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Report #1

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

Annual Progress Report

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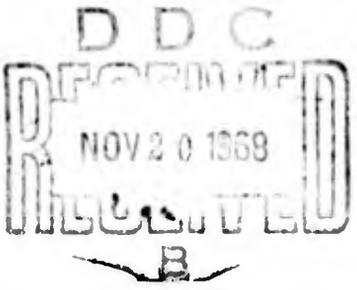

SUMMARY OF WORK

This work was undertaken to investigate effectiveness of various therapeutic trials in experimental and clinical respiratory distress. Using an experimental model of fat embolism, continuous positive pressure breathing, intermittent positive pressure breathing, oxygen, and corticosteroid have been evaluated. Continuous positive pressure breathing has provided better oxygenation at lower minute ventilation than intermittent positive pressure breathing. The use of oxygen does not appear to be beneficial in these experimental animals. Corticosteroids have been valuable in the treatment of clinical fat embolism but have not improved results in experimental animals.

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. Dr. T. Uzawa assisted in the experimental work and 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 Animal 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 distress and respiratory failure following non-thoracic and thoracic trauma are a significant cause of mortality and morbidity in both military and civilian casualties. In this group of patients fat embolism may play a major role in the development of respiratory failure. At present no specific treatment is available for the prevention of fat embolism. Therapeutic efforts must therefore be directed towards effective treatment of the physiological derangements seen in massive systemic fat embolism. Since respiratory failure is a major cause of death in patients with fat embolism, therapeutic efforts of this investigation have been directed towards the causes and treatment of respiratory failure associated with fat embolism.

II. BACKGROUND

Numerous reports have now documented the respiratory failure seen with severe fat embolization following injury. In a report by Peltier[1] on the effect of neutral fat and free fatty acids on the lung, a theory was presented that neutral fat emboli in the lungs and other organs were broken down into free fatty acids which in turn caused a severe hemorrhagic edema in the lung. This work confirmed earlier reports by Scuderi[2] and Jefferson[3] on the effect of free fatty acids on the lung. Previous work in this laboratory confirmed these observations and documented the severe respiratory failure that occurred following the injection of small amounts of oleic acid.[4] Death in these experimental animals was caused by severe progressive hypoxemia. This hypoxemia was accompanied by extreme tachypnea, dyspnea, and intercostal retractions. Circulatory failure did not occur until after respiratory arrest. These initial laboratory studies were stimulated by clinical observations in patients with acute respiratory distress following a variety of injuries and illnesses including fat embolism.[5] These patients developed severe tachypnea, dyspnea, cyanosis, and loss of lung compliance. The syndrome carried a high mortality, but observations indicated that controlled ventilation with continuous positive pressure was effective in maintaining oxygenation of the blood. With this background further experimental and clinical studies were undertaken.

III. EXPERIMENTAL APPROACH

The experimental approach to this problem has evolved around the systematic testing of various therapeutic measures using the experimental model previously developed, whereas the clinical approach has been to use those therapeutic measures that have proven successful in previous patients.

The experimental method is described in previous reports[4] and in the contract application. Indices measured were respiratory frequency, tidal volume, minute ventilation/m^2, dynamic lung compliance, cardiac output, and cardiac index, heart rate, systemic and pulmonary artery blood pressures, and systemic arterial and pulmonary arterial blood gases and hemoglobin. Oxygen consumption and oxygen transport were calculated. A minimum of ten valid experiments were run with each trial therapeutic measure.

IV. RESULTS AND DISCUSSION

A. The use of continuous positive pressure breathing (CPPB) versus intermittent positive pressure breathing (IPPB) on experimental respiratory distress:

