Oxygen Toxicity

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OXYGEN inhalation is not without complications. Although most types of hypoxemia are relieved and tissue hypoxia is alleviated, several changes in the body occur when tissue hypoxia is abolished. Anaerobic processes which normally take place in some cells are suppressed.[6] Some enzyme systems in the cells are inhibited,[1, 10, 11, 12, 16, 21] thus interfering with cellular function. The absorption of gases from closed spaces in the body is accelerated.[8, 20] The action of oxygen on the specialized receptor cells of the carotid body inhibits respiratory impulses arising in these cells, and vagal inhibition of cardiac output occurs in normal man.[9] The rapid absorption of gas from closed spaces and the cellular toxicity bring about the collapse of such spaces, the engorgement of surrounding tissues, and the transudation of proteinaceous fluid from the vascular bed into the space.[3, 5, 13, 22]

Not all individuals are equally susceptible to the effects of breathing oxygen.[2, 7, 19] Also, attendant circumstances minimize or accentuate the effects in any individual.[4, 14, 15] The concentration of oxygen, duration of its administration, and in special circumstances the ambient barometric pressure can be varied. The skillful management of supplementary oxygen is the sign of a thoughtful physician. Some of the factors relating to oxygen toxicity are outlined below.

Tissue Oxygen Tension

Tissue oxygen tension varies throughout the body because of variations in the rate of cellular oxygen uptake, differences in the rate of bloodflow to the different tissues, inequality in the distance through which oxygen must diffuse from the blood to the cells, and spacing of the cells along the capillaries, some upstream, closer to the arterial end of the capillary, and others downstream, closer to the venous end. Not all cells in the body receive as much oxygen as they need for aerobic metabolism. Some cells receive their energy principally from anaerobic processes, the end-products being oxidized elsewhere in the body. While the total ventilation and cardiac output vary in proportion to tissue demands, the local bloodflow and vascularity also vary according to local demands.

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Effect of Oxygen on Overall Ventilation and Cardiac Output

Administering oxygen suppresses the impulses arising from the cells in the carotid body. Ordinarily, the slight drop in pulmonary ventilation is counteracted by the increased activity of the respiratory center resulting from the rise in arterial P_{CO_2}, thus restoring ventilation to normal. Nevertheless, during prolonged hypoxia, the respiratory center is driven more by the hypoxic stimulus via the carotid body than by CO_2. On inspiring pure oxygen, the ventilation drops abruptly due to abolition of the carotid body stimulus. Under the influence of sedation, or in many patients with pulmonary disease, alveolar ventilation decreases when breathing oxygen. Similarly, the cardiac output diminishes in normal people when they breathe oxygen, but this effect can be abolished by giving atropine, and hence appears to be vagal in action. Normal man, exercising at altitude, and some patients who have cardiac disease and hypoxia, improve their cardiac output during oxygen therapy, because the factor limiting cardiac output may be oxygen supply to the myocardium.

Effect of Oxygen on Regional Bloodflow

Pulmonary Circulation. Breathing oxygen decreases the pulmonary vascular resistance in some patients who have pulmonary hypertension, thus relieving part of the right heart strain.

Retinal Circulation. Breathing oxygen decreases the blood supply to the retina in premature infants. When the infant returns to breathing air, the retinal ischemia may be followed by retinal fibrosis. This effect of oxygen, known as retrolental fibroplasia, can be prevented by keeping the inspired oxygen at less than 40 per cent, and giving it for less than seven days, to premature infants. However, it is the arterial, not the inspired, O_2 tension which produces the effect. Therefore, if higher concentrations are required to saturate the arterial blood, they may be used for short periods.

Absorption of Gas from Closed Spaces

The gas within spaces in the body is subjected to nearly atmospheric pressure transmitted from the surface of the body through the soft tissue. This enclosed gas will go into solution in the surrounding tissues and blood supplying them if the sum of partial pressures of the gases in the closed space is greater than the sum of partial pressures of gases in the blood and tissues. Breathing oxygen from airtight systems, by eliminating the inert gas normally dissolved (nitrogen), lowers the sum of partial pressures in the blood and tissues around a closed space. This causes a diffusion gradient for gases, which then move from the gas space toward the blood. Because of the solubility of the gas in blood and the blood-flow, the gases which diffuse from the enclosed space are carried away. When there is no inert gas in the blood as during a period of oxygen breathing, the gases in the cavity are all carried away faster than they are when breathing air. The ensuing subatmospheric pressure in the gas space causes collapse of its walls. If the difference between pressure in the space and the surrounding hydrostatic pressure exceeds the colloid osmotic pressure, fluid and plasma proteins will be transuded into the closed space. Two examples of gas absorption are pulmonary atelectasis and retraction of the ear drums.

