# Liquid breathing

JOHANNES A. KYLSTRA

*F. G. Hall Laboratory for Environmental Biomedical Research, Duke University Medical Center, Durham, North Carolina 27710*

Kylstra, J. A. 1974. Liquid breathing. Undersea Biomed. Res. 1(3):259-269.–Adult anesthetized dogs can breathe oxygenated isotonic salt solutions or fluorocarbon liquids, resume gas breathing, and survive without lasting lung damage. The lungs of man can, one at a time, safely be ventilated with isotonic saline. Immediately following liquid ventilation the lung contains a residual volume of liquid, the pulmonary gas exchange is impaired, and the lung is less compliant but it functions normally again within a few days. Measurements of the flow rate of saline from human lungs indicate that the minute volume of ventilation in a saline-breathing man could be greater than 4 liters but probably will not exceed 6 liters. The diffusive mixing of dissolved oxygen and carbon dioxide in saline-filled lungs of man appears to be complete within 30 seconds. Calculations based on an assumed effective alveolar ventilation of 3 liters/min and the $O_2$ and $CO_2$ content at $PA_{O_2}$ = 1755 mm Hg and $PA_{CO_2}$ = 40 mm Hg, respectively, of a 30% (by volume) emulsion of FC-80 fluorocarbon liquid in a 0.3 molar THAM solution adjusted to pH 7.4 at 37°C predict a $\dot{V}_{O_2}$ of 1.1 liter/min.

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| liquid breathing | lung lavage | maximum minute ventilation |
| gas exchange | diffusion dead space | pressure |
| fluorocarbon emulsions | effective alveolar ventilation | decompression |

Some of the hazards which man faces when he ventures into the ocean's depths could be avoided if he were to breathe a liquid instead of gas. This idea may have occurred first to Stein and Sonnenschein (1950), who wrote:

"Water with oxygen dissolved under pressure and properly adjusted for osmotic, ionic, and density characteristics, et cetera, conceivably may sustain life when it surrounds the man and fills his lungs. The other components and adjustments necessary are still unknown, except that carbon dioxide will have to be removed chemically. There is no reason why, with water as a diluent for oxygen, man may not be able to work safely at any depth to which a fish may go . . . ."

As it turns out, the situation is more complicated. I shall first review the currently available experimental evidence and then discuss a possible solution to the problem of $CO_2$ retention which, thus far, seemed to preclude a practical application of the liquid-breathing concept.

## EXPERIMENTS WITH WHOLE ANIMALS

### GAS EXCHANGE AND VENTILATION

Mice and rats have stayed alive up to 18 hours while submerged in salt solutions equilibrated with oxygen at high pressure (Kylstra 1962a, 1962b; Kylstra, Tissing, and van

der Mäen 1962; Goodlin 1962; Pegg, Horner, and Wahrenbrock 1963). The animals appeared to inhale and exhale the salt solution, responded to external stimuli when not previously anesthetized, and were obviously capable of extracting adequate amounts of dissolved oxygen from their aqueous environment. Mice submerged in a hyperbarically oxygenated balanced salt solution to which the carbon dioxide buffer THAM (Tris-hydroxymethyl aminomethane) had been added lived markedly longer than in an identical but unbuffered salt solution (Kylstra et al. 1962). In a tracheostomized rat submerged in plain hyperbarically oxygenated saline, $Pa_{CO_2}$ was 174 mm Hg and pHa was 6.61 after 30 min, but in another rat who, under otherwise identical conditions, breathed saline to which 0.4% THAM had been added, a $Pa_{CO_2}$ of 50 mm Hg and a pHa of 7.00 was measured 30 min after the beginning of the experiment (Pegg et al. 1963).

