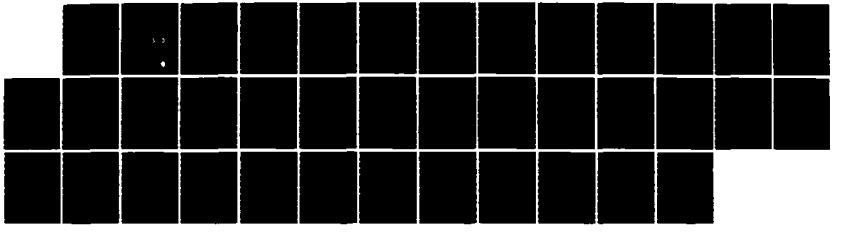
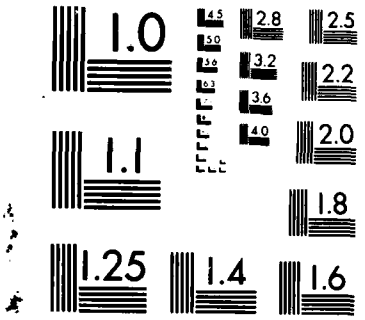
AD-A173 602 VENTILATION CRITERIA FOR AEROMEDICAL EVACUATION(U) 1/1
STATE UNIV OF NEW YORK AT BUFFALO PULMONARY DIV
R A KLOCKE ET AL. SEP 86 USAFSAM-TR-86-3
UNCLASSIFIED F33615-83-D-0603 F/G 6/11 NL





USAFSAM-TR-86-3

VENTILATION CRITERIA FOR AEROMEDICAL EVACUATION

Robert A. Klocke, M.D.
Alan T. Aquilina, M.D.
Brydon J. B. Grant, M.D.
Alan R. Saltzman, M.D.
Patricia A. Land, Captain, USAF, NC (USAFSAM/VNC)
Neel B. Ackerman, Jr., Major, USAF, MC (USAFSAM/VNC)

Department of Medicine
Pulmonary Division
State University of New York at Buffalo
Buffalo, NY 14215

September 1986

Final Report for Period April 1984 - December 1985

Prepared for

USAF SCHOOL OF AEROSPACE MEDICINE
Aerospace Medical Division (AFSC)
Brooks Air Force Base, TX 78235-5301

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION / AVAILABILITY OF REPORT Approved for public release; distribution is unlimited.
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S) USAFSAM-TR-86-3
6a. NAME OF PERFORMING ORGANIZATION Dept of Medicine Pulmonary Division 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION USAF School of Aerospace Medicine (VNC)
6c. ADDRESS (City, State, and ZIP Code) State University of New York at Buffalo Buffalo, NY 14215	7b. ADDRESS (City, State, and ZIP Code) Aerospace Medical Division (AFSC) Brooks AFB, TX 78235-5301
8a. NAME OF FUNDING / SPONSORING ORGANIZATION 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER F33615-83-D-0603
8c. ADDRESS (City, State, and ZIP Code)	10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
62202F	7930	16	4A

11. TITLE (Include Security Classification)
Ventilation Criteria for Aeromedical Evacuation

12. PERSONAL AUTHOR(S) Klocke, R.A.; Aquilina, A.T.; Grant, B.J.B.; Saltzman, A.R.; Land, P.A.; Ackerman, N.B., Jr.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Final	FROM 1 Apr 84 TO 1 Dec 85	1986, September	39

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
06	11		Aeromedical evacuation; Ventilatory requirements; Air evacuation; and Mechanical ventilation.
06	12		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)
Air evacuation of patients requiring mechanical ventilation exposes these individuals to a barometric pressure that is approximately 25% less than normal. This limits the maximum inspired oxygen tension that can be provided as well as possibly altering ventilatory requirements. We investigated this problem in two ways. First, we used a theoretical analysis to set tolerance limits on vital physiological functions. Oxygen delivery, the product of cardiac output and arterial oxygen concentration, is the most important factor in ensuring survival. Surprisingly, overall ventilation could be reduced substantially without resulting in an unfavorable outcome. In the second portion of the study, we induced the respiratory distress syndrome in anesthetized dogs and then exposed them to a reduced barometric pressure similar to that encountered with aeromedical evacuation. These experiments demonstrated no change in ventilatory requirements but indicated that reduced inspired oxygen tension resulted in substantial hypoxemia. Using these data, we have proposed guidelines for selecting candidates for aeromedical evacuation and determining optimal inspired oxygen concentration during air transport.

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	UNCLASSIFIED

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL
Erika J. Poleschner, 2d Lt, USAF	512-536-2937	USAFSAM/VNC

DD FORM 1473, 84 MAR 83 APR edition may be used until exhausted. All other editions are obsolete.

TABLE OF CONTENTS

List of Illustrations

List of Tables

VENTILATION CRITERIA FOR AEROMEDICAL EVACUATION

INTRODUCTION

Severe trauma, whether the result of natural disaster, industrial accident or armed conflict, often occurs in remote areas of the world. Medical stabilization of patients prior to transportation is desirable but may not be feasible due to either the lack of adequate local medical facilities or a large number of injured personnel that could overwhelm the available health care system. Thus, the need exists to be able to transport patients rapidly to medical centers where appropriate treatment can be instituted. By nature these individuals will be medically unstable and many will require mechanical ventilatory support during transportation. Air transportation is the most efficient approach to this problem, and this burden will fall primarily upon the Military Airlift Command of the U.S. Air Force.

Because aircraft cabins are not pressurized to sea-level conditions (760 mmHg), care for injured personnel becomes complicated. A cruising altitude of 40,000 feet (12,200 m) is not unusual which results in cabin pressures as low as 560 mmHg--an equivalent altitude exposure of 8,000 feet (2,400 m). Oxygenation of blood in the lungs depends upon the actual pressure of oxygen in the alveolar gas rather than on the fractional oxygen concentration. Hence, a 25% reduction in barometric pressure that can accompany air transportation will result in a similar reduction in alveolar oxygen tension when the same inspired oxygen mixture is breathed. This has serious implications for patients with severe respiratory disease. Finally, with barometric pressure reduced, each volume delivered by a respirator will contain less gas molecules because ventilators deliver gas volumes under ambient conditions. From a theoretical standpoint, this might be expected to have little impact on pulmonary gas exchange. Unfortunately, no experimental studies to date either support or refute this position.

Despite past large-scale transportation of injured personnel and an obvious need for scientific guidelines in this matter, the medical literature has a paucity of relevant studies. Some are anecdotal reports of one or more cases. Many other studies involve large numbers of patients and were reported during or just after World War II; they therefore lack information pertinent to current medical therapy.

Kirby et al. (1) described the function of the Bird Mark VIII positive-pressure ventilator at altitude. They studied normal dogs at altitude and concluded that this particular ventilator, even though its delivery characteristics varied substantially at altitude, was adequate to maintain ventilation

of a healthy animal. They did not study animals with abnormal lungs. In an elegant, technically difficult study, Henry et al. (2) documented severe arterial hypoxemia in casualties being evacuated from the Republic of Viet Nam to Japan. These patients were all reasonably stable from a medical standpoint; none required mechanical ventilation. Unfortunately, we find no studies that describe the physiological consequences of exposure to reduced barometric pressure in either humans or animal models that require mechanical ventilation to sustain life.

These considerations have led us to investigate three potential problems that may occur with exposure to reduced barometric pressure during air transportation:

1. Reduction in arterial oxygenation accompanying exposure to reduced inspired-oxygen tension

2. Possible alterations in ventilatory requirements for maintaining acid-base homeostasis

3. Effect on gas exchange of a sudden decompression accompanying loss of cabin pressure and a reduction of ambient pressure to less than 20% of ground-level pressure

Although the main thrust of this work was directed towards gas exchange in the abnormal lung, control measurements in normal lungs were necessary to separate the influence of disease from the effect of lowered barometric pressure. The animal model of acute lung disease used in these experiments was induced by intravenous injection of oleic acid. This model presents a pathological and physiological picture similar to that accompanying the adult respiratory distress syndrome (ARDS) in humans. The oleic acid model was chosen because ARDS is the most common form of acute lung injury seen in humans after trauma or inhalational exposure to toxic substances.

Our first approach was to use a computer simulation of gas exchange in normal and abnormal lungs during exposure to reduced barometric pressure. For the abnormal lungs, we chose physiological parameters to duplicate reported values in ARDS in humans. This theoretical approach has the advantage of testing changes of many variables without resorting to innumerable, complex experiments. These computations highlighted the major potential problems associated with altitude exposure and identified those requiring particular attention. Next, to determine the actual effects of altitude exposure, we designed and performed experiments in both normal dogs and those injured with oleic acid. This report is written to follow this investigative approach.

THEORETICAL ANALYSIS

Computer Model

We developed a computer model of pulmonary gas exchange typical of a patient with ARDS. The model simulates a patient being ventilated artificially, with ventilation held constant. Other assumptions of the model include continuous alveolar ventilation rather than tidal breathing, continuous rather than pulsatile pulmonary blood flow, and a constant metabolic rate. Dead space of the ventilator and regulatory mechanisms such as hypoxic pulmonary vasconstriction or the effects of hypoxia and hypercapnia on cardiac output are not taken into account.

The pulmonary gas exchange abnormality of ARDS is based on data of Dantzker et al. (3) and is simulated with a 10-compartment lung model. The compartments are ventilated and perfused in parallel, so collateral ventilation does not occur. One compartment is designated as shunt; the others are assigned ventilation-perfusion ratios from 0.005 to 100.0, equally spaced on a logarithmic scale. The model is assigned a shunt of 48%. Apart from the shunt, the dispersion of ventilation-perfusion ratios in ARDS is mild (3). Therefore, we generated a narrow degree of ventilation-perfusion inequality distributed with a small log (natural) standard deviation of 0.25, using techniques described in detail elsewhere (4). Because of the narrow dispersion, only two compartments received appreciable blood flow (greater than 10^{-6} L/min). To reduce computation time, we reassigned to these two compartments the trivial amount of blood flow to other compartments.

In addition to the computer model of ARDS, for comparison purposes we simulated gas exchange in a model of a normal subject being ventilated mechanically. The model consisted of a single homogeneous compartment. Because its effects on gas exchange are small (5), we ignored the minor degree of alveolar ventilation-perfusion mismatch that occurs in normal subjects.

Input Data

Under all conditions body temperature was held at 37° C, respiratory exchange ratio was maintained at 1.0, P_{50} was specified as 26.8 at pH 7.4, and nitrogen exchange and base excess were assumed to be zero. Baseline values assigned to other variables were hemoglobin concentration, 15 g/dl; hematocrit, 0.45; oxygen uptake, 300 ml/min; carbon dioxide output, 300 ml/min; and cardiac output, 6.0 L/min. Both the normal and ARDS models were ventilated to an arterial carbon dioxide tension (P_aCO_2) of 40 mmHg, which required an alveolar ventilation of 6.47 L/min for the normal lung and 8.73 L/min for the ARDS model.

Computer Program

The computer program was written in FORTRAN and executed on a VAX computer. For most calculations we assumed complete equilibration between alveolar and end-capillary blood gases (i.e., no diffusion defect). Since diffusion limitation has been demonstrated even in normal subjects at marked altitude, we incorporated this factor into calculations where it could have a significant effect on gas exchange. To take diffusion into account, we used a Bohr integration procedure that has been described in detail previously (6). For this procedure we assumed a constant ratio (0.533) of membrane diffusing capacity for oxygen (D_mO_2) to capillary blood volume (V_c). The fraction of D_mO_2 assigned to each compartment (except shunt) is directly dependent on compartmental blood flow. These relations are likely to occur if increased pulmonary blood flow results in recruitment of capillaries. This simplifying assumption enables compartmental V_c to be estimated from compartmental D_mO_2, and the transit time in each lung compartment to be estimated from its V_c and blood flow. For this procedure, the membrane diffusing capacity for carbon dioxide was assumed to be 20 times the corresponding value for oxygen. The multiple chemical reactions involved in carbon dioxide transfer are described by a single exponential reaction with a half-time of 0.15 s. We assumed that oxygen saturation changes took place with rates described by Staub et al. (7). An important assumption is that these reaction rates, which were measured in vitro, can be used to simulate events occurring in vivo.

