OXYGEN TOXICITY
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General Effects of Hyperbaric Oxygen

If the arterial partial pressure of oxygen is raised to over 2.25 ATA there is sufficient oxygen dissolved in the plasma to supply the body's needs. So a person can be kept alive even if his haemoglobin is useless. This effect is made use of in treating carbon monoxide poisoning with hyperbaric oxygen. At the same time the partial pressure of oxygen throughout the body will be raised well above normal, which is used clinically in the treatment of gas gangrene.

However high partial pressures of oxygen have their inevitable effects. Above 2.25 ATA the haemoglobin remains fully saturated so carbon dioxide transport is interfered with. There is vasoconstriction and damage to various organs and enzymes. The organs that have been shown to be adversely effected by raised oxygen partial pressures include the central nervous system, the lungs, the eye, the bone marrow, the kidneys, the gonads and the liver. I will mainly be discussing the effects of oxygen on the central nervous system and the lungs.

Tissue Effects of Hyperbaric Oxygen

Life developed when the atmosphere contained little or no oxygen but plenty of carbon dioxide and water. Oxygen release into the atmosphere started as a result of photosynthesis. Enzyme systems developed and are now adapted to work at 0.21 ATA oxygen. It is not surprising that we get trouble when we expose these enzyme systems to higher pressures of oxygen. Oxygen is known to be biochemically toxic at a number of sites. Some of these are sulphydryl enzymes; thio containing co-enzymes, such as lipoic acid, co-enzyme A and reduced glutathione (GSH); flavoprotein enzymes, particularly those containing non-haem iron and sulphydryl groups; enzymes requiring pyridoxal phosphate as a co-enzyme (of particular interest here is glutamic acid decarboxylase (GAD) which forms gamma-amino butyric acid (GABA) in the nervous system); and lipids undergo peroxidation. Possible mechanisms involved in the inactivation of enzymes by oxygen are; firstly an enzyme with two SH groups could have them both oxidised to form a disulphide linkage, this may be the mechanism for the inactivation of Glyceraldehyde phosphate dehydogenase (GAPD); secondly, an enzyme with a single SH group could react with another enzyme molecule also carrying a single SH group but this reaction is not as likely as the third reaction which represents the prior oxidation of non-protein cellular compound such as glutathione, followed by mixed disuphide formation. This last reaction is reversible and is also the reaction by which oxidised SH enzymes can be reactivated, by a substance such as reduced glutathione (CSH).

There are two possible ways that sulphydryl groups can be oxidised. Increased concentrations of oxygen may drive, by mass action, reactions such as the oxidation of glutathione towards the right. An alternative is that free radicals are formed during hyperbaric oxygenation and that these inactivate the sulphydryl groups by forming disulphide linkages and water.

Carbohydrate mechanisms are susceptible to the toxic effects of oxygen in at least five places.

1. In glycolysis, glyderaldehyde phosphate dehydrogenase is quite easily inactivated. It can be reactivated by incubation with an SH donating agent.
2. The next step that has been found to be inactivated by oxygen is the oxidation of pyruvate, and this may involve the oxidation of either lipoic acid or co-enzyme A.

3. In the tricarboxylic acid cycle several dehydrogenases contain SH groups which have been demonstrated, in vitro, to be inactivated by oxygen.

4. In the respiratory chain there are a number of flavoprotein enzymes that are exceptionally vulnerable to oxygen toxicity.

5. Finally oxidative phosphorylation, the formation of ATP linked to the reactions of the respiratory chain, is also vulnerable to oxygen as it depends on the presence of free SH groups.

Not all enzyme systems are oxygen sensitive, some are oxygen resistant such as the gas concentrating mechanism of the swimbladder of fish. Below 100 metres (11ATA) swimbladder gas is 85-95% oxygen. The swimbladder P O2 can be approximated to 0.09 x depth in metres, which gives pressures of 100 to 200 ATA in some species. It is thought that the low temperature at which deep sea fish exist (less than 5°C) may protect against oxygen toxicity as may pressure itself by preventing any oxidation in which water is an end product.