In anesthetized, intubated, or tracheostomized spontaneously breathing hypothermic dogs submerged in hyperbarically oxygenated unbuffered saline, arterial blood gas analyses revealed adequate oxygenation, but retention of carbon dioxide (Kylstra and Tissing 1964). Intrathoracic pressure fluctuations in these saline-breathing animals reflected the effort required to move liquid instead of air through the trachea and bronchi. The pressure in the right atrium ranged from 40 mm Hg below, during inspiration, to 15 mm Hg above atmospheric pressure during expiration, and expiration lasted twice as long as inspiration.

The pulmonary gas exchange during liquid breathing was measured in anesthetized normothermic dogs who were ventilated mechanically with a hyperbarically oxygenated modified Ringer solution (Kylstra, Paganelli, and Lanphier 1966). The minute volume of liquid ventilation ranged from 1 to 4 liters at respiratory frequencies ranging from 6 to 21 breaths per min. The arterial oxygen tension varied between 18 and 1790 mm Hg, and the oxygen consumption between 31 and 93 ml/min at inspired oxygen tensions ranging from 1380 to 3640 mm Hg. The respiratory exchange ratio ranged from 0.3 to 0.7 at arterial carbon dioxide tensions from 43 to 80 mm Hg, indicating deficient carbon dioxide elimination. The $CO_2$ partial pressure in end-tidal liquid, i.e. following exhalation of 82-93% of the tidal volume, ranged from 28 to 74% of the simultaneously measured $Pa_{CO_2}$, suggesting the presence of stratified inhomogeneity of dissolved alveolar gas. There was a clear, although statistically not significant, trend for the end-tidal $P_{CO_2}$ to approach $Pa_{CO_2}$ as the respiratory frequency decreased and more time was available for the diffuse mixing of dissolved alveolar gas.

Clark and Gollan (1966) first used a fluorinated hydrocarbon (FX-80)[1] as a breathing fluid. At 37°C, solubility of $O_2$ in this liquid is approximately 20 times, of $CO_2$ 3 times as great as in unbuffered isotonic salt solutions; nevertheless $CO_2$ retention occurred in fluorocarbon-breathing cats and dogs. Modell, Newby, and Ruiz (1970) also reported respiratory acidosis (with arterial $CO_2$ partial pressures up to 80 mm Hg) in anesthetized dogs who were ventilated with bubble-oxygenated FX-80 fluorocarbon liquid. However, Sass, Ritman, Caskey, Banchero, and Wood (1972) were able to maintain the arterial $P_{CO_2}$ of anesthetized dogs who were ventilated mechanically with oxygenated FX-80 fluorocarbon liquid between 16 and 40 mm Hg, but the pH of the arterial blood progressively decreased to values near 7.0 at the end of 4 hours of liquid breathing.

Lundgren and Örnhagen (1972) measured the oxygen consumption of mice who breathed oxygenated fluorocarbon liquid without mechanical assistance. The body temperature of the

[1] FX-80 (now designated FC-80) is the trade name of a fluorocarbon liquid manufactured by the 3M Company, St. Paul, Minnesota.

animals was varied between 16 and 37°C, and the oxygen pressure in the liquid ranged from 1.0 to 7.8 atm. It was found that the oxygen uptake was not influenced by the inspired oxygen pressure, up to a body temperature of about 22°C. At higher body temperatures, the inspired oxygen pressure had to be increased to about 3.5 atm to maintain a normal oxygen uptake. Intraperitoneal THAM injections did not appreciably influence survival time. Oxygen uptake increased with body temperature, reaching (by extrapolation) about 2.8 ml $O_2$ per gram body weight per hour at 37°C as compared to 1.6 ml $O_2$ per gram body weight per hour at 37°C in oxygen-breathing, Nembutal-anesthetized mice. The difference was attributed to the greater than normal work required to breathe a liquid instead of gas.

