0090-3493/90/1811-1257$02.00/0
CRITICAL CARE MEDICINE

Vol. 18, No. 11
Printed in U.S.A.

High-frequency oscillation during simulated altitude exposure

ALAN R. SALTZMAN, MD; ROBERT A. KLOCKE, MD; NEEL B. ACKERMAN, JR, MD; PATRICIA LAND, RN; BRYDON J. B. GRANT, MD; ALAN T. AQUILINA, MD

Ventilatory requirements using high-frequency oscillation (HFO) during simulated altitude exposure were investigated in control dogs and animals with oleic acid-induced lung injury. F_{IO_2} values of 0.21 and 1.0 were supplied by bias flow to the normal and injured dogs, respectively. After a control period, animals were exposed to a simulated altitude of 8,000 ft (barometric pressure 564 torr), followed by a second control period at ground level. Both experimental groups had similar values of P_{aCO_2} at ground level and during exposure to reduced barometric pressure. The tidal volume necessary to maintain eucapnia was higher in oleic acid-injured animals compared with the control group; cardiac output and functional residual capacity were lower. The alveolar-arterial oxygen difference was substantially larger in the oleic acid group. Adequate gas exchange can be maintained with HFO during exposure to altitude provided that ventilation and inspired P_{O_2} are not reduced below normobaric levels. (Crit Care Med 1990; 18:1257)

Patients with respiratory failure requiring mechanical ventilation (MV) occasionally must be transported by air to other medical facilities. Significant hypoxemia can occur during air transport even in patients who are in stable condition (1). Cabin pressures at altitudes reached with maximum aircraft performance are substantially lower than atmospheric pressure (2), leading to a reduction in inspired P_{O_2}.

Previous work (3) from our laboratory established ventilatory criteria for conventional MV during aeromedical evacuation. Adequate gas exchange was achieved during exposure to altitude in animals with acute oleic acid-induced lung injury. This required maintenance of ventilation at normobaric levels and an increment in F_{IO_2} to compensate for the reduction in barometric pressure. The present study was conducted to determine the effect of altitude on gas exchange during ventilation with high-frequency oscillation (HFO).

From the Department of Medicine, State University of New York at Buffalo, Buffalo, NY (Drs. Saltzman, Klocke, Grant, and Aquilina), and the United States Air Force School of Aerospace Medicine, Brooks AFB, TX (Dr. Ackerman and Capt. Land).

This study was supported, in part, by a grant from the Southeastern Center for Electrical Engineering Education and Program Project grant HL-34323 from the National Heart Lung and Blood Institute. Dr. Grant is the recipient of the National Institutes of Health Research and Career Development Award HL-01418.

The opinions expressed herein are those of the authors and do not necessarily reflect those of the United States Air Force or the Department of Defense.

Address requests for reprints to: Alan R. Saltzman, MD, SUNYAB-ECMC, 462 Grider Street, Buffalo, NY 14215.

MATERIALS AND METHODS

Male mongrel dogs (16.6 ± 1.8 [SD] kg) were anesthetized with 4% thiamylal (6 mg/kg) iv followed immediately by administration of α-chloralose in sodium tetraborate buffer. The initial iv dose of α-chloralose (120 mg/kg) was supplemented continuously with 43 mg/kg·h by infusion pump. After demonstrating adequate anesthesia with α-chloralose, muscle paralysis was achieved with iv pancuronium bromide. The initial dose of 0.1 mg/kg was supplemented with doses of 0.04 mg/kg administered as needed. At the conclusion of the experiment, the animal was killed by rapid iv injection of 50 ml saturated KCl during ECG monitoring.

Animals were intubated with a cuffed No. 10 oral endotracheal tube. The oleic acid model of adult respiratory distress syndrome was induced in five of ten experimental animals by injection of oleic acid (0.1 ml/kg) into the right atrium via a pulmonary artery catheter at a rate of 0.4 ml/min. The dogs were allowed to breathe spontaneously from a reservoir containing 100% oxygen. Arterial blood gases were monitored and, if needed, the animals were ventilated intermittently with an Ambu bag to prevent severe respiratory acidosis. Ninety minutes after the oleic acid infusion, the animals were placed on HFO.

