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MEDICAL GRAND ROUNDS

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OXYGEN - A DRUG

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Despite the fact that the adverse effects of high concentrations of inspired oxygen were well described by Lorrain Smith as early as 1897(1), and that enough work had been performed on the subject to allow Bean to collect 350 references by 1945(6), administration of oxygen by precise dosage received little attention in the clinical literature until relatively recently. The major recent stimuli to investigation of the toxic effects of oxygen have been the space program and the advent of hyperbaric oxygen therapy; however, the publications emanating from such investigations did not find their way into commonly read clinical journals. The realization of the potentially harmful effects of oxygen has not kept pace with the increasing use of pieces of equipment which may

administer very high concentrations of oxygen. To quote an editorial in the New England Journal of Medicine, "It is remarkable that with other potent pharmacologic agents both governmental agencies and persons entrusted with the care of patients insist on precise dosage, whereas in the case of oxygen, one of the most potent therapeutic agents at the disposal of medical science, facilities for administration are unreliable, and administration itself is haphazard."(5).

There are four general manifestations of oxygen toxicity: systemic effects of hyperbaric oxygen; local pulmonary toxicity of oxygen; absorption atelectasis; and the metabolic effects of oxygen at ambient pressure, including retrolental fibroplasia and hematologic changes. In addition to oxygen toxicity, too high a concentration of inspired oxygen may cause respiratory depression in a patient with carbon dioxide retention. This review will be concerned primarily with the pulmonary effects of oxygen, and with the delivery techniques suitable for various types of patients.

PATHOLOGICAL CHANGES IN OXYGEN TOXICITY

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16. Gable, Walter D., and Frank M. Townsend: Lung morphology of individuals exposed to prolonged intermittent supplemental oxygen. Aerospace Med. 33:1344, 1962.

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The pathological findings in the lungs caused by oxygen toxicity has been studied extensively in a variety of laboratory animals. There is marked variability in time of onset not only between different species but also between members of the same species. In all animals there is a latent period during exposure to high oxygen concentrations in which no lesions can be detected by light or electron microscopy; on average, this is 24 to 72 hours. Once lesions have appeared the pathological findings do not vary much from one animal species to another.

Most animals die of respiratory distress and hypoxemia during the exposure to high oxygen concentrations. Terminally, serosanguineous, foamy exudate drips from the nose and mouth. The lungs are extremely heavy with patchy, dark red areas which tend to coalesce. Large areas of lung are airless due in part to atelectasis and in part to extensive pulmonary edema. In contrast, the lungs of the few animals that survive into a chronic phase appear nearly bloodless and are tan or yellowish-gray with an almost dry surface. Nevertheless, they are extremel heavy, and sink in water.

The earliest lesions seen by light microscopy are areas of interstitial edema surrounding moderate sized blood vessels. In the fully developed syndrome changes are seen in the alveo-capillary region distributed focally over the entire lung. The inter-alveolar septa are markedly thickened with fluid and cells. Alveoli are filled with a partly hemorrhagic exudate containing fibrin, numerous leukocytes, and macrophages filled with PAS-positive, acidophilic granules. Eosinophilic, PAS-positive membranes, sometimes 5 to 10 microns thick, cover a large number of alveoli, alveolar ducts and respiratory bronchioles; that is, hyaline membranes consisting of fibrin have formed. In the subacute syndrome lesions consist of variable amounts of proliferation of pulmonary interstitum and hyperplasia of the alveolar lining epithelium. In the alveoli there is often a resolving exudate containing fibrin with entrapped neutrophils, mononuclear phagocytic cells, and an occasional desquamated alveolar cell. Hyaline membranes have largely disappeared.

The earliest changes observed by electron microscopy are a marked widening of interstitial spaces by edema fluid that contains fibrin strands, leukocytes, thrombocytes, and macrophages. Edema fluid occurs before obvious damage to endothelial cells, but as the lesion progresses there is obvious damage to these cells which become partially detached from basement membranes. In the final stage of endothelial cell destruction the capillary is bounded exclusively by its basement membrane which is in direct contact with erythrocytes. In spite of the drastic destruction of the endothelial cells, the alveolar epithelium shows relatively little change. In some areas, however, the entire air-blood barrier appears torn, so that a continuity is established between the blood vessels and interstitial and alveolar spaces. The alveolar spaces are frequently obliterated by a heterogeneous exudate which contains fibrin strands, cell debris, and a myelin material.