General forms of Oxygen Toxicity

The two major forms of oxygen toxicity were both described many years ago. In three years time it will be 100 years since Paul Bert described convulsions in animals exposed to high pressures of oxygen. Twenty years later in 1899 J Lorraine Smith described the other important effect of breathing increased partial pressures of oxygen. This came on at lower pressures and was the inevitable result of breathing oxygen at more than 0.5 ATA. This form of oxygen toxicity affects the lungs leading through a sequence of sore chest, a decreased vital capacity, cough, increased respiratory rate and eventually to respiratory failure and death. That is of course in animals as experimental humans are not usually exposed long enough to develop respiratory failure. If an animal is exposed to high oxygen pressures and convulses to death it does not live long enough to develop the toxic changes in the lungs.

Oxygen toxicity can creep up on us completely unexpectedly. There is a disease called retrolental fibroplasia which causes blindness in babies. It occurs occasionally and the pathology is a growth of fine blood vessels into the vitreous humour of the eye, which is normally without blood vessels, and then cellular infiltration blocking light from reaching the retina. About 25 years ago there was a sudden epidemic of retrolental fibroplasia in premature infants. After a few years it was worked out that this was due to the apparently commendable practice of giving extra oxygen to all premature babies as they lay in their humidicribs. Stopping the oxygen stopped the epidemic, although sporadic cases still occur. That was oxygen at less than 1 ATA.

Oxygen at 3 ATA is toxic to the eye and three hours exposure has led to a symmetrical contraction of the visual fields. Vision remained but had been reduced to a cone of 10° and the normal field is a cone varying between 60° and 80°. The subjects in this experiment retained their limited vision until they went unconscious from the other central nervous system effects of oxygen. Within an hour of being returned to sea level their vision had been fully restored. But another man was not so fortunate. He had had eye symptoms, due to retrobulbar neuritis, some time previous to his exposure to oxygen at 2 ATA. By the end of two hours he had developed almost complete loss of vision in the eye that had been affected before. He had been exposed to less oxygen than most patients having hyperbaric oxygen therapy. He was most unlucky and was left with a permanent visual defect in the middle of the field of the affected eye.

Even if we keep the oxygen partial pressure down below 0.5 ATA we can cause the body trouble if there is no other gas present. Gemini 4, 5 and 7 were space flights where the oxygen pressure was below 0.5 ATA and above 0.21 ATA. There was no other gas present in the space craft. The crews all suffered from a large decrease in the red blood cell mass. There was a similar but smaller decrease in red blood cell mass in the crew of Apollo 9 but no change occurred in the crews of Apollo 7 and 8. The difference was that the Apollo missions started with 0.6 ATA of nitrogen in the cabin atmosphere. Apollo 7 and 8 retained this nitrogen for the whole trip but Apollo 9 was depressurised in flight for a space walk and repressurised with oxygen only. So the crew was exposed to 6 days of pure oxygen.

Central Nervous System Oxygen Toxicity

We know that high oxygen partial pressures decrease GABA levels in the brain, that the decrease precedes the convulsions, and is reversible, the decrease is specific for GABA among amino acids. Susceptibility to convulsions correlates with the rate of GABA decrease for different species, for different pressures and for different carbon dioxide concentrations. The same oxygen pressure that produces convulsions decreases GABA. And GABA given intraperitoneally protects some animals from oxygen convulsions.

GABA oxyglutaric transaminase, the enzyme that destroys GABA is normally only found in the mitochondria. Glutamic acid decarboxylase, the GABA forming enzyme is found normally in the nerve endings astride the mitochondria. GABA levels are normally determined by the GAD activity rather than the ABA-T activity. Membrane permeability probably plays a major role in the control of GABA levels by keeping GABA away from GABA-T. Extracellular GABA is involved in the inhibition or modulation of nerve transmission. The reductions in brain GABA, induced by high oxygen partial pressure, could be brought about by any one of the following mechanisms.

