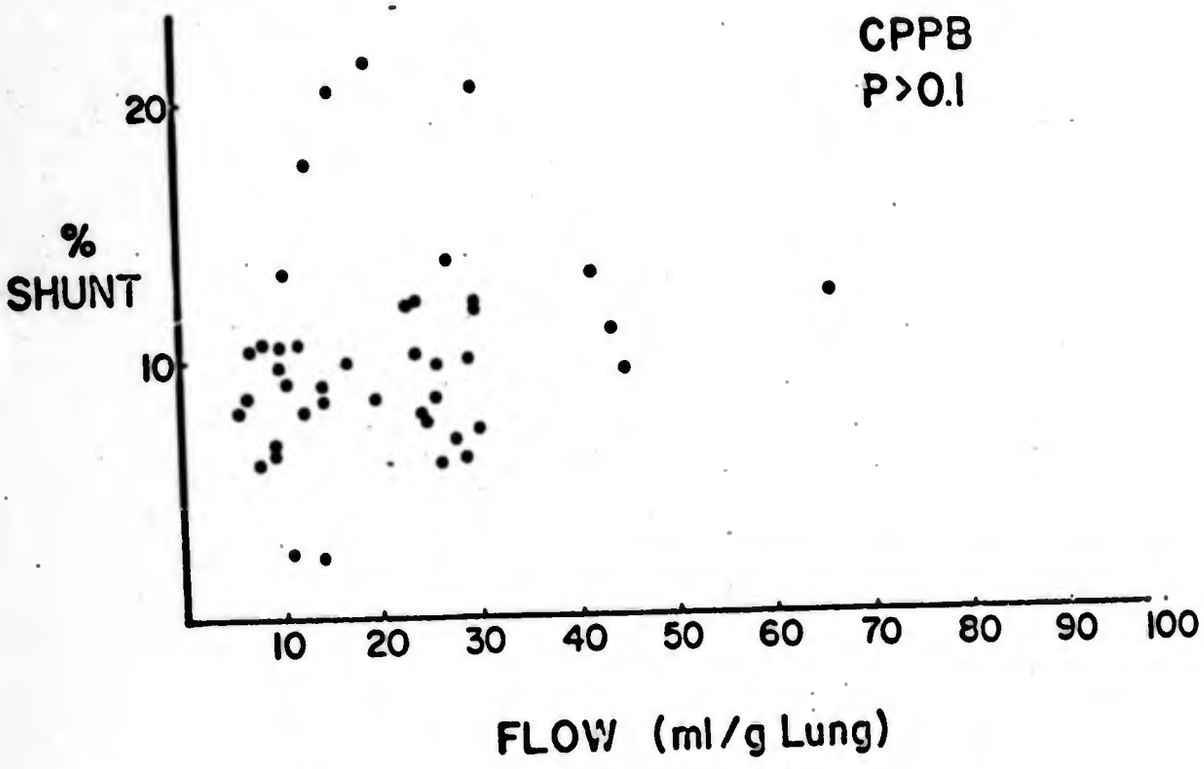

Figure 10 No correlation is shown between shunt and flow/gram of lung weight with CPPB (calculated linear regression line).