The computer program uses an iterative technique (Newton-Raphson) to estimate the end-capillary blood gas tensions within each lung compartment for a given barometric pressure and the inspired and mixed venous blood gas compositions. Arterial blood gas composition is estimated from the flow-weighted mean of the end-capillary blood gas contents of each compartment. From cardiac output, the mixed venous and arterial blood gas composition, oxygen uptake ($\dot{V}O_2$), and carbon dioxide output ($\dot{V}CO_2$) are estimated. Then mixed venous blood gas composition is adjusted by another iterative process to produce $\dot{V}O_2$ and $\dot{V}CO_2$ values equal to the preassigned values. Nitrogen exchange is also taken into account in individual alveoli; it is assumed that no net nitrogen exchange occurs across the lung as a whole.

Sensitivity Analysis

To determine the relative importance of the gas exchange variables on the system, we performed a sensitivity analysis. Because of their clinical pertinence to the problem at hand, we selected five factors that affect pulmonary gas exchange: alveolar ventilation, cardiac output, hematocrit, metabolic rate, and D_mO_2. Each parameter was varied over a wide range to determine at what level pulmonary gas exchange is compromised to a point that life is apt to not be sustained. We arbitrarily

chose the limits to be a decrease of mixed venous oxgen tension below 10 mmHg or a decrease in arterial pH to less than 7.1 units. The latter is associated with an increase in the P_aCO_2 to 80 mmHg.

Results of the Theoretical Study

Control Data

Table 1 compares the published data on gas exchange variables in patients with ARDS to the values obtained in the computer model for breathing oxygen at sea level. The computer-model values are all within one standard deviation of those reported in ARDS patients (3), which indicates the computer model's close simulation of pulmonary gas exchange in ARDS.

TABLE 1. COMPARISON OF GAS EXCHANGE VARIABLES

Gas Exchange Variable[a]	ARDS Patients[b]	ARDS Model[c]
F_IO_2	.83 ± .16	.99
$\dot{V}_A$ (L/min)	9.3 ± 1.9	8.7
$\dot{Q}$ (L/min)	6.7 ± 2.6	6.0
Shunt (%)	48 ± 15	48
P_aO_2 (mmHg)	66 ± 19	52
P_vO_2 (mmHg)	36 ± 7	35

[a]Inspired gas fraction (F_IO_2), alveolar ventilation ($\dot{V}_A$), cardiac output ($\dot{Q}$), percentage of $\dot{Q}$ shunted from pulmonary to systemic circulation (shunt), arterial blood oxygen tension (P_aO_2), mixed venous blood oxygen tension (P_vO_2).

[b]Means ± 1 S.D. of gas exchange variables in a group of patients (3).

[c]Values of gas exchange variables in the computer model.

Table 2 provides the values of arterial and mixed venous blood oxygen tensions for both the normal and the ARDS computer models under each of the five conditions: breathing air at sea level and 8,000 feet and breathing oxygen at sea level, 8,000 feet, and 40,000 feet. Barometric pressures of 564 and 141 mmHg were assumed for conditions of 8,000 and 40,000 feet. With increasing altitude, differences between normal and ARDS lungs diminish because the falling inspired oxygen tension, rather than shunt, becomes the dominant cause of hypoxemia.

TABLE 2. COMPARISON OF BLOOD OXYGEN TENSIONS AT DIFFERENT ALTITUDES

Variable		Air		Oxygen		
		Sea Level	8,000 Feet	Sea Level	8,000 Feet	40,000 Feet
P_aO_2[a]						
	N[b]	109	68	666	472	53
	ARDS[c]	42	38	52	49	37
P_vO_2[a]						
	N	43	40	53	51	35
	ARDS	29	27	35	33	26

[a]Arterial and mixed venous blood oxygen tensions expressed in mmHg.

[b]Computer model of normal lung.

[c]Computer model of patients with ARDS.

Sensitivity Analysis

To determine the values that result in a limitation of pulmonary gas exchange, we systematically varied alveolar ventilation, cardiac output, hematocrit, metabolic rate and D_mO_2. Not surprisingly, the major limit for gas exchange due to reduced alveolar ventilation at ground level breathing air (Figure 1) is a rising P_aCO_2 and falling arterial pH. Hypercapnia and respiratory acidosis also limit gas exchange at ground level and 8,000 feet when oxygen is inspired. Oxygenation is a limiting factor at 8,000 feet breathing air and 40,000 feet inspiring oxygen. Nevertheless, the limiting values for alveolar ventilation for the ARDS lung and the normal lung are similar.

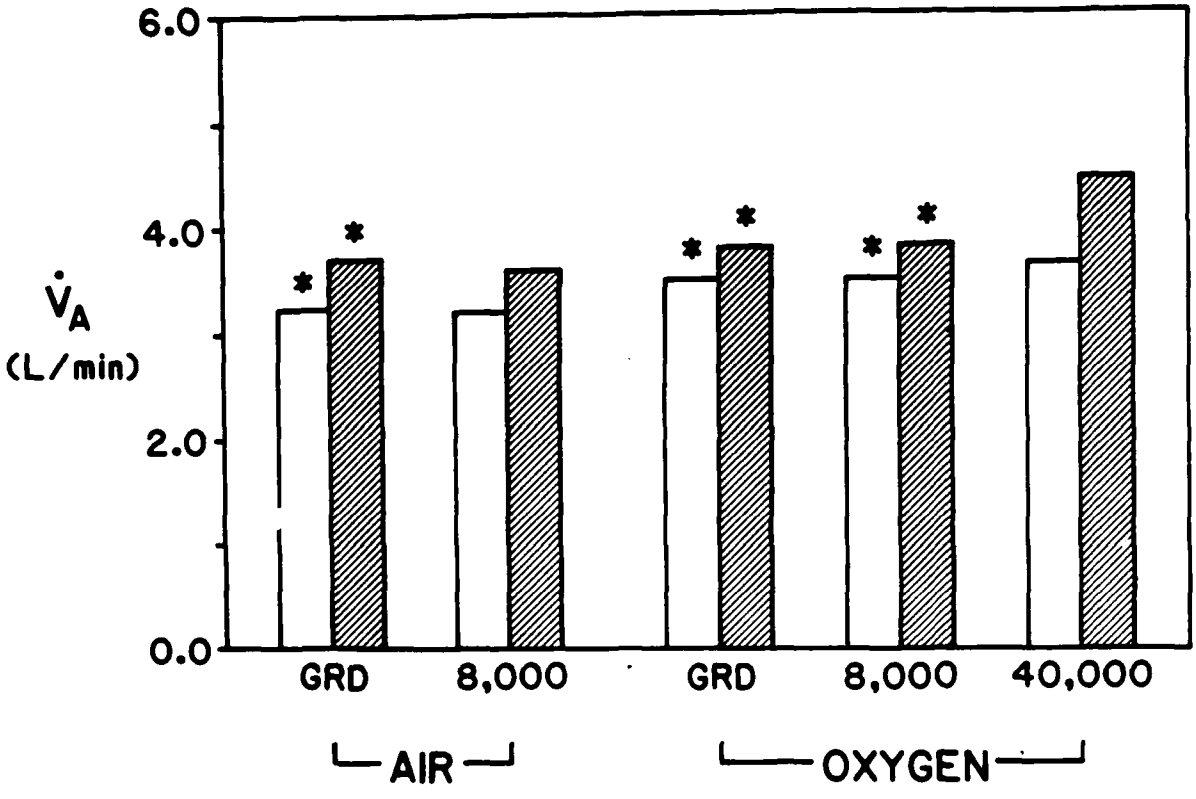


Figure 1. Lowest levels of alveolar ventilation that can be tolerated in normal (clear columns) and ARDS (shaded columns) lungs stressed to preassigned limits. The asterisk indicates that the limiting factor is a decrease of arterial pH to 7.1 and an increase of P_aCO_2 to 80 mmHg. At 40,000 feet a decrease in P_aO_2 to less than 10 mmHg limits the ventilation decrease that can be tolerated.

In contrast, reduced cardiac output is poorly tolerated in the ARDS lung compared with the normal lung (Figure 2). This intolerance, however, is affected only to a small extent by inspired oxygen fraction (F_IO_2) or altitude.

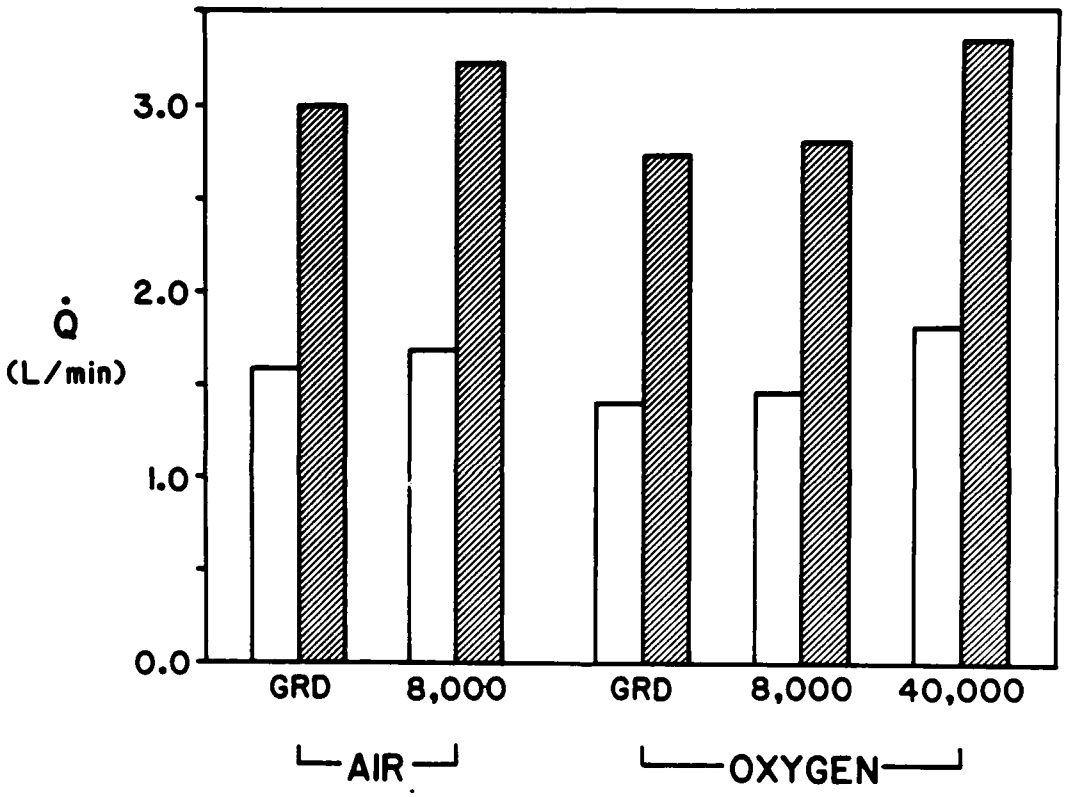


Figure 2. Cardiac output ($\dot{Q}$) levels that can be tolerated in normal (clear columns) and ARDS (shaded columns) lungs stressed to preassigned limits. In all cases a decrease in P_vO_2 to less than 10 mmHg limits the cardiac output decrease that can be tolerated.

A similar pattern of results was obtained by varying hematocrit (Figure 3). These results confirm the concept that oxygen delivery to the tissues (the product of cardiac output and arterial oxygen content) is a critical factor in determining survival.

