LIQUID BREATHING

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As some of you may recall, during the Second World Congress of Underwater Activities held in London in 1962, Jacques Cousteau startled his audience with a vision of the diver of the future - homo aquaticus - a human creature with liquid-filled lungs, breathing like a fish, with a surgically implanted gill. Homo aquaticus would be free to roam the oceans from the surface to great depths, protected against decompression sickness by an incompressible liquid in his lungs. As all of you know, one of the main hazards in diving is the presence of compressed air in the lungs, which prevents the chest from being crushed while, at the same time, sustaining life. The pressure causes gases to dissolve in the blood, with potentially serious consequences. At heightened concentrations in the blood and tissues, most gases are toxic: oxygen can cause lung damage and convulsions; nitrogen can produce a state of altered consciousness, and usually incapacitates a diver at a depth of 300ft or thereabouts. These complications can be avoided by using helium, which is not narcotic at high partial pressures, and by minimising the fractional concentration of oxygen in the inspired gas mixture so that the partial pressure of oxygen remains within safe limits.

However, regardless of the gas mixture used, the inert gas dissolves in the blood and tissues and, whenever a diver surfaces too rapidly from depth, releases bubbles that result in decompression sickness. Theoretically, decompression sickness and gas toxicity could both be avoided by filling the diver’s lungs with a liquid instead of compressed gas. This liquid would resist the external pressure without a change in the volume of the chest and, at the same time, no gas would dissolve in the blood flowing-through the lungs since there would be no gas in the lungs in the first place.

To supply the diver with enough oxygen and an avenue for the disposal of the carbon dioxide that is continually being produced in his body would necessitate the use of a device similar to the ones now being used by surgeons to keep patients alive while repairing their hearts; an artificial lung, but this time fashioned after the gills of fish, et voila - homo aquaticus.

The essential feature of homo aquaticus is the incompressible liquid in his lungs. The artificial gill - a technical and surgical “tour de force” - is necessary to protect him from drowning, or is it? Could not the diver’s liquid-filled lungs be made to function like gills? As it turns out, the answer is “Yes”, and the advantages over the surgically implanted artificial gill are obvious.

Animal life on our planet began in the sea in an environment in which oxygen is relatively scarce. Early forms of animal life, making the best of the conditions imposed by the environment, evolved breathing organs such as gills that are capable of extracting adequate amounts of oxygen from water. Eventually the evolution of lungs made it possible for animals to emerge from the sea and to benefit from the physical characteristics and advantages of an oxygen-rich gaseous environment. Throughout the span of evolution, however, the function of the respiratory organs has remained basically the same: in both gills and lungs oxygen diffuses from the environment, across thin membranes, into the blood, and carbon dioxide coming out of the blood diffuses in the opposite direction to be discharged into the environment. Nevertheless, to reverse evolution and to resume water breathing presents formidable problems for a mammal. I have already mentioned one: the fact that under normal conditions, at ordinary atmospheric pressure, water contains too little dissolved oxygen. Another problem lies in the fact that natural water, be it fresh or seawater, usually has a composition which is very different from that of blood. Hence, when such water is inhaled it causes lung tissue damage and, provided enough of it is inhaled, fatal alterations in the volume or composition of the body fluid.

Now it is a simple matter to prepare a liquid that overcomes both of these difficulties. Suppose we take an isotonic salt solution that is like blood plasma in composition, and charge this solution with oxygen under greater-than-normal pressure: the solutions' similarity to the blood will prevent any alterations in the volume or composition of body fluid by diffusion or osmosis. Under pressure, the solution can be charged with about the same concentration of oxygen as is normally present in air at sea level. Could a mammal breathe such a solution?

Using a small pressure chamber partly filled with an isotonic salt solution, I performed the first experiment, with a mouse, at the University of Leiden in 1961. The mouse was introduced at the bottom of the pressure chamber through a lock like the escape hatch of a submarine; the chamber had transparent walls so that the mouse could be observed. In the first few moments after entering the chamber , the animal tried to swim to the surface of the water, but was prevented from doing so by a grid below the water level. After a short period the mouse quieted down and did not seem to be in any particular distress; it made slow rhythmic movements of respiration - apparently inhaling and exhaling the liquid. It moved about in the chamber occasionally and would respond to a rap on the wall. Some of the mice so tested survived for many hours, the length of survival depending on the particular conditions of the experiment such as temperature and the chemical composition of the liquid. In each case, however, the mouse eventually ceased his respiratory activity.