1. Inhibition of glutamic acid decarboxylase

2. Activation of GABA oxyglutaric transanimase.

3. Increased membrane permeability which would allow GABA more rapid access to GABA-T.

There is good evidence that glutamic acid decarboxylase is inhibited by high oxygen pressures and that increased catabolism by GABA oxyglutaric transanimase also occurs, which is thought to be due to greater permeability of the membranes to GABA.

GABA is an inhibitory transmitter in the central nervous system and it is assumed that the oxygen induced decrease of GABA reduces CNS inhibition so allowing the incoordinate actions that lead to convulsions.

For the diver the most important form of oxygen toxicity is the acute nervous system effect as this can lead, without warning, to convulsions and if you have a convulsion underwater and lose your breathing apparatus you drown. It is also highly inconvenient for a patient to have a convulsion in the confined space of a single man hyperbaric chamber.

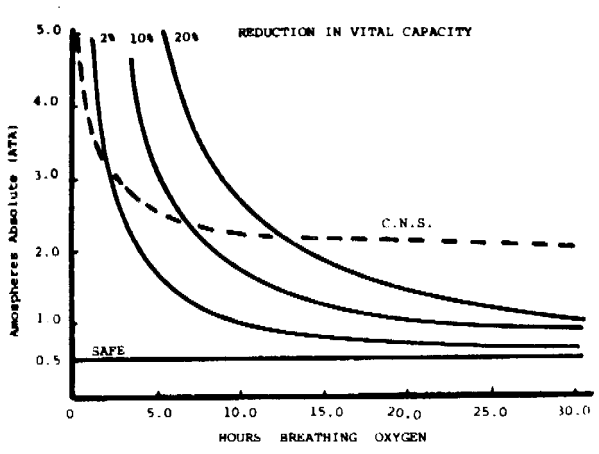
The toxic effects of high oxygen pressure on the central nervous system can be likened to acute poisoning. The victim suffers cerebral changes, twitches, inco-ordination and convulsions. The symptoms often occur immediately after the oxygen pressure has been reduced and before the arterial partial pressure has had time to drop. In one series 40% of convulsions occurred during decompression. We know that there is an

extreme variation of tolerance to oxygen not only between individuals but also for the same individual on different days. The time of exposure before the onset of symptoms is decreased as the pressure is increased. Symptoms occur sooner with men in water than with men in a dry chamber. Work greatly reduces the tolerance to high oxygen pressures. Both these effects are probably due to increased P CO2, the result of the inability of the standard oxygen diving set to absorb completely high carbon dioxide outputs.

In one experiment firemen, who might have had to fight fires in pressurised tunnels, were exercised wearing oxygen sets in a pressure chamber at the RN Physiological Laboratory at pressures equivalent to depths of 20- 47 feet of seawater. They were wearing 57.5 lb of equipment and were exercised for 40 minutes, 2 minutes work and one minute rest, at a rate that left them almost exhausted. They had approximately 87% oxygen in the breathing bag. There were no signs or symptoms in these men working hard at pressures equivalent to 20 to 23 feet of seawater. The first signs of oxygen toxicity that occurred were fasiculations and small twitches of the facial muscles (described as "the lips"). After 29 feet, which is just below two atmospheres, approximately 50% of the men had "the lips". They were not usually noticed by the subject, appeared during rest periods and disappeared during exercise. There was no trouble keeping the mouthpiece in place. These were the minor symptoms.

Young defined major symptoms as those that endanger a man under pressure, severe nausea, dizziness, light-headedness, confusion, euphoria and convulsions. One man convulsed during exercise and one during decompression. These serious symptoms started at 35 feet, just over 2 ATA, and became more frequent after 41 feet. The signs that these men had intensified during decompression while they were still breathing oxygen. 14% of the signs started during decompression, usually within 5 seconds of starting decompression and always within 10 minutes. They diminished rapidly during decompression and were gone by surfacing.