Pulmonary Complications

During oxygen breathing, or immediately following its cessation, the rapid absorption of gases from closed off alveoli results in atelectasis. Since obstructive or absorptive atelectasis is accompanied by a negative pressure, there is a consequent engorgement of the capillaries, a right to left shunting of blood leading to reduced arterial oxygen tension, and transudation of fluid and proteins into the lungs. During inhalation of the high oxygen concentrations, the lungs are exposed to the full tension of the inspired oxygen (760 mm. of mercury at sea level) minus water vapor tension (47 mm. of mercury at 37° C.) and minus alveolar CO_2 tension (40 mm. of mercury) whereas the peripheral tissues of the body are exposed to much lower tensions of oxygen; hence, the lungs bear the brunt of a chemical effect of oxygen on the alveolar tissues. After a few days of breathing oxygen, the alveoli of most mammals show cellular changes evidenced by edema, transudation, and a fibrinous deposit. As a result, the lungs behave functionally as they do in pulmonary edema, alveolo-capillary block, atelectasis, and pneumonia, combined in varying degrees. In animals these effects can be accentuated by the administration of adrenocorticotrophic hormone or adrenal cortical steroids during the period of oxygen breathing. The effects of oxygen toxicity on the lungs are less in animals in whom the adrenal glands or pituitary have been removed. Thus, the usually "anti-inflammatory" effects of corticosteroids are reversed in oxygen poisoning of the lungs. There is no reason to think that man would differ from other mammals in response to oxygen when receiving steroids. Periodic deep inflations of the lungs are useful in order to prevent or reverse at least part of the collapse of the lungs which many view as a result of breathing 100 per cent oxygen.

Cerebral Complications of CO_2 Retention

In some patients with pulmonary disease in whom ventilation is decreased by breathing oxygen, certain cerebral complications ensue and these are attributable to increasing CO_2 tension. Even though oxygen administration is continued, these complications can be relieved by assisting respiration to provide adequate ventilation of the lungs and thus reversing the CO_2 retention. The manifestations of increased CO_2 retention in such patients include inability to be aroused (*i.e.*, coma), increased cerebrospinal fluid pressure (pseudo-

tumor cerebri), and arterial blood changes indicative of respiratory acidosis, including increased arterial P_{CO_2}, and decreased arterial *p*H; partial restoration of *p*H is achieved if the kidneys excrete buffer base.

Convulsions Resulting from Breathing Oxygen at Increased Ambient Pressure

When oxygen is breathed at 3 or 4 atmospheres of pressure, epileptic seizures usually occur in about half an hour. These are not caused by CO_2 retention, because CO_2 is adequately eliminated by the lungs and, despite the slight inhibition of the Bohr shift, by the blood flowing through the tissues. Nevertheless, increasing the arterial CO_2 tension increases the cerebral bloodflow, raises the mean capillary and mean cerebral tissue P_{O_2}, and brings on oxygen convulsions more rapidly.[17, 18] The convulsions appear to be caused by the toxic chemical effect of oxygen on the cerebral tissues, which are exposed, at these pressures, to an oxygen tension similar in magnitude to that which produces chemical damage to the alveolar tissues of the lungs when breathing oxygen at one atmosphere.

Theories to Explain the Chemical Effect of Oxygen on Tissues

The oxygen present in the atmosphere is generated by plant photosynthesis. Before animal life had evolved, plants had developed processes of protein synthesis and ion transport utilizing energy derived from anaerobic processes. Even now, in animals and man, much of muscular contraction, retinal energy, embryonic development, liver metabolism and nerve conduction is anaerobic. Some animals, particularly the tortoise, alligator, duck and seal, are able to go for long periods while breathholding, using little oxygen. These animals derive their muscular energy from the glycolysis of sugars, or suppress their metabolism until oxygen is available. Life in the sea evolved with low surrounding oxygen tensions, and the tissues of present day higher animals, including man, are at a low oxygen tension. Artificially raising the O_2 tension of all the tissues for a long time is not necessarily beneficial to their function. Animals are built to withstand hard exercise. During this, they build up an oxygen debt, accumulate lactic acid, and these processes result in flushing the tissues with blood, in suppression of bacterial growth, and in stimulation of vascularization of the tissue.

There are theories concerning the mechanism of adverse chemical effects of high oxygen concentrations on cells. One theory postulates that oxygen inhibits certain enzymes in the tricarboxylic acid cycle, particularly those containing sulfhydryl groups. This inhibition can be demonstrated *in vitro*. The main lines of evidence for this action *in vivo* are that reduced glutathione yields some protection against oxygen poisoning, that cupric ions, which are a catalyst for the oxidation of SH groups by oxygen, accentuate oxygen toxicity, that suppressing the normally present metallic ions with ethylenediaminetetraäcetic acid (EDTA) decreases the cellular toxicity of oxygen. Oxygen also has been postulated to be toxic through liberating excess free radicals capable of oxidizing sites such as SH groups similar to those mentioned above. The main evidence for this view is that roentgen-ray irradiation, which liberates free radicals, mimics many of the effects of oxygen poisoning, and that roentgen rays and high oxygen, given together, have a summed action. Furthermore, glutathione partly protects cells against roentgen-ray toxicity as well as against high oxygen.