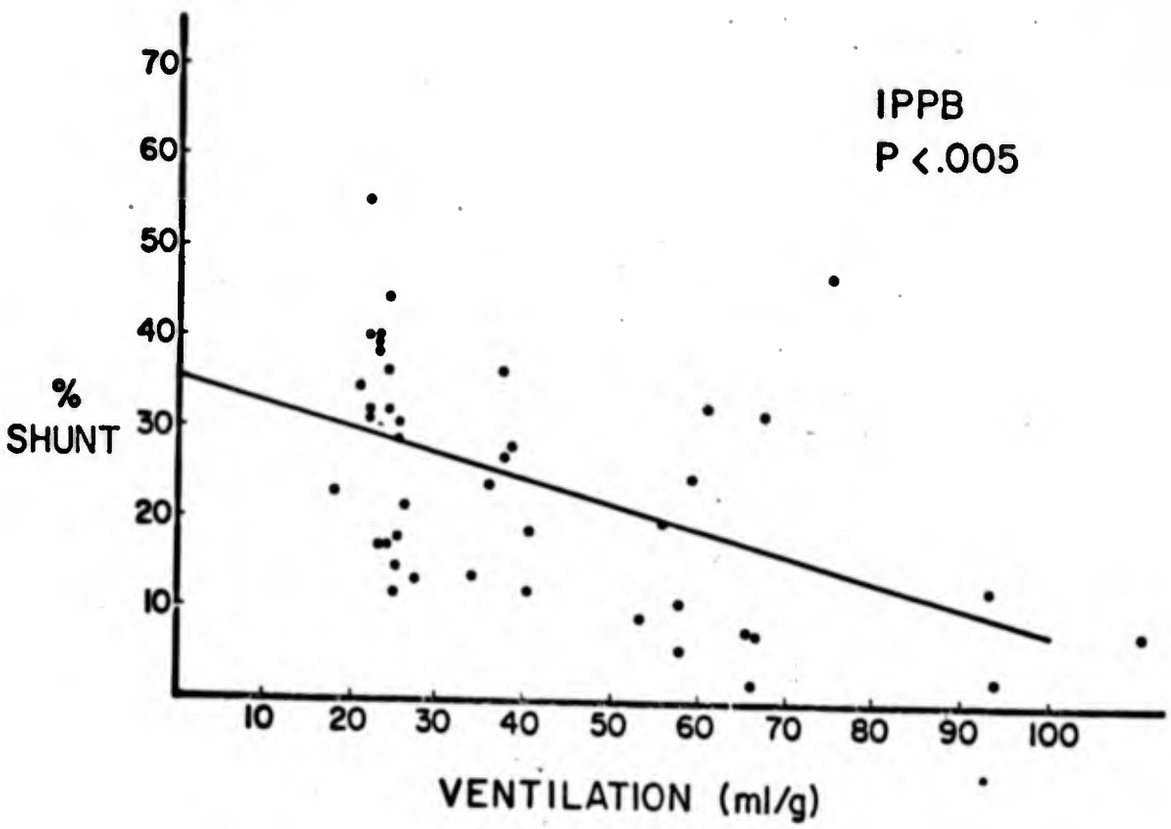

Figure 11 Correlation between shunt and ventilation/gram of lung weight with IPPB (calculated linear regression line).