In the Navy oxygen sets are limited to a depth of 25 feet, a total pressure of 1.75 ATA, which has been shown to be safe for the endurance of the sets. This graph shows the levels of oxygen exposure, expressed as pressure and time, at which one may expect central nervous system and pulmonary toxicity. The dotted line marked CNS shows the exposures at which central nervous system toxicity leading to convulsions can be expected. The solid line across the bottom shows the level at which no toxic effect on central nervous system or lungs have been reported, although blood changes do occur at this level. It appears to be safe to breath oxygen at 0.5 ATA in nitrogen indefinitely. The other three curves show the exposures that have been found to give the indicated reductions in vital capacity. A small reduction in vital capacity develops quite quickly even when breathing oxygen at 1 ATA.



Patients in hyperbaric chambers are usually exposed to pressures of 2.25 to 2.5 ATA for periods of not more than two hours which gives them all the advantages of, and as few of the disadvantages of, hyperbaric oxygen treatment. They are in the safe zone. Safe from central nervous system toxicity, unless they are very intolerant

of oxygen, and safe from the pulmonary effects while their bodies are being drenched in oxygen. They are at rest which reduces the chances of CNS symptoms.

Divers being treated for decompression sickness are usually given oxygen at 60 feet, 2.8 ATA, and oxygen breathing is interrupted every 20 minutes by 5 minutes air breathing, which retards the onset of oxygen toxicity and also allows the patient to drink if he wants to. He doesn't always want to, as nausea and vomiting are some of the earliest symptoms of oxygen toxicity. My authority for this statement is Geoff Macfarlane, who has had considerable experience treating divers who have developed decompression sickness in Bass Strait. Even with air breathing to delay the onset of toxicity, therapeutic exposure to oxygen at 60 feet, 2.8 ATA, is limited to a total of 60 minutes, in all 75 minutes at 60 feet after which the chamber is depressurised to 30 feet, 1.9 ATA. Again the patient is at rest. Divers who have decompression sickness are exposed to high oxygen levels in an effort to increase the excretion of inert gases from their blood into their lungs. So one is walking a tightrope between oxygen toxicity and inadequate excretion of inert gas. This becomes quite a problem after long exposures to high pressures.

Pulmonary Oxygen Toxicity

Divers breathing compressed air are breathing more than 0.5 ATA below 50 feet. However the effects of nitrogen narcosis will come on and incapacitate them long before they reach 300 feet, the level at which the partial pressure of oxygen in compressed air is 2 ATA. 2 ATA of oxygen is known to have caused convulsions in divers. Luckily humans are more resistant to the pulmonary effects of oxygen than most experimental animals. A few hours exposure to a raised oxygen partial pressure, followed by a rest period on the surface, does not appear to do any permanent damage. But for saturation dives it is normal practice to keep the oxygen levels below 0.5 ATA to prevent the onset of pulmonary oxygen toxicity.

One situation where non-divers may develop pulmonary oxygen toxicity is in being rescued from a submarine. Australian submarines are fitted with buoyant ascent equipment. The sub has an egress hatch surrounded by a twill trunking coming down close to the deck. To escape the compartment is flooded, compressing the air in it to the outside pressure when it is possible to open the hatch. The twill trunking prevents the air from whooshing out of the line hatch. Each man in turn dips under the trunking, inflates his life jacket, and is borne irresistibly upwards. Over his head is a plastic hood, open at the bottom to vent excess gas, which allows him to breathe normally on the way up. Such ascents have been made by the RN from as deep as 300 feet. But the escapees are exposed to the risks of decompression sickness and of being lost when they surface. Another approach is that used by the USN and the Swedish Navy. They have built and are building underwater rescue vessels designed to mate with a hatch on the stricken sub and transfer the crew at failure. So we are forced back to the animal model and the nearest animal to humans that has been well documented histologically is the monkey (Macaca Mulatta).

Many reports of patchy collapse as a complication of breathing pure oxygen 1 ATA have been published based on postmortem evidence. However Kapanci and his co-workers showed that this is a postmortem effect, and that if the lungs are fixed in the inflated position immediately after death there is quite a different picture. It is from their work that this section of my presentation is taken. Their monkeys were exposed to oxygen at 1 ATA for up to 13 days.