From the results of variations of the applied environmental conditions, it appeared that the decisive factor, limiting the survival of the mice was not the lack of oxygen - which could be supplied in ample amounts simply by increasing the oxygen partial pressure in the liquid - but the difficulty of eliminating carbon dioxide at the required rate. The mousse that survived for the longest time - 18 hours was assisted by the addition to the solution of a small amount of tris(hydroxymethyl)-aminomethane, which is a substance that minimizes the untoward effects of carbon dioxide retention in animals and man. Lowering the temperature of the solution to 20°C, about half the mouse's normal body temperature, also lengthened the survival time by cooling the animal and thus reducing his metabolic rate, and consequently his rate of carbon dioxide production.

Now with mice in a small pressure chamber it is difficult to determine how much oxygen is actually taken up by the lungs, how well the arterial blood is oxygenated, and how much carbon dioxide the animal retains. Consequently, my associates and I resorted to more elaborate procedures using dogs in a large pressure chamber provided with additional equipment.

The entire chamber was pressurised with air and an anaesthetized dog was lowered into a tub of oxygenated saline. The animal was kept cool at about 32°C in order to reduce his oxygen requirement. While submerged, the dog continued to breathe, and jets of water rising from the surface showed clearly that he was pumping the solution in and out of his lungs. At the end of the observations, the dog was lifted out of the tub and his lungs were drained of water and re-inflated with air. One of these dogs was later adopted as a mascot by the crew of the Royal Netherlands Navy vessel HMS Cerberus.

We had now shown in measurable terms that under certain conditions a mammal could indeed maintain respiration by breathing water for a limited period of time. The blood pressure of the dog was slightly below normal while he was breathing the oxygenated liquid, but it remained stable; his heart rate and respiration were low but regular and his water breathing kept the arterial blood fully saturated with oxygen. However, the carbon dioxide content of the blood steadily increased, indicating that the dog’s vigorous respiratory efforts were not enough to remove sufficient amounts of carbon dioxide from the body.

I continued my studies at the State University of New York at Buffalo, using apparatus that makes it possible to measure the actual exchange of gases taking place in the lungs of water-breathing dogs. As before, an anaesthetized dog breathed the salt solution oxygenated under pressure. This time, however, the animal did not have to move the water into and out of the lungs on his own, and it was possible to measure accurately the gas content of the inhaled and exhaled water. Oxygenated liquid was delivered to the dog via a tube from a reservoir, and was drained back into a reservoir underneath the dog. A motor driven valve system regulated the respiration. The amount of oxygen taken up from the liquid in the lungs, and the amount of carbon dioxide discharged into it, was measured by comparing the relative amounts of these gases in the inspired and expired liquid. Samples were taken, so we knew the oxygen content of the liquid going into and out of the lungs; the dog was not cooled , and it extracted about the same amount of oxygen from water as it normally would have from air. However, in spite of the mechanical assistance to its water breathing, the animal did not eliminate sufficient amounts of carbon dioxide in the exhaled water, so that the partial pressure of carbon dioxide in the arterial blood gradually increased. At the end of the period of water breathing, which lasted up to three-quarters of an hour, the water in the dog’s lungs was drained by gravity through a tube in the trachea and the animal’s lungs were inflated with a few breaths of air blown into the tube. Several of these water-breathing dogs later became healthy and pleasant family pets.

It was now abundantly clear that inadequate elimination of carbon dioxide was the main problem in water breathing. There are two reasons for this. First of all, we now know that when a breath of fresh air or water is drawn into the air sacs of the lung, the oxygen molecules are at first concentrated in the centre of the sacs and have to traverse a substantial distance by diffusion before they reach the walls to enter the bloodstream; this distance is many times greater than the thickness of the membranes that normally separate air from blood in the lungs. If the breathing medium is air, the situation is of little consequence: oxygen diffuses in air so rapidly that freshly inhaled oxygen is distributed homogeneously in a matter of milliseconds. However, when the medium is water, in which the respiratory gases diffuse about 6,000 times slower than in air, a gradient of oxygen tensions persists over the distance between the centre of the air sacs and the walls at the periphery. Throughout the cycle of each respiration the oxygen tension is greater at the centre than at the walls; the same being true of carbon dioxide discharged from the blood: it is more concentrated near the transfer membranes than at the centre of the sacs. Thus, at a normal resting respiratory frequency, the average carbon dioxide partial pressure in exhaled water is considerably lower than in exhaled air, at the same partial pressure of carbon dioxide in the arterial blood. Furthermore, the situation may be expected to get worse as the respiratory frequency increases and less time is available for carbon dioxide to diffuse during each breath.