The high-frequency oscillator consisted of a Teflon piston 2.5 inches in diameter contained within a brass cylinder (Fig. 1). A threaded Plexiglas head tapered to a 0.5-inch ID outlet was attached to the end of the brass cylinder with an O-ring seal. The piston was driven by a ¼-hp motor with frequency adjusted by a silicon-controlled rectifier. Control and oleic acid-injected animals were ventilated at constant rates of 15.4 and 15.9 Hz, respectively. Stroke volume of the oscillator (0 to 100 ml) was adjusted by altering the position of the drive shaft on a motor-driven cam. Initial piston stroke volume was set at 3 ml/kg and P_{aCO_2} was determined. If the P_{aCO_2} was outside the normal range, the stroke volume was adjusted until eucapnia was achieved as confirmed by arterial blood gas analysis. No further

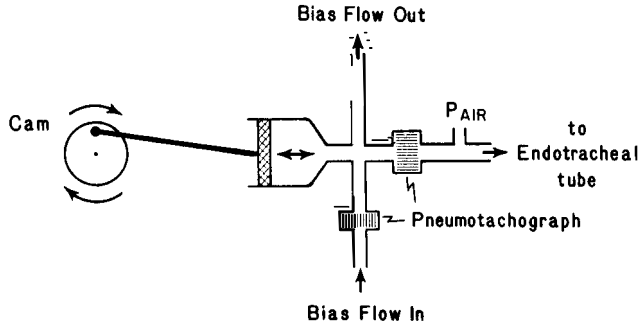

FIG. 1. High-frequency oscillator and bias flow circuit. Bias flow enters the system between the oscillator and the pneumotachograph. Measured tidal volume does not include any portion of the oscillator stroke volume which may have been diverted into the bias flow. Airway pressure is monitored at the proximal end of the endotracheal tube.

adjustments were made in oscillator settings during the experiment. Bias flow entered the circuit between the oscillator and a No. 3 Fleisch pneumotachograph (Dynasciences, Blue Bell, PA), which measured the delivered tidal volume (VT). Bias flow was monitored using a No. 1 pneumotachograph in the inspiratory bias flow line. Pressure changes across the pneumotachographs were measured with variable reluctance transducers (MP-45, Validyne, Northridge, CA). The expiratory bias flow passed through approximately 200 cm of ¼-inch ID flexible plastic tubing, which served as a low pass filter. The bias flow was held constant throughout the entire experimental period. Mean bias flow was slightly higher in the oleic acid-injected animals (14.9 L/min) than in normal animals (13.1 L/min). The control group received an F_{IO_2} of 0.21 via the bias flow, while an F_{IO_2} of 1.0 was administered in the oleic acid group to prevent severe hypoxemia.

A jugular venous catheter was inserted for fluid and drug administration. A femoral artery catheter was utilized for BP monitoring and collection of arterial blood samples. Body temperature was maintained with a heating blanket. A triple-lumen pulmonary artery thermodilution catheter was used to monitor pulmonary artery (PAP) and pulmonary wedge pressures (WP) and to sample mixed venous blood. Body temperature was monitored with a thermistor located at the tip of the pulmonary artery catheter.

Hemodynamic and respiratory data were recorded simultaneously with both an eight-channel chart recorder (2800, Gould, Cleveland, OH) and an eight-channel FM tape recorder (3968A, Hewlett-Packard, San Diego, CA). The variables recorded were ECG, BP, and PAP (P-23Db transducers, Gould), WP, airway pressure ($\overline{Paw}$) at the proximal end of the endotracheal tube (MP-45, Validyne), bias flow, tracheal air flow, and delivered VT obtained by electrical integration of the pneumotachograph flow signal. The chart recorder was used only for monitoring during the experiment.