Changes in Lung Tissue in Monkeys

In the monkey 15% of lung volume is tissue and the rest is air. After a week of breathing oxygen there is a vast decrease in normal lung tissue. After twelve days the lungs have virtually no normal tissue left and the total tissue volume has nearly doubled. Some monkeys removed from oxygen and allowed to recover. To get them out of the oxygen environment safely they had to be weaned by gradually reducing the oxygen partial pressure as rapid reductions made them anoxic. The monkey which was sacrificed 56 days after its 7 day exposure recovered so that almost three-quarters of its lung was normal tissue but it still had more lung tissue than the controls. The monkey sacrificed 84 days after its 13 day exposure had about 90% of its lung tissue normal and the septal volume was almost back to normal. Both had patches of abnormalities scattered haphazardly throughout the lung. The abnormalities were of various grades of disorganisation.

Both monkeys and humans have a destructive and exudative phase as the first signs of pulmonary oxygen toxicity. There was a steady increase in interstitial thickness with exposure to oxygen. During the first few days this was due to an increase in interstitial fluid which more than replaced the volume of the cells destroyed. This was the early destructive and exuderive phase. If the monkey survived this there was a later proliferative phase in which there was a steady increase in the volume of cells and fibres.

After four days the alveolar walls were severely damaged. The alveoli contained oedema fluid and cellular debris and macrophages. 90% of the membranous, type 1, pneumatocytes were damaged. The cells were swollen and had ruptured membranes and fragmented cytoplasm. Some were detached from the basement membrane which was left bare or covered with fibrin strands. There was a small increase in the air-blood barrier. By seven days the type 1 pneumatocytes, normally 85% of the alveolar lining, had been almost completely destroyed. Their replacement by type 11, granular, pneumatocytes thickened the alveolar walls. The epithelial part of the air blood barrier was now 1.7 mu instead of 0.6 mu in the controls. The endothelium varied in thickness from region to region and the interstitum was filled with fibroblasts and leucocytes. About this stage many of the monkeys died from respiratory failure.

At 12 days the alveoli were lined by cuboidal, type 11, cells. The alveolar spaces were decreased by increase in volume of the septa which were thickened by many fibroblasts and inflammatory cells as well as by the thicker epithelial cells. The air blood barrier was over three times as thick as in the control animals.

Following exposure to oxygen there is a large increase in the volume of the epithelium complete destricution of the type I, membranous, pneumatocytes and overgrowth of the type II, granular, pneumatocytes. In those animals that survived exposure the normal proportion of epithelial cell types was not restored even after many weeks.

To recap. The main changes in monkey's lungs are a large increase in epithelial thickness, a lesser increase in interstitial thickness and little change in endothelial thickness. The process can be divided into an early destructive and exudative phase, peaking at about 4 days, and a later proliferative phase.

Species differences exist in response to the same exposures. The rate doubles the thickness of his blood air barrier in three days while the monkey in the same time has no significant change.

Human Symptoms and Signs

Now to leave the animal world and come to humans. Clark and Lambertsen reported the symptoms that were complained of by people exposed to oxygen at 2 ATA. The symptoms started with mild carinal irritation on deep inspiration, went on to occasional coughing, then pain on inspiration, then frequent coughing, intense carinal irritation, uncontrollable coughing, severe pain on inspiration and then dyspnoea. The decrease in vital capacity was correlated with the symptoms but came on before the subject complained. Clark and Lambertsen chose the decrease in vital capacity because it was something that they could measure, whereas symptoms are very difficult to measure. It would be very nice to have this early evidence of oxygen toxicity when treating patients in a recompression chamber. But there are problems. Water spirometers are excellent until the pressure is reduced and the air in them expands and water goes everywhere. Electrically driven portable spirometers like the Vitalograph cannot be used in pressure chambers if you do not want to risk a fire as it is inadvisable to take electric motors into high oxygen environments. There is a mechanically driven recorder on the market but it is made by the Japanese for the Japanese and has a maximum of 4.5 litres which is not large enough to cope with the average Australian diver. Vane spirometers, such as the Wright Respirometer and the Drager Volumeter, are affected by the increased density of the compressed gas and the rate of flow past the vanes.