Secondly, at normal body temperature, the solubility of carbon dioxide in water is less than in air, which is to say that water contains fewer carbon dioxide molecules than an equal volume of air at the same partial pressure. Hence, an increase in the partial pressure of carbon dioxide in the arterial blood, and consequently, in the air sacs in the lungs, would eventually restore the balance of the production of carbon dioxide in the body and elimination through the liquid-filled lungs. Unfortunately, the body tolerates only minor variations of carbon dioxide partial pressures in the arterial blood. Obviously then if we put all these factors together, we find that in order to maintain his arterial carbon dioxide partial pressure within tolerable levels - to prevent a sense of suffocation or even loss of consciousness - a water-breathing diver would have to move a substantially greater volume of water per minute in and out of his lungs than the air-breathing diver moves air. At first sight this would not seem to be an insurmountable problem, since a suitable motor-driven pump could relieve the diver of the extra work of breathing, but unfortunately the maximum rate at which air or water can flow out of the lungs is effort independent: the flow initially increases with the increase in expiratory effort, but only up to a point, after which the flow no longer increases no matter how much pressure is applied to the lungs. The reason for this is the pliability of the walls of the airways so that they collapse once the critical expiratory flow has been reached.

David Leith and Jerry Mead at the Harvard School of Public Health, Boston, have measured the maximum expiratory flow of water from the lungs of dogs, and on the basis of their findings predicted that the maximum minute ventilation of a saline breathing diver would be approximately 3.5 litres. If one realises that a resting man must breathe normally almost twice this amount of air per minute and much more when he is performing work, then it becomes clear that the water-breathing diver could not possibly eliminate carbon dioxide at the necessary rate, even if he remained absolutely at rest in the water.

Now does this mean that we must find other ways to eliminate carbon dioxide from the body such as, for instance, an artificial gill? Not necessarily. Theoretically, the problem could be solved by using a liquid in which carbon dioxide is more soluble than in water, or by adding a substance which chemically binds carbon dioxide; the effect of either of these measures would be the same, namely to increase the number of carbon dioxide molecules present in the exhaled liquid at a given partial pressure.

We are mainly interested in the solubility of carbon dioxide at a partial pressure of 40 millimetres of mercury; that is a partial CO pressure normally found in arterial blood. Under these conditions, one litre of saline contains approximately 30 millilitres of carbon dioxide, while FC80 - a synthetic fluorocarbon liquid - contains 84 millilitres (almost three times as much), whereas one litre of air at the same partial pressure contains approximately 60 millilitres. A solution of tris(hydroxymethyl)-aminomethane in a 0.3 molar concentration and adjusted to a pH of 7.4 contains 320 millilitres of carbon dioxide per litre.

Since, in normal resting conditions a man produces about 250 millilitres of carbon dioxide per minute, it would follow that carbon dioxide elimination might not be a problem if a diver were breathing a tris buffer solution, even if his maximum minute ventilation were no more than 3.5 litres, as predicted by Leith and Mead. In fact it can be shown that such a diver would be able to perform work requiring up to 1,300 millilitres of oxygen per minute - that is, approximately four times as much as under resting conditions - and still have a normal partial pressure of carbon dioxide in his arterial blood.

Unfortunately, the solubility of oxygen in a tris buffer solution is no different from that in normal saline, thus an inspired oxygen partial pressure of approximately 18 atmospheres would be required to provide the diver with the 1,300 millilitres of oxygen per minute. If our diver were to breathe fluorocarbon liquid instead, his maximum oxygen consumption at a normal arterial carbon dioxide partial pressure would only be about 300 millilitres per minute - barely enough to support him while completely at rest. On the other hand, only one half of an atmosphere of inspired oxygen pressure would be needed to provide him with the necessary amount of oxygen.

In general then, the high carbon dioxide-carrying capacity of a tris buffer solution would allow productive physical activity of a liquid-breathing diver but, with the oxygen solubility being so low, prohibitively high partial pressures of inspired oxygen would be necessary. The solubility of oxygen in a fluorocarbon liquid is high enough to provide the diver with sufficient oxygen at safe inspired partial pressures, but the solubility of CO in fluorocarbon liquids is still not good enough: even at complete rest in the water and while breathing at his maximum capacity, the diver would barely be able to maintain a normal carbon dioxide partial pressure in his arterial blood.