Following the injection of oleic acid animals were ventilated either with a pressure respirator using 20 to 30 cm H_2O pressure, or with a volume respirator using controlled ventilation and 10 cm H_2O of end expiratory pressure. Prolonged survival was noted in

both groups when compared to controls receiving no ventilatory assistance. Animals treated with continuous positive pressure breathing (CPPB) maintained a higher P_aO_2 and better lung compliance at lower minute ventilation than did animals treated with intermittent positive pressure breathing (IPPB). Respiration was easier to control with CPPB than IPPB. The IPPB animals and control animals both developed extreme tachypnea and respiratory effort. Coincident with this respiratory effort, these two groups had a higher oxygen consumption than did the CPPB group. Cardiac index was decreased in the CPPB group to a greater degree than the IPPB or control group. CPPB may cause a serious reduction in cardiac output when the lungs are normally compliant. While the effect on cardiac output is less with IPPB than CPPB, this effect is least prominent when the lungs are less compliant. That is to say, CPPB may seriously impair cardiac output when the lungs are normal, but has little effect when the lungs are stiff and congested. The comparison of these two therapeutic modalities would indicate that CPPB is more effective than IPPB in maintaining oxygenation, in controlling ventilation, and in reducing oxygen consumption in this experimental model.

B. Effect of IPPB and CPPB using 100% oxygen:

Since the principal cause of death in the control group was hypoxemia, another series of experiments were undertaken to determine the effect of oxygen on experimental respiratory distress. Although all experiments have not been completed in this group, certain trends are again evident.

Following the injection of oleic acid, control animals were allowed to spontaneously breathe 100% oxygen. These animals develop tachypnea, dyspnea, and hypoxemia in much the same degree as did control animals breathing room air, but the onset of symptoms is delayed and life may be prolonged in some of the animals. Animals treated with 100% oxygen delivered via a pressure respirator show an initial rise in P_aO_2. As edema and hemorrhage in the lung develops, the P_aO_2 falls in these animals below 100% (P_IO_2 = 560-580 at 5,280 feet altitude). CPPB treated animals maintain a high P_aO_2' with a much smaller $P_IO_2 - P_aO_2$ difference than the IPPB animals. Survival time in this series seems comparable to the initial series. Data on lung compliance and cardiac output in this series has not been analyzed as yet since the series is incomplete with regard to number of experiments in each group.

These initial observations suggest that the cause of hypoxemia in this experimental preparation is due to shunting of blood past non-ventilated alveoli rather than a diffusion block. If impairment were strictly diffusion, this should be corrected by administration of 100% oxygen, whereas shunting of blood will not be corrected with 100% oxygen. Oxygen without assisted ventilation neither prevents nor ameliorates the acute hemorrhagic edema that occurs following injection of oleic acid. Oxygen with IPPB improves oxygenation only slightly but oxygen with CPPB results in sustained high levels of P_aO_2. This suggests that CPPB maintains better alveolar ventilation. Since alveolar ventilation is primarily

impaired by edema fluid, CPPB must reduce the amount of pulmonary edema seen in these animals. Atelectasis which may be accentuated by breathing 100% oxygen is also partially prevented by the increase in functional residual capacity that occurs with CPPB. Since the changes in the lung are identical in the series with and without oxygen, oxygen toxicity is not implicated as a causative or contributive factor.

C. The effect of corticosteroids on experimental fat embolism:

A series of experiments is currently in progress designed to test the efficacy of pretreatment with corticosteroids prior to and following injection of oleic acid*. This experiments was based on the clinical observation that corticosteroids could dramatically reverse the respiratory failure associated with fat embolization. The experimental evidence indicates that corticosteroids are ineffective in preventing the acute hemorrhagic edema caused by the injection of oleic acid into the pulmonary artery. This discrepancy with clinical observations may be related to the instantaneous mass effect of oleic acid in the experimental model compared to a slower release of free fatty acids in the clinical situation.

D. Effect of oleic acid injection on atrial and pulmonary venous pressures:

A series of five animals had polyethylene catheters placed in the left atrium and in a pulmonary vein at thoracotomy. The catheters were then buried subcutaneously and the animal allowed to recover. Following recovery from the operation, animals were re-anesthetized and the catheters recovered from their subcutaneous pouches. Pressures in the pulmonary artery, left atrium, and left pulmonary vein, and a systemic artery were measured before and after injection of oleic acid. No consistent pattern has been seen in the pulmonary venous or left atrial pressures in these few experiments and further experiments will need to be done before any statement can be made concerning the effect of oleic acid on left atrial pressures.

