

ORIGINAL PAPERS

Foreword by Ken Locklear: The following paper is reproduced exactly as written. It was originally published in the *Journal of Cardiovascular Surgery* in 1959. This is one of the most often cited papers in all of hyperbarics, yet it is extremely difficult to find because of its age. We have reproduced it here as a reference, as well as foundational support for future indications that have anemia as a primary or secondary symptom. The ultimate findings of this paper are so profound that many don't realize how it underpins so many major diseases that we see today. I want to point out how crucial these findings are to sustaining or improving life in indications where oxygen transport has been compromised for any reason – frostbite, arterial occlusion of any kind, stroke, heart attack, chemotherapy, radiation therapy, etc.) Hyperbarics is not a cure in any of these indications, but as stated in this paper, it can sustain life until other interventions can be arranged.

Life Without Blood

(A study of the influence of high atmospheric pressure and hypothermia on dilution of the blood)

by

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When in 1948 we (first al research) started our experiment on hypothermia^{11 13} our ultimate aim was to reduce the metabolism of a warm-blooded animal to such an extent that all the physiological processes would almost come to a standstill.

If successful, this would enable the heart to be clamped off for a period long enough to allow for a major intracardiac operation to take place. When, however, we presented our results to the Netherlands Society of Surgeons in 1950 this aim had not been achieved by any means. In a hypothermic animal at about 27°C., the circulation could be stopped with good chances of survival for about twice as long as in a normothermic animal. The gain in time, about 100 percent, was relatively great, but absolutely it was very modest, amounting to about five minutes; the reason for this was that below 26°C the physiology was altered too much and the normal harmony of life processes disturbed too much to allow for continuation of life or normal recovery by warming up.

Efforts to achieve safe conditions at a lower level of hypothermia so as to gain a greater period of time for clamping off the heart failed until recently, at any rate for animals with the same weight as human patients. So in 1956 we presented a series of experiments which showed that it was possible to clamp off the circulation for a greater length of time without lowering the temperature further than 27°C.^{17 18} We operated on the animal in a pressure chamber at an absolute pressure of three atmospheres. The animal breathed pure oxygen, the investigators naturally breathed air.

Through the combination of inhaling pure oxygen and being under three atmospheres of pressure, the whole body was supersaturated with oxygen in physical solution.

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reduction of oxyhaemoglobin or even haemoglobin itself would no longer be necessary. Other investigators have also come to this conclusion.²⁴¹⁹

However, different organs need different quantities of O_2 . The brain is particularly vulnerable in this respect. According to Lambertsen the arteriovenous difference in oxygen content in the brain is 6.1 vols. percent or slightly below the quantity of O_2 in physical solution at 3.5 atmospheres, but slightly above our calculated figure at three atmospheres which comes to a content of about 4.5 vols. percent in plasma. So it appears doubtful whether breathing O_2 at three atmospheres will provide enough transport of O_2 to the tissues by means of physical solution only. Furthermore it is not clear that the normal physiological behavior of the body will not upset our expectations. It is well known that breathing O_2 at increased pressure for a certain length of time will be followed by dangerous symptoms which are usually considered to be signs of oxygen intoxication. Enzymatic processes in all cells of the body are affected. The brain and the lungs especially are in danger, psychical changes and lung oedema developing in animals as well as in man during the experiments. However, if the O_2 pressure is not raised too much and the time of exposure not extended for too long the dangers may be avoided. In our opinion the great disagreements in the literature may be ascribed to the great differences in the pressures which are used. The effects of pressures of up to 5, or 8 and even more atmospheres are examined experimentally. The conclusions from these experiments are most confusing probably because the results at one level of pressure are often applied and accepted to be true also for lower levels of pressure. So we used only pressures which are expected to be useful in surgery without being harmful to the subject or the operating team in the pressure chamber. Furthermore it is no use leaving the animal in a state of abundance of O_2 for a longer period of time than is necessary for a normal operation.