## SURVIVAL AND RECOVERY

One out of six dogs who had breathed a pressure-oxygenated salt solution for 20 minutes without mechanical assistance survived the experiment and was in good health for many years afterwards (Kylstra and Tissing 1964). Six out of 16 dogs who had been ventilated mechanically with a hyperbarically oxygenated salt solution for up to 58 min survived without grossly apparent ill aftereffects. Three of these dogs were sacrificed 22, 90, and 116 days after the experiment. Only minor pathological changes were found in the lungs of two of these animals but, in the third, masses of eosinophilic material surrounded by small round cells embedded in scarred areas and dense eosinophilic membranes in association with chronic inflammatory cells and fibroblasts were seen in alveolar and bronchiolar lumina of the lungs (Kylstra et al. 1966).

Ten out of 10 dogs who had been ventilated with hyperbarically oxygenated saline for 15 min survived (Blenkarn and Hayes 1970). Forty-eight hours after the experiment the arterial oxygen and carbon dioxide partial pressures were normal while the animals breathed room air. Morphologic changes observed up to 24 hours after the liquid ventilation consisted of patchy atelectasis and intrabronchial froth. Mild interstitial edema and distention of the rough endoplasmic reticulum was observed at 2 and 6 days after the experiments.

Modell, Hood, Kuck, and Ruiz (1971) reported that all of a series of 36 dogs who had been ventilated for 1 hour with oxygenated fluorocarbon liquid survived. For several days afterwards, the arterial oxygen tension of these animals was lower than normal when they breathed air. This was attributed to residual fluorocarbon in the lungs and/or partial airway closure. Pathologic examination of the lungs 3 hours after the liquid ventilation had been terminated disclosed an acute exudative inflammatory reaction which was confined largely to the bronchioles. By 72 hours, the acute reaction had subsided and the dominant change consisted of vacuolated intra-alveolar macrophages, presumably containing fluorocarbon. At 10 days, the macrophages were still present, but generally in much smaller numbers. After 18 months, the lungs appeared normal.

Saga, Modell, Calderwood, Lucas, Tham, and Swenson (1973) ventilated the lungs of 11 dogs with a highly purified fluorocarbon liquid, Caroxin-F, for 1 hour. All animals survived the experiment. During the period of liquid breathing there was an increase in $Pa_{CO_2}$ and a decrease in pHa, but these values returned to normal immediately after the animals resumed gas breathing. Twenty-four hours later, the mean $Pa_{O_2}$ was 84 mm Hg and the mean $Pa_{CO_2}$ was 34 mm Hg while the dogs breathed air. An increase in the airway resistance and a decrease in the lung compliance was found 24 hours after the ter· ination of liquid breathing, but these parameters returned to normal within 72 hours. The temporary

impairment in pulmonary function following the breathing of Caroxin-F was attributed to residual fluorocarbon liquid in the lung.

## EXPERIMENTS WITH ISOLATED LUNGS

### GAS EXCHANGE

West, Dollery, Matthews, and Zardini (1965) studied the distribution of ventilation and blood flow in excised lungs of greyhound dogs, filled with saline, suspended in a saline bath, and perfused with blood. The distribution of blood flow was measured by injecting aggregated $I^{131}$-labeled albumin into the pulmonary artery and scanning the lung from bottom to top when the particles had been trapped by the small vessels. After equilibrating the alveolar saline with more inhaled iodinated albumin and scanning again, they could calculate blood flow per unit alveolar volume. With vascular pressures which have been shown to cause great topographical inequality of blood flow in the gas-filled lung, blood flow was evenly distributed, on the average, in the saline-filled preparation, presumably because the hydrostatic pressure differences in the blood vessels were balanced by corresponding pressures in the airways. The topographical distribution of a single breath of iodinated albumin in saline was found to be uniform but there was strikingly stratified inhomogeneity along the airways. This was due to the slow diffusion rate of albumin in saline. Similar effects were seen with inhaled radioactive oxygen and carbon dioxide dissolved in saline.