Data collected on the FM tape were digitized off-line with a 16-bit analog to digital converter (DT2801, Data Translation, Marlborough, MA) in a personal computer, and stored on floppy disk. Data from the FM tape were sampled over 20-sec periods at 50 Hz. Mean values of $\overline{Paw}$, PAP (MPAP), WP, and BP (MAP) were obtained by numerical integration of the respective phasic pressure signals. Ventilator rate and delivered VT were determined from the integrated pneumotachograph signal. Arterial and mixed venous blood samples were obtained and analyzed at 37°C. Since animal temperature was maintained between 36° and 38°C, blood gas values were not corrected for these minor temperature variations. Cardiac output ($\dot{Q}t$) was determined by thermodilution using a cardiac output computer (9510A, Baxter Edwards Laboratories, Irvine, CA). Values obtained from three to five sequential 10-ml injections of saline at room temperature were averaged. Functional residual capacity (FRC) was estimated by N_2 dilution using closed circuit rebreathing.

The initial data at ground level (GRD-I) were collected on two occasions 20 to 30 min apart. After data collection, the hypobaric chamber in which the animal was situated was decompressed to a simulated level of 8,000 ft (barometric pressure equal to 564 torr). Two sets of altitude data (ALT) were collected 20 to 30 min apart. The hypobaric chamber was returned to ground level and another two sets of measurements (GRD-II) were obtained. After any change in barometric pressure, no measurements were made for 25 to 30 min to ensure that a steady state was reached. During this period vascular and $\overline{Paw}$ transducers were recalibrated. The pneumotachographs were not recalibrated. There were no significant differences between the first and second data sets collected under either ground or altitude conditions. The average of both sets of data for each condition is provided in Table 1.

Data were analyzed with analysis of variance for a repeated-measures experimental design (4). For all statistical comparisons, significance was accepted at the 5% level.

RESULTS

Effective alveolar ventilation, as estimated by Pa_{CO_2}, was normal in both oleic acid-injected and control animals (Table 1). There was no change with altitude. The pHa was also normal in both groups. To maintain eucapnia, the oleic acid-injected animals required an average delivered VT that was 50% greater than that provided to the control group. Respiratory frequency was essentially the same for all animals.

The delivered VT obtained from the integrated flow signal decreased slightly with altitude. There was a tendency for VT to decrease with time as evidenced by the difference between the two ground-level observa-

TABLE 1. Physiologic variables at ground level and simulated altitude (mean ± SD)

Variable	Group	GRD-I	ALT	GRD-II
pH	C	7.41 ± 0.06	7.40 ± 0.06	7.39 ± 0.06
	O	7.38 ± 0.03	7.40 ± 0.03	7.38 ± 0.03
Pa_{CO_2} (torr)	C	37.4 ± 3.6	39.5 ± 4.2	38.9 ± 5.9
	O	40.3 ± 3.5	38.7 ± 7.2	39.4 ± 7.6
VT (ml)[b,i]	C	54.4 ± 9.5	51.7 ± 8.7	53.1 ± 9.5
	O	87.1 ± 20.3	80.9 ± 19.7	70.8 ± 18.7
$\overline{Paw}$ (mm Hg)[b,g]	C	5.6 ± 1.4	5.8 ± 1.7	6.1 ± 1.9
	O	8.5 ± 2.3	8.7 ± 2.2	10.2 ± 2.9
FRC (ml)[b]	C	954 ± 168	1049 ± 402	952 ± 254
	O	608 ± 241	490 ± 189	581 ± 125
$\dot{Q}t$ (L/min)[b,h]	C	2.7 ± 0.7	2.6 ± 0.5	2.3 ± 0.4
	O	1.7 ± 0.6	1.7 ± 0.4	1.7 ± 0.4
MAP (mm Hg)[f]	C	106 ± 11	112 ± 11	113 ± 10
	O	134 ± 18	134 ± 18	128 ± 12
MPAP (mm Hg)[e,g]	C	19.1 ± 7.0	24.3 ± 8.0	20.6 ± 6.9
	O	29.1 ± 14.6	28.9 ± 14.1	32.3 ± 15.2
WP (mm Hg)[d]	C	6.0 ± 2.7	5.4 ± 2.2	7.4 ± 2.9
	O	6.1 ± 3.4	3.2 ± 6.0	5.5 ± 2.9
Pa_{O_2} (torr)[c]	C	99 ± 7	63 ± 8	97 ± 10
	O	172 ± 146	157 ± 136	199 ± 186
$P\bar{v}_{O_2}$ (torr)[c]	C	45 ± 4	38 ± 2	43 ± 3
	O	40 ± 5	35 ± 5	36 ± 6
$P(A\text{-}a)O_2$ (torr)[a,c,f]	C	3 ± 7	−2 ± 6	3 ± 4
	O	484 ± 151	321 ± 140	457 ± 193

C, control group; O, oleic acid-injured group.