E. Miscellaneous observations:

If injection of oleic acid is made into either the right or left pulmonary artery or into a lobar artery, the remainder of the lung is spared the effects of oleic acid. These animals, depending on the amount of involved or uninvolved lung, have a prolonged survival compared to animals where the lesion is diffuse. All animals with lobar involvement alone survive the experimental period. They develop, however, necrosis and infection in the involved lobe and die of sepsis. Several important conclusions may

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*In an attempt to minimize errors in technique, and possible changes related to seasonal effects in animals, several different experimental series are being run concurrently rather than running a single series of animals in succession.

be drawn from this observation:

(1) In order to achieve a bilateral diffuse lesion, oleic acid must be injected into the main pulmonary artery. This is best achieved by withdrawing the catheter to a position just below the pulmonary valve where complete mixing and bilateral distribution will occur.

(2) The effect of oleic acid on the lung is maximal on the first passage through the pulmonary circulation with little or no effect due to recirculation.

(3) Infection is an invariable complication in these damaged lungs if the animal survives the initial acute episode. While animals in the acute experiments have not been covered with antibiotics, animals in survival studies and certainly patients should be treated prophylactically and therapeutically with antibiotics.

(4) The site of injection may also determine amount of oleic acid needed to cause pulmonary damage. Previous investigators used relatively larger amounts of oleic acid than used in this study; however, oleic acid was injected intravenously at some distance from the lungs. The longer exposure to circulating blood prior to contact with a capillary bed may have allowed binding of protein and oleic acid with neutralization in part of the toxic effects of this acid.

F. Clinical observations:

In the eight months of the duration of this grant, no patients with severe respiratory failure secondary to fat embolism have been seen. Two patients with milder forms of fat embolism have been observed but did not require respiratory support and did not receive steroids. Data from the first 21 patients with severe respiratory distress seen at this hospital have been reported and are currently in press in the Journal of Thoracic and Cardiovascular Surgery. (Copies of this report have been previously sent to the contracting officer.) Since that report, five patients with severe respiratory distress have been managed on the wards of Colorado General Hospital. In four of these patients, acute respiratory distress was secondary to gram-negative-septicemia and acute tubular necrosis. All of these patients died from overwhelming sepsis. Two of these patients did not receive continuous positive pressure breathing. Both patients were in profound shock and CPPB was thought to be contra-indicated.

A third patient was treated with CPPB and survived the episode of acute respiratory distress. She ultimately died of sepsis and bilateral bronchopneumonia. The fourth patient was seen in septic shock and severe respiratory distress one week following severe multiple trauma. Dye dilution cardiac output studies on this patient demonstrated a hyperdynamic state despite hypotension. For this reason CPPB was begun even in the face of hypotension. The patient survived the episode of acute respiratory distress, but died

from continued sepsis. These four patients represent a group in the spectrum of diseases or illnesses that may precipitate respiratory distress. Failure to control the precipitating illness ultimately causes death.

The fifth patient developed respiratory distress following multiple injuries including a flail chest, head trauma, and numerous fractures. The episode of acute respiratory distress occurred on his fourth post-injury day. Prior to the episode of respiratory distress, he had been continuously treated with a volume respirator without end-expiratory retard. CPPB was initiated at the onset of severe respiratory distress. Improvement in arterial oxygenation was immediate. Clearing of pulmonary infiltrates occurred more slowly, but recovery was eventually complete.

G. Discussion:

The following illnesses and/or injuries have been implicated in respiratory distress:

1. Shock.
2. Fat embolism.
3. Sepsis.
4. Aspiration.
5. Direct trauma to the lung.
6. Viral pneumonia.
7. Head injuries.
8. Cardiopulmonary bypass.
9. Oxygen toxicity.
10. Diffuse intravascular coagulation.

Despite the variety of etiologic factors, a common denominator seems to be the development of interstitial and intra-alveolar edema, vascular congestion, and atelectasis secondary to direct injury to the lung capillaries. This injury may be caused by ischemia as suggested by Willwerth et al.[6] and Henry et al.[7] Recent studies by Lucas et al.[8] and McLaughlin et al.[9] have demonstrated that the hypoxemia seen following trauma and shock is almost entirely due to shunting of blood across the lungs. This explanation is undoubtedly true as well in the patients in our series since raising the P_IO_2 alone has little effect on P_aO_2. This shunt is most likely a physiologic shunt rather than an arteriovenous shunt, with collapsed or edema-filled alveoli being perfused but not ventilated.