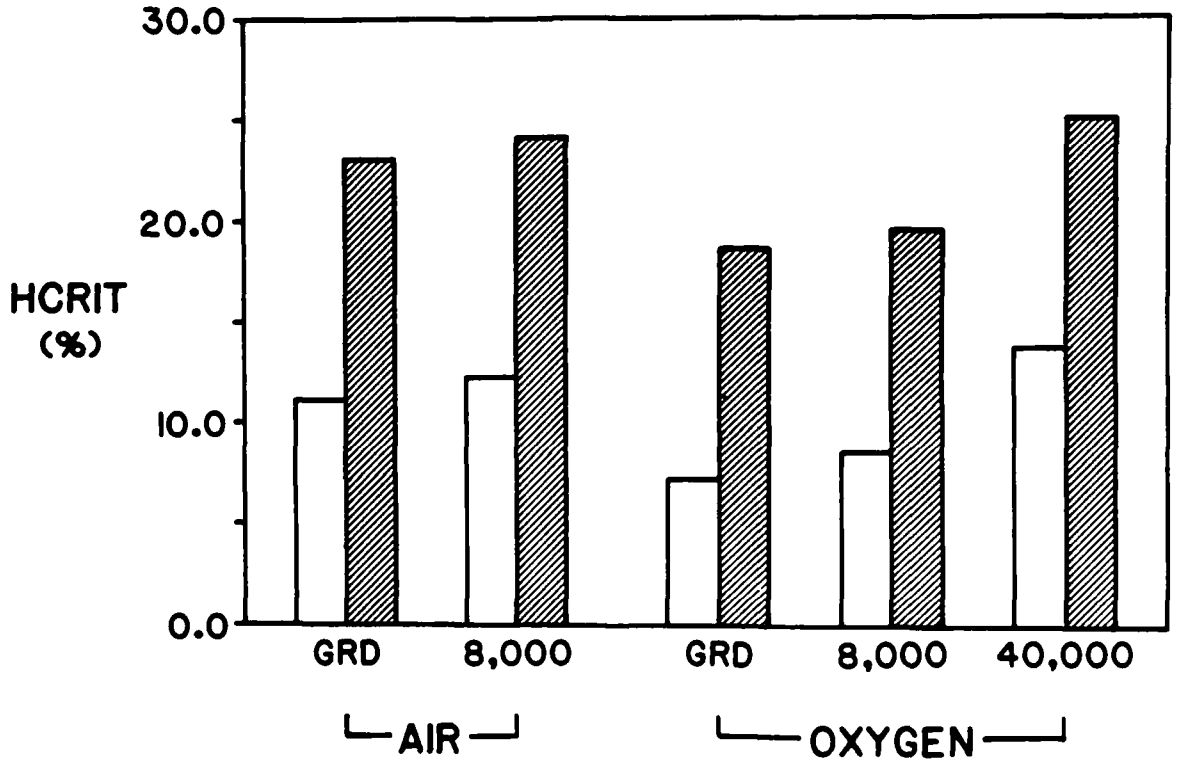


Figure 3. Hematocrit levels that can be tolerated in normal (clear columns) and ARDS (shaded columns) lungs stressed to preassigned tolerance limits. In all cases a decrease in P_vO_2 to less than 10 mmHg limits the hematocrit decrease that can be tolerated.

Patients with ARDS are frequently infected or stressed as a result of tissue catabolism and multiple-organ failure. As a result, an increased metabolic rate is imposed on an already compromised gas-exchange function. At both ground level and altitude, when air is inspired the ARDS lung is less tolerant of increasing metabolic rate than is the normal lung (Figure 4). On the other hand, when pure oxygen is inspired this difference is considerably reduced at all three altitudes, but not abolished.

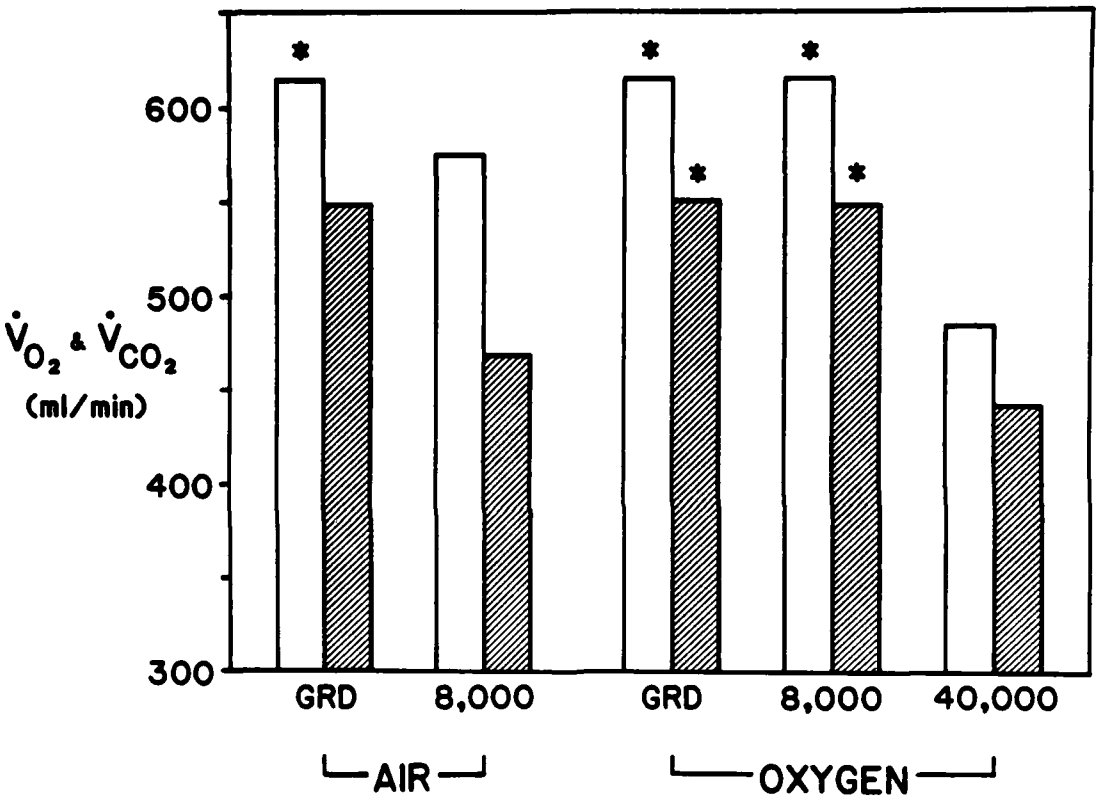


Figure 4. Levels of oxygen uptake and carbon dioxide output that can be tolerated in normal (clear columns) and ARDS (shaded columns) lungs stressed to preassigned limits. Oxygen uptake and carbon dioxide output (displayed on the ordinate) are equal in magnitude. The asterisk indicates that the limiting factor is a decrease of arterial pH to 7.1 and an increase of P_aCO_2 to 80 mmHg. Data without an asterisk indicate that a decrease in P_vO_2 to less than 10 mmHg limits the increase in oxygen uptake and carbon dioxide output that can be tolerated.

Abnormal diffusion primarily affects oxygen transfer but also can impact carbon dioxide transfer. When oxygen is inspired, impairment of carbon dioxide transfer limits gas exchange at sea level and 8,000 feet (Figure 5). For the other conditions, oxygen transfer is limiting. This analysis is based on the assumption that the diffusing capacity is identical in both normal and abnormal lungs; thus it is not surprising that similar reductions in D_mO_2 are tolerated in both situations. However, this assumption may be erroneous, and the importance of the diffusing capacity has been assessed in a second circumstance in which it is reduced in the ARDS lung in direct proportion to the degree of shunting. It seems logical that a pathological process that causes a reduction in functioning alveoli likewise may produce a similar reduction in D_mO_2.

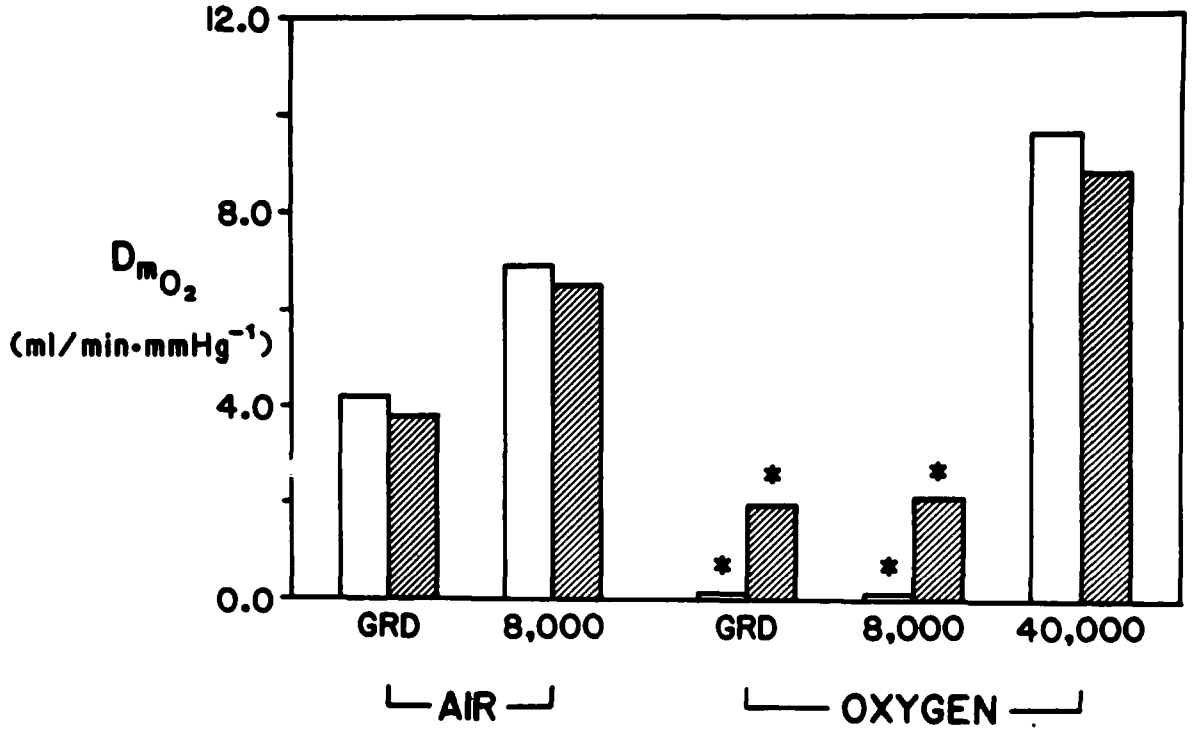


Figure 5. Levels of D_mO_2 that can be tolerated in the normal (clear columns) and ARDS (shaded columns) lungs stressed to preassigned limits. The asterisk indicates that the limiting factor is a decrease of arterial pH 7.1 and an increase of P_aCO_2 to 80 mmHg. Data without an asterisk indicate that a decrease in P_vO_2 to less than 10 mmHg limits the decrease that can be tolerated.

Table 3 indicates the maximum change in any of the five tested parameters, expressed as a percentage of the baseline value, that can be tolerated under the different conditions of altitude and F_IO_2. The table indicates that the two variables most sensitive for gas exchange limitation are cardiac output and hematocrit. Supplemental oxygen only partially diminishes the adverse effects of altitude.

TABLE 3. LIMITING VALUES OF PARAMETERS[a] AS PERCENTAGE OF BASELINE

	$\dot{V}_A$[b]	$\dot{Q}$	Hcrit	$\dot{V}O_2$ & $\dot{V}CO_2$	D_mO_2[c]	D_mO_2[d]
Breathing air						
Sea level						
N	57 *	27	25	205 *	11	11
ARDS	42 *	50	51	183	10	18
8,000 feet						
N	57	28	28	191	17	17
ARDS	44	68	54	156	17	32
Breathing 100% O_2						
Sea level						
N	57 *	23	16	205 *	<2 *	<2 *
ARDS	44 *	45	41	192 *	5 *	9 *
8,000 feet						
N	57 *	23	18	200 *	<2 *	<2 *
ARDS	44 *	46	44	193 *	5 *	10 *
40,000 feet						
N	57	30	30	161	24	24
ARDS	52	55	56	147	22	42

[a]Alveolar ventilation $\dot{V}_A$; cardiac output, $\dot{Q}$; hematocrit, Hcrit; oxygen uptake and carbon dioxide output, $\dot{V}O_2$ and $\dot{V}CO_2$; membrane diffusing capacity for oxygen, D_mO_2.