Would it be possible to combine the advantages of a fluorocarbon liquid and of a tris buffer solution by mixing the two in suitable proportions? Fluorocarbon liquids do not mix with water and are in general very poor solvents for all but a few organic substances. However, it is possible to make stable emulsions of fluorocarbon liquid droplets in physiological salt solution containing tris buffers. Such emulsions have been prepared as a blood substitute, the fluorocarbon liquid droplets functioning as liquid blood cells to carry oxygen from the lungs to the tissues.

We can now estimate the maximum oxygen uptake through human lungs filled with different liquids at various arterial carbon dioxide partial pressures. The calculations are based on the known oxygen and carbon dioxide solubilities of various liquids, on an estimated maximum effective alveolar ventilation of three litres per minute, a minimum arterial oxygen pressure of 100 millimetres of mercury and a gas exchange ratio of 0.8. On the basis of such calculations one can predict that the maximum oxygen uptake of a saline-breathing diver could be no more than one third of his resting oxygen requirement at a normal arterial carbon dioxide pressure, that is to say, he could not survive under these conditions. In order to be able to extract the minimum required 300 millilitres of oxygen per minute from the oxygenated saline in his lungs, the partial pressure of carbon dioxide in his arterial blood would rise to 110mm of mercury and cause him to lose consciousness. As you may recall, these predictions are in accordance with the experimental findings in saline-breathing animals which I discussed earlier.

If a diver were to breathe FX80 Fluorocarbon liquid instead of saline, the situation would be somewhat better: the estimated maximum oxygen uptake would be slightly greater than his minimum oxygen requirement at a normal arterial carbon dioxide partial pressure. However, the slightest amount of physical activity, raising his demand for oxygen by no more than about 60 per cent, would cause an increase in his arterial carbon dioxide partial pressure to 60mm of mercury, and give rise to a sensation of impending suffocation. For this reason a fluorocarbon-breathing diver would not be of much use in the water.

If we estimate the maximum uptake of oxygen through the lungs of a diver breathing an emulsion of fluorocarbon liquid in an isotonic tris buffer solution, the prospects brighten considerably: the diver would be able to perform work that requires an oxygen uptake of 1,100 millilitres per minute, at a normal arterial CO_2 pressure of 40mm of mercury, and he could increase his oxygen consumption to almost 1,500 millilitres per minute before he would be so short of breath that he would have to stop. The diving women of Korea, who harvest abalone and oysters and other materials from the seabed at depths of up to 60ft, require about 1,200 millilitres of oxygen per minute while they are working underwater. So this would seem to be a reasonable figure for a reasonably active diver.

I have prepared a Graph showing the relationship between oxygen uptake, effective alveolar ventilation, and oxygen and carbon dioxide partial pressures in the arterial blood of a hypothetical fluorocarbon emulsion-breathing diver. As you can see, the effective alveolar ventilation increases linearly with an increase in the oxygen consumption, while the arterial carbon dioxide and oxygen partial pressures at the end of an expiration remain 40 and approximately 1,300mm of mercury, respectively. Once the maximum alveolar ventilation of three litres per minute has been reached - which occurs at an oxygen consumption of approximately 1,100 millilitres per minute - a further increase in activity and consequently in the oxygen consumption, causes a rise in the arterial carbon dioxide partial pressure and a drop in the arterial oxygen partial pressure. An inspired oxygen partial pressure of approximately 4 atmospheres was chosen to prevent blackout as a result of arterial hypoxaemia before the diver’s arterial carbon dioxide tension rises to a value that would force him to rest. In spite of the high inspired oxygen partial pressure, the partial pressure of oxygen in the arterial blood remains within acceptable limits, at least for a dive that would not last much longer than an hour or so. With liquid-filled lungs that would be long enough to descend several thousand feet into the water, work at depth for perhaps half an hour and return safely to the surface - all within an hour.

Granted that it has been shown that animals can breathe oxygenated salt solution or fluorocarbon liquid; granted that my estimate of the respiratory capabilities of a hypothetical fluorocarbon emulsion-breathing diver is approximately correct, what evidence is there that a real diver could tolerate the sensations arising from the presence of a liquid instead of air in his lungs?