Regardless of the etiology, the acute initial lesion is remarkably consistent and similar. If these patients die from respiratory failure at this point in time, the lungs are heavy, violaceous, and congested. Little crepitance is noted on palpation. The bronchi and larger airways are patent. Microscopic sections of these lungs demonstrate the aforementioned edema, congestion, and atelectasis. Hyaline membranes are commonly found. If death from acute respiratory failure is prevented, patients may follow one of three general courses.

(1) Many patients, particularly when trauma or fat embolism is the primary etiologic agent, recover rather dramatically over a period of three to five days. This group of patients has had the most dramatic and gratifying response to CPPB. Prior to the use of CPPB, most of these severely ill patients died in the acute stage from hypoxemia. Although corticosteroids appear beneficial in fat embolism, they have not had any effect on other patients in this group.

(2) The second group of patients recovers more slowly but eventually recovers completely. In this group are patients with aspiration pneumonia, septicemia, and viral pneumonias. The technique of CPPB allows effective oxygenation and ventilation during the recovery period which may last up to 14 days. While corticosteroids have been used in these patients, no dramatic effects have been noted and the role of corticosteroids remains difficult to assess. Recovery in the first two groups is apparently complete. Pulmonary function tests and blood gas analysis performed up to one year after recovery in several patients have all been normal. Surviving patients not already studied are being recalled for these studies.

(3) The third group of patients have been kept on CPPB and usually a high inspired oxygen concentration for up to three weeks with evidence of steadily worsening gas transport. Almost invariably these patients have had uncontrolled sepsis frequently combined with other serious illnesses such as acute hemorrhagic pancreatitis and acute tubular necrosis. At necropsy these lungs show diffuse organizing pneumonia combined with acute and massive interstitial fibrosis. Normal architecture of the lung is almost completely destroyed. The etiology of this intense fibroblastic response remains unclear. Oxygen toxicity must be considered yet other patients that recovered received high concentrations of oxygen for prolonged periods. My personal opinion is that this represents an abnormal response to injury and continued insult with fibroblasts replacing irreparably damaged capillary beds in the lung. More work needs to be done on this particular aspect of the respiratory distress syndrome.

V. CONCLUSIONS

(1) Both experimental and clinical studies performed with the support of this contract have confirmed the efficacy of the treatment of respiratory distress with CPPB. By increasing functional residual capacity, more alveoli are ventilated, edema is reduced, and oxygenation improved. CPPB should not be used in the presence of hypovolemic shock since this technique may decrease venous return and cardiac output especially when the lungs are relatively compliant.

(2) Corticosteroids appear to be effective in clinical fat embolism but have not been effective in the experimental model. This discrepancy of effect may be due to the relative amounts of free fatty acid released in the lung in the two situations.

(3) Oxygen in high concentrations is not effective therapy unless combined with respiratory support. The large physiologic shunts produced in these illnesses do not respond to high concentrations of oxygen. Improved ventilation particularly with CPPB will overcome a portion of these shunts.

VI. RECOMMENDATIONS

CPPB is recommended for the treatment of patients with severe respiratory distress following shock, trauma, sepsis, and other causes. It is particularly valuable in the presence of hypoxemia that does not respond to increasing concentrations of inspired oxygen. Corticosteroids are recommended for the treatment of acute respiratory failure secondary to fat embolism in man. This statement is based on clinical observations and has not been substantiated in the laboratory.

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13. ABSTRACT

This work was undertaken to investigate effectiveness of various therapeutic trials in experimental and clinical respiratory distress. Using an experimental model of fat embolism, continuous positive pressure breathing, intermittent positive pressure breathing, oxygen, and corticosteroid have been evaluated. Continuous positive pressure breathing has provided better oxygenation at lower minute ventilation than intermittent positive pressure breathing. The use of oxygen does not appear to be beneficial in these experimental animals. Corticosteroids have been valuable in the treatment of clinical fat embolism but have not improved results in experimental animals.

