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The maximum effective alveolar ventilation ($V_A^e max$) in healthy young liquid breathing men is approximately 3 l/min. This estimate is based on measured expiratory flows of saline and FC-80 fluorocarbon liquid from excised dogs' lungs and maximum expiratory flow and gas exchange in saline ventilated lungs of men. At a solubility of CO_2 in saline of 0.742 ml STPD/l/mmHg, a $V_A^e max$ of 3 l/min precludes the feasibility of saline breathing in man.

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20. Abstract

Normothermic anesthetized dogs ventilated with oxygenated FC-80 fluorocarbon liquid can be maintained at a normal $PaCO_2$ for 1 hr. This indicates that the solubility of CO_2 in FC-80 fluorocarbon liquid is approximately 3 ml STPD/l/mmHg, which is considerably higher than reported in the literature. It should be possible for a healthy man breathing oxygenated FC-80 fluorocarbon to maintain a normal $PaCO_2$ while at rest. This would make possible the rapid escape from disabled submarines at great depths. The use of an emulsion of 1% (by volume) of 2 M NaOH in FC-80 fluorocarbon liquid should permit a liquid breathing diver to perform work requiring a $\dot{V}O_2$ of approximately 1 l STPD/min while maintaining a normal $PaCO_2$. Microscopic examination of the lungs of dogs and rats that had breathed oxygenated FC-80 fluorocarbon liquid or an emulsion of 1% (by volume) of 2 M NaOH in FC-80 fluorocarbon liquid revealed the transient presence of increased numbers of mononuclear cells but no other pathologic changes.

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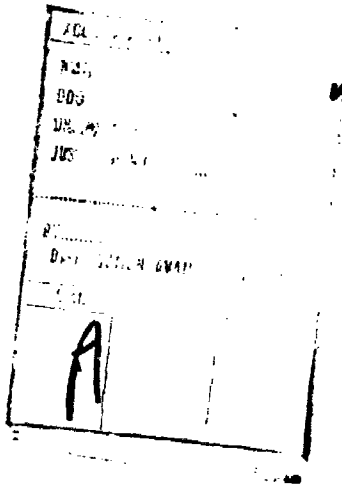

INTRODUCTION

Decompression sickness could be eliminated if the inert gas in the breathing mixtures which currently are being used in diving could be replaced by a noncompressible liquid. Furthermore, liquid breathing would make it possible to study the biological effects of pressure per se in mammals without the interference of pharmacological effects of compressed gases, provided that thermal, metabolic and respiratory homeostasis could be maintained during the hydraulic compression of the experimental animals.

The research on liquid breathing dating back to 1962 has been reviewed earlier elsewhere (10). In this report, the work performed under ONR contract N00014-67-A-0251-0007 between May 1, 1969 and October 31, 1975 is summarized. The activities aimed primarily at assessing the feasibility of liquid breathing in man are discussed in Section I. Other investigations dealing with the physiological responses to a hyperbaric environment are summarized in section II. A complete chronological bibliography of scientific publications emanating from the contract is given in section III.

I. LIQUID BREATHING

In all experiments prior to 1969, adequate arterial oxygenation could be maintained but the experimental animals invariably developed a severe respiratory acidosis. The elimination of CO_2 through liquid filled lungs depends upon the solubility of CO_2 in the alveolar liquid (αCO_2) and the effective alveolar ventilation (V_A^e) which may be defined as the virtual volume of exhaled liquid in which the partial pressure of CO_2 is the same as in the arterial blood, or more conventionally, as the difference between the minute volume of ventilation ($\dot{V}_E$) and dead space ventilation ($\dot{V}_D$). Thus, under steady state conditions when the inspired liquid does not contain CO_2, $PaCO_2 = \dot{V}CO_2/\dot{V}_A^e \cdot \alpha CO_2$. Hence, if a normal $PaCO_2$ cannot be maintained at a given $\dot{V}CO_2$, then either $\dot{V}_A^e$ or αCO_2 or both are too low. To assess the feasibility of liquid breathing in man, it was therefore deemed to be of prime importance to establish the limits of $\dot{V}_A^e$ during ventilation with various liquids and to explore possibilities of increasing αCO_2.