[b]Absolute values of $\dot{V}_A$ in normal and ARDS lungs (6.47 and 8.73 L/m respectively) were chosen to maintain a P_aCO_2 of 40 mmHg. Baseline values of $\dot{Q}$, Hcrit, and $\dot{V}O_2$ and $\dot{V}CO_2$ are the same for normal and ARDS lungs.

[c]Baseline is assumed to be equal in normal and ARDS lungs.

[d]Absolute value of baseline in the ARDS lung is assumed to be 52% of the normal-lung volume—analogous to a 48% shunt in the latter case.

*These limiting bounds are the result of a decrease in arterial pH to 7.1 and an increase in P_aCO_2 to 80 mmHg. In all other cases the limiting value is reached when P_vO_2 falls below 10 mmHg.

Supplemental Oxygen

The ARDS lung can sustain pulmonary gas exchange at 40,000 feet as long as supplemental oxygen is provided. To determine the minimum oxygen fraction required to prevent limitation of oxygen transfer, we progressively reduced the inspired oxygen fraction at this altitude. Figures 6 and 7 show the P_aO_2 and P_vO_2 resulting from these reductions. The results indicate that at least 65% oxygen is required to avoid limiting oxygen exchange for both the normal and ARDS lung. In addition, the smaller increases of the P_aO_2 and P_vO_2 that accompany increases in F_IO_2 indicate that the hypoxemia of ARDS is more resistant to supplemental oxygen than is hypoxemia in the normal lung.

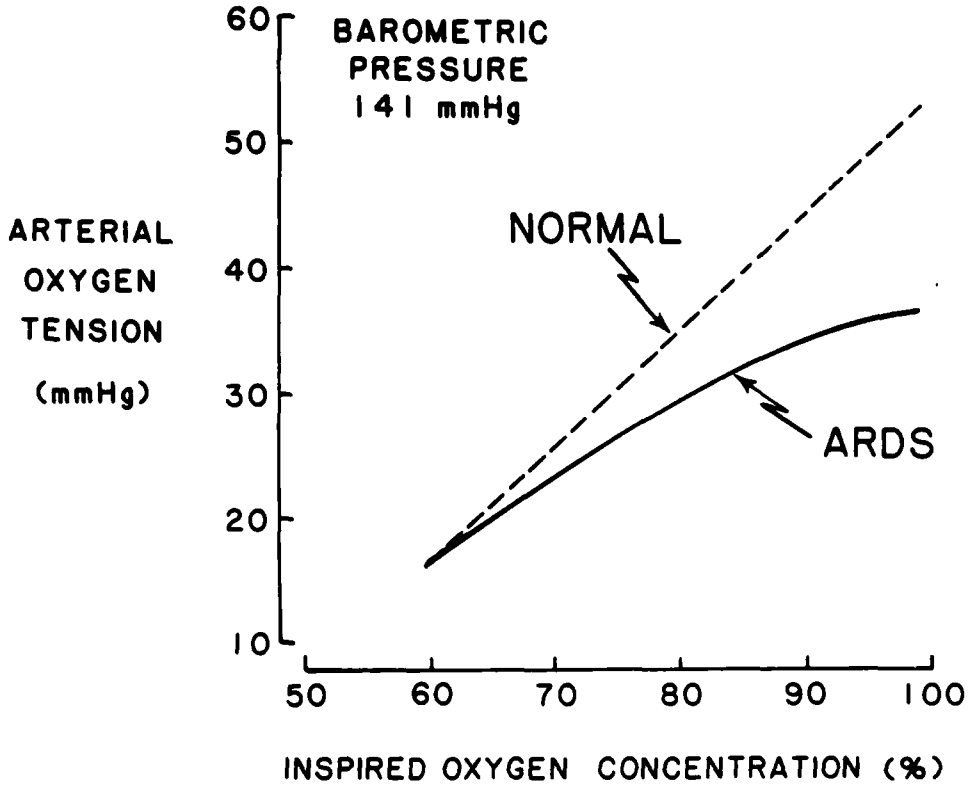


Figure 6. Effects of changing F_IO_2 (abscissa) on P_aO_2 at a barometric pressure of 141 mmHg (40,000-ft altitude) for normal (dashed lines) and ARDS (solid lines) lungs.

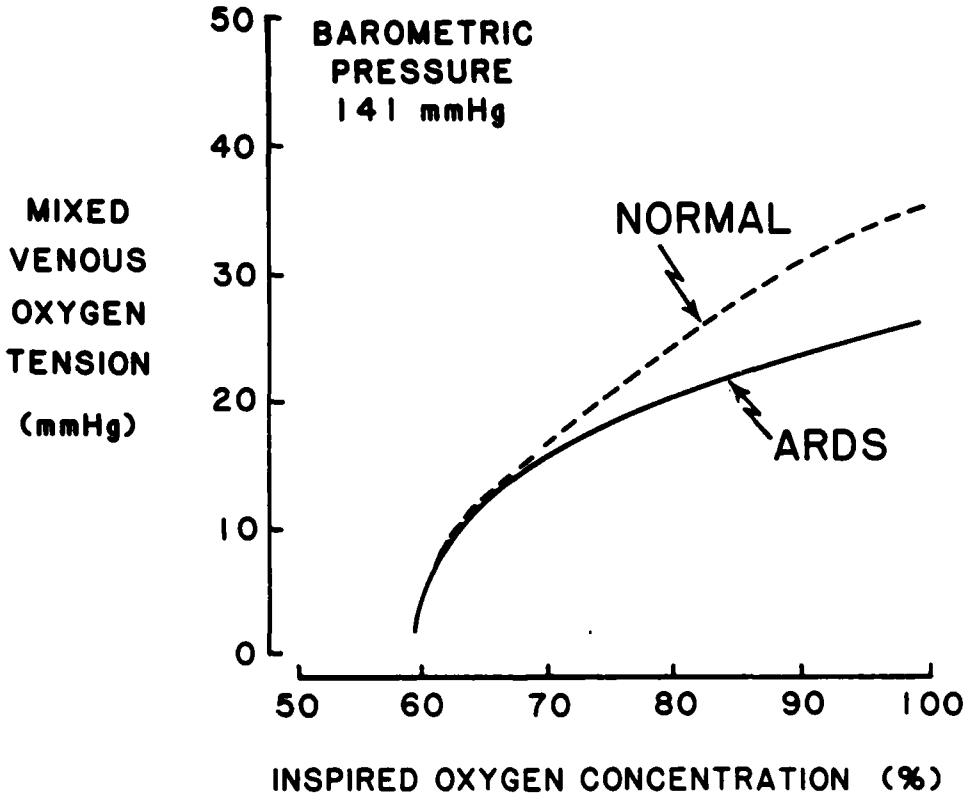


Figure 7. Effects of changing F_IO_2 (abscissa) on P_vO_2 at a barometric pressure of 141 mmHg (40,000-ft altitude) for normal (dashed lines) and ARDS (solid lines) lungs.

EXPERIMENTAL STUDIES

Experimental Methods

Preliminary animal studies were performed at the contractor's laboratory to validate measurement techniques and to establish the protocol used to create the canine oleic acid model of ARDS. The studies reported here were performed at the United States Air Force School of Aerospace Medicine.

Male mongrel dogs were premedicated with 4% thiamylal (6 mg/kg) given by rapid intravenous bolus injection. Anesthesia was induced with an alpha-chloralose/sodium tetraborate solution (120 mg/kg, IV) and maintained by a continuous infusion of alpha-chloralose (42.8 mg/kg per hour). A constant-infusion pump was used to maintain accurate infusion rate. Alpha-chloralose is an effective anesthetic agent for nonsurvival animal experiments. (In pilot experiments a single intravenous bolus dose of alpha-chloralose maintained anesthesia for at least 6 h.) A steady level of anesthesia was insured by continuous infusion throughout the study period. For muscle paralysis, an initial dose of 0.1 mg/kg pancuronium bromide (IV) was given; supplemental doses of 0.04 ml/kg were administered as needed; and no data collections were obtained for at least 10 min after an injection. Each dog was intubated with a cuffed oral endotracheal tube and ventilated with a Harvard constant-volume ventilator. Initial tidal volume was set at approximately 15 mg/kg with a respiratory rate of 12 to 16 breaths/min. Adjustments in ventilator rate were made prior to data collection to insure adequate gas exchange as determined by blood gas analysis. No further adjustments were made in ventilator settings.

The dogs were instrumented with a jugular venous catheter for fluid and drug administration and a femoral arterial catheter for blood pressure monitoring and collection of arterial blood samples. A heating blanket was used to maintain body temperature. A triple-lumen Swan-Ganz thermodilution catheter was placed in the pulmonary artery via a femoral vein for pulmonary artery and pulmonary capillary pressure wedge monitoring and collection of mixed venous blood samples. Body temperature was monitored by the thermistor located at the tip of the Swan-Ganz catheter.

The oleic acid model of ARDS was induced by injection of 0.1 ml/kg oleic acid infused via the right atrial port of the Swan-Ganz catheter at a rate of 0.4 ml/min. In some animals oleic acid was injected through a second catheter positioned in the right atrium. The dogs were allowed to breathe spontaneously from an inspired source containing 100% oxygen. Arterial blood gases were monitored, and if necessary, the animal was ventilated intermittently with an Ambu bag to prevent severe respiratory acidosis. Approximately 1.5 h after the oleic acid infusion,

when P_aO_2 stabilized, the animals were placed on the ventilator. When blood gases were stable (approximately 2 h after oleic acid infusion), we began data collection.

We recorded data with both a Gould 8-channel recorder (used for on-line monitoring) and a Hewlett-Packard 8-channel FM tape recorder. All calculations were obtained from tape recorder data as described below. The variables recorded were EKG, systemic and pulmonary artery pressures, pulmonary artery wedge pressure, airway pressure at the proximal end of the endotrachial tube, airflow (obtained from a Fleish pneumotachograph placed between the ventilator and the endotracheal tube), inspired volume (by electrical integration of the inspiratory flow signal), and end tidal oxygen and carbon dioxide concentrations (from a Perkin-Elmer mass spectrometer). The end tidal sample site was at the proximal end of the endotracheal tube. In addition, mixed expired oxygen and carbon dioxide were obtained from a mixing chamber attached to the expiratory port of the ventilator. Arterial and mixed venous blood samples were obtained and analyzed at 37°C with a Corning blood gas analyzer. Since all animal temperatures ranged between 36°C and 38°C, no blood gas corrections were made for these minor variations. With an Edwards cardiac output computer, we made three to five sequential cardiac output determinations using 10-cc injections of saline at room temperature. The computer continually monitored the temperature of the injectate solution. We estimated lung volume by nitrogen dilution, using a closed-circuit rebreathing technique.

We used the same data collection protocol for both control and oleic acid animals. After placing them on the constant-volume ventilator, we obtained several preliminary arterial blood gases at 15-20 min intervals. When both P_aO_2 and P_aCO_2 were stable, we began data collection. We collected the initial ground-level data on two occasions, 20-30 min apart. All parameters were measured each time except for lung volume, which was determined only with the second collection of each set. After these data collections, the hypobaric chamber containing the animal was closed and decompressed to a simulated level of 8,000 feet (barometric pressure equal to 564 mmHg). The rate of ascent and descent to and from 8,000 feet was 2,000-5,000 feet/min. Once altitude was reached, all pressure transducers (airway, systemic, and pulmonary artery pressure) were recalibrated. After a 25-30 min stabilization period, we collected two sets of altitude data using the same protocol as during ground-level conditions. The hypobaric chamber was returned to ground level, pressure transducers were recalibrated, and after 25-30 min stabilization, we obtained another two sets of measurements. Table 4 summarizes the data collection protocol. At the conclusion of the experiments, animals were euthanized by rapid intravenous injection of a saturated KCl solution.