The vital capacity decreases and other oxygen toxicity effects do not clear up immediately. The vital capacity changes in three individuals who had been breathing oxygen at 2 ATA were all different. All subjects had a continuing decrease in vital capacity in the first four hours post-oxygen when they were breathing air. The man with the least decrease in vital capacity had returned to a normal vital capacity by the third day after discontinuing oxygen. The man with the greatest decrease however had a normal vital capacity by the second day, while the man with the intermediate decrease took eleven days to regain a normal vital capacity. This emphasises the individual variation in susceptibility to oxygen toxicity.

To sum up

Oxygen is not a harmless drug if given for long periods at more than 0.5 ATA. Certainly if given for 24 hours at 0.75 ATA the subject will complain of chest symptoms and will have suffered a decrease in vital capacity. At higher pressures pulmonary toxicity comes on quicker and progresses more rapidly. At pressures above 2 ATA central nervous system symptoms and signs can be expected. This is a limitation in hyperbaric therapy. In treating decompression sickness in divers who have been deep and so require a prolonged therapeutic decompression pulmonary oxygen toxicity can be a complication of great severity preventing the use of raised oxygen partial pressures. The only way to avoid oxygen toxicity is to keep within the experimentally determined safe limits and even then there can be surprises owing to the great variations in individual susceptibility.

Clyde Cameron, when Minister for Science (September 1975) put the case against ill considered scientific programs very succinctly. “To repose confidence in crash programs in science is as realistic as advising a woman that she could produce a baby in a month by putting nine men on the job.” Such remarks surely require no relating to diving to be worth repeating!

References and further reading

1. Clark JM and Lambertsen CJ. Rate of development of pulmonary toxicity in man during O2 breathing at 2 ATA. *J App Physiol*. 1971; 30: 737-752.

2. Clark JM and Lambertsen CJ. *Pulmonary Oxygen Toxicity: A Review. Pharmacological Reviews*. 1971; 22: 37-133.

3. Kapanci Y, Weibel ER, Kaplan HP and Robinson FR. Pathogenesis and Reversibility of the pulmonary lesions of oxygen toxicity in monkeys. 11 Ultrastructural and morphometric studies. *Laboratory Investigation*. 1969; 20: 101-118.

4. Kapanci HP, Robinson FR, Kapanci Y, and Weibel ER. Pathogenesis and reversibility of the pulmonary lesions of oxygen toxicity in monkeys. 1 Clinical and light microscopical studies. *Laboratory Investigation*. 1969; 20: 94-100.

5. Winter PM and Smith G. The toxicity of oxygen. *Anesthesiology*. 1972; 37: 210-241.

6. Wood JD. In *Oxygen Toxicity in the physiology and medicine of diving and compressed air work*. Eds Bennett PB and Elliott DH. London: Bailliere Tindall and Cassell, 1969.

Books

1. Miles S. *Underwater Medicine*. London: Staples Press, 1969.

2. *Medical Aspects of Small Submersible Operations*. Bethesda, Maryland: Undersea Medical Society.

3. Lambertsen CJ, Ed. *Underwater Physiology*. New York and London: Academic Press, 1971.

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Commons' Speaker: "Rigs are Ships"

The UK House of Commons was in uproar (28 May 1976) , the votes evenly decided as to whether Oil Rigs were ships, so should be Nationalised, or Oil Rigs. The Speaker had the casting vote and disregarded the Government's wishes by His decision that such platforms would be included in the assets that would be Nationalised. He also voted to ensure that the bill was passed. Everyone being displeased, a brawl ensued. As Divers in Australia seem to be governed under the Scaffolding Acts we can hardly laugh too loud.

Graeme Henderson, the Perth maritime archaeologist investigating the wreck of the James Matthew in Cockburn Sound, has disproved the cherished mariners' theory that if you tickle an octopus it becomes your friend. Mr Henderson was measuring timbers when a large tentacle grabbed his steel tape measure. He tried the tickle test, but the octopus made a grab for his watch. Mr Henderson wants to pass on the information that octopuses are the bowerbirds of the sea .... so avoid swimming wearing anything that glitters. (Australian 31 March 1976)