

OXYGEN THERAPY : STATE OF ART

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Abstract: The primary goal of oxygen therapy is to correct alveolar and or tissue hypoxia. Oxygen is a drug. Unlike most pharmaceutical agents, oxygen either has been taken for granted or ignored as a therapeutic drug. It should be prescribed in a dose and therapy has to be continuously monitored and dose adjusted to ensure adequate oxygenation and to save precious oxygen from wastage. The oxygen therapy should be evaluated clinically and by the help of pulse oximeter. At the same time, oxygen toxicity, although, uncommon occurring in many forms, must be kept in mind.

INTRODUCTION

Oxygen (O₂) therapy has played a vital role in health care since the early nineteenth century. After the introduction of oxygen as the therapeutic agent by Alvin Barach¹, it has been widely available and frequently used. The delivery of O₂ to the tissues depends upon adequate function of cardiovascular (cardiac output and flow), hematological (Hb and its affinity for O₂) and the respiratory (arterial O₂ pressure) systems. Thus tissue hypoxia is not only relieved by O₂ therapy but it needs functioning of all three oxygen systems². Though the advances in respiratory therapy have made it possible to administer O₂ properly and assess its effectiveness through invasive and non-invasive means, yet very few physicians, nurses and allied health professionals understand O₂ therapy³. Very few prescriptions in hospital practice specify the correct dosages and methods of administration of oxygen. Many workers^{4,5,6,7} have reviewed the role of oxygen therapy and its toxicity in various clinical situations in the past. Through this article, an attempt has been made to further review in great details the physiology of tissue oxygenation, current indications and guidelines of O₂ therapy, role of short term/long term O₂ therapy, administration devices and pathophysiological basis of O₂ toxicity with its overuse.

PHYSIOLOGY OF O₂ DELIVERY AND UPTAKE

Oxygen is the second most common gas forming the normal external air (20.93%), preceded only by nitrogen (78.10%). O₂ is vital to sustain life. The partial pressure of O₂ in inspired air at sea level is about 160 mmHg. Total body O₂ uptake (VO₂) is the difference between total O₂ delivery and the amount of oxygen that returns in the mixed venous blood and is given by $VO_2 = Q_t X (CaO_2 - CVO_2)$, where Q_t is the cardiac output and CaO₂ and CVO₂ are O₂ contents of arterial and venous blood respectively. The O₂ uptake is determined by cellular O₂ demand. When total O₂ delivery falls to a certain level, which differs from organ to organ, it results in decreased O₂ uptake (VO₂) and tissue hypoxia. The cellular O₂ tension at which tissue hypoxia begins to develop is known as critical O₂ tension and is usually less than 5 mmHg⁸. The main consequence of hypoxaemia is tissue hypoxia, which usually manifests as organ dysfunction and/or metabolic acidosis. Acute hypoxaemia leads to series of physiological responses which increase the O₂ delivery to tissues⁹. The dissociation and the binding of oxygen by haemoglobin are not directly proportional to the pO₂ of its environment but instead exhibit a sigmoid-curve relationship, i.e. the haemoglobin-oxygen dissociation curve.

The shape of this curve is very important physiologically, as it permits a considerable amount of oxygen to be delivered to the tissues with a small drop in oxygen tension. For example, in the environment of lungs, where the partial pressure of oxygen (oxygen tension), measured in millimeters

of mercury (Hg), is nearly 100 mmHg, the haemoglobin molecule is almost 100% saturated with oxygen (point A, as shown in Figure I). As the RBC travels to tissues where the partial pressure of oxygen drops to an average 40 mmHg (mean venous oxygen tension), the haemoglobin saturation drops to about 75% saturation, releasing about 25% of oxygen to tissues (point B). In situations such as hypoxia, a compensatory "shift to the right" of haemoglobin-oxygen dissociation curve occurs to alleviate a tissue oxygen deficit (Figure 2).