During the past six or seven years my colleagues and I at Duke University Medical Center have been treating patients suffering from a variety of lung diseases by rinsing their lungs with a physiological salt solution in order to remove harmful secretions.

The patients are anaesthetised and a double tube catheter is inserted into the trachea: one lung breathes anaesthetic gas and oxygen while the other has its air replaced by physiological salt solution at normal body temperature. Once all the gas in the lung has been replaced by liquid, the rinsing procedure, which more or less resembles the normal breathing process, begins. A tidal breath of 500 millilitres of saline is made to flow into the liquid-filled lung and immediately after this the same volume of liquid is siphoned off. We continue this treatment for up to two hours and may use as much as 10 gallons of salt solution on one lung; so far we have done this on about 200 occasions, and the patients have suffered no harmful effects.

The same procedure was performed on a healthy volunteer whose windpipe was anaesthetised to introduce the catheter; he otherwise received no medication and was wide awake throughout the entire experiment. He told me afterwards that the liquid-filled lung had not felt noticeably different from the gas filled one, and that he had experienced no unpleasant sensations arising from the flow of saline in and out of his lung. Of course, such a test is very different from trying to breathe liquid with both lungs, but it did at least show that filling the human body with liquid will not necessarily damage the tissues or produce unacceptable sensations, provided a suitable liquid is used and provided the proper technique is employed.

With the advent of this volume-controlled lung lavage technique it has also become possible to measure accurately the rate at which a saline solution can flow out of the human lung. We have been able to drain 500cc of saline from one lung in 7 seconds, so it should be possible to exhale twice that amount, that is one litre of saline, from both lungs in the same time and, since inhalation and exhalation normally require about the same amount of time, it should be possible to move more than 4 litres of saline per minute into and out of both lungs. This is slightly better than Leith and Mead’s estimate of 3.5 litres per minute.

The total amount of liquid inhaled and exhaled per minute will always be greater than the effective alveolar ventilation since part of it is wasted in ventilating the dead space. Consequently, the maximum effective alveolar ventilation may be expected to be somewhat less than 4 litres per minute, depending upon the size of the anatomical dead space, the respiratory frequency, the distribution of the flow of inhaled liquid and blood in the lung, and the presence of absence of partial gas pressure gradients within the liquid-filled gas exchange units of the lung.

During volume-controlled lung lavage in patients and again in a healthy volunteer, my colleagues and I found that diffusive mixing in the liquid-filled gas exchange units of the human lung is complete, provided that the respiratory frequency is no more than two or three breaths per minute. In addition, we found no evidence of a gross imbalance between the flows of inspired liquid and blood in the saline filled human lungs which, by the way, is in complete agreement with observations in dogs' lungs made several years ago by John West and his Clinical Research Physiology Group at Hammersmith Hospital in London.

It seems therefore safe to conclude that at a respiratory frequency of two or three breaths per minute the physiological dead space in a liquid-breathing man would not be much greater than the anatomical dead space of some 200 millilitres. Thus, with 4 litres ventilation per minute the effective alveolar ventilation of a liquid breathing diver could be as high as 3.5 litres per minute. As you will recall, my predictions were based on the assumption of an effective alveolar ventilation of 3 litres per minute, so they are in fact a little bit on the safe side.

This is in essence what is known now - 12 years after it was first shown that mice could be kept alive breathing on their own in oxygenated salt solution, instead of air. Many questions remain unanswered and much work remains to be done. Nevertheless, looking to the future, it seems likely that some day - soon, perhaps - some courageous man will take a deep breath of specially prepared liquid and that, by the turn of the century, divers with liquid-filled lungs will carry out critical rescue and salvage operations at great depths in the oceans, where gas-breathing divers would have failed.

Surgeon Commodore Rawlins: I think our last speaker gave an extremely interesting and erudite presentation, but I have always personally felt that homo aquaticus could be equated with man-powered flight: extremely interesting but not too practical, I could be wrong about that.

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Brief Profile

Johannes A Kylstra, widely known for his liquid breathing experiments, is Associate Professor of Medicine and Assistant Professor of Physiology at America's Duke University. Born in the Netherlands - he received a medical degree from the University of Leiden in 1952. From 1952 to 1954 he was an intern at Albany, NY, and from 1955 to 1958 he was a Lieutenant in the Royal Netherlands Navy Medical Corps.

In 1958 he obtained his PhD in physiology from the University of Leiden, and after three more years in the US, he served from 1961 to 1963 as Assistant Professor of Physiology at that University.

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