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14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Continuous Positive Pressure Breathing						
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Corticosteroids						
Oxygen						
Lung Compliance						
Respiratory Distress						
Cardiac Index						

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APPENDIX

The following Tables I-VI with appropriate captions represent data collected on dogs either breathing room air or ventilated with room air using IPPB or CPPB. These tables are taken from a paper submitted to the Journal of Applied Physiology.

CAPTIONS

TABLE I - Mean body weight and mean body surface area ± 2 standard errors of the mean are present for control IPPB and CPPB groups.

TABLE II - Mean valves ± 2 standard errors of the mean for P_aO_2, P_aCO_2, pH, and S_aO_2 in the three groups before and after injection of oleic acid. Pre-injection valves represent a mean of all animals prior to injection.

TABLE III - Changes in mean (±2SE) arterial pressure (AP), pulmonary artery pressure (PAP), heart rate, and cardiac index (CI) are presented for the three groups.

TABLE IV - Changes in mean (±2SE) tidal volume (V_t), respiration rate (f) and minute ventilation ($\dot{V}$).

TABLE V - Changes in mean (±2SE) dynamic lung compliance (C_L), total compliance (C_T), transtracheal pressure (P_T), and transpulmonary pressure fall (P_{TP}). P_T in the control groups was atmospheric pressure and total compliance could not be measured in the control group by our methods.

TABLE VI - Changes in mean (±2SE) oxygen transport and oxygen consumption.

TABLE I

	Mean Body Wt.	Mean Body Surface Area
Controls	18.40 ± 2.84 Kg	.7866 ± 0.08 m^2
IPPB	18.1 ± 2.21 Kg	.7680 ± .06 m^2
CPPB	15.7 ± 1.77 Kg	.6990 ± .05 m^2

TABLE I

	P_aO_2 mm Hg			S_aO_2 %			P_aCO_2 mm Hg			pH (arterial)		
	Control	IPPB	CPPB	Control	IPPB	CPPB	Control	IPPB	CPPB	Control	IPPB	CPPB
Injection	60 ± 2.7			88.8 ± 2.6%			37.8 ± 2.9			7.35 ± .02		
30 min	44 ± 4.5	55.1±6.8	71.3±5.7		84.7± 3.7	92.3±4.1	41.1± 7.4	32.3±2.6	30.1±5.8	7.31±.03	7.35±.03	7.36±.05
1 hr	37.5± 5.8	50.1±7.3	66.9±4.8		81.6± 6.1	89.9±4.0	36.8± 6.2	31.4±4.4	32.8±6.4	7.32±.05	7.37±.03	7.30±.05
2 hr	31.8±11.1	47.2±5.5	65 ±5.3		78.3± 8.5	86.6±6.8	45.2±10.3	24.3±2.7	33.4±6.5	7.25±.08	7.44±.04	7.29±.05
3 hr		45.5±6.3	67 ±3.9		76 ± 9.3	89.6±3.0	-	26.1±3.3	34.9±6.5		7.44±.04	7.29±.05
5 hr		44.3±5.9	61 ±3.3		78.2± 8.6	87 ±3.5		26 ±4.7	36.4±6.7		7.42±.06	7.29±.06
8 hr		48.7±6.1	60 ±6.6		78.6±11.1	84.1±6.3		18.8±2.6	35.9±4.0		7.38±.08	7.27±.05

TABLE III

	AP mm Hg			PAP mm Hg			Heart Rate			CI L/min/m^2		
	Control	IPPB	CPPB	Control	IPPB	CPPB	Control	IPPB	CPPB	Control	IPPB	CPPB
Injection	139 ± 11			15 ± 2			163 ± 13			3.83 ± .55		
30 min	113±10	108±14	93±16	15±3	14±2	15±3	113±20	141±18	140±22	2.53±.45	2.25±.45	1.32±.26
1 hr	135±11	106±14	111±13	17±5	14±2	19±3	127±21	163±21	156±26	2.89±.42	2.66±.46	1.69±.31
2 hr	137±14	114±13	141±11	24±4	24±4	14±2	116±14	180±17	177±22	3.47±.93	2.34±.30	1.78±.34
3 hr		123±13	133±11		17±2	23±4		172±26	166±18		2.51±.40	1.53±.3
5 hr		117±10	140±11		19±3	30±6		182±26	189±18		2.70±.47	1.89±.51
8 hr		109±20	130±13		22±4	33±8		201±36	184±15		2.96±.98	2.56±.68