1. Experiments with Excised Dogs' Lungs

Volume-flow characteristics of saline and FC-80 fluorocarbon filled excised dogs' lungs were compared by using volume-displacement plethysmography (17). In these experiments, expiratory flow started from a lung volume at which the static recoil pressure of the same lung filled with air had been 20 cm H_2O. The maximum flows of saline and fluorocarbon were compared over the first 50% of the total volume expired. The mean flows were 121 $\pm$ 32 ml/sec for the saline filled lungs and 104 $\pm$ 46 ml/sec for the fluorocarbon filled lungs. At comparable lung volumes, the static recoil pressure of FC-80 filled lungs was found to be greater than in saline-filled lungs, indicating that alveolar surface tension is not abolished in a fluorocarbon-filled lung (8).

2. Observations in Man

It is possible to ventilate one lung of man with saline while the other lung is ventilated with oxygen (7). Such a procedure is by now a generally

accepted method of treating patients with alveolar proteinosis and has also been used successfully as an adjunct in the treatment of patients suffering from bronchiectasis, cystic fibrosis of the pancreas, or intractable asthma. Bronchoalveolar lavage has been used prophylactically to remove accidentally inhaled radioactive plutonium from the lungs of a healthy man.

(a) *Gas Exchange*

During lavages of the lung of a patient with alveolar proteinosis and a 49 year old healthy volunteer, the PO_2 and PCO_2 of end-tidal liquid remained virtually unchanged as the time between the beginning of infusion to the end of drainage of a tidal volume increased from less than 30 to more than 200 sec. Also, the arterial and mixed venous PO_2 and PCO_2 remained essentially the same, suggesting that diffusive gas tension equilibrium between alveolar capillary blood and alveolar contents was established within 30 sec in these saline filled human lungs (9). The computed difference between the mean end-capillary and alveolar CO_2 partial pressure was, on the average, less than 1 mmHg in the 28 year old patient with alveolar proteinosis indicating that ventilation and perfusion were adequately matched in the liquid filled lung.

(b) *Ventilation*

In the anesthetized volunteer, the maximum expiratory flow of saline from the left lung was measured by applying and gradually increasing suction at the outflow tube until the rate of flow of saline ceased to increase. The minimum time required to remove 500 ml saline, starting from a lung volume of 2000 ml was 9.4 sec. The computed total lung capacity (TLC) of the left lung (0.45 x TLC of both lungs measured the day before the experiment) was 2900 ml. Assuming that the time required for inspiration is equal to the time required for expiration, and assuming an equal maximal expiratory flow rate for both lungs, the maximum minute ventilation of this man, if he were breathing saline, would be 3.2 liters, at a tidal volume of 1 liter and with expirations starting at 70% of TLC. In the patient with alveolar proteinosis, 500 ml saline was drained from the left lung in 7 sec, starting at TLC. Making the same assumptions as before, the maximum minute volume of ventilation in this patient, if he were to breathe saline, would be 4.2 liters at a tidal volume of 1 liter and with expiration starting from TLC.

The maximum expiratory flow of either gas or liquid is dependent upon the recoil tendency of the lung and limited by dynamic compression of the airways. Therefore, the maximum expiratory flow cannot be increased by mechanical assistance, i.e. by artificially applying a greater than normal difference in pressure between the alveoli and the mouth. However, the inspiratory flow is not limited by dynamic airway compression, so that, theoretically, the inspiratory flow should continue to increase as the difference between the pressure in the alveoli and at the mouth increases. It had been found earlier that the inspiratory flow in spontaneously saline breathing dogs was about twice as great as the expiratory flow (6). As a result, the minute volume of ventilation was 33% greater than would have been the case if inspiration and expiration would have lasted equally long. By increasing the inspiratory flow rate, as the saline breathing dog did, the 49 year old volunteer's maximum minute volume of saline ventilation could be 4.3 liters. The maximum minute volume of ventilation in the 28 year old patient with alveolar proteinosis, if he were breathing saline, could

be 5.6 liters at a tidal volume of 1 liter with expirations starting from TLC. Diffusive mixing in saline filled gas exchange units of the human lung appears to be complete within 30 sec and theventilation and perfusion of saline filled lungs appears to be matched adequately (9). The expiratory flow of saline and fluorocarbon from liquid filled excised dogs' lungs was very similar (17). Hence, it seems reasonable to conclude that the effective alveolar ventilation in a healthy young saline or fluorocarbon breathing diver could be 3 liters/min.