Significant difference between C and O: [a]($p < .01$), [b]($p < .05$).

Significant difference between GRD and ALT values: [c]($p < .001$), [d]($p < .05$).

Greater effect of ALT on control animals: [e]($p < .001$); greater effect of ALT on oleic acid-injured animals: [f]($p < .001$).

Significant differences between GRD-I and GRD-II values: [g]($p < .001$), [h]($p < .05$).

tions. However, this did not achieve statistical significance since only three observations were made in the oleic acid-injected animals during the GRD-II period. In the other two experiments, the pneumotachograph became contaminated with pulmonary edema fluid, invalidating the VT measurements during the final ground observations.

The $\overline{Paw}$ measurement was higher in the oleic acid-injected animals compared with the control group, probably because of the larger delivered VT and decreased compliance in the oleic acid-injected animals. Resistance to air flow also was increased because of the decrease in FRC in the oleic acid-injected animals. FRC was approximately 75% larger in the control group. Observed changes in FRC with altitude were not statistically significant.

$\dot{Q}t$ was significantly lower in the oleic acid group. MAP was higher in the oleic acid-injected animals than in the control group. This finding, combined with the decreased $\dot{Q}t$ noted in the oleic acid-injected dogs, reflects elevation of peripheral vascular resistance.

The MPAP measurement was higher in the oleic acid group, but this difference failed to reach statistical significance. PAP increased during altitude exposure in the control group, but not the oleic acid-injected animals. This finding is a result of hypoxic vasoconstriction occurring in the control animals in response to the lower Pa_{O_2} present at altitude. In the oleic acid-injected animals, an F_{IO_2} of 1.0 prevented substantial hypoxemia and an increase in PAP. Mean WP was similar in both groups of animals.

Oxygen exchange was grossly abnormal in the oleic acid-injured animals. Despite an F_{IO_2} of 1.0, mean Pa_{O_2} was 186 torr during the ground-level observations. The Pa_{O_2} varied widely in the oleic acid-injured animals; the lowest Pa_{O_2} was 68 torr. At 8,000 ft, inspired P_{O_2} was 517 torr, but mean Pa_{O_2} was only 157 torr. The mean alveolar-arterial oxygen pressure difference ($P[A\text{-}a]O_2$) in the oleic acid group was 471 torr at GRD-I and GRD-II, but decreased to 321 torr at altitude.

Blood gas values in the control animals under ground-level conditions were unremarkable. At 8,000 ft, inspired P_{O_2} decreased to 108 torr. This decrease in inspired P_{O_2} of 39 torr from ground conditions resulted in an average decrease in Pa_{O_2} of 35 torr, from 98 torr (GRD-I and GRD-II) to 63 torr during altitude exposure.

The $P\bar{v}_{O_2}$ measurement was slightly, but not significantly, higher in the control group than in the oleic acid group. A small but statistically significant decline in $P\bar{v}_{O_2}$ occurred with altitude, paralleling the decrease in Pa_{O_2}.

DISCUSSION

The influence of decreased barometric pressure on the efficacy of HFO has not been examined previously. It is not possible to predict this effect on theoretical grounds because the role of different mechanisms of gas transport in HFO has not been delineated (5). In this study, we used an empirical approach to determine if HFO would be affected by hypobaric conditions. The fact that Pa_{CO_2} did not change during hypobaric conditions indicated that HFO supplied constant effective alveolar ventilation throughout the experiments. Because the mechanisms underlying HFO are poorly understood, Pa_{CO_2} is the only practical means to judge the effectiveness of ventilation (5). These data indicate that as long as the oscillator maintains its stroke volume at altitude, no change in Pa_{CO_2} or acid-base status will occur.