TABLE 4. DATA COLLECTION PROTOCOL

Parameter	Ground 1	Ground 2	Alt. 1	Alt. 2	Ground 3	Ground 4
Airway Pressure	X	X	X	X	X	X
Arterial Pressure	X	X	X	X	X	X
Pulmonary Artery Pressure	X	X	X	X	X	X
Pulmonary Wedge Pressure	X	X	X	X	X	X
Ventilator Flow	X	X	X	X	X	X
Ventilator Volume	X	X	X	X	X	X
End Tidal CO_2	X	X	X	X	X	X
End Tidal O_2	X	X	X	X	X	X
Mixed Expired CO_2	X	X	X	X	X	X
Mixed Expired O_2	X	X	X	X	X	X
Arterial Blood Gas	X	X	X	X	X	X
Mixed Venous Blood Gas	X	X	X	X	X	X
Cardiac Output	X	X	X	X	X	X
Lung Volume (FRC)		X		X		X

At our laboratory we analyzed the data collected on the FM tape recordings. The tape was replayed and the signals digitized by a 12-bit analog-to-digital converter in a NorthStar Horizon computer and stored on floppy disc. Data from the recorder were sampled over 20-s periods at a rate of 50 Hz. Mean values for heart rate, airway pressure, and pulmonary wedge pressure were obtained as well as systolic and diastolic systemic and pulmonary arterial pressures. Ventilator rate and inspired volume also were determined. Mixed expired gas concentrations were used to calculate carbon dioxide production ($\dot{V}CO_2$). Inspired and alveolar oxygen pressures were calculated, as was the alveolar-arterial oxygen difference $(A\text{-}a)O_2$. The cardiac outputs determined at each data collection time were averaged, and lung volume was calculated from mixing syringe volume and nitrogen dilution data.

We used analysis of variance for two factor experiments to analyze data, using a factorial experiment-design analysis technique (8,9). This approach allowed comparison of control with oleic acid animals as well as examining the effects of altitude and changes that may have occurred over time within each group. Statistical significance was assumed at the 5% level. For analysis of lung volume, we used t-tests and the Bonferroni correction for multiple samples to analyze results within the control or oleic acid groups under the ground-level and altitude conditions. This approach was necessary since incomplete data collection occurred in three experiments. By a t-test, we compared the mean lung volume of the controls and the oleic acid animals.

Experimental Results

Twelve mongrel dogs were required for 10 successful experiments (two oleic acid animals died before measurements were completed). Dogs weighed between 14.4 and 27.2 kg. The five dogs used as controls (20.6 kg) did not significantly differ in weight from the five oleic acid animals (19.1 kg).

Results are summarized in Table 5. The respirator delivered a constant tidal volume at both ground-level and altitude conditions. Its performance was not affected by a simulated altitude of 8,000 feet. Ventilator frequency was also constant. Airway pressure was higher in the oleic acid animals than in the controls, probably related to a decreased lung compliance secondary to the oleic acid lung injury in that group. An increased resistance to airflow may have also been present, related to the decreased lung volume in the oleic acid animals; airway resistance is known to be inversely related to lung volume. Functional residual capacity (FRC) was approximately 3 times larger in the controls than in the oleic acid group ($p<.001$).

Arterial carbon dioxide tension, P_aCO_2, was higher in the oleic acid animals than in the controls, despite a similar minute ventilation in both groups. This information, when combined with the finding that $\dot{V}CO_2$ was actually lower in the oleic acid animals, suggests that major alterations in gas exchange occurred in the oleic acid animals. These data indicate that physiologic dead space and the dead space to tidal volume ratio (V_D/V_T) were both increased in these animals. The elevated P_aCO_2 noted in this group produced a decrease in their arterial pH compared to that of the controls.

Oxygen exchange was also grossly abnormal in the oleic acid group. Despite being ventilated with 100% oxygen, which resulted in an inspired PO_2 of approximately 700 mmHg at ground level, these animals had a mean P_aO_2 of 174 mmHg for the four ground-level observations. There was a wide range of P_aO_2 in this group, and prealtitude (ground levels 1 and 2) P_aO_2 ranged from 62 to 344 mmHg. At 8,000 feet, inspired PO_2 was 521 mmHg and the mean P_aO_2 was 103 mmHg. The $(A-a)O_2$ of the group was 462 mmHg at ground level (observations 1-4) and 365 mmHg at altitude. This large $(A-a)O_2$ on 100% oxygen is evidence of a large right-to-left intrapulmonary shunt, as would be expected in a model of lung injury simulating ARDS.

The control group had normal values for P_aO_2 and $(A-a)O_2$ under ground-level conditions. At 8,000 feet, the inspired oxygen tension (P_IO_2) had decreased from about 147 mmHg under ground conditions to 108 mmHg. This 39 mmHg decrease resulted in an average decline in P_aO_2 of 25 mmHg, from 92 mmHg (ground levels 1 and 2) to 67 mmHg during the first altitude period. During the second altitude period, two control animals received 30% oxygen rather than room air. The higher F_IO_2 resulted in a 35-mmHg increase in P_IO_2 and restored P_aO_2 to ground-level values in these two animals. The mean values (± S.E.) for P_aO_2 during the ground-level periods bracketing the altitude mean values are shown in Figures 8 and 9 for the control and the oleic acid groups respectively.

Mixed venous blood oxygen tension was lower in the control than in the oleic acid group. This is not unexpected since the oleic acid animals all received 100% oxygen and had much higher P_aO_2. A slight, but statistically significant, decrease in P_vO_2 occurred over time in both groups.

Heart rate and cardiac output were significantly lower in the oleic acid group than in the controls. A small but steady decrease in cardiac output occurred in the oleic acid animals over time. This can be seen in Figure 10, which plots the mean cardiac output during the ground-level periods as well as at altitude. Figure 11 shows similar data for the normal animals, and the relative stability of cardiac output in this group is apparent.

Mean systemic arterial blood pressure was lower in the oleic acid animals than in the controls, probably due to the decreased cardiac output noted in the former group. Mean pulmonary artery pressure was higher in the oleic acid group, probably as a result of their lung injury and hypoxemia. The mean pulmonary artery pressure tended to increase over time in the oleic acid animals, but this did not reach statistical significance. Pulmonary artery wedge pressure was similar in both oleic acid and control groups.

Pathologic changes in the lungs of the oleic acid group showed patchy areas of pulmonary edema, as expected with administration of oleic acid. The extent of the injury varied considerably. We noted no gross abnormalities in the control group.

TABLE 5. SUMMARY OF RESULTS

PARAMETER		GROUP	GROUND 1	GROUND 2	ALTITUDE 1	ALTITUDE 2	GROUND 3	GROUND 4
Tidal Vol (cc_{BTPS})		Control	413 ± 126	412 ± 125	411 ± 121	416 ± 116	417 ± 122	411 ± 122
		Oleic	413 ± 31	412 ± 32	410 ± 31	410 ± 35	411 ± 31	412 ± 36
Resp Rate (breaths/min)		Control	19 ± 3	19 ± 3	19 ± 3	19 ± 3	19 ± 3	19 ± 3
		Oleic	20 ± 4	20 ± 4	20 ± 4	20 ± 4	20 ± 4	20 ± 4
$\dot{V}CO_2$ STPD (cc/min)	a	Control	79 ± 28	77 ± 24	74 ± 22	74 ± 18	73 ± 19	72 ± 16
		Oleic	68 ± 25	63 ± 21	64 ± 22	61 ± 17	62 ± 22	61 ± 25
P_{Airway} (mmHg)	b	Control	6 ± 1	7 ± 1	6 ± 1	6 ± 1	7 ± 1	7 ± 1
		Oleic	8 ± 2	9 ± 2	9 ± 2	9 ± 2	10 ± 2	10 ± 2
FRC (cc_{BTPS})	c	Control		908 ± 322		670 ± 41		872 ± 288
		Oleic		319 ± 116		249 ± 74		252 ± 88
$P_{Art,Mean}$ (mmHg)	d	Control	128 ± 14	126 ± 13	122 ± 12	120 ± 18	119 ± 16	119 ± 14
		Oleic	108 ± 20	110 ± 17	108 ± 20	110 ± 19	109 ± 19	110 ± 20
$P_{Pulm,Mean}$ (mmHg)	e	Control	13 ± 3	14 ± 2	16 ± 2	13 ± 4	13 ± 2	13 ± 2
		Oleic	17 ± 5	19 ± 7	20 ± 4	21 ± 6	21 ± 6	21 ± 6
$P_{Wedge,Mean}$ (mmHg)		Control	3 ± 3	3 ± 3	4 ± 2	3 ± 3	4 ± 3	4 ± 3
		Oleic	3 ± 2	4 ± 2	5 ± 1	5 ± 2	4 ± 2	5 ± 2
Heart Rate (beats/min)	f	Control	110 ± 32	106 ± 34	102 ± 21	103 ± 25	101 ± 23	100 ± 25
		Oleic	71 ± 14	79 ± 12	80 ± 11	83 ± 16	88 ± 20	88 ± 21
$\dot{Q}$ (L/min)	g	Control	2.8 ± .8	3.2 ± 1	3.3 ± .7	3.3 ± .9	3.0 ± .7	2.9 ± .7
		Oleic	2.2 ± .8	2.3 ± .7	2.1 ± .6	2.0 ± .4	1.8 ± .4	1.9 ± .3
pH_a	h	Control	7.42 ± .08	7.40 ± .09	7.43 ± .11	7.44 ± .10	7.44 ± .12	7.45 ± .10
		Oleic	7.34 ± .07	7.35 ± .07	7.36 ± .08	7.36 ± .07	7.36 ± .07	7.37 ± .08

P_aCO_2 (mmHg)	i	Control	35 ± 7	36 ± 7	34 ± 8	33 ± 7	33 ± 9	31 ± 7
		Oleic	47 ± 6	46 ± 6	44 ± 8	43 ± 7	43 ± 8	42 ± 8
P_aO_2 (mmHg)	j	Control	92 ± 6	92 ± 3	67 ± 11	82 ± 15	100 ± 6	103 ± 4
		Oleic	209 ± 138	172 ± 125	106 ± 67	100 ± 61	157 ± 131	159 ± 134
P_vO_2 (mmHg)	k	Control	45 ± 3	36 ± 20	32 ± 18	33 ± 19	25 ± 23	34 ± 19
		Oleic	52 ± 13	50 ± 15	43 ± 13	41 ± 12	42 ± 12	42 ± 11
$(A-a)O_2$ (mmHg)	l	Control	15 ± 20	13 ± 18	-1 ± 19	4 ± 16	7 ± 21	6 ± 18
		Oleic	420 ± 147	465 ± 134	362 ± 75	368 ± 67	478 ± 130	485 ± 136

[a] $\dot{V}CO_2$ Control > Oleic, $p<.01$

[b] P_{Airway} Oleic > Control, $p<.01$

[c] FRC Control, Altitude n = 3; Oleic, Ground #1 n = 4
No difference within Control or Oleic groups by ANOVA or t-test for multiple samples.
Control > Oleic by t-test, $p<.001$

[d] $P_{Art,Mean}$ Control > Oleic, $p<.01$

[e] $P_{Pulm,Mean}$ Oleic > Control, $p<.01$

[f] Heart Rate Control > Oleic, $p<.01$

[g] $\dot{Q}$ Cardiac Output: Control > Oleic, $p<.01$
$\dot{Q}$ falls with time: Ground 1,2 > Ground 3.4; $p<.05$ (due to Oleic values)