In the studies of human oxygen toxicity (17, 21, 22) electron microscopy is not available, but gross and light microscopic changes are the same as those described for the acute phase of oxygen toxicity in animals. These lesions are similar to those in infants with respiratory distress and hyaline membrane disease. Nash, et al, (22) found that there was a definite correlation with prolonged ventilator therapy utilizing high concentrations of inspired oxygen. There was no significant correlation of these changes with the duration of artificial ventilation when the concentration of oxygen was not taken into account. The term "respirator lung syndrome", therefore, is a misnomer.

The studies by Pratt (13) and Gable and Townsend (16) describe a different syndrome which, if confirmed, would be of considerable interest. Pratt feels that he can detect pulmonary alterations

consisting of capillary congestion and proliferation after as little as two days of oxygen breathing by nasal catheter, which gives a relatively low concentration of inspired oxygen. After continuous inhalation for approximately two weeks, he finds diffuse fibrosis. Gable and Townsend reviewed histological material from the lungs of 50 flight crew personnel with over 500 hours of jet aircraft time. They found the presence of large numbers of pigment laden macrophages with some cases showing positive staining for iron, and patchy capillary prominence and septal widening in a few cases. They suggest that these changes may be due to repeated oxygen inhalation by these personnel.

BIOCHEMICAL ASPECTS OF OXYGEN TOXICITY

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Since my own areas of expertise do not include biochemistry, I do not feel competent to carefully evaluate the articles dealing with the effects of oxygen at a cellular level. Therefore, I have not reviewed articles relating to this subject. Interested persons are referred to these review articles and the articles contained in their bibliographies.

SURFACTANT CHANGES IN OXYGEN TOXICITY

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Since pulmonary atelectasis and edema are important features of oxygen toxicity, and since the surface tension properties of the lining layer of alveoli are important in maintaining alveolar stability and in maintaining fluid filtration and absorption balance in the lung, the effects of oxygen toxicity on surfactant have been extensively studied. The results are conflicting; some investigators find no change in surface active properties following oxygen exposure and others find a decrease in surface tension lowering properties (i.e. a decrease in surfactant). It is likely that part of the discrepancy is related to experimental technique, and it may be that different animal species react differently in this regard. Morgan, et al, (28) found that surface tension lowering properties were normal in dogs that were not allowed to progress to the point of pulmonary edema, while surface tension lowering properties were abnormal in dogs with pulmonary edema due to oxygen. Thus, it may be that decreased surfactant depends on the stage of disease. The issue is not just of academic interest, since techniques to replace surfactant in patients with diseases related to a deficiency of this material are being studied.

DOSE TIME RELATIONSHIPS OF OXYGEN TOXICITY

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Normal man experiences respiratory symptoms in from 6 to 30 hours after onset of exposure to breathing 100% oxygen at atmospheric pressure (760 mm Hg). The symptoms normally described include substernal distress, paresthesia, nausea and vomiting, general malaise and fatigue. Substernal distress appears to be a symptom common to all and should be relied on as a prime index of impending oxygen toxicity. Normal voluntary tolerance for exposure to one atmosphere of oxygen appears to be on the order of 53 to 75 hours, based on data collected on 14 test subjects. Maximum reported tolerance time has been 110 hours and involved 2 test subjects.

Although atelectasis should occur more commonly when 100% oxygen is breathed at barametric pressures less than 760 mm Hg (i. e. high altitude) compared to breathing a lower concentration of inspired oxygen at atmospheric pressure but resulting in the same alveolar P_{O2}, such has not been found to be the case. Therefore, it is permissible to utilize data from the space program which has been collected while breathing 100% oxygen at lower than atmospheric pressure in computing the probable time of onset

of oxygen toxicity at less than 100% inspired oxygen at atmospheric pressure. When such data is used, normal man has been found to withstand inspired oxygen concentrations equivalent to 55% for 7 days; each subject experienced substernal pain from the second day onward (34). In a separate experiment, normal subjects were able to withstand the equivalent of approximately 35% inspired oxygen concentration for 30 days without demonstrable deleterious effects (42). Since 55% oxygen caused early symptoms of toxicity, although not necessitating abandoning the experiment, while 35% oxygen was well tolerated, it is reasonable to believe that normal man's tolerance for oxygen for any protracted period lies between these two values.