The normal animals exhibited an average decrease in Pa_{O_2} at 8,000 ft of 35 torr, approximately equal to the decrease in inspired P_{O_2} of 39 torr that occurred with the transition to altitude. The normal group also had a significant increase in MPAP at a simulated altitude of 8,000 ft. If inspired P_{O_2} were increased at altitude to the same value present at ground level, neither the hypoxemia nor the hypoxic pulmonary vasoconstriction would occur (3). This situation could be achieved

by administering an F_{IO_2} of 0.29 at 8,000 ft, resulting in the same inspired P_{O_2} (149 torr) present at sea level. Thus, it is sufficient to administer an F_{IO_2} of ~0.30 during air transport to prevent undesirable effects of hypoxemia in patients with normal lungs who require MV.

The five animals with oleic acid-induced lung injury had markedly elevated $P(A\text{-}a)O_2$ measurements occurring as a consequence of diffuse lung injury. Potential errors associated with measurement of high partial pressures of oxygen in blood could affect the calculated $P(A\text{-}a)O_2$ in these animals. However, the difference in $P(A\text{-}a)O_2$ between the two experimental groups is far too great to be the result of this relatively minor problem. The changes in Pa_{O_2} with altitude were greater in animals with lung injury than in the control group. In the latter, alveolar P_{O_2} (P_{AO_2}) and Pa_{O_2} decreased in an approximately equal manner. In the oleic acid-injured animals, the decrease in P_{AO_2} with altitude was much greater than the decline in Pa_{O_2}. Mean P_{AO_2} was 657 torr at ground level and 476 torr at altitude. This difference of 181 torr in P_{AO_2} between ground and altitude resulted in only a mean decrease of 29 torr in Pa_{O_2}. This is the corollary to the usual clinical situation seen in patients with the adult respiratory distress syndrome in which Pa_{O_2} is relatively insensitive to increases in F_{IO_2} (6).

The decrease in oxygenation occurring in patients exposed to reduced barometric pressure is a function of $P\bar{v}_{O_2}$, the degree of ventilation/perfusion inequality, and the magnitude of right-to-left shunt. These factors vary widely from patient to patient and their impact on Pa_{O_2} cannot be predicted with sufficient accuracy to avoid hypoxemia during air transport in some individuals. The best means of ensuring adequate oxygenation in patients transported by air is to maintain inspired P_{O_2} at the value required to produce adequate oxygenation at ground level. There is considerable risk that severe hypoxemia may develop during air transportation in a patient who requires an F_{IO_2} of 1.0 at sea level to maintain a Pa_{O_2} <100 torr.

In conclusion, exposure to reduced barometric pressure during air transport will not have a deleterious effect on a patient as long as inspired P_{O_2} and minute ventilation are not altered. The former can be achieved by increasing F_{IO_2}. The latter is a function of ventilator performance and is not dependent on whether the patient is receiving conventional MV or HFO.

ACKNOWLEDGMENTS

The authors thank Erika Poleschner, 2d Lt, USAF, Ernest Roy, T. Sgt, USAF, Jerald Duffman, M. Sgt, USAF, and Larry Warfel, T. Sgt, USAF, for technical assistance during the performance of these experiments; Edmund Egan, MD, for use of the high-frequency oscillator; and Kevin Freiert for data reduction and analysis.

REFERENCES

1. Henry JN, Krenis LJ, Cutting RT: Hypoxemia during aeromedical evacuation. *Surg Gynecol Obstet* 1973; 136:49
2. Cottrell JJ: Altitude exposures during aircraft flight. *Chest* 1988; 92:1
3. Saltzman AR, Grant BJB, Aquilina AT, et al: Ventilatory criteria for aeromedical evacuation. *Aviat Space Environ Med* 1987; 58:958
4. Snedecor GW, Cochran WG: Statistical Methods. Seventh Edition. Iowa City, Iowa Press, 1980, pp 267–269
5. Chang HK, Harf A: High frequency ventilation: A review. *Respir Physiol* 1984; 57:135
6. Dantzker DR, Brook CJ, Dehart P, et al: Ventilation-perfusion distributions in the adult respiratory distress syndrome. *Am Rev Respir Dis* 1979; 120:1039