Symposium on HYPERBARIC MEDICINE

Oxygen Toxicity

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Oxygen is essential for maintenance of all forces, forms of plants and animal life except for some anaerobic organisms. Paradoxically, this substance has toxic effects on these organisms if presented in concentrations slightly higher than that present in the air. The knowledge of the toxic effects of oxygen is as old as the discovery of oxygen itself.

Paul Bert concluded that oxygen was a protoplasmic poison and produced toxicity possibly by inhibiting "fermentative" reactions in the cell. He predicted that 60% of 1 atm of oxygen was the highest safe limit.

Lorrain Smith demonstrated toxic effects of oxygen on lungs. Mice when exposed to 1 atm oxygen for 4 days showed congestion and consolidation in lungs. There was rapid reversibility of effects if oxygen was stopped. Oxygen toxicity in lungs is known as "Lorrain Smith effect". Hill recognised the importance of oxygen toxicity in caisson disease. Dean and Rottschaffer and Gersh et al did complex experiments by sections of brain at various levels and demonstrated that there was global involvement producing convulsions. EEG pattern showed non-specific grand mal type activity.

The present interest in the field has been due to the findings that oxygen increases the sensitivity of some tumours to radiation and because of the increasing use of HBO in surgery and medicine. This increasing use has also led to studies in the mechanisms of oxygen toxicity.

Clinical Features

Oxygen is a protoplasmic poison and does affect most of the body cells that contain the susceptible enzymes. In vitro and in vivo studies have demonstrated effects on metabolism of CNS, lungs, heart, liver, testes and other organs. Some of the demonstrable effects are discussed below.

Central Nervous System Toxicity

Two types of crises have been described. Minor crisis is characterised by facial pallor, twitching of eye lids and alae nasi, sweating, bradycardia, nausea, dizziness, vertigo, dimness of vision and minor changes in behaviour. Major crisis is preceded by the above symptoms of minor crisis followed by vertigo, convulsions and collapse. The convulsions are grand mal type. Tonic phase, which may last for about 30 seconds, is followed by clonic contractions lasting for about one minute. Following convulsions, there is hyperventilation due to excessive accumulation of carbondioxide during fits. There are no hypoxic effects (like cyanosis) which may differentiate it from epilepsy.

There are wide individual variations in tolerance to HBO. Oxygen at 2ATA upto 3 hrs produces no fits. In one study, convulsions were seen in 2 out of 4 cases in 43—44 min at 3 ATA. Oxygen at 5-7 ATA causes convulsions in 4½ min.

Toxicity on Lungs (Lorrain-Smith Effect)

It is a dose and duration relationship. We are interested in this because of requirements of space flight conditions and the choice of breathing mixture for astronauts. Oxygen breathed at 250 mm Hg upto 30 days in space flights has not shown any adverse effects. Exposure to 1 atm oxygen for 24 hours led to pulmonary naso pharyngeal and conjunctival irritation. On 2nd day there was reduction in vital capacity and slight paraesthesia of fingers ; on 3rd day, there were complaints and symptoms of bronchitis, pneumonia, irritation behind sternum on coughing and deep inspiration. There was reduction in diffusive capacity of lungs to 81% after 48 hours oxygen breathing and to 73% after 74 hours.

Toxic Effects on Other Tissues

Eyes— In pre-mature infants, even with oxygen at 1 ATA, there is retrolental fibroplasia, a condition with extensive vascular obliteration and fibroblastic infiltration in the retina leading to permanent blindness. It is related to prematurity as it does not occur in adults even at higher oxygen pressures. It causes retinal vaso constriction. The vaso obliteration is inversely proportional to maturity. Oxygen at 1 ATA has been known to cause conjunctivitis, iritis, hypotony and retinal detachment in animals.

Blood and haemopoietic system — Oxygen at 0.5 ATA for 14 days causes reduction in haemoglobin synthesis; there is increased capillary fragility and acceleration of haemolysis. The increase in RBC fragility is suspected to be due to formation of lipid peroxides in RBC walls. There is a reduction in haemopoietic factor in prolonged space flights where the atmosphere is maintained with 100% oxygen.

Mechanism of Oxygen Toxicity

The exact mechanism of oxygen poisoning and the nature of cellular resistance to the oxygen are not very well understood. There is an increasing amount of evidence from 'in vitro' and 'in vivo' studies that oxygen interferes with cellular metabolism leading to disturbed tissue function. The final toxic effect of hyperbaric oxygen can be described as a condition of "Hyperoxic Hypoxia" leading to cellular death and disruption. The possible physiological sites which are said to be affected and which lead to production of oxygen toxicity can be at the level of cell membrane, synapses in the central nervous system, contractile proteins in the muscle, nerve endings or a combination of these sites.