TABLE IV

	V_t ml			f/min			$\dot{V}$ min		
Pre Injection	Control	IPPB	CPPB	Control	IPPB	CPPB	Control	IPPB	CPPB
	282 ± 41			24 ± 7			6.1 ± 1.2		
30 min	102±12	418±120	327±27	109±13	19± 6	20 ±0	11.0±2.2	6.4±1.9	6.6± .6
1 hr	137±18	398±127	350±26	119±24	23± 6	20 ±0	13.2±3.1	7.6±1.6	7.0± .5
2 hr	120±14	375± 93	352±28	105±30	27± 9	20 ±0	15.1±3.9	9.2±2.1	7.1± .5
3 hr		374± 89	370±26		48±23	20 ±0		14.2±4.4	7.4± .6
5 hr		342± 86	390±21		55±21	20.8±1		17.0±4.2	8.1± .5
8 hr		326± 69	442±80		59±19	21 ±1		17.3±4.9	9.3±1.7

TABLE V

	C_L L/cm H_2O			C_T L/cm H_2O		P_T cm H_2O		P_{TP} cm H_2O		
Pre Injection	Control	IPPB	CPPB	IPPB	CPPB	IPPB	CPPB	Control	IPPB	CPPB
	.043 ± .008							5 ± 2		
30 min	.012±.003	.026±.010	.031±.008	.015±.004	.027±.006	16±1	19±3	8±2	11±2	8±2
1 hr	.008±.002	.027±.009	.037±.006	.017±.006	.027±.004	16±2	18±1	13±3	11±2	7±2
2 hr	.006±.001	.025±.007	.037±.011	.016±.004	.028±.006	18±1	19±3	19±4	13±2	7±3
3 hr		.019±.005	.033±.006	.013±.004	.026±.005	22±3	20±2		14±3	8±2
5 hr		.021±.004	.034±.005	.012±.003	.027±.003	22±3	20±2		14±3	8±2
8 hr		.019±.008	.028±.008	.011±.004	.023±.006	23±4	20±3		17±5	10±3

TABLE VI

	Oxygen transport ml/min/m^2			Oxygen consumption ml/min/m^2		
	Control	IPPB	CPPB	Control	IPPB	CPPB
Pre Injection		639 ± 99			128 ± 15	
30 min	422±40	357± 64	255± 45	128±14	119±18	117±20
1 hr	331±82	425± 80	328± 61	152±22	123±20	126±28
2 hr	272±47	386± 62	329± 57	162±22	135±18	120±23
3 hr		389± 74	295± 68		153±22	111±19
5 hr		447± 86	361± 92		158±29	135±26
8 hr		571±175	436±106		147±21	141±32

CAPTIONS

TABLE VII - Changes in P_aO_2, P_aCO_2, pH in animals breathing 100% oxygen. Control animals (8) breathed from a reservoir through a one-way valve. IPPB and CPPB animals were ventilated with 100% O_2.

TABLE VIII - Changes in pulmonary artery pressure and cardiac index in dogs breathing or ventilated with 100% air.

TABLE IX - Changes in respiratory rate (f) and minute ventilation ($\dot{V}$) in dogs breathing or being ventilated with 100% oxygen.

TABLE X - Changes in lung compliance (C_L) and dynamic total compliance (C_T) in dogs breathing or ventilated with 100% oxygen.

TABLE XI - Oxygen transport and oxygen consumption in dogs breathing or ventilated with 100% oxygen.