[h] pH_a Control > Oleic, $p<.01$

[i] P_aCO_2 Oleic > Control, $p<.01$

[j] P_aO_2 Oleic > Control, $p<.01$
P_aO_2 falls with altitude, both groups, $p<.05$
Note: 2/5 Controls on 30% O_2 for Altitude 2

[k] P_vO_2 Oleic > Control, $p<.01$
P_vO_2 falls with altitude, both groups, $p<.01$

[l] $(A-a)O_2$ Oleic > Control, $p<.01$
Decrease with altitude, both groups, $p<.01$
Oleic shows greater decrease with altitude than control, $p<.05$

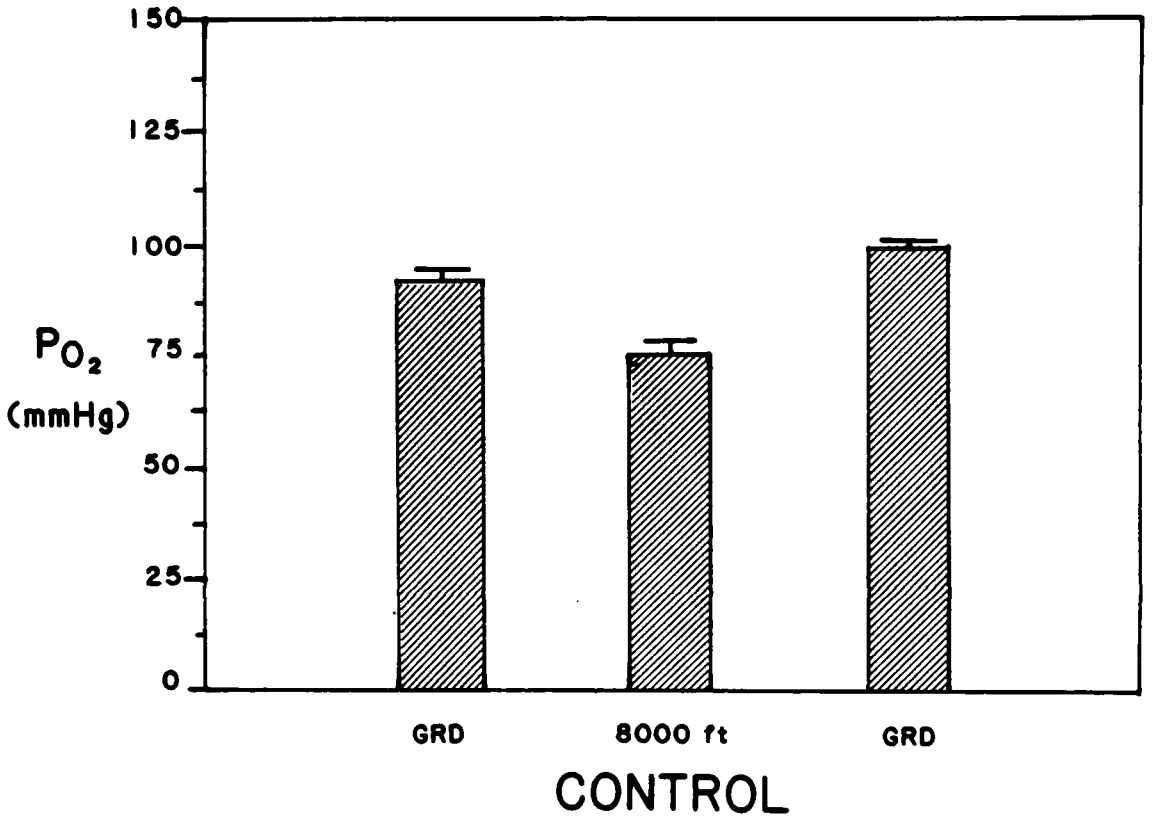


Figure 8. Arterial PO_2 in normal dogs during the three experimental periods. Bars in the figure indicate standard errors of the means.

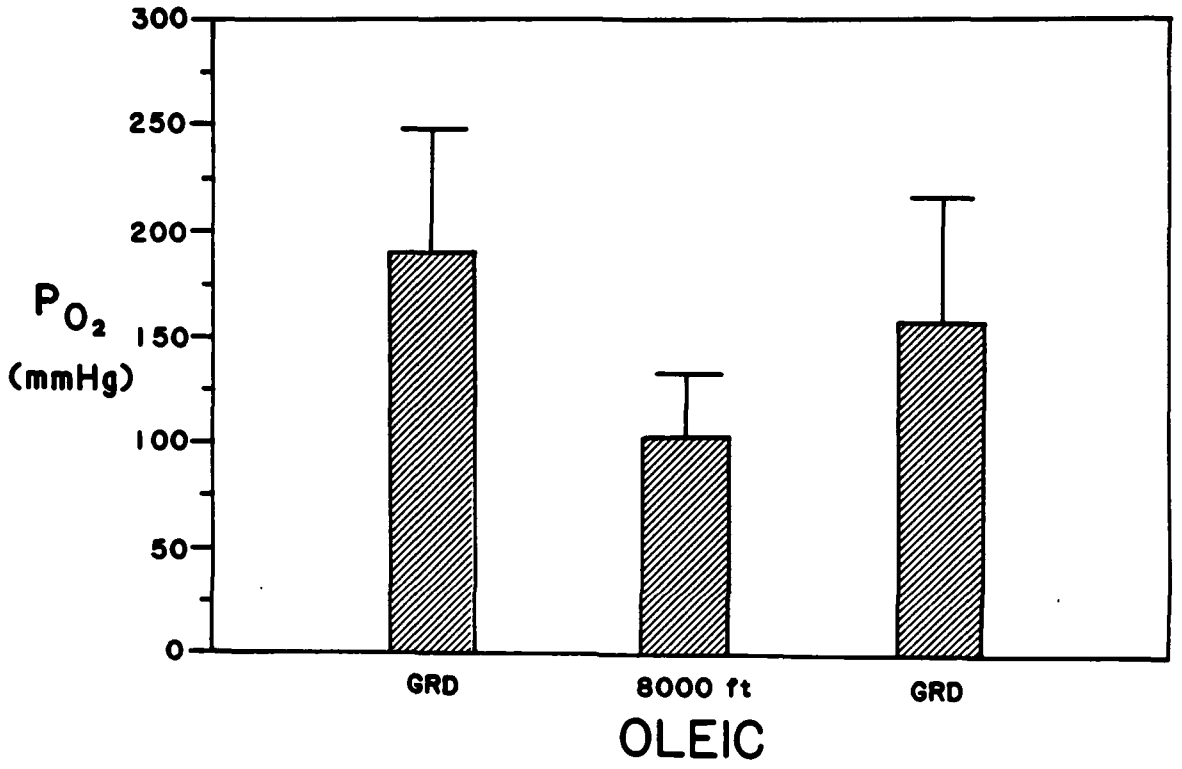


Figure 9. Arterial PO_2 in dogs given intravenous oleic acid during the three experimental periods. Bars in the figure indicate standard errors of the means.

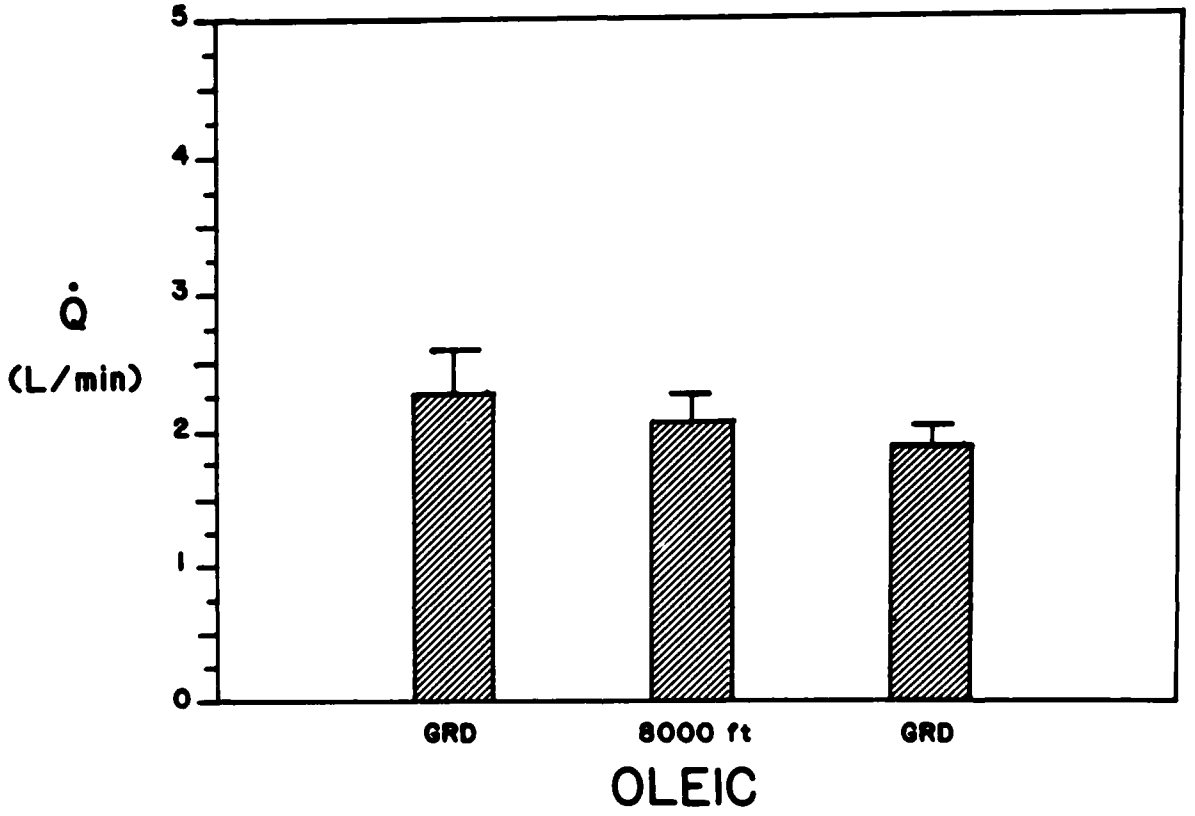


Figure 10. Cardiac output in dogs given intravenous oleic acid during the three experimental periods. Bars in the figure indicate standard errors of the means.

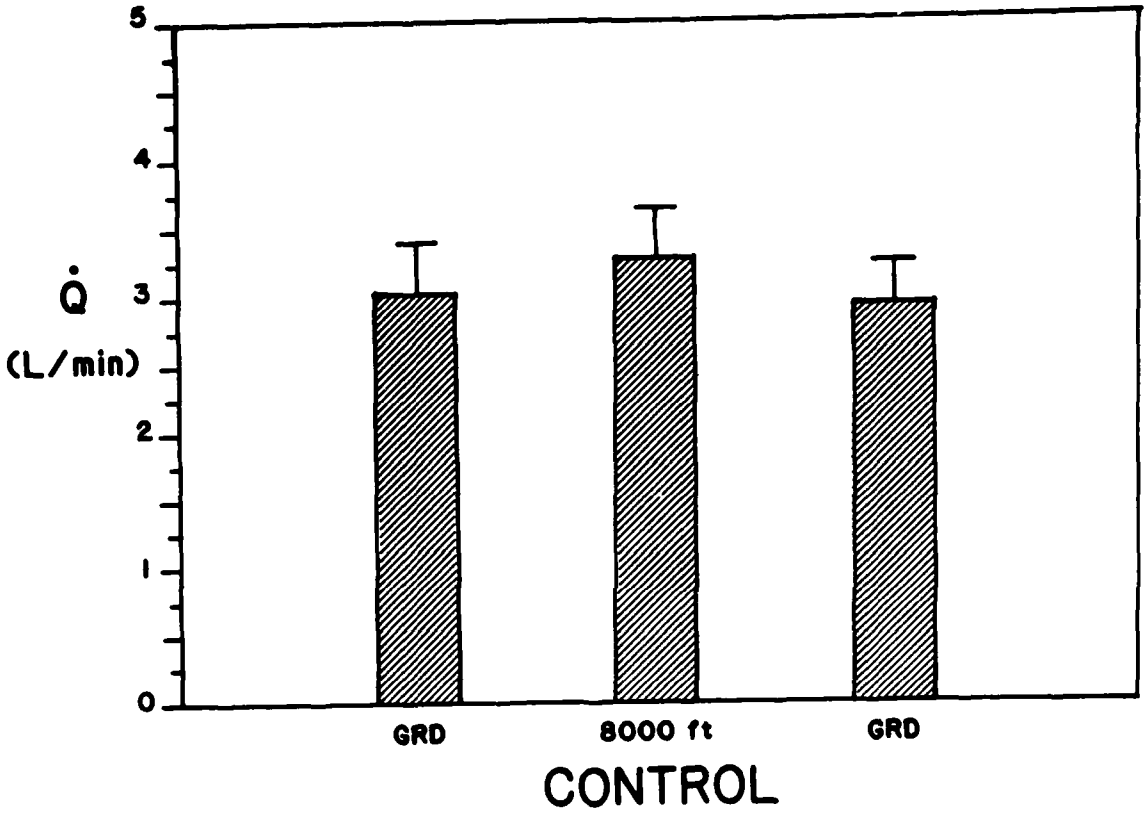


Figure 11. Cardiac output in normal dogs during the three experimental periods. Bars in the figure indicate standard errors of the means.