(c) *Recovery following Lung Lavage with Saline*

Chest x-rays taken shortly after a lung lavage usually show a diffuse opacification of the washed lung, but the lung is clear again after 24 hours (7). Serial pulmonary function tests following lavage of a lung of the volunteer revealed a decrease in the vital capacity, TLC and FEV_1; a PaO_2 of 76 mmHg; and a $PaCO_2$ of 37 mmHg 24 hours after the procedure but these parameters returned to prelavage control levels in 72 hours and remained at these levels during the following 2 years. Static pressure-volume relationships of the left lung and chest of the anesthetized and curarized volunteer revealed a considerable decrease in compliance immediately following the lavage, as compared to the measurements made just before the lavage. This can be explained by the diminished volume or air in the lung caused by the presence of residual saline and by the surface tension at the interface between residual liquid and air.

(d) *Subjective Acceptability*

The healthy volunteer whose larynx and trachea had been anesthetized to facilitate intubation, but who otherwise received no medication, did not experience intolerable sensations arising from the flow of saline into and out of his lungs and seemed not to be aware of the presence of residual liquid in his lung after the lavage.

3. The CO_2 Carrying Capacity of Various Breathing Fluids

At a maximum $\dot{V}_A^e$ of approximately 3 1/min and a solubility of CO_2 in saline at 37°C of 0.724 ml STPD/l/mmHg, the $\dot{V}CO_2$ is limited to 87 ml STPD/min at $PaCO_2$ = 40 mmHg. Hence, it will obviously be impossible to maintain respiratory homeostasis in a saline breathing diver. The solubility of CO_2 at 37°C in FC-80 fluorocarbon was found to be approximately 3 ml STPD/l/mmHg (12). Therefore, it should be possible for a fluorocarbon breathing diver who produces no more than 360 ml STPD of CO_2/min to maintain a normal $PaCO_2$. While this would probably suffice to escape from disabled submarines, it would preclude the use of liquid breathing under circumstances where appreciable work has to be performed by a diver. For this reason, several possibilities of increasing the CO_2 carrying capacity of a liquid have been explored.

(a) *The Addition of THAM*

The addition of THAM to the inspired salt solution markedly prolonged survival of liquid breathing mice (5) and rats (18). To evaluate quantitatively the increase in the CO_2 carrying capacity of a saline breathing fluid caused by the addition of THAM, an isotonic 0.3 Molar THAM solution, titrated to pH 7.4 was equilibrated with various gas mixtures containing CO_2 at partial pressures ranging from 7 to 70 mmHg. The CO_2 content of the gas-equilibrated

THAM solution was then determined by the method of Van Slyke. The CO_2 content of an isotonic 0.3 Molar THAM solution at pH 7.4 equilibrated with carbon dioxide at a partial pressure of 40 mmHg was approximately 390 ml STPD/l. In contrast, a liter of saline under these conditions contains only 29 ml STPD of CO_2 (17).

If a diver were to breathe an isotonic 0.3 Molar THAM solution titrated to pH 7.4 at an effective alveolar ventilation of 3 l/min, then he would be able to eliminate 3 x 390 = 1170 ml STPD of CO_2 per min at a $PaCO_2$ of 40 mmHg and thus be able to perform work which requires an oxygen uptake of 1462 ml STPD per minute, assuming that R = 0.8. However, the solubility of oxygen in a 0.3 Molar THAM solution is no greater than in saline (0.0299 ml STPD/l per mmHg at 37°C) so that a partial pressure of 16,300 mmHg or 21.45 atm of oxygen, at least, would be required in the inspired THAM solution to supply the 1462 ml of oxygen per minute. Such partial pressures of oxygen are prohibitively toxic.