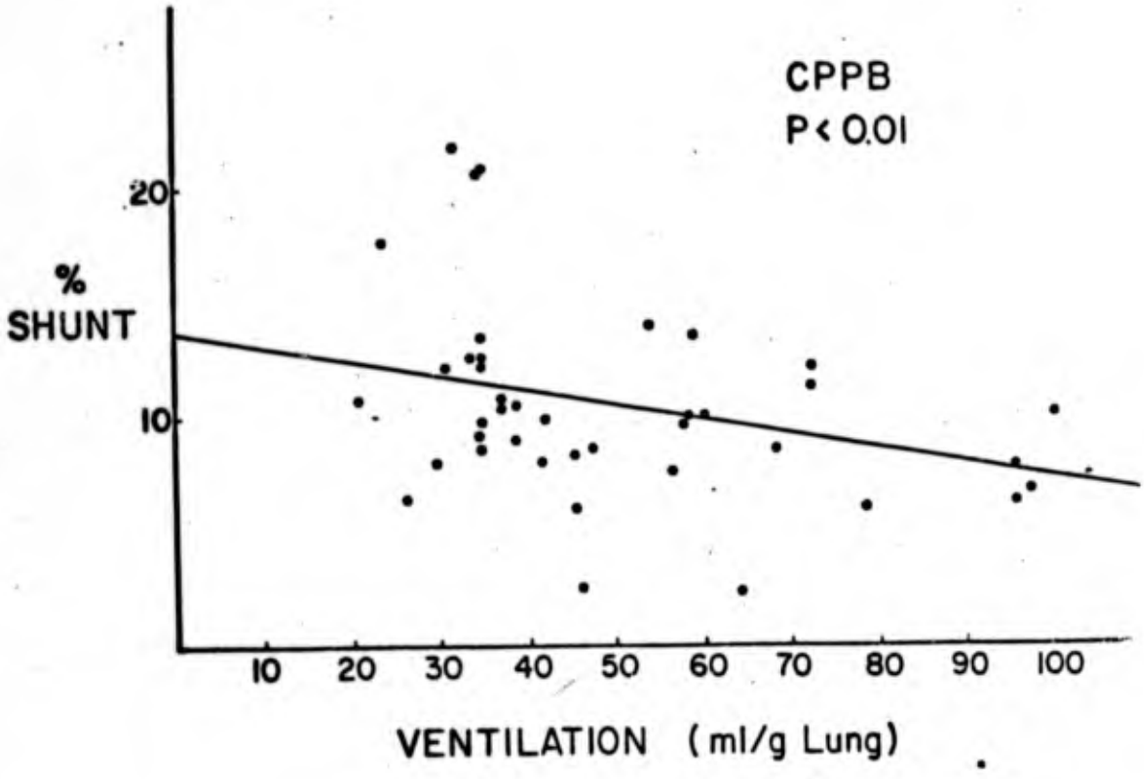

Figure 12 Correlation between shunt and ventilation/gram of lung weight with CPPB (calculated linear regression line).