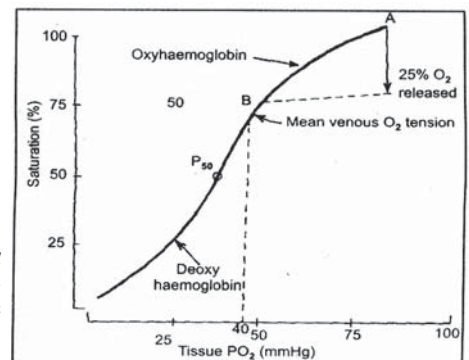


Fig. I
Showing normal
haemoglobin-
oxygen
dissociation curve

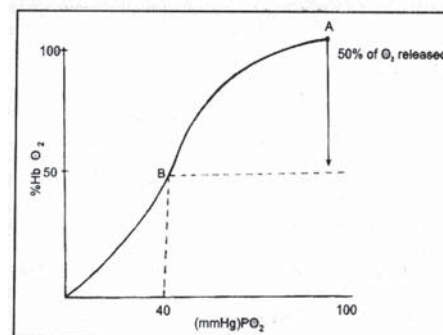


Fig. 2 Showing
right-shifted
haemoglobin-
oxygen
dissociation
curve

This rightward shift of the curve, mediated by increased levels of 2,3-DPG results in a decrease in haemoglobin's affinity for the oxygen molecule and an increase in oxygen delivery to tissues. Note that the oxygen saturation of haemoglobin in the environment of the tissues [40 mm Hg pO₂ (see point in the Figure II)] is now only 50%; the other 50% of the oxygen is being released to the tissues. The RBCs thus have become more efficient in terms of oxygen delivery. Thus, a patient who is suffering from anaemia due to loss of RBCs may be able to compensate by shifting the oxygen dissociation curve to the right, making the RBCs, while few in number, more efficient. Some patients may be able to tolerate anaemia better than others because of the compensatory mechanism. A shift to the right may also occur in response to acidosis or a rise in body temperature. This shift to the right of the haemoglobin-oxygen dissociation curve is

only one way in which patients may compensate for various types of hypoxia. Other ways include an increase in total cardiac output and increase in erythropoiesis.

A "shift to the left" of the haemoglobin-oxygen dissociation curve leads to an increase in haemoglobin-oxygen affinity and decrease in oxygen delivery to tissues (Figure 3).

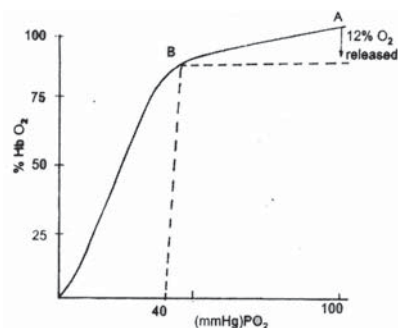


Fig. 3 Showing left shifted haemoglobin-oxygen dissociation curve

With such a dissociation curve RBCs are much less efficient since only 12% of oxygen can be released to the tissues (point B). Various conditions associated with this left shift include alkalosis, increased quantities of abnormal haemoglobins; such as methaemoglobin and carboxy haemoglobin; increased quantities of HbF; or multiple transfusions of 2,3-DPG-depleted stored blood.

TYPES OF HYPOXIA

Clinically hypoxia is of 4 types:-

A) HYPOXAEMIC HYPOXIA: Hypoxia is lack of O_2 at the tissue level while hypoxaemia means a low arterial O_2 tension below normal expected value (85-100 mmHg). A precise PaO_2 which will result in hypoxia can not be identified because various other factors (like Hb, oxyhaemoglobin affinity, cardiac output) interact in a complex manner to deliver O_2 to the tissues. In most of the clinical situations, the direct determination of PaO_2 and arterial O_2 saturation are the only parameters available to the clinician¹⁰. Hypoxaemia may be mild, moderate or severe. Mild hypoxaemia i.e. $PaO_2 = 60-79$ mmHg is generally not associated with hypoxia but O_2 therapy may be useful in reducing the strain on cardiopulmonary system. Moderate hypoxaemia (i.e. $PaO_2 = 45-59$ mmHg) may be associated with tissue hypoxia if cardiovascular system is unable to provide increased cardiac output to meet the tissue O_2 demands. Thus the presence of hypoxaemia does not necessarily indicate the presence of hypoxia. In other situations, hypoxia may be present in the absence of hypoxaemia such as in severe anaemia. Severe hypoxaemia (i.e. $PaO_2 = 45$ mmHg) is always associated with hypoxia and needs correction without delay.

Various causes of hypoxaemia:

- 1. Relative shunting:** In this the amount of O_2 available in alveolar capillary units is insufficient (i.e. low PaO_2) to oxygenate the normal volume of blood perfusing alveoli resulting in low ventilation perfusion ratio. Hypoxaemia due to relative shunting in obstructive airway diseases is usually corrected by O_2 therapy, increased O_2 supply and partial pressure in units with relative shunting.
- 2. Defective ventilation (hypoventilation):** Various causes are:-
 - a) Respiratory centre depression e.g. (i) drugs such as narcotics, anaesthetics and sedatives (ii) cerebral infarction (iii) cerebral trauma.
 - b) Neuromuscular disorders i.e. (i) myasthenia gravis (ii) Guillain-Barre syndrome (iii) brain or spinal injuries; (iv) polio, porphyria, botulism etc.
 - c) Airways obstruction: (a) COPD (b) acute severe asthma
 - d) Restrictive defects; (i) interstitial lung disease; (ii) kyphoscoliosis,

ankylosing spondylitis (iii) severe obesity; (iv) bilateral diaphragmatic palsy.