It must be emphasized that all of the available data has been collected in normal subjects. There is no data available to indicate in what manner previously existing lung disease effects man's tolerance for oxygen. Thus, no definitive dose-time relationship for oxygen toxicity can be given for oxygen therapy employed in patient care.

PHYSIOLOGICAL CHANGES DUE TO OXYGEN

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It is difficult to equate the various physiological studies that have been performed on normal subjects while breathing high concentrations of oxygen, since many investigators use 100% oxygen at 2 atmospheres to hasten the onset of symptoms and shorten the experiment. One cannot relate the time of response in these circumstances to studies breathing 100% oxygen at one atmosphere. Probably the best over-all assessment was that by Caldwell, et al, (49) who exposed 4 volunteers to 98% oxygen at 760 mm Hg for 30, 48, 60, and 74 hours. There was a fall in vital capacity which was rapidly progressive after 60 hours of exposure, and the 3 subjects exposed longer than 30 hours had decreases in pulmonary diffusing capacity. Results of studies on the effect of oxygen on compliance have been variable. In my opinion, the best work is that of Burger (51) and Burger and Mead (55) who found that compliance changed only at high lung volumes, and only in those subjects who experienced substernal pain. Both symptoms and pressure volume changes were reversed with repeated deep breaths. This strongly suggests

that the changes observed were due to atelectasis and were preventable by deep breathing.

In a single additional subject, Burger and Mead prevented atelectasis by having the patient reproduce his vital capacity 3 times every 15 minutes throughout the course of an 11 hour exposure to pure oxygen at 2 atmospheres. Nevertheless, after 6 hours the subject experienced symptoms of chest pain and cough which increased in intensity throughout the rest of the experiment. The symptoms were not relieved by the deep breaths. Finally, his respiratory rate increased to 45 breaths per minute, his tidal volume decreased, and functional residual capacity increased. In spite of the intensity of the symptoms, and the persistance of the symptoms for two hours post exposure, the subject's pressure volume characteristics were normal. In the authors' opinion, these findings appeared to be a different process than simple atelectasis and were thought to represent an example of a direct toxic effect of oxygen.

CLINICAL REPORTS OF OXYGEN TOXICITY

57. Fuson, Robert L., Herbert A. Saltzman, Wirt W. Smith, Robert E. Whalen, Suydam Osterhout, and Roy T. Parker: Clinical hyperbaric oxygenation with severe oxygen toxicity. New Eng. J. Med. 273:415, 1965.

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59. Hyde, Richard W., and Arnold J. Rawson: Unintentional iatrogenic oxygen pneumonitis-response to therapy. Ann. Int. Med. 71:517, 1969.

Although many clinical reports of patients with a variety of pulmonary diseases maintained on mechanical ventilators refer to the development of oxygen toxicity in a fraction of their patients, there have been few reports dealing exclusively with this syndrome. The report by Hyde and Rawson (59) of 5 patients with respiratory insufficiency secondary to muscular weakness who developed diffuse pulmonary disease while on ventilators with high concentrations of oxygen is the most impressive that I have seen. Four of the 5 patients became markedly better within 2 to 5 days after reduction of the expired oxygen concentration from 87% to 40%. Pulmonary infiltrates by x-ray decreased in 1 to 4 weeks and disappeared in 3 to 7 weeks. The one patient studied 11 weeks later had normal pulmonary function.

FACTORS POSSIBLY MODIFYING OXYGEN TOXICITY

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Several drugs have been noted to modify the course of oxygen toxicity. However, no observations have been made in man, and the amount of drug necessary for protection of experimental animals is frequently in a toxic range. The most promising drugs for possible clinical application are buffers. Both TRIS and sodium lactate have been shown to be protective in laboratory animals. Tris has only been used in experiments involving oxygen at pressure greater than one atmosphere, but sodium lactate has been used in oxygen toxicity produced at atmospheric pressures (65).