As Behnke came to the conclusion that breathing O_2 at three atmospheres can be continued without harm for three hours, we decided to use a pressure of three atmospheres in our pressure chamber to be used for operations, and never to keep the animal, and in due course the patient, at this pressure for more than three hours. So it seems that the increase of the O_2 tension in the blood is better tolerated than a decrease (see von Euler et al.).

Nevertheless there is an important alteration in the physiology in particular while we were decreasing the quantity of haemoglobin in animals at various atmospheric pressures. When the critical level had been reached the haemoglobin content was again raised to a normal level. Besides this, the experiment was only considered successful when the animal woke up and showed postoperatively the same normal behaviour as previous to the experiment. As it is well known that signs of damage may occur long after treatment in a high pressure tank the animal ought to survive the experiments for several weeks if one is to speak of success.

We diluted the blood by extracting it via a tube in the femoral artery and infusing a clear fluid not containing haemoglobin into the femoral vein. The rate at which plasma was run in was regulated by measuring the rate of spontaneous outflow from the femoral artery so as to make the inflow rate at any moment almost exactly the same as the outflow rate.

In our first experiments we used plasma. Very large quantities of plasma are needed. As the blood of pigs is available in slaughterhouses in any quantity required we used piglets as experimental animals twenty-seven times. Heparin was added to this blood and plasma obtained by centrifugation.

We later abandoned the plasma and used macrodex. To saltless macrodex containing 6 percent dextran and 5 percent glucose, salts were added to form a solution similar to that of Ringer's solution.

In blood plasma the oxygen is kept in simple physical solution, in equilibrium with the O_2 tension in the alveolar air. So by altering the O_2 tension in the lung alveoli the solubility in the plasma is directly influenced. Even a small lowering of this tension is known to be followed by alterations in respiration and circulation.^{5 17}

The partial O_2 tension in the alveoli can be increased to about five times its normal value by breathing pure O_2 instead of air. When in addition the pressure of the inhaled O_2 is raised to three atmospheres the solubility of the O_2 in the plasma increases three times again. Thus the physical solution of O_2 in plasma, which when breathing air under normal atmospheric conditions comes to 0.3 volumes per cent, may increase to $0.3 \times 5 \times 3 = 4.5$ volumes per cent when breathing O_2 under a pressure of three atmospheres.

According to Campbell^{14 15} the solubility of O_2 in fluids increases by 2.3 volumes per cent for every increase of one atmosphere. So according to this calculation the O_2 in physical solution may rise to 6.9 volumes percent at a pressure of three atmospheres of pure oxygen. Naturally these calculations do not apply completely in practice. For instance the gas in the alveoli is never pure O_2 as it is mixed with expiratory gases from the blood, and moreover it is not certain whether this abnormal condition does not affect the simple diffusion via the alveolar membranes between the gas in the alveoli and the blood in the capillaries. Lambertsen, who measured the quantity of O_2 in physical solution in the blood after breathing O_2 at a pressure of 3.5 atmospheres, found this to be 6.5 volumes percent.^{23 26} That this percentage was even higher than that which we had first calculated was of course unpredictable. It was an unexpected advantage in our aims which are described below.

This increase of O_2 in physical solution is not confined to the blood plasma but it may be expected that the whole body, including the interstitial fluid and even the cells, may have the same increase of dissolved O_2 . So the body is capable of storing more O_2 when O_2 is breathed at a pressure of three atmospheres. As this rise in the level of physically dissolved O_2 is not followed, at rest, by an increase in O_2 consumption,^{14 15 20 21} this large reserve of O_2 in the body enabled us to stop the circulation for many more minutes than at normal pressure. This will be especially so when the need of oxygen of the body is decreased by hypothermia. This may be of great importance in surgery on the open heart. This supposition was confirmed by our experiments published in 1956.

In 1879 Fontaine had the same idea of increasing the solubility of gases in the blood by raising the atmospheric pressure of the inhaled gases. He raised the pressure by only 1/5 or 1/4 of an atmosphere in order to increase the quantity of N_2O dissolved in the blood by which means he intended to improve N_2O anaesthesia. He intended to build a high pressure operating theatre but did not succeed in doing so. As far as we know the idea of raising the percentage O_2 in solution was never suggested as an aid in operative surgery. An operating theatre for operations in a high pressure chamber has now been built in Amsterdam.