TABLE VII

	P_aO_2 mm Hg (100% inspired O_2)			P_aCO_2 mm Hg			pH		
	Control	IPPB	CPPB	Control	IPPB	CPPB	Control	IPPB	CPPB
Pre-injection	43±11*	61±5*	375± 99	34±5.6	31± 2.8	29± 6.0	7.35±.21	7.36±.21	7.41±.09
30 min	199±101	247±68	416± 40	43±6.4	38± 7.8	31±10.6	7.22±.13	7.26±.27	7.32±.27
1 hr	145± 60	124±46	359± 75	37±3.5	32± 4.9	26± 9.8	7.25±---	7.31±.11	7.32±.19
2 hr	107± 75	73±15	365± 60	36±5.6	28± 5.6	28± 9.8	7.31±.18	7.32±.23	7.34±.32
3 hr	126± 70	68±23	329± 84	32±5.6	27± 6.0	25± 5.3	7.33±.13	7.35±.29	7.37±.22
5 hr	154±104	69± 8	293±103	29±6.8	29± 7.5	27± 5.3	7.35±.29	7.31±.22	7.34±.03
8 hr	122± 95	67±13	229± 99	37±9.0	35±22.0	29± 6.9	7.25±.11	7.28±.37	7.36±---

*Room air.

TABLE VIII

	Pulmonary Artery Pressure mm Hg			Cardiac Index L/min/m^2		
	Control	IPPB	CPPB	Control	IPPB	CPPB
Pre-injection	14.5±3.2	15.7±4.1	15.3±4.1	4.8±1.28	3.9±.78	4.1±1.96
30 min	12.6±2.0	11.8±3.5	15.7±2.9	3.3±1.05	2.6±.64	3.0±1.96
1 hr	11.6±2.1	14.9±3.2	14.6±3.0	2.9± .98	2.4±.35	2.5±1.21
2 hr	11.0±2.2	18.2±4.6	16.8±3.2	2.5± .45	1.9±.35	2.3±1.21
3 hr	16.2±4.5	19.5±4.6	17.3±3.6	2.5± .38	1.8±.29	2.0± .83
5 hr	17.1±4.8	22.0±6.8	20.7±1.0	2.5± .63	1.6±.45	2.3±1.21
8 hr	17.0±2.6	23.3±7.1	21.6±2.4	2.6± .90	1.6±.57	2.2± .58

TABLE IX

	f/min			$\dot{V}$ L/min		
	Control	IPPB	CPPB	Control	IPPB	CPPB
Pre-injection	16± 6.9	19±13.0	20±0	6.26±2.81	5.71±2.26	9.10±2.39
30 min	71±20.6	10± 3.5	20±0	11.36±2.65	7.42±1.40	8.97±1.86
1 hr	62±19.9	15± 4.3	20±0	12.78±4.53	10.31±2.44	8.90±1.97
2 hr	51±14.9	27± 8.8	20±0	13.84±3.97	11.75±2.80	8.85±1.69
3 hr	55±17.8	18± 3.8	20±0	14.65±6.74	10.43±2.11	8.03±2.25
5 hr	82±26.3	29±13.7	20±0	20.86±9.83	11.16±4.06	8.10±1.90
8 hr	79±21.7	43±12.3	20±0	14.23±4.26	12.28±4.52	7.43±1.70

TABLE X

	C_L L/cm H_2O			C_T L/cm H_2O	
	Control	IPPB	CPPB	IPPB	CPPB
Pre-injection	.050±10	.074±39	.057±15	------	.032± 8
30 min	.044±34	.049±12	.048±13	.035±8	.034±11
1 hr	.038±19	.046±10	.048±18	.032±6	.033±10
2 hr	.029±10	.039± 9	.042±15	.025±5	.032±10
3 hr	.032±15	.039±15	.044±23	.027±4	.030±11
5 hr	.029±13	.030± 9	.034±15	.022±6	.025±10
8 hr	.020± 4	.024±10	.023±11	.019±8	.017± 4

TABLE XI

	Oxygen Transport ml/min			Oxygen Consumption ml/min		
	Control	IPPB	CPPB	Control	IPPB	CPPB
Pre-injection	720±204	697±156	706±433	174± 52	176±49	125± 48
30 min	419±124	497±190	685±492	91± 45	137±56	148± 94
1 hr	402±131	490± 82	566±307	123± 60	116±16	125± 56
2 hr	406±131	387± 94	498±293	120± 45	124±34	107± 53
3 hr	388± 82	394±106	404±192	137± 35	130±56	107± 49
5 hr	405± 56	337± 89	472±364	155± 89	96±20	135±12
8 hr	359±129	360± 80	426±120	261±184	137±77	99± 12