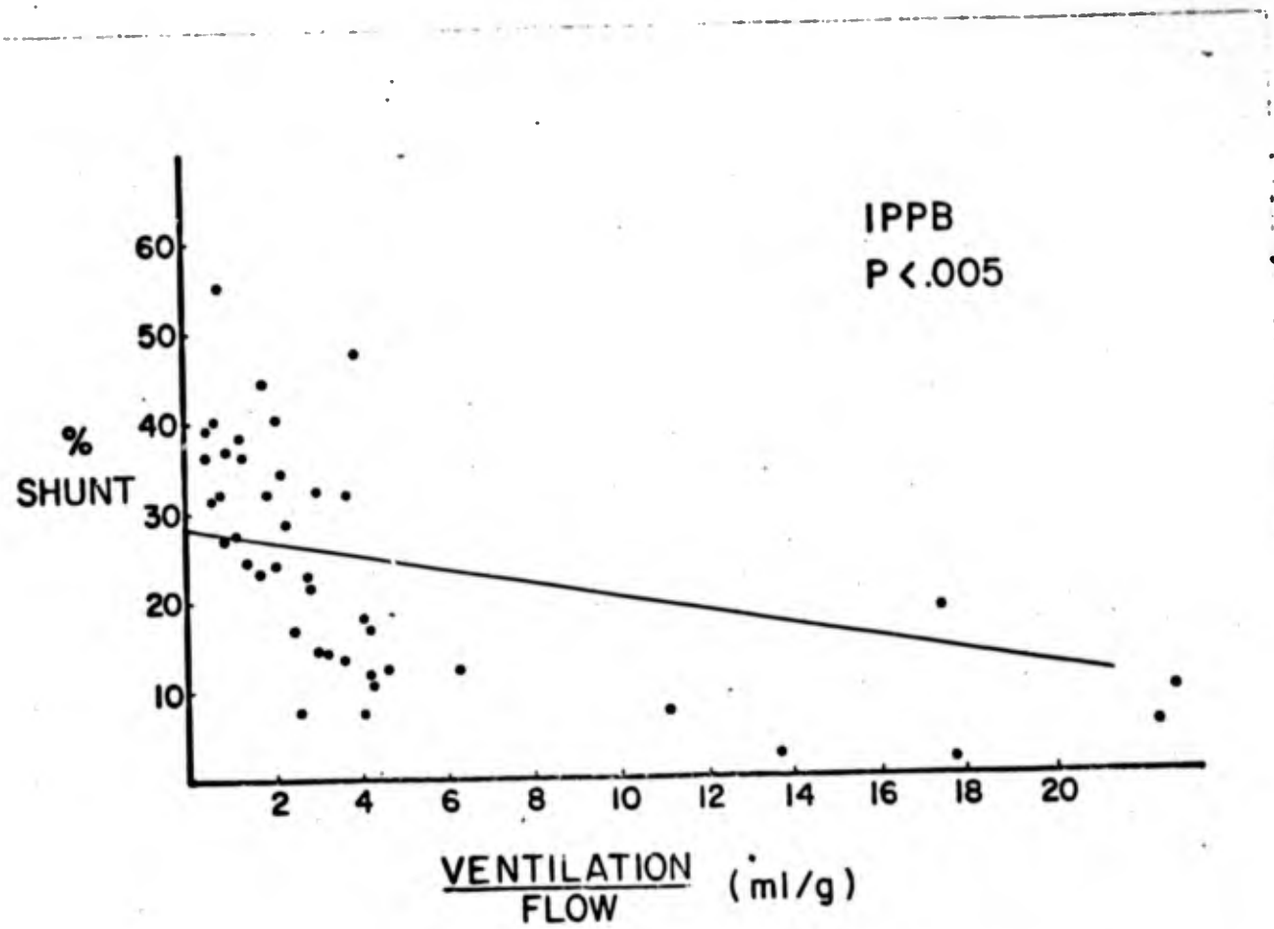

Figure 13 Correlation between shunt and ventilation/perfusion per gram of lung weight with IPPB (calculated linear regression line).

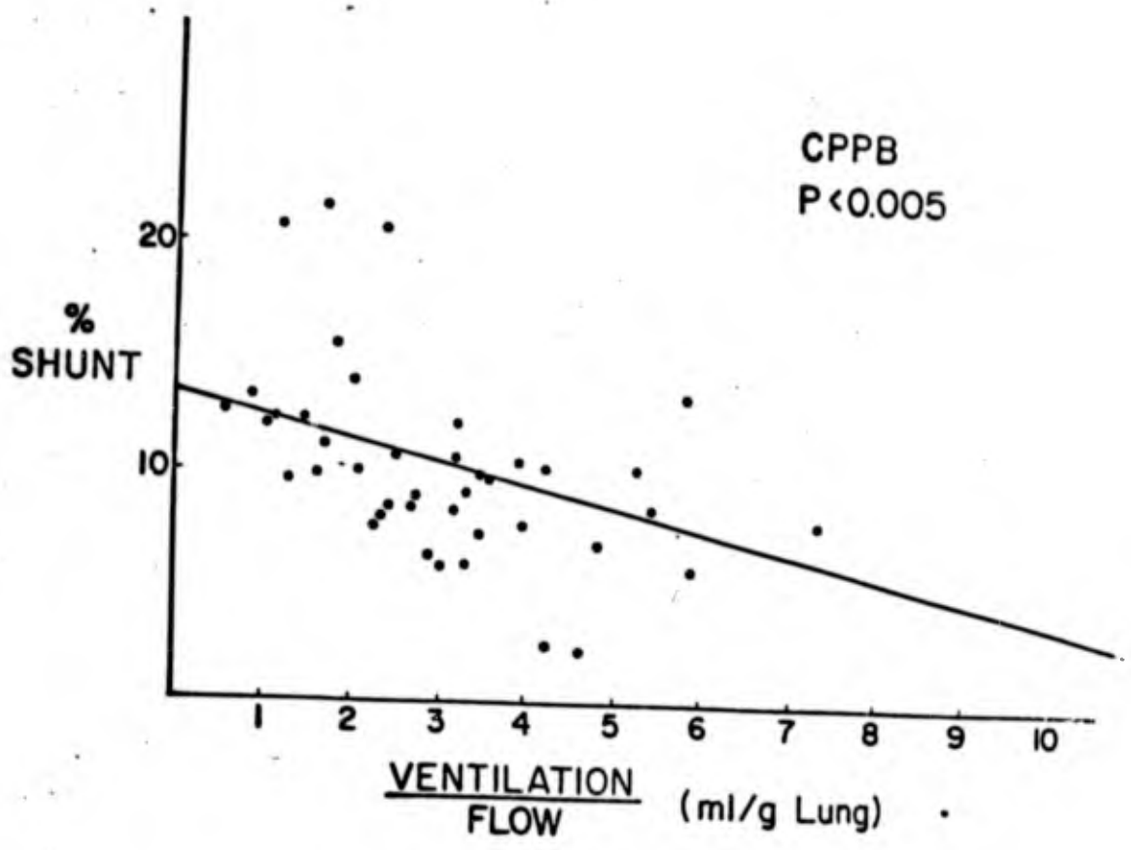

Figure 14 Correlation between shunt and ventilation/perfusion per gram of lung weight with CPPB.