Stratified inhomogeneity of dissolved radioactive Xenon, persisting for more than 30 sec but less than 3 min, was demonstrated in a subsequent series of experiments. In addition to stratification of alveolar dissolved gas there was evidence of stratification of alveolar capillary blood flow, which would seem to impair the efficiency of gas transfer in saline-ventilated lungs (West, Maloney, and Castle 1972).

### VENTILATION

Leith and Mead (1966) recorded pressure-volume and maximum expiratory flow-volume curves from air-filled and gas-free, saline-filled dog and rat lungs suspended in volume or pressure plethysmographs. In the saline-filled lungs, the static recoil pressures were less than half of the ones in air-filled lungs and maximum expiratory flows were about 100 times smaller than in air-filled lungs. On the basis of these results, a maximum saline ventilation in man of about 3.5 liters per minute (1/m) was predicted. Hamosh and Luchsinger (1968) also measured the maximum expiratory flow of saline from excised dogs' lungs and essentially confirmed the findings of Leith and Mead.

Volume-flow characteristics of saline and FC-80 fluorcarbon-filled excised dogs' lungs were compared by Schoenfisch and Kylstra (1973) using volume-displacement plethysmography. 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 ml/sec for the saline-filled lungs and 104 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 (Kylstra and Schoenfisch 1972).

## TOLERANCE OF LIQUID BREATHING MAMMALS TO PRESSURE AND DECOMPRESSION

### PRESSURE

To separate the effects of pressure from pharmacological effects of compressed gases, Kylstra, Nantz, Crowe, Wagner, and Saltzman (1967) observed the behavior of hydraulically compressed fluorocarbon-breathing mice. The measured partial pressures of oxygen in the fluorocarbon liquid were 700 mm Hg or less; the temperature of the liquid ranged from 17° to 25°C. Forty liquid-breathing mice were subjected to hydrostatic pressures up to 166 atm. The first pressure effect observed in most animals was trembling of the limbs, and voluntary movements became jerky and uncoordinated. When the pressure was increased further, generalized tonic convulsions were observed. These tremors, uncoordinated limb movements, and tonic convulsions, which were absent in control animals, occurred at pressures ranging from 50 to 100 atm. Three mice were compressed with helium to 100 atm. Tremors and uncoordinated movements, but no tonic convulsions, were observed. Five mice were precooled in a water bath until the rectal temperature had dropped to approximately 20°C. When the animals were then compressed with helium, tonic convulsions, similar to the ones observed in hydraulically compressed mice, occurred in three animals at pressures ranging from 69 to 86 atm.

Örnhagen and Lundgren (1972) studied the influence of compression rate and body temperature on the pressure tolerance of fluorocarbon-breathing mice. The pressure of oxygen in the liquid was 4 atm. The limit of hydrostatic pressure tolerance was defined as respiratory standstill. The mean pressure tolerance limit was 150 atm at a rectal temperature of 17°C, 220 atm at 21°C, 220 atm at 27°C, 125 atm at 31°C. The rate of compression had no marked effect on the pressure tolerance although 6 atm/min appeared less favorable than a slower rate. Pressure-induced convulsions began to appear at between 80-100 atm. With the highest compression rate, tonic convulsions were particularly marked and long lasting (>1 min). At a body temperature of 17°C, the convulsions were long lasting (>1 min) compared to the short bursts (<10 sec) of convulsive activity seen at 27°C and 31°C.

The respiratory frequency and heart rate decreased in a roughly linear fashion with increasing pressure. This was particularly evident in animals studied at body temperatures of 21°C and 27°C. For instance, at 21°C and 50 atm, the mean heart rate was 104 beats/min and the mean respiratory frequency, 17 breaths/min. At 150 atm the mean heart rate had fallen to 77 beats/min and the respiratory frequency to 5 breaths/min. Except for a prolongation of the P-Q interval in some animals and a general tendency for the amplitude to be less at increasing pressures, the electrocardiograms were normal. Although no special emphasis was placed on saving the animals, some of them recovered and appeared normal several months after exposure to pressures of up to 250 atm (8250 fsw).