Winter, et al, (67) reported that experimentally produced right to left shunts of a magnitude sufficient to produce arterial hypoxemia while animals breathed 100% oxygen at greater than one atmospheric pressure were protective against the development of the pulmonary lesions of oxygen toxicity. This implied that the alveolar oxygen tension was not the important factor in producing the pulmonary lesion of oxygen toxicity. However, Miller, et al, (68) in a similar experiment showed that arterial hypoxemia did not protect dogs against pulmonary injury from 100% oxygen at one atmosphere.

GOALS OF OXYGEN THERAPY

69. Fishman, Alfred P., Harry W. Fritts, Jr., and Andre Cournand: Effects of acute hypoxia and exercise on the pulmonary circulation. Circulation. 22:204, 1960.

70. Kellogg, Ralph H.: Central chemical regulation of respiration, in Handbook of Physiology, Section 3, Vol I, American Physiological Society, 507, 1964.

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Tissue hypoxia may result from 1.) Inadequate oxygenation of arterial blood (hypoxemia), 2.) A reduction in the oxygen carrying capacity of blood, 3.) Inadequate tissue perfusion due to a diminished cardiac output or poor regulation of peripheral blood flow, 4.) or from an inability of cellular enzymes to utilize the oxygen presented. Although the enrichment of inspired air by additional oxygen may modestly improve tissue hypoxia in the latter 3 circumstances, oxygen therapy is maximally effective only in patients whose cardiopulmonary apparatus cannot effectively oxygenate the arterial blood. In circumstances where arterial blood is well oxygenated, the small addition of dissolved oxygen (0.003 ml/mm Hg/100 ml blood) caused by

breathing high concentrations of inspired oxygen is rarely worth the risk of oxygen toxicity involved.

In normal man with a normal oxygen carrying capacity of blood (approximately 20 ml/100 ml blood) the physiological responses to hypoxemia are inversely related in a linear fashion to the arterial oxygen content. Hence, the physiological responses to hypoxemia are also linearly related to the saturation of hemoglobin. However, because of the shape of the oxygen dissociation curve, physiological responses are related to arterial P_{O2} in a curvilinear manner. It has been demonstrated that physiological responses to hypoxemia such as an increased cardiac output and pulmonary hypertension (69), augmentation of ventilation (70, 71, 74), and an increase in red cell mass (72) begin to occur at an arterial oxygen saturation of approximately 90% (i. e., a P_{O2} of approximately 60 mm Hg).

The bend of the oxygen dissociation curve occurs at a P_{O2} of approximately 60 mm Hg and a hemoglobin saturation of approximately 90%. Increases in the arterial oxygen content above this bend are rather inefficient, in that large increases in P_{O2} are required for small increases in saturation. On the other hand, below this point small changes in P_{O2} cause large changes in arterial oxygen content.

These data suggest that a reasonable goal of oxygen therapy in hypoxemic patients is an arterial oxygen saturation of approximately 90% corresponding to an arterial oxygen tension of approximately 60 mm Hg. To increase the saturation above this point adds relatively little oxygen to blood and may necessitate high concentrations of inspired oxygen causing some risk of oxygen toxicity. Allowing the arterial oxygen saturation to be below this value invokes physiological responses that imply tissue hypoxia. These values refer to patients with a normal hemoglobin. In patients with a reduced oxygen carrying capacity, it might be necessary to strive for higher values, although information is not available to substantiate this assumption.

ROUTINE OXYGEN DELIVERY DEVICES

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There is no way of accurately predicting the fraction of inspired oxygen (F_{IO_2}) when using routine oxygen delivery devices. The F_{IO_2} will vary considerably depending on the patient's minute ventilation and the position of the device relative to the patient. In addition, clinical flow meters, even of the pressure compensated type, may be considerably inaccurate.

Studies to determine the approximate F_{IO_2} from various devices have encountered difficulty in sampling techniques. Probably the best is the work by Shumman (80) in which the arterial oxygen tension caused by various devices in normal subjects was measured. The following table is a back calculation to F_{IO_2} from his data. It is indicated only as a very rough guide.