O_2 therapy corrects hypoxaemia associated with hypoventilation but does not correct hypercarbia and acidosis associated with hypoventilation.

3. Diffusion defects (impaired diffusion and gas exchange):

Various causes are: (a) pulmonary oedema (b) acute respiratory distress syndrome (ARDS) (c) pulmonary thromboembolism (PTE) (d) pulmonary fibrosis

O_2 therapy in such conditions increases PaO_2 thereby increasing the driving pressure of O_2 across the alveolar capillary membrane.

4. Ventilation perfusion abnormalities: Various causes are (i) COPD (ii) pulmonary fibrosis (iii) ARDS (iv) PTE.

5. Absolute shunting: O_2 therapy is usually ineffective to correct hypoxaemia due to absolute shunting because O_2 never reaches blood which is perfusing collapsed or consolidated alveoli as seen in pulmonary edema. However O_2 therapy is given in cases of absolute shunting because probably there is some relative shunt component in all hypoxaemia¹⁰.

B) ANAEMIC HYPOXIA: It is due to decreased O_2 carrying capacity of blood due to low Hb or decreased ability of Hb to carry O_2 in conditions like carbon monoxide poisoning and methemoglobinemia. O_2 therapy in anemic hypoxia produces little benefit by increasing O_2 content through small increase in dissolved O_2 at higher PaO_2 ¹¹.

C) CIRCULATORY HYPOXIA: It is due to arterial - venous shunting as in sepsis or capillary stagnation of blood on account of low cardiac output. It is rarely associated with hypoxaemia. O_2 therapy produces only marginal benefit.

D) HISTOTOXIC HYPOXIA: It is due to inability of the tissues to utilize available O_2 , as seen in cyanide poisoning.

EFFECTS OF HYPOXIA

The general features attributable to mild to moderate hypoxaemia are restlessness palpitation, sweating, altered consciousness, headache, confusion, tachypnoea and tachycardia, occurring as a result of vasoconstriction of vascular beds supplying skin, muscles and abdominal viscera as well as vasoconstriction of pulmonary vascular beds. Severe hypoxia may result in cyanosis, bradycardia, hypertension and or hypotension, somnolence and confusion. Hypercapnia accompanies hypoxaemia in conditions responsible for defective ventilation or hypoventilation as listed above.

INDICATIONS FOR OXYGEN THERAPY

Oxygen can be administered either as high or low concentration in all the conditions associated with hypoxaemia. In conditions like COPD in which there is a risk for hypercarbia, low concentration should be used. In acute lung conditions (without underlying chronic lung disease) like pulmonary embolism, pneumonia, tension pneumothorax, acute severe asthma, pulmonary edema or myocardial infarction, a higher concentration of O_2 can be given. Similarly in fibrosing alveolitis, there is no retention of CO_2 , so high concentration can be given as in such conditions, there is no risk of induction of hypoventilation. Maintaining PaO_2 above 60 mmHg gives O_2 saturation of 90%. During acute exacerbation of COPD, chemoreceptor drive for ventilation is eliminated which leads to reduced alveolar ventilation. Hypoxaemia should be reduced immediately by giving O_2 generally in a concentration of 24% to improve oxygenation without losing the respiratory stimulant effect. O_2 can be given as short term or long term therapy.

INDICATIONS OF SHORT TERM OXYGEN THERAPY

a) Hypoxia: As explained earlier, hypoxemia is the major indication for O_2 therapy. Severe hypoxaemia (PaO_2 45 mmHg) is almost always associated with tissue hypoxia and needs correction without delay. In mild and moderate hypoxaemia, tissue hypoxia may be prevented by appropriate response of cardiopulmonary system. O_2 therapy in such cases decreases the "excessive work of breathing and excessive myocardial work". Hypoxaemia due to relative shunting responds

best to O₂ therapy followed by hypoxemia due to impaired diffusion as explained earlier.