(b) *Emulsions of Fluorocarbon in THAM Solutions*

A stable emulsion can be prepared by subjecting a mixture of 30% (by volume) FC-80 fluorocarbon; a 0.3 Molar THAM solution titrated to pH 7.4 with HCl; and 0.04 g F68 Pluronic surfactant per milliliter FC-80 to ultrasonic energy (11). The emulsion has a density of 1.24 g/ml; an absolute viscosity of 2.4 centipoise; and an approximate fluorocarbon droplet diameter of 3 μ. The approximate CO_2 content of the emulsion at partial pressures ranging from 30 to 60 mmHg is 132 ml STPD/liter + (5.5 x PCO_2). The O_2 content in ml STPD/liter equals 0.213 x PO_2 (mmHg). Since the density and the viscosity of the emulsion are somewhat greater than of saline, the maximum $\dot{V}_A^e$ can be expected to be somewhat less. However, to permit work requiring 1 l STPD/min of oxygen, a diver breathing the emulsion would need a $\dot{V}_A^e$ of only 2.3 l/min. in order to eliminate the 800 ml STPD of CO_2 produced by his tissues each minute and yet maintain a $PaCO_2$ of 40 mmHg. However, at a $\dot{V}O_2$ of 1 l STPD/min and a $\dot{V}_A^e$ of only 2.3 l/min, a PIO_2 of at least 2100 mmHg would still be needed to maintain adequate arterial oxygenation.

(c) *Emulsions of NaOH in Fluorocarbon*

It is possible to make emulsions consisting of a continuous phase of fluorocarbon liquid in which are suspended small droplets of NaOH surrounded by surfactant molecules. Such an emulsion combines the high oxygen solubility of fluorocarbon with the high CO_2 combining capacity of NaOH. The CO_2 can diffuse through the continuous fluorocarbon phase into the NaOH droplets, whereas the NaOH cannot diffuse through the water immiscible fluorocarbon phase and, therefore, is prevented from coming in contact with the alveolar wall (13). The total CO_2 capacity of the emulsions is the sum of the amount of CO_2 physically dissolved in the FC-80 fluorocarbon plus the amount of CO_2 which is bound chemically by the NaOH when Na_2CO_3 is formed. At a PCO_2 of 40 mmHg, a 1% 2 Molar NaOH in FC-80 fluorocarbon emulsion contains approximately 300 ml STPD of CO_2.

The absolute viscosity of the 1% (by volume) 2.0 M NaOH in FC-80 fluorocarbon emulsion is 1.17 centopoise which is nearly equal to the absolute viscosity of FC-80 alone. The density of the emulsion is also

approximately the same as of FC-80 fluorocarbon so that the maximal $\dot{V}_A^e$ of a diver breathing the emulsion would be the same as if he were breathing FC-80 fluorocarbon. At a $\dot{V}_A^e$ of 3 l/min, a diver breathing a 1% (by volume) 2.0 M NaOH in FC-80 fluorocarbon emulsion would be able to eliminate approximately 900 ml STPD of CO_2 per minute at a $PaCO_2$ of 40 mmHg. To ascertain adequate arterial oxygenation at a $\dot{V}O_2$ of 1125 ml STPD/min (assuming that R = 0.8), a PIO_2 of only 700 mmHg would suffice. Moreover, a NaOH in fluorocarbon emulsion would offer important advantages over a fluorocarbon in THAM emulsion: (1) return to spontaneous air breathing would be easier since the surface tension of residual liquid in the lung would be much lower; (2) no untoward water and electrolyte shifts between liquid in the lungs and blood in the alveolar capillaries could occur.