DISCUSSION

An interesting feature of the model computations is the demonstration that the P_aO_2 is relatively more resistant to change during hypobaric hypoxia in the ARDS lung than in the normal lung. As seen in Table 2, ascent to 8,000-ft altitude results in a decrease in P_aO_2 of 41 mmHg (from 109 to 68 mmHg) in the normal lung. In the ARDS model under the same circumstances, the P_aO_2 decreased only 4 mmHg to 38 mmHg. When pure oxygen is inspired, this difference between normal and ARDS lungs is even more prominent. Alterations in altitude result in changes of several hundred mmHg in the normal lung, but in the ARDS model the total range of PO_2 is only 15 mmHg. These differences stem largely from the nonlinear characteristics of the oxygen dissociation curve. In these calculations, for the most part gas exchange in the normal lung takes place on the upper portion of the dissociation curve. The slope of this portion of the curve is much less steep than the portion utilized in exchange in the ARDS lung. Calculation of arterial oxygen content emphasizes this point. Assuming an oxygen capacity of 20 vol% in blood, ascent to 8,000 feet while breathing air causes similar decreases (0.99 and 1.07 vol%) in the normal and ARDS lungs. When oxygen is breathed during ascent to 8,000 and 40,000 feet from ground-level, arterial oxygen content decreases 0.64 and 4.46 vol% in the normal lung; comparable changes in the ARDS model are 0.51 and 3.35 vol%. The effect of the slope of the dissociation curve on PO_2 is further illustrated by the mixed venous data. In both the ARDS and normal lungs, P_vO_2 lies on the steep, relatively linear portions of the curve. Under this circumstance, while air or oxygen is breathed the changes in P_vO_2 during ascent to altitude are quite similar in both normal and ARDS models. In a sense these findings are not surprising because it is the converse of the more common clinical circumstance--the abnormal P_aO_2 in ARDS is relatively resistant to correction by normobaric hyperoxia.

Sensitivity Analysis

Figure 1 illustrates that the ARDS and normal lungs have similar lower limits of alveolar ventilation necessary for survival by the criteria chosen. However, since the absolute quantity of ventilation required for maintenance of eucapnia is greater in the ARDS lung (8.73 vs. 6.47 L/min), it can tolerate a greater relative reduction in ventilation than can the normal lung (Table 3).

Tolerated reductions in ventilation are limited by elevation of P_aCO_2 (and accompanying reduction in pH) except during air breathing at 8,000 feet and oxygen inhalation at 40,000 feet. Under the conditions of these calculations (R=1.0), an elevation in alveolar carbon doxide tension (P_ACO_2) is equal to an accompanying reduction in alveolar oxygen tension (P_AO_2). Hence,

a 40-mmHg elevation of P_ACO_2, the maximum change under the criteria chosen, is accompanied by a 40-mmHg decrease in P_AO_2. Because of the shape of the oxygen dissociation curve, a 40-mmHg drop in P_AO_2 does not produce sufficient hypoxemia to reach the assigned limits of P_vO_2 except when the initial P_AO_2 is lower than normal. At 40,000 feet, barometric pressure is only 141 mmHg so inspired oxygen, even when pure oxygen is breathed, is only 94 mmHg. Under these circumstances, reductions in P_AO_2 caused by decreases in ventilation produce severe hypoxemia before the concomitant increases in P_ACO_2 reach an intolerable level. During inspiration of air at 8,000 feet the initial P_AO_2 is only 68 mmHg. A further decrease in P_AO_2 resulting from decreased ventilation produces intolerable hypoxemia. In all other circumstances the initial P_AO_2 is greater than 100 mmHg and reductions in P_AO_2 can be tolerated.

The data illustrating limitations imposed by reductions in cardiac output and hematocrit (Figures 3 and 4) are remarkably similar. These results confirm the concept that oxygen delivery to the tissues (the product of cardiac output and arterial oxygen content) is a critical factor in determining survival. Reductions in either parameter are poorly tolerated in the ARDS lung. In contrast, under normal conditions either blood flow or hematocrit can be reduced to approximately one-half the lower limiting value seen in the ARDS lung. Interestingly, tolerated reductions in both models are influenced relatively little by either altitude or F_IO_2. This appears to be related to the maintenance of a fairly high P_aO_2 under the five conditions studied (Table 2). Under these conditions, the maximum tolerable reduction in oxygen delivery, achieved either by a decrease in cardiac output or hematocrit, is proportional to P_aO_2.

Increases in metabolic requirements are tolerated less in the ARDS than in the normal lung, but the differences are relatively small in most cases. The maximum possible increase in metabolic rate that can be tolerated under the criteria chosen is an approximately twofold increase over the baseline value. In this sensitivity analysis, we held ventilation constant. As a result, a twofold increase in carbon dioxide production results in an approximate doubling of P_ACO_2, and hence, P_aCO_2. A doubling of the baseline 40 mmHg P_aCO_2 reaches the preset limit of 80 mmHg because distribution of both ventilation and blood flow remain invariant in this analysis. As indicated in Figure 4, tolerable metabolic requirements did not increase more than twofold in any circumstance; in most circumstances when this twofold increase was achieved hypercapnia was the limiting factor. When tolerable increments in metabolic rate were substantially less than twice the baseline value, reduction in oxygen delivery with a fall in P_vO_2 to less than 10 mmHg uniformly set the tolerable limit. In these cases the reduced oxygen delivery appeared to be the result of two factors: first, the reduction in P_aO_2; second, an increase in P_aCO_2 which shifted the position of the oxygen dissociation curve.

The effect of diffusion limitation on gas exchange in ARDS is unknown. In normal subjects D_mO_2 is estimated to be 40 ml/min per mmHg or greater (10), but it is unknown in patients with ARDS. Substantial reductions in D_mO_2 can be tolerated, especially when supplemental oxygen is administered (Figure 5). The reduction in D_mO_2 is overcome by increasing the gradient of oxygen tension across the alveolar-capillary membrane. Alveolar PO_2 is incremented with supplemental oxygen, and the resulting increased partial pressure gradient augments oxygen transfer into the capillary blood. The reduction in D_mO_2 that can be tolerated under the circumstances investigated in this theoretical study is largely a function of the P_AO_2 since P_vO_2 remained relatively constant (Table 2). Because of the uncertainty of the effect of ARDS on the D_mO_2, we made our calculations with two baseline values of D_mO_2 in the ARDS model. A normal baseline value of D_mO_2 was assumed initially; for the second set of calculations, the baseline value was reduced in proportion to the quantity of shunted blood in the ARDS model. The results differed quantitatively to a moderate degree, but not qualitatively (Table 3).

Impaired carbon dioxide exchange, with resulting hypercapnia, can occur when D_mO_2 is extremely reduced while oxygen is breathed. When air (21% O_2) is inspired, the D_mO_2 would be progressively reduced and result in increasing hypoxemia as oxygen transfer is reduced. Death would occur before the D_mO_2 could be reduced to a level that would influence carbon dioxide exchange. However, inhalation of pure oxygen increases the driving force for oxygen diffusion into the blood almost fivefold. Under these circumstances oxygen transfer is sufficient to maintain life, and progressive reduction of the D_mO_2 begins to affect carbon dioxide transfer from blood to alveolus. The diffusion coefficient for carbon dioxide is twentyfold greater than that for oxygen because of the differing aqueous solubilities of the two gases. However, the driving gradients for the gases are far different because of the differing slopes of the dissociation curves. As a result, the gradient for carbon dioxide transfer--the difference between P_vCO_2 and P_ACO_2--is only 6 mmHg under normal conditions. This is one-tenth of the normal oxygen driving gradient and sharply reduces the advantage in gas transfer imparted by the high solubility of carbon dioxide. As indicated in Figure 5, under conditions of severely reduced D_mO_2 and inhalation of pure oxygen, the impaired carbon dioxide, not oxygen, exchange is the factor that limits survival. Oxygen transfer can be enhanced by increasing the F_IO_2, thereby increasing the driving force for oxygen diffusion. Because air is free of carbon dioxide, the driving force for carbon dioxide exchange cannot be increased by altering the F_IO_2.

Survival is theoretically possible in ARDS even with decompression to 40,000-ft altitude. In this circumstance a high F_IO_2 (at least 65%) must be maintained (Figures 6 and 7). The

low barometric pressure (141 mmHg) sets a limit of 94 mmHg as the maximum possible P_AO_2. A patient who is mechanically ventilated at this altitude is at a disadvantage compared to one who is breathing spontaneously, even if the ventilator does not fail due to decompression. With fixed ventilation, P_ACO_2 will remain at 40 mmHg, reducing P_AO_2 from the inspired value of 94 mmHg (breathing 100% O_2) to 54 mmHg. The patient who is breathing spontaneously will increase ventilation as a result of the hypoxic stimulus, thus lowering P_ACO_2 and increasing P_AO_2. This is a normal response to altitude exposure and is thought to be a major compensatory mechanism in this circumstance (11).

The data in Figure 6 are somewhat surprising in that, in both the normal and ARDS lungs, the P_aO_2 and P_vO_2 show relatively little difference. However, this finding is consistent with the observation made in 1946 that right-to-left shunting has little effect on the $(A\text{-}a)O_2$ when P_AO_2 is reduced to a low level (12).

This study addresses only the aspect of gas exchange during air transportation of ARDS patients. Although the ARDS lung tolerated 40,000 feet when ventilated with enriched oxygen mixtures, sudden decompression at this altitude would likely result in severe hypothermia, barotrauma, and other serious complications that could cause death. Nevertheless, the results of this theoretical study indicate that air transportation of ARDS patients is feasible and that these patients could possibly survive sudden decompression.

The experimental portion of this study was performed to determine the ventilatory criteria for successful aeromedical evacuation of patients with respiratory failure requiring mechanical ventilation. Initially this issue was approached experimentally by evaluating cardiorespiratory and gas exchange information obtained from normal, anesthetized, apneic animals ventilated under ground-level conditions and at a simulated altitude of 8,000 feet. This altitude is similar to that maintained with commercial and military aircraft flying at an altitude of approximately 40,000 feet. After these experiments, acute lung injury was induced in a second group of animals by intravenous injection of oleic acid. Oleic acid produces a lung injury similar to that seen in the adult respiratory distress syndrome (ARDS). These animals were ventilated with 100% oxygen and the same hemodynamic and gas exchange measurements were made in these animals as in the control group.