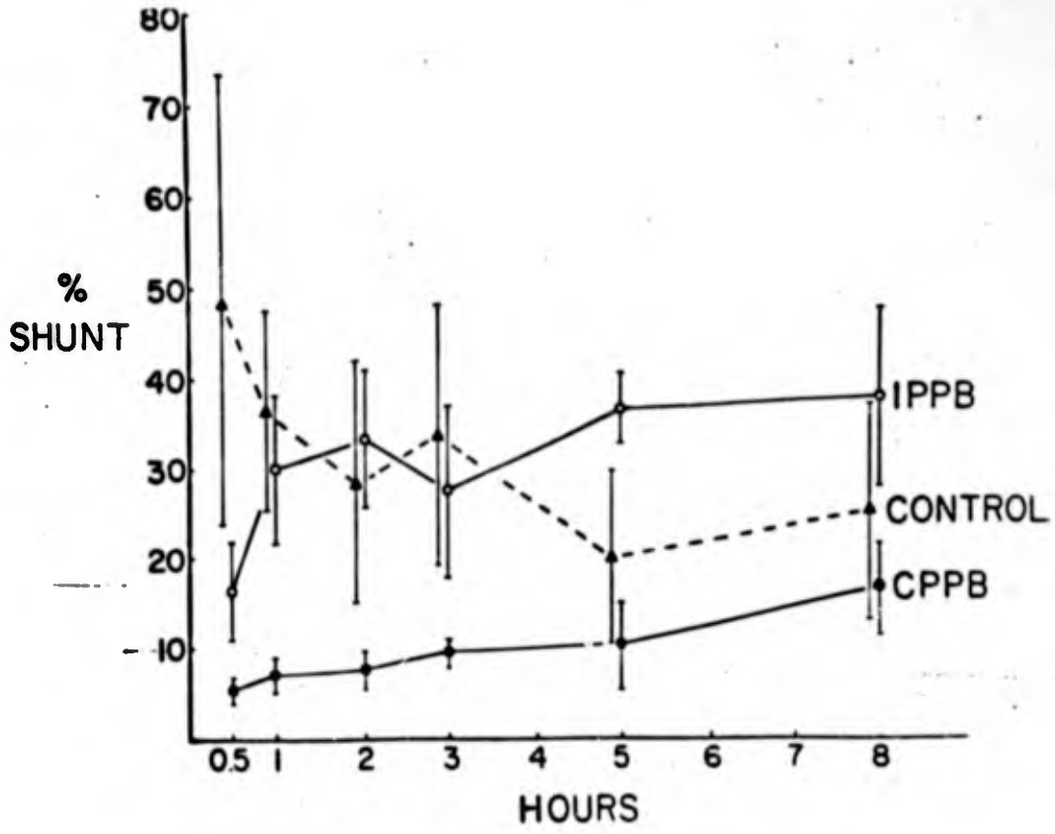

Figure 15 Percent shunt in hemorrhagic edema. (Mean values ± 2 SE) Animals were allowed to breath spontaneously or were ventilated with IPPB or CPPB.