Besides the problem of increasing the amount of stored O_2 in solution in a high pressure chamber, another problem concerning the transport of O_2 has arisen. Normally the O_2 is transported practically exclusively by means of oxyhaemoglobin.

In the tissue capillaries O_2 spreads from the plasma into the tissues and to the cells, the loss of O_2 dissolved in the plasma being made up immediately by the O_2 given off by oxyhaemoglobin. The oxyhaemoglobin, however, is not completely reduced, the extent of reduction being dependent on the activity and consequently the need of oxygen of the tissues.

At rest in the body as a whole the oxyhaemoglobin of 19 vols. percent in the arteries is reduced to 14 vols. percent in the capillaries. The need of the tissue at rest is thus seen to be 5 vols. percent. Probably the physically dissolved O_2 is almost entirely available for the tissues. So, if a level of 5 vols. percent of O_2 in physical solution in the plasma could be reached, the necessary transport of O_2 from the lungs to the tissues could be provided by the plasma alone;

It proved to be very important at any given moment to replace exactly the amount of blood taken from the artery. The temperature of the infused fluid should be the same as that of the animal.

The animals were anaesthetized with Nembutal and pethidine and breathed pure oxygen. Curare was given in very low quantities only when shivering disturbed the ECG readings. We found that spontaneous respiration stayed almost normal even when the haemoglobin was very low. The corneal reflexes remained present. The respiration was often too superficial, however, so that there was a tendency for the pH to fall. As the experiment developed, we therefore used artificial respiration by means of an intratracheal tube. The blood pressure was read by means of a mercury manometer connected with a plastic tube introduced into the other femoral artery.

In three pigs weighing about 12 Kg, the blood was washed out of the circulation as described above by means of plasma or macrodex under normal atmospheric conditions. In all cases the results were about the same. When the level of the haemoglobin fell to 10, 11 or 12 percent Sahli, the ECG showed disturbances (S—T depression) which were interpreted as signs of severe anoxia of the heart muscle. At this moment the blood pressure usually dropped. The inflow and outflow were then stopped. This level was maintained for fifteen minutes. If the ECG abnormalities did not then indicate a recovery from the cardiac ischaemia, it was concluded that the lowest tolerable level of haemoglobin had been reached. Stored blood of other pigs was then infused until the preoperative haemoglobin level was reached. The ECG almost immediately showed normal oxygenation of the heart muscle. The animals left the operation table in good condition and showed no disturbances during the next few weeks.

We may therefore conclude that a haemoglobin percentage (Sahli) of lower than 10 will not be tolerated by the working heart muscle at normal pressure. Even when breathing oxygen, the physically dissolved oxygen does not exclude the need for haemoglobin.

The same experiment was repeated in a high pressure tank where the atmospheric pressure was increased three times. The animal, during artificial respiration by means of an intratracheal tube, was consequently oxygenated by oxygen at a pressure of three atmospheres. Now we found that the haemoglobin level could be decreased much lower than at normal pressure. When after several experiments all the difficulties were mastered, and we saw that the animals survived the experiments, we were finally able to wash out practically all of the red cells. In the last series all the animals survived. The lowest haemoglobin levels were 0.6, 0.5 and once even 0.4 percent.

In the last cases macrodex was used instead of plasma. Even here the results were good.

Summary

The authors lowered the level of haemoglobin in young pigs to 0.4 per cent, exchanging the blood by plasma or by rheomacrodex. The animals, breathing oxygen at a pressure of 3 atmospheres in a high pressure tank, lived for 45 minutes with a level of haemoglobin not compatible with life when at normal atmospheric pressure.

During all this time the EEG showed no pathological changes, the circulation and blood pressure remained spontaneously normal.

Recovery was uneventful after re-infusion of normal blood.

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