### DECOMPRESSION

Gollan and Clark (1967) submersed mice in fluorocarbon liquid which had been bubble-oxygenated for 10 min at atmospheric pressure. The beaker containing the mouse was then encased in a gas-impermeable Mylar membrane, put into a small steel chamber, and exposed to an air pressure of 33 atm (1124 fsw) for 10 minutes. After decompression of the chamber, which required about 5 sec, the mouse was removed from the liquid, held head down to drain the liquid from its lungs, and placed in an atmosphere of gaseous oxygen.

Fourteen such liquid-breathing animals survived, while the same number of control animals died upon removal from the chamber.

Kylstra et al. (1967) reported that a fluorocarbon-breathing mouse survived uniform compression to 100 atm for 30 sec; it was decompressed in 3 sec, resumed air breathing, and was alive and in apparent good health 1 month after the experiment. Such a rate of decompression is equivalent to surfacing from 3300 fsw (1000 m) underwater at a vertical speed of 700 mph (1200 km/hr) without signs of decompression sickness.

## OBSERVATIONS IN MAN

It is now possible to *ventilate* one lung of man with saline while the other lung is ventilated with oxygen. Such a procedure is occasionally used to treat patients with various diseases of the lung (Ramirez-R 1966; Kylstra, Rausch, Hall, and Spock 1971; Rogers, Braunstein, and Shuman 1972).

### GAS EXCHANGE

During lavages of the lung of a patient with alveolar proteinosis and a healthy volunteer, the $P_{O_2}$ and $P_{CO_2}$ 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 $P_{O_2}$ and $P_{CO_2}$ 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 (Kylstra, Schoenfisch, Herron, and Blenkarn 1973). The computed difference between the mean end-capillary and alveolar $CO_2$ partial pressure was, on the average, less than 1 mm Hg in the 28-year-old patient with alveolar proteinosis but 9 mm Hg in the 40-year-old volunteer.

### 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. (These observations were made during volume-controlled lung lavage in a study by Kylstra et al. [1971].) 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 × 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.

### RECOVERY

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. Serial pulmonary function tests

following lavage of a lung of the volunteer revealed a decrease in the vital capacity, TLC, and $FEV_1$; a $Pa_{O_2}$ of 76 mm Hg; and a $Pa_{CO_2}$ of 37 mm Hg 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 was attributed primarily to a diminished volume or air in the lung caused by the presence of residual saline and to the surface tension at the interface between residual liquid and air (Kylstra et al. 1971).

## SURFACTANT IN THE LAVAGE EFFLUENT

Kylstra et al. (1971) studied the surface tension of the lavage effluent from the lungs of a normal volunteer and four patients with asthma. They found minimal surface tensions well in excess of 12 dynes/cm. Rogers and Sonne (1970) examined the effluent from the lungs of 10 patients. They collected the effluent serially in 1500-ml bottles and centrifuged a 500-ml sample of each bottle. The centrifugate was resuspended in 40 ml of saline and placed in a modified Wilhelmi balance. A minimum surface tension below 13 dynes/cm was found in at least one bottle of the lavage effluent of each patient, and in two of five bottles in seven patients. When all of the effluent liquid was mixed in a large container and a 500-ml centrifuged sample was examined, the minimum surface tension was similar to the one reported by Kylstra et al. (1971). Rogers, Sonne, and Shuman (1971) also noted a shift in the pressure-volume curve of the lung, downward and to the right, immediately following a lavage. However, the pressure-volume curve returned to normal by 24 to 72 hours.

## SUBJECTIVE ACCEPTABILITY

Ramirez-R (1966) initially performed lung lavage in awake patients; only the larynx and trachea were anesthetized topically. Nevertheless, the patients tolerated the procedure. Kylstra (1968) reported that a healthy volunteer whose larynx and trachea had been anesthetized to facilitate intubation, but who otherwise received no medication, did not experience unpleasant sensations arising from the flow of saline into and out of his lungs or from the presence of residual liquid in his lung after the lavage.