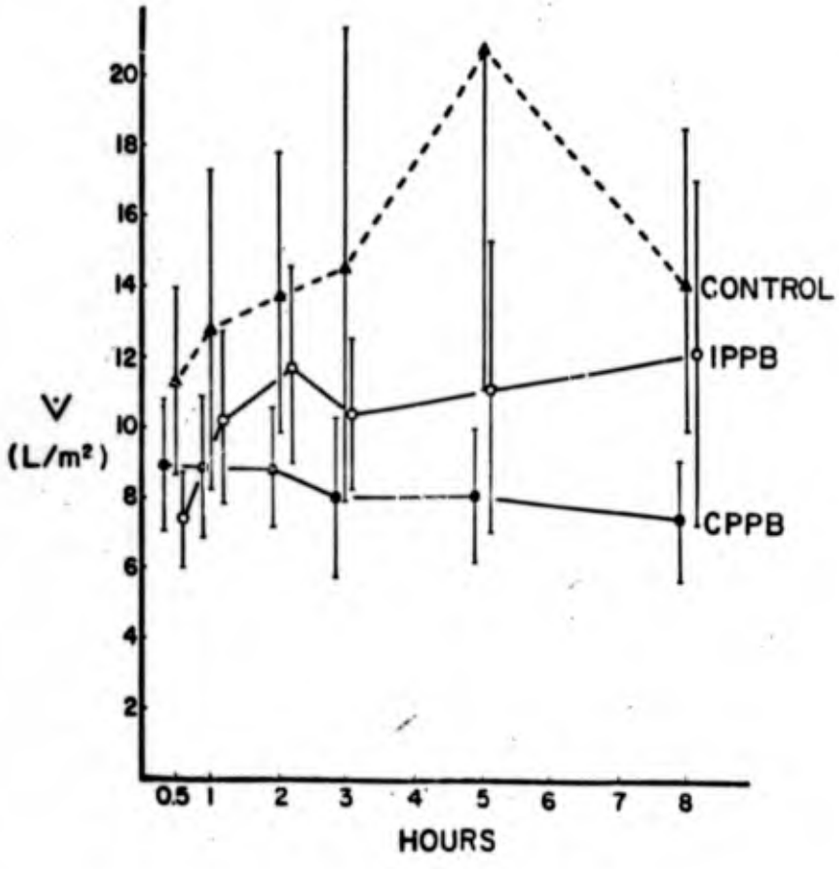

Figure 16 Minute ventilation during spontaneous breathing, IPPB, or CPPB in hemorrhagic edema. (Mean values $\pm$ 2 SE)

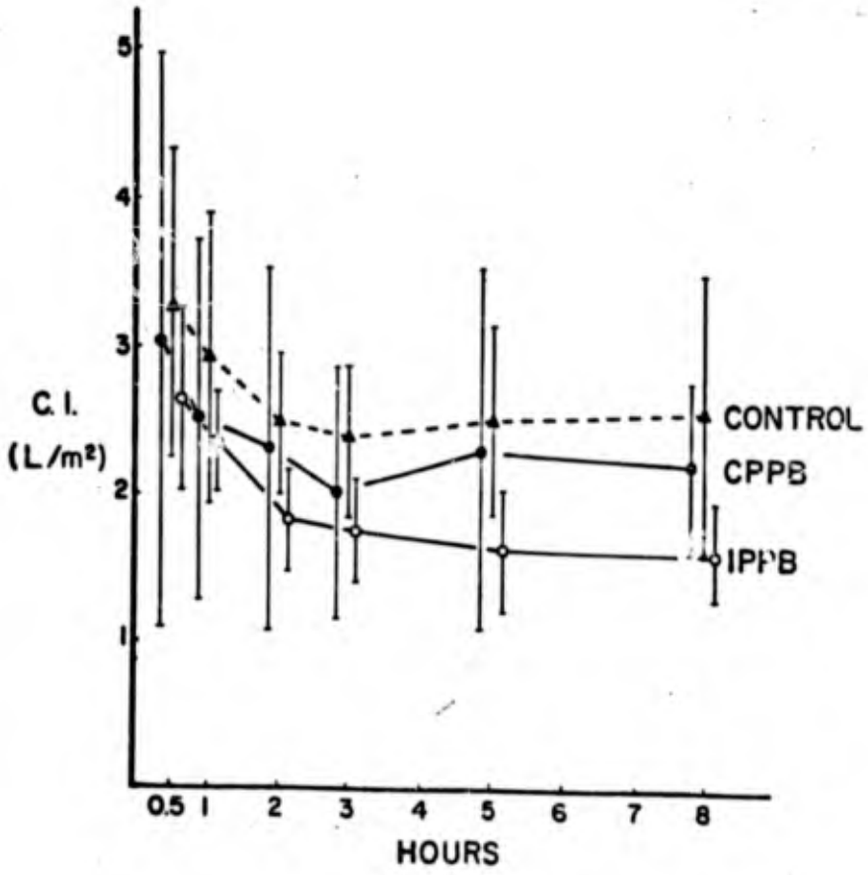

Figure 17 Cardiac index during spontaneous breathing IPPB or CPPB in hemorrhagic edema. (Mean values ± 2 SE)

	Mean	± 1 S.D.	Probability
% Shunt			
IPPB	20.0	7.72	P less than
CPPB	9.6	3.23	0.005.
CI (L/m^2)			
IPPB	2.261	0.627	No significant
CPPB	2.085	0.783	difference.
$\dot{V}$ (L/m^2)			
IPPB	7.22	1.95	No significant
CPPB	7.25	1.50	difference.

Table I Percent shunt open chest animals ventilated with IPPB or CPPB. No occlusion of artery or bronchus. Differences in percent shunt are highly significant despite no significant differences in perfusion or ventilation.