The Clinical Implications of Oxygen Toxicity

Since we have little scientific information on man, any conclusions about the safety or danger of administering a specific concentration of oxygen over a given period of time are somewhat speculative and are based on an educated guess. Most of us would be reluctant to give 100 per cent O_2 using an airtight system for more than a day or two because of the possible chemical action on the alveolar epithelium. On the other hand, many investigators believe that 60 per cent oxygen can be given over a period of days or weeks without major hazard. However, even within these limits, the complications of atelectasis resulting from gas absorption, or coma resulting from increased CO_2 tension may occur and may require treatment by

means of periodic deep inflation of the lungs or assisted ventilation to increase the rate of alveolar ventilation.

Similarly, in infants, pediatricians prefer to use less than 40 per cent oxygen to avoid retrolental fibroplasia. However, the use of higher concentrations for short periods may be justified if such concentrations are needed to fully saturate the arterial blood. This is because it is the arterial, not the inspired oxygen tension, which when high, constricts the retinal vessels. In short, oxygen, like other therapeutic agents, should be prescribed according to the physiological requirements of the body, but not in excessive amounts because, like other agents, it may produce side effects or cellular toxicity if given in too high a concentration over too long a period of time.

Summary

The administration of high oxygen concentration using an airtight system results in the rapid absorption of gases from closed spaces in the body. Atelectasis, accompanied by engorgement of the lungs and by right to left shunting of blood, may ensue. There is some suppression of the respiratory impulses arising from the carotid body, and hence a decreased ventilatory stimulus. This may result in an increase in arterial P_{CO_2} if the ventilatory response to CO_2 is not adequate. These effects are counteracted by assisted ventilation. In normal man, there is a decrease in cardiac output when breathing oxygen, but this is abolished by atropine. In patients, oxygen may improve cardiac function. In premature infants, the administration of more than 40 per cent oxygen may result in constriction of the retinal vessels. On return to air, retinal fibrosis (retrolental fibroplasia) may ensue. When administered over a period of days, oxygen may produce chemical effects in the alveolar cells resulting in a picture of pulmonary edema, atelectasis, pneumonia, and alveolo-capillary block. At 3 atmospheres, pure oxygen brings on convulsions owing to the chemical action of O_2 on the brain cells. The chemical effects probably are due to inhibition of cellular metabolic processes by oxidation of certain enzymes, and the presence of ionizing radiation accentuates these effects.

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METABOLIC ALKALOSIS Several parameters of ventilation were studied in two subjects in whom steady-state metabolic alkalosis had been induced by sodium bicarbonate ingestion. Respiratory compensation for metabolic alkalosis was evidenced by increased arterial carbon dioxide tensions. Lung function and gas exchange were unaffected by alkalosis in both subjects. Ventilatory response to carbon dioxide was diminished during metabolic alkalosis. Possible explanations for this observation include increased buffering capacity of blood during metabolic alkalosis or a direct action of bicarbonate ion on the respiratory center. (*Stone, D. J.: Respiration in Man During Metabolic Alkalosis, J. Appl. Physiol. 17: 33 (Jan.) 1962.*)

LUNGS DURING BYPASS Effect of cardiopulmonary bypass on the lungs was studied in 29 dogs. Studies of blood gases, pulmonary compliance and peripheral systemic vascular resistance were done during 60 to 80 minutes of normothermic perfusion at 80 to 100 cc./kg./minute and a mean arterial blood pressure of 80 to 110 mm. of mercury. A Kay-Cross disc pump-oxygenator was utilized into which 2 per cent carbon dioxide in oxygen was run at 3 to 4 liters/minute. The lungs were subjected to three conditions: no inflation, intermittent positive pressure at 1 to 6 liters/minute ventilation, and static inflation at 7 to 15 cm. water pressure. Determinations were carried out with the aorta and pulmonary artery cross-clamped and unclamped. Pulmonary compliance was unchanged following either no inflation or static inflation; it was slightly decreased following IPPB. Peripheral vascular resistance was unchanged for 40 minutes, after which it rose slightly. Oxygen saturation and acid-base balance in pulmonary venous blood was well maintained with static inflation of the lungs if the aorta and pulmonary artery were cross-clamped and the heart was in anoxic arrest, thereby perfusing the lungs with oxygenated bronchial collateral flow only; however, without cross-clamping and with a functioning heart, the perfusion of the lungs with mixed bronchial, azygos and coronary venous blood necessitated IPPB to avoid significant decreases in oxygen saturation and *p*H. (*Cartwright, R. S., and others: Pathophysiological Changes in the Lungs During Extracorporeal Circulation, Circulat. Res. 10: 131 (Feb.) 1962.*)