The lungs from rats that had breathed a 1% (by volume) 2.0 M NaOH in FC-80 fluorocarbon emulsion for 15 minutes, subsequently returned to air breathing and then were sacrificed after 3 hours, appeared normal. Eight days after breathing these emulsions, the only pathological findings consisted of some macrophages in the alveoli near the alveolar ducts. Thirty days after breathing the emulsion, the lungs contained a greater number of macrophages in the alveoli and there was some perivascular edema. There were also lymphocytes in some alveoli, but other than that, no pathology was seen.

4. Maintenance of Respiratory Homeostasis in Normothermic Liquid Breathing Dogs

The experimental conditions necessary to differentiate between pressure and the pharmacologic effects of compressed gases have been realized so that it will be possible in the future to study the immediate and long term effects of pressure per se in liquid breathing dogs.

Ten anesthetized, paralyzed, purebred beagle dogs were ventilated for 45 and 60 min with oxygenated (PIO_2 = 685 mmHg) FC-80 fluorocarbon liquid at 38°C. In five dogs, the $PaCO_2$ remained constant at approximately 43 mmHg during 60 min of liquid ventilation (mean tidal volume = 290 ml, mean respiratory frequency = 2.8 breaths/min). Histological examination by light as well as scanning electron microscopy of the lungs of dogs sacrificed 10, 30 or 180 days after liquid ventilation revealed no pathological changes except for a slight increase in the number of macrophages, especially around the alveolar ducts (12).

II. PHYSIOLOGICAL RESPONSES TO ALTERATIONS IN AMBIENT PRESSURE AND THE COMPOSITION OF BREATHING MIXTURES

1. Pulmonary Gas Exchange

Theoretically, $P(A-a)O_2$, i.e. the difference between the mean alveolar and arterial PO_2, due to imbalance of ventilation and perfusion, should vanish if the inert gas in a breathing mixture is replaced by oxygen. This can be done without changing the PIO_2 by lowering the ambient pressure in an altitude chamber. This theoretical prediction has been verified experimentally (14). Increasing the inert gas fraction in a breathing mixture

(as is done in diving practice to avoid oxygen toxicity) should, theoretically, cause an increase in $P(A-a)O_2$ caused by ventilation-perfusion imbalance. This was also verified experimentally (15). Since the distribution component of $P(A-a)O_2$ can be eliminated by oxygen breathing at simulated altitude, and since the shunt component of $P(A-a)O_2$ can be minimized by lowering the PIO_2 to around 60 mmHg, the remaining $P(A-a)O_2$ must be due to incomplete diffusive equilibrium between alveolar gas and end-capillary blood. It was found that, in normal men, there was no measurable diffusion component of $P(A-a)O_2$ at rest, but that it was present when the men performed exercise (1).

The principle of abolishing $P(A-a)O_2$ by breathing 100% oxygen at a simulated altitude was also tested to explain an unexplained drop in PaO_2 upon immersion up to the neck which occurred in two Navy divers. It was found that, in some men, this drop in PaO_2 upon submersion up to the neck in water is caused by a ventilation-perfusion imbalance but that in others it is caused primarily by an increase in true venous admixture (2).

2. Effect of Pressure on Ventilation and Gas Exchange in Man

In six men breathing various gas mixtures at different ambient pressures, the $PaCO_2$ increased rectilinearly with ambient pressure but the change in $PaCO_2$ was not related to other experimental variables. This would indicate that the regulation of breathing somehow is affected by pressure *per se* (16).

3. Maximum Expiratory Flow

The maximum expiratory flow of various breathing mixtures (gas as well as liquid) can be calculated for Weibel's lung model, using the equal pressure point (EPP) concept and standard fluid dynamics equations. The computed maximum expiratory flow of air and of oxygen-helium mixtures over a range of ambient pressures from 1 to 53 atmospheres was in good agreement with measurement reported in the literature (3). It would, therefore, seem possible to predict a diver's maximum expiratory flow at great depths (when breathing gas or liquid) from measurements made at the surface and at shallow depths while breathing air.

4. Pharmacological Properties of Helium

Reports in the literature that helium breathed at normal atmospheric pressures reduces the incidence of cardiac arrhythmias following coronary artery ligation in dogs could not be confirmed (4).

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