## THE PROBLEM OF $CO_2$ ELIMINATION

In all but one (Sass et al. 1972) of the thus far reported series of experiments with saline- or fluorocarbon-breathing animals, the elimination of carbon dioxide through the liquid-filled lungs was found to be inadequate, in spite of the fact that the animals were anesthetized. Clearly, this would seem to preclude a practical application of liquid breathing since a diver, in order to perform useful work, should be able to increase his carbon dioxide production well above resting levels without experiencing a sense of suffocation, or worse, losing consciousness as a result of an increase in the carbon dioxide partial pressure in his blood.

The elimination of carbon dioxide through liquid-filled lungs ($\dot{V}_{CO_2}$) depends upon the solubility of carbon dioxide in the alveolar liquid ($\alpha_{CO_2}$), the partial pressure of carbon dioxide in the arterial blood ($Pa_{CO_2}$), and the effective alveolar ventilation ($\dot{V}_A{}^e$), which may be defined as the virtual minute volume of exhaled liquid in which the partial pressure of carbon dioxide is the same as in the arterial blood, or more conventionally, as the

difference between the minute volume of ventialtion ($\dot{V}_E$) and the dead space ventilation ($\dot{V}_D$). Thus, under steady state conditions, i.e. when the production of carbon dioxide in the tissues equals the elimination of this gas through the lungs, and assuming that the inspired liquid contains no carbon dioxide:

$$Pa_{CO_2} = \frac{\dot{V}_{CO_2}}{\dot{V}_A{}^e \cdot \alpha_{CO_2}}$$

where the units of $\dot{V}_{CO_2}$, $Pa_{CO_2}$, $\alpha_{CO_2}$, and $\dot{V}_A{}^e$ are ml/min (STPD), mm Hg, ml/ml (STPD) and mm Hg, and ml/min respectively. If $CO_2$ elimination in liquid-filled lungs is inadequate, as evidenced by a greater than normal $Pa_{CO_2}$, either $\dot{V}_A{}^e$ or $\alpha_{CO_2}$ or both must be deficient and should be increased.

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 (Mead, Turner, Macklem, and Little 1967). 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. Interestingly, the inspiratory flow in spontaneously saline-breathing dogs was about twice as great as the expiratory flow (Kylstra and Tissing 1964). 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.

The maximum expiratory flow of saline from the left lung of the 40-year-old healthy volunteer would correspond to a maximum minute volume of 3.2 liters saline, at a tidal volume of 1 liter starting at 70% of TLC, if the duration of inspiration and expiration were equal. By increasing the inspiratory flow rate, as the saline-breathing dog did, the volunteer's maximum minute volume of saline ventilation could be 4.3 liters. Likewise, 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 instead of 4.2 liters at a tidal volume of 1 liter with expirations starting from TLC. Since diffusive mixing in saline-filled gas exchange units of the human lung appears to be complete within 30 sec (Kylstra et al. 1973), and since the ventilation and perfusion of saline-filled lungs appears to be matched adequately (West et al. 1965; Kylstra et al. 1973), it would seem reasonable to estimate that the effective alveolar ventilation in a saline-breathing diver could be 3 liters/min.

The addition of THAM to the inspired salt solution effectively increases $\alpha_{CO_2}$ and markedly prolongs survival of liquid-breathing mice (Kylstra et al. 1962) and rats (Pegg et al. 1963). To evaluate quantitatively the increase in $\alpha_{CO_2}$ caused by the addition of THAM to a saline-breathing fluid, 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 mm Hg. 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 mm Hg was approximately 390 ml (STPD)/liter. In contrast, 1 liter of saline under these conditions contains only 29 ml (STPD) of $CO_2$; 1 liter of FC-80 fluorocarbon liquid, 84 ml (STPD) of $CO_2$ (Schoenfisch and Kylstra 1973).