Molecular oxygen can be considered to be a potent enzyme inhibitor. Oxygen can also oxidise some of the important non-protein constituents of the cells into inactive forms. The possible important mechanisms of oxygen toxicity are :—

1) Oxidation of sulfhydryl (SH) containing co-enzymes such as lipoic acid and co-enzyme A.
2) Inactivation of enzymes with sulfhydryl groups essential for their activity.
3) Inhibition of iron and SH containing flavo-proteins.
4) Damage to cellular membranes by lipid peroxidation.
5) Oxidation of glutathion, ascorbic acid and possibly other oxidisable tissue components.

Factors that influence toxicity

Many studies on 'in vitro' preparations and animals have suggested that toxic effects of oxygen can be influenced. It is difficult to accurately ascertain the extent of damage by oxygen. On experimental animals, incidence of convulsions or time elapsed before convulsions and lung damage as ascertained by change in weight or gross appearance are the events that are determined. Various factors that may influence toxic effects of oxygen are discussed below :

a) *Carbondioxide*

The safe latent period can be prolonged by hyperventilation by causing diminution of carbondioxide in the body. It can be shortened by breathing low concentration of carbondioxide in the breathing mixture. Vasodilation and increased blood flow to brain, with resultant rise in brain pO_2, rather than the increased brain pCO_2 and lowered pH, per se, are the important factors in shortening the time to onset of convulsions.

b) *Physical activity*

The incidence and rate of development of oxygen convulsions is increased by exercise. This fact is of great importance in diving operations which are associated with physical activity. The mechanism is not yet established but CO_2 retention due to increased production, faulty absorption in the closed circuit breathing system and interference with alveolar ventilation due to increased resistance to airflow in respiratory passages or breathing apparatus, have been incriminated.

c) *Hypothermia*

The observation that cold blooded animals are resistant to HBO and become prone to toxicity when their body temperature is raised has lead to utilisation of artificial hypothermia and hyperoxia during surgical operation. The safe latent period is increased by combining these 2 procedures.

d) *Intermittent exposure to HBO*

It has been demonstrated by Lambertson that intermittent return of animals to lower pO_2 would allow one to extend the total time of exposure to HBO without development of serious toxicity. The survival time and the safe latent period is considerably increased and the animal receives almost continual hyperoxygenation with this procedure.

e) *Hormones*

Hypophysectomy reduces the susceptibility to HBO especially in the lungs. This benefit is counteracted by administration of thyroid hormone. Adrenalectomy also gives some protection and adrenaline injections increase the sensitivity to HBO. Ganglion blocking drugs like tetraethylammonium and hexamethonium reduce the pulmonary toxicity without much significant effect on convulsions. This suggests that hyperactivity of sympathetic nervous system is the factor primarily responsible for pulmonary toxicity of HBO.

f) *Anaesthetic agents*

Some anaesthetic agents offer protection against oxygen toxicity. It has been thought to be due to depression of metabolism. Phenobarbitone decreases oxygen damage in lungs and delays convulsions in rats exposed to 5 ATA. There are conflicting reports about the beneficial effects of anaesthesia. It has been agreed that anaesthetic agents, though they delay the onset of convulsion, do not affect the cellular damage which continues unabated.

g) *Antoxidants*

Vitamin E deficient rats develop toxic manifestations earlier than those fed on normal Vitamin E diet. Administration of Vitamin E has been known to delay the onset of convulsions. Lipid peroxides were found in measurable quantities in erythrocytes of Vitamin E deficient mice exposed to HBO and not in erythrocytes from normal rats under normal conditions. Vitamin K (K1 and K3) and substance 2,5-bis hydroquinone also give some protection.

Treatment of Oxygen Toxicity

The logical treatment of oxygen poisoning is to reduce the partial pressure of oxygen in the breathing air and return it to normal levels. In case of convulsions, care of the patients should be on the same lines as for convulsions due to any other cause, viz., care of the upper respiratory tract, bite-block to prevent injury to the tongue and moderate degree of restraint. Decompression should not be done during the convulsions since expanding gases in the lungs may lead to serious lung injury and fatal

pulmonary air embolism in presence of laryngospasm and incoordinated thoracic movements. Once the convulsions stop and rhythmic movements of chest return one can proceed with the decompression with proper care of the upper airway After return of consciousness the patient may be irritable and confused. Assurance and tranquillizers may be required.

Lung damage may present as atelectasis, pulmonary oedema, bronchopeumonia and disturbances in pulmonary gas exchange leading to acidosis, hyperbaric hypoxia and death In mild cases one would do well with antibiotics, atropine, artificial respiration and reduction of pO_2 in the lungs. A level not more than 60% of that at sea level has been recommended as higher pO_2 would possibly aggravate existing pulmonary pathology. In severe cases, there is anoxaemia even at very high pO_2 in the lungs. It is a point of no return unless a heart lung machine can be used. No other measure will cause reversal of severe pulmonary damage. Reduction in pO_2 in lungs will aggravate anoxaemia and treatment of reduced arterial pO_2 with normal or high pressure will further increase the existing damage.

It is the pulmonary toxicity which is the limiting factor in the use of hyperbaric oxygen and should be given the most serious attention.