FRACTIONAL CONCENTRATION OF INSPIRED OXYGEN USING VARIOUS MODES OF DELIVERY (Ref. 80)

METHOD	Flow L./Min.	Concentration Range	Mean
Nasal Catheter	5	32-42%	37
	10	39-54%	[illegible]
	15	45-63%	54
Nasal Cannula (Mouth Closed)	5	31-41%	36
	10	38-53%	45
	15	42-62%	52
Nasal Cannula (Mouth Open)	5	31-39%	35
	10	36-48%	42
	15	37-57%	47
Face Mask	5	27-41%	34
	10	33-45%	39
	15	33-53%	43
Aerosol Mask	5	34-44%	39
	10	45-61%	53
	15	49-71%	60
Rebreathing Mask, Polyethylene	5	40-60%	50
	10	51-69%	60
	15	61-75%	65
Rebreathing Mask Vinyl	5	43-61%	52
	10	54-70%	62
	15	61-75%	68
Face Tent	5	31-45%	38
	10	37-57%	47
	15	37-63%	50
Face tent with baffle	5	36-51%	
	10	50-64%	
	15	58-72%	
High Altitude Mask	5	53-81%	
	10	64-90%	
	15	77-93%	
BLB Mas	5	54-74%	
	10	72-89%	
	15	75-92%	

OXYGEN DELIVERED BY VENTILATORS

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When pressure limited ventilators (Bird or Bennett) are driven by compressed oxygen with the air mix Venturi operating, there is no way of predicting the F_{IO2}. The variables include the patient's respiratory rate and pattern of respiration; the effective compliance of the patient and the connection of the machine to the patient; the particular characteristics of the Venturi system of the machine in use and the manner of powering the mainstream and medication nebulizers. One does know, however, that the F_{IO2} will exceed 40%, the figure frequently quoted by the manufacturers and by many physicians. In various measurements values from 52% to 97% mean inspired oxygen have been obtained. The usual values have been in excess of 70%. To achieve lower concentrations of oxygen requires that the machine be powered by compresssed air; additional oxygen may be bled into the system. There are several methods of accomplishing such oxygen enrichment, but there is no way of predicting the F_{IO2} that will be achieved. The variables include not only the ones listed above, but also the volume of machine from the mainstream nebulizer to the patient.

One must set the oxygen bleed by trial and error and monitor the inspired oxygen concentration. A more satisfactory device (86) has been described, and even more superior devices for controlling the inspired oxygen concentration are available commercially. Unfortunately, each such device is more expensive than the ventilator it serves, and hance there are not many such available in most hospitals.

OXYGEN THERAPY FOR PATIENTS IN RESPIRATORY FAILURE

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The ventilation of patients with hypercapnia may be depressed by small increases in the concentration of inspired oxygen, and hence the concentration must be controlled within a narrow range. The Venturi principle is used to dilute 100 per cent oxygen with room air; a metered flow of oxygen through a jet causes a partial vacuum in the vicinity of the jet which entrains room air to form the desired concentration of oxygen. A high flow of the desired oxygen mixture into the nose, mouth or tracheostomy is necessary otherwise, the patient's inspiratory flow may exceed the flow of the air oxygen mixture and the desired oxygen concentration will be diluted by additional room air pulled in at the mask. The Venturi also causes such a high flow. For example, to dilute 7 l/min of 100 per cent oxygen to an ultimate concentration of 40 per cent, an additional 21 L/min of room air must be mixed with the oxygen resulting in a total flow of 28 L/min.

Convenient, disposable, plastic face masks operating on the Venturi principle are commercially available to supply a prescribed concentration of oxygen (in the 24 to 32 per cent range). These masks are excellent for emergency therapy in patients with chronic obstructive lung disease and respiratory depression, but they are not ideal for more than emergency care, because the only moisture provided is from an unheated humidifier. Heated nebulizers available commercially may be used to give accurate concentrations of inspired oxygen by the high flow principle. If the nebulizer is driven by 100 per cent oxygen, a Venturi device allows enough air mixing to cause the final oxygen concentration to be 40 per cent. However, in many patients with respiratory depression due to hypercapnia 40 per cent oxygen will depress ventilation. To provide lesser concentrations of inspired oxygen, the heated nebulizer is driven by compressed air, the Venturi device left open to create a high flow, and enough oxygen delivered into the nebulizer top from a separate supply to give the desired final concentration.