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, he would be able to eliminate $3 \times 390 = 1170$ ml

(STPD) of $CO_2$ per minute at a $Pa_{CO_2}$ of 40 mm Hg, 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/l per mm Hg at 37°C) so that a partial pressure of 16,300 mm Hg 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. If the diver were to breathe FC-80 fluorocarbon (assuming that his effective alveolar ventilation would be the same), his oxygen consumption at a normal $Pa_{CO_2}$ would be 315 ml (STPD)/min, which would be just enough to satisfy his basal metabolic requirements. Obviously, such a fluorocarbon-breathing diver would not be of much use in the water.

In general, the carbon dioxide-carrying capacity of THAM solutions would be adequate but the solubility of oxygen in aqueous solutions is so low that prohibitively high partial pressures of inspired oxygen would be necessary. The solubility of oxygen in FC-80 fluorocarbon liquid (0.638 ml/l per mm Hg at 37°C) is high enough, but the solubility of $CO_2$ in FC-80 fluorocarbon liquid (2.105 ml/l per mm Hg at 37°C) is not, so that, even at complete rest in the water, a fluorocarbon-breathing diver would barely be able to maintain a normal arterial $CO_2$ partial pressure while breathing at his maximum ventilatory capacity.

A combination of the advantages of a fluorocarbon liquid and a carbon dioxide-binding aqueous solution might be the answer. Fluorocarbon liquids do not mix with water. However, it is now possible to make stable emulsions of fluorocarbon liquid droplets in aqueous solutions with the aid of suitable emulsifiers (pluronics[2]). Such emulsions have already been prepared in a number of laboratories to be used as a blood substitute in which the fluorocarbon liquid droplets function as red blood cells, carrying oxygen from the lungs to the tissues (Clark, Becattini, Kaplan, Obrock, Cohen, and Becker 1973).

If we calculate the pulmonary gas exchange of a diver who would be breathing an emulsion of 30% (by volume) of FC-80 fluorocarbon liquid in an isotonic 0.3 molar THAM solution at pH 7.4 (assuming again a maximum effective alveolar ventilation of 3 l/min), then it turns out that, at a $Pa_{CO_2}$ of 40 mm Hg, he would be able to eliminate $3 \times [(0.7 \times 390) + (0.3 \times 40 \times 2.105)] = 895$ ml (STPD) of $CO_2$ per minute. At a normal respiratory gas exchange ratio of 0.8, this diver's oxygen uptake would be 1118 ml (STPD)/min. To supply this amount of oxygen each minute, the partial pressure of oxygen in the inhaled emulsion should be at least $1118/3 \times [(0.7 \times 0.0299) + (0.3 \times 0.638)] = 1755$ mm Hg, i.e. less than 3 atm. Such an inspired oxygen partial pressure is acceptable for exposures lasting approximately 1 hour, particularly since the mean arterial oxygen partial pressure would be appreciably lower. The estimated oxygen uptake of the hypothetical fluorocarbon-THAM emulsion breathing diver is similar to the oxygen requirements of the diving women of Korea and Japan who harvest abalone, pearl oysters, and other valuable materials from the seabed at depths up to 60 fsw (Yokoyama and Iwasaki 1965).

## CONCLUSION

Liquid breathing could be of great value in providing a diver with immunity against the hazards of decompression sickness, gas embolism, inert gas narcosis, and, probably, underwater explosions. As a result, it would not be necessary to expose divers to dangerous conditions for more than an hour or so during critical rescue or salvage operations at great depths, instead of the days or even weeks required with current diving techniques.

[2]Trade name, BASF Wyandotte Corporation, Wyandotte, Michigan.

The further development of liquid breathing would seem to hinge primarily on the preparation and biological testing of an optimal breathing liquid, probably a fluorocarbon emulsion.

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