Previous studies had shown that some commercially available ventilators decreased volume output at altitude. By using the Harvard piston pump ventilator, this important variable was controlled. Our results indicated that the tidal volume delivered by the ventilator remained constant at both ground level and 8,000 feet. Because of this, in the control group, the P_aCO_2, pH, and carbon dioxide output remained unchanged during ground-level conditions and at altitude. The oleic acid animals

showed evidence of impaired gas exchange in terms of carbon dioxide elimination, probably related to an increased physiological dead space in this group. Nonetheless, even in the face of their lung injury, P_aCO_2 and carbon dioxide output remained constant at ground level and altitude. We can therefore conclude that as long as a ventilator delivers the same tidal volume at altitude as it does at ground level, no change in P_aCO_2 or carbon dioxide output will occur. If ventilation, as assessed by P_aCO_2, is adequate at ground level in patients with respiratory failure, ventilation should not change during aeromedical evacuation if the ventilator maintains rate and volume delivery.

At 8,000 feet the normal animals exhibited a drop in P_aO_2 approximately equal to the decrease in P_IO_2 that occurred from ground level to altitude. At ground level, barometric pressure was approximately 747 mmHg and P_IO_2 was 147 mmHg; at 8,000 feet, they were 564 mmHg and 108 mmHg respectively. When F_IO_2 was increased to 30% at 8,000 feet, the P_IO_2 was 155 mmHg, slightly greater than that at ground level. Two control animals were evaluated at 8,000 feet while breathing 30% oxygen. This increment in F_IO_2 restored P_aO_2 in both animals to values observed at ground level. Most control animals had a slight increase in pulmonary artery pressures when taken to a simulated altitude of 8,000 feet. Pressures in the two animals given 30% oxygen decreased noticeably with administration of this mixture. These findings indicate that administering only 30% oxygen during aeromedical evacuation is sufficient to prevent alteration of physiological parameters in a patient whose normal lungs require mechanical ventilation, e.g., respiratory failure caused by neuromuscular disease.

The five animals with lung injury induced by oleic acid had markedly elevated $(A\text{-}a)O_2$ differences. However, since all were ventilated with 100% oxygen, none were severely hypoxemic at ground level. Several animals did become hypoxemic at altitude. Arterial oxygen tension approached 40 mmHg in several cases. These data show that a patient who requires 100% oxygen at ground level and has a P_aO_2 less than 100 mmHg is at significant risk of developing severe hypoxemia during air transportation. This could adversely affect the likelihood of successful aeromedical evacuation.

The best means of ensuring adequate oxygenation in patients who are being evacuated by air is to maintain the P_IO_2 at a value that produced adequate oxygenation at ground level. To do this, simply increase the F_IO_2 at altitude to an extent that will counteract the decrease in barometric pressure. Table 6 is a guide to therapy for patients requiring supplemental oxygen during aeromedical evacuation. This table lists the F_IO_2 necessary to maintain P_IO_2 at the same value that was present at sea level when different oxygen mixtures were breathed. For

TABLE 6. INSPIRED OXYGEN CONCENTRATION (F_IO_2) REQUIRED TO MAINTAIN INSPIRED OXYGEN TENSION (P_IO_2)

Barometric Pressure: (mmHg)	760	656	609	564
Equivalent Altitude: (ft)	0	4000	6000	8000
P_IO_2	F_IO_2			
149	.21	.25	.27	.29
214	.30	.35	.38	.41
285	.40	.47	.51	.55
366	.50	.60	.65	.71
428	.60	.70	.76	.83
499	.70	.82	.89	.97
517	.725	.85	.92	1.00
562	.79	.92	1.00	
570	.80	.94		
609	.85	1.00		

example, as previously noted, P_IO_2 can be maintained at 149 mmHg at an 8,000-ft altitude if F_IO_2 is increased to just under 30%. If 50% oxygen were required to maintain adequate oxygen exchange at sea level, then 71% oxygen would be necessary at 8,000 feet. Note that if the F_IO_2 exceeds .725 at sea level, the equivalent P_IO_2 cannot be achieved at 8,000 feet. This suggests an upper limit in F_IO_2 for patients being evaluated for possible aeromedical evacuation. If an F_IO_2 of greater than 0.70 at sea level is needed to maintain a satisfactory P_aO_2, deterioration in P_aO_2 will almost certainly occur at altitude even if 100% oxygen is inspired. This could have an adverse effect on patient outcome. The risk-benefit ratio of transporting such a patient would have to be carefully weighed.

For patients requiring very high oxygen concentrations, an alternate choice would be to transport at lower altitudes to maintain cabin pressure at a higher value. The intermediate altitudes shown in Table 6 would permit transportation of patients with greater oxygen requirements.

If patients had to be transported under conditions that would result in lowered P_IO_2, the consequent fall in arterial oxygenation is difficult to predict. This decrease in oxygenation would be a function of the mixed venous oxygen tension, the degree of ventilation-perfusion inequality, and the magnitude of right-to-left shunt. These factors could vary widely from one patient to another.

This approach to oxygen therapy depends upon being able to measure arterial blood gases prior to evacuation. If under extremely adverse circumstances this is not possible, the most expedient approach would be to administer 100% oxygen to all patients requiring mechanical ventilation. The risk of oxygen toxicity while breathing 100% oxygen for less than 24 h is extremely small in normal individuals. For a patient who has a lung lesion, however, no data is available to predict the effect of pure oxygen. However, it seems likely that this risk is less than the consequences of possible severe hypoxemia.

If cabin decompression is thought to be possible, the only means of ensuring potential survival (for both normal and severely ill individuals) is to increase the inspired oxygen concentration to extremely high levels, preferably 100%.

CONCLUSIONS

1. Exposure to decreased barometric pressure accompanying ascent to altitude does not change mass ventilatory requirements. Tidal volume and respiratory frequency that are adequate at ground level will suffice at altitude.

2. Patients who require mechanical ventilation can be adequately oxygenated during aeromedical evacuation if the P_IO_2 is kept constant by incrementing the F_IO_2 as the barometric pressure is lowered.

3. Even in severely ill patients with adult respiratory distress syndrome (ARDS), adequate gas exchange can be maintained during decompression to an altitude of 40,000 ft as long as ventilation is maintained with 100% oxygen.

REFERENCES

1. Kirby, R.R.; A.J. DiGiovanni; R.W. Bancroft; and R.G. McIver. Function of the Bird respirator at high altitude. Aerospace Med 40:463-469, 1969.

2. Henry, J.N.; L.J. Krenis; and R.T. Cutting. Hypoxemia during aeromedical evacuation. Surg Gyn Obstet 136:49-53, 1973.

3. Dantzker D.R.; C.J. Brooks; P. Dehart; J.P. Lynch; and J.G. Weg. Ventilation-perfusion distributions in the adult respiratory distress syndrome. Am Rev Resp Dis 120: 1039-1052, 1979.

4. West J.B.; and P.D. Wagner. Pulmonary gas exchange. In Bioengineering Aspects of the Lung. New York: Dekker, 1977. vol. 3, pp. 361-457.

5. West J.B. Regional differences in gas exchange in the lungs of erect man. J Appl Physiol 17:893-898, 1962.

6. Wagner P.D.; and J.B. West. Effects of diffusion impairment on O_2 and CO_2 time course in pulmonary capillaries. J Appl Physiol 33:62-71, 1972.

7. Staub N.C.; J.M. Bishop; and R.E. Forster. Importance of diffusion and chemical reaction rates in O_2 uptake in the lung. J Appl Physiol 17:21-27, 1962.

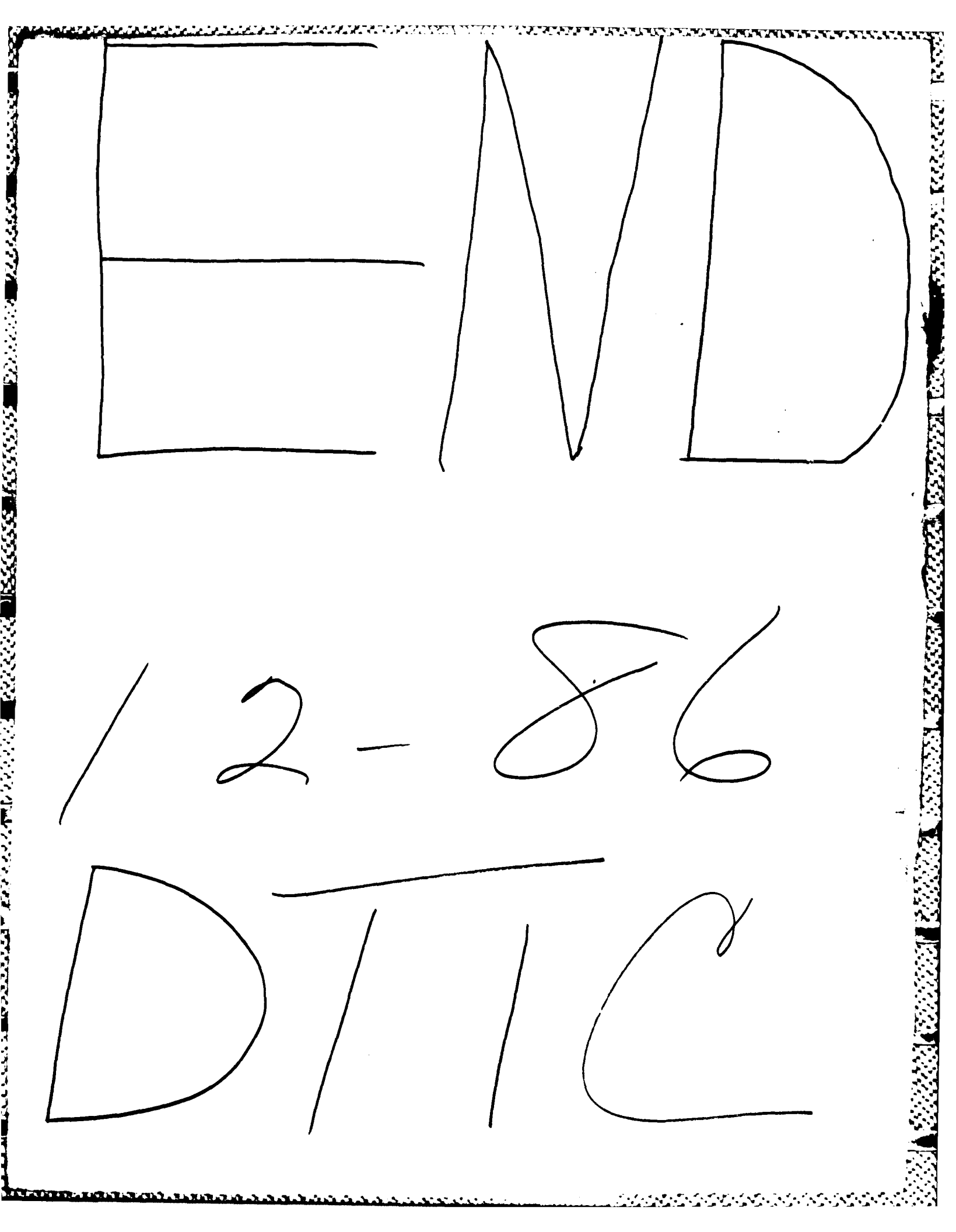
8. Snedecor, G.W.; and W.G. Cochran. Statistical Methods. Sixth Edition. Iowa City: Iowa Press, 1967.

9. Cochran, W.G.; and G.M. Cox. Experimental Designs. Wiley: New York, 1953.

10. Johnson, R.L., Jr. Pulmonary diffusion as a limiting factor in exercise stress. Circ Res 20-21 (Suppl I):154-160,1967.

11. West, J.B. Man at extreme altitude. J Appl Physiol 52:1393-1399, 1982.

12. Lilienthal, J.L., Jr.; R.L Riley; D.D Proemmel; and R.E. Franke. An experimental analysis in man of the oxygen pressure gradient from alveolar air to arterial blood during rest and exercise at sea level and at altitude. Am J Physiol 147:199, 1946.


END
12-86
DTIC