- b) **Acute myocardial infarction:** Therapeutic or prophylactic use of low flow oxygen 2 lits/min should be used routinely. However there is lack of data to suggest that acute O₂ therapy alters the mortality in acute uncomplicated MI.
- c) **Co-poisoning and carboxyhemoglobinaemia:** In Co-poisoning, the O₂ transportation is reduced by formation of carboxyhemoglobin and also release of O₂ to the tissues is reduced by shifting of O₂ dissociation curve to the left. The administration of high concentration (100%) O₂ decreases the half life of carboxyhemoglobin from 320 minutes to 60 minutes and increases the total arterial O₂ content by increasing the dissolved O₂ and also increased PaO₂ helps in dissociation of Hb Co. By using hyperbaric oxygen, the results achieved are faster¹².
- d) **Methemoglobinaemia:** 100% oxygen is the treatment of choice while reversing the cause of methemoglobinaemia.
- e) **Sickle cell crisis:** Although the clinical response to supplemental O₂ is variable, initial therapy with 100% O₂ is advisable.
- f) **Spontaneous pneumothorax and pneumomediastinum:** In pneumothorax less than 15% of hemithorax, the rate of pleural air absorption can be increased using 100% of oxygen. It increases ten times the gradient for movement of gas from capillaries in parietal and visceral pleura to air in pleural cavity by replacing nitrogen with oxygen in capillaries¹³. Such a modality should not be used beyond 12-16 hours to avoid oxygen toxicity.
- g) **Gas gangrene:** If available hyperbaric O₂ is life saving in treating patients seriously infected with clostridium perfringes. Increased O₂ tension in tissues can inhibit the growth of organisms and toxin production¹⁴.
- h) **Severe pneumonia:** In severe acute bacterial or viral pneumonias, there may be hypoxaemia and respiratory failure. O₂ is given at a flow rate of 4-6 L/min to achieve PaO₂ above 60 mmHg. Bronchial hygiene and treatment with antibiotics and other drugs is further continued.
- i) **Interstitial lung disease:** Patients may have respiratory failure due to fulminant onset or because of intercurrent infection. The lungs are stiff and have low compliance. As these patients need oxygen for prolonged periods, one should wean oxygen to FiO₂ of about 40% as early as possible. Some patients may become dyspnoeic even after mild exertion and such cases benefit from O₂ administration before and after physical activity.
- j) **Acute severe bronchial asthma (status asthmaticus):** These patients have severe airways obstruction and inflammation. They are usually having hypoxaemia which is corrected by giving O₂ at a flow rate of 4-6 L/min to achieve FiO₂ of 35-40%. Flow rate may be adjusted to maintain PaO₂ of about 80 mmHg or more. The risk of hypercarbia and Co₂ narcosis is more in COPD rather than acute severe asthma and such cases need assisted ventilation. Sedatives and tranquilizers should never be given since they may precipitate Co₂ retention in patients of COPD and bronchial asthma.
- k) **ARDS:** In such cases to correct hypoxaemia, ventilator controlled administration of O₂ often with PEEP (positive end expiratory pressure) is required. The desirable PaO₂ of about 60 mmHg with lowest possible FiO₂ is achieved with PEEP of about 10-15 cm H₂O. After the initial 24 hours, FiO₂ should not exceed 60% (to reduce the risk of O₂ toxicity).
- l) **Pulmonary thromboembolism:** Hypoxaemia in the presence of pulmonary thromboembolism is common but not essential. O₂ is required when there is breathlessness and hypoxaemia which depends upon the amount of pulmonary circulation occluded. Pulmonary infarction is prevented by alveolar oxygen and systemic bronchial vascular anastomosis which can be enriched with O₂ therapy.

Goals of Oxygen therapy : The goal is to relieve hypoxaemia by increasing

alveolar tension, to reduce the work of breathing and to decrease the work of myocardium. Oxygen should be used like a drug and its dose should be individualized. Arterial blood gases should be measured repeatedly in patients with acute respiratory failure on O₂ therapy. The goal is to maintain PaO₂ above 60 mmHg. O₂ should be given in low dose continuously since small increase in FiO₂ causes increase in PaO₂ as most patients of COPD lie on the steep part of haemoglobin dissociation curve¹⁵.

INDICATIONS OF LONG TERM OXYGEN THERAPY (LTOT)

This should only be prescribed for patients who have been on maximal medical therapy for atleast 30 days prior to ordering oxygen¹⁶. LTOT may be *continuous, nocturnal or exercise*. **Indications for continuous LTOT** :- (i) PaO₂ ≤55 mmHg measured at rest during non-recumbent position. (ii) PaO₂ 56-59 mmHg with evidence of organ dysfunction (secondary pulmonary hypertension, corpulmonale, secondary erythrocytosis, CNS dysfunction) attributable to hypoxia.

Indications for nocturnal LTOT¹⁸: PaO₂ ≤55 mmHg (or SaO₂ ≤88%) during sleep associated with organ dysfunction attributable to hypoxia.

Indications for exercise LTOT¹⁸: PaO₂ ≤55 mmHg (or SaO₂ ≤ 88%) during exercise. Thus the indications of LTOT are broadly summarized as :- 1) Common pulmonary conditions which require LTOT: (a) COPD (b) Diffuse interstitial lung disease (c) Cystic fibrosis (d) Bronchiectasis. 2) Non-pulmonary conditions which may require LTOT includes: (a) Pulmonary hypertension (b) Recurrent CHF due to cor-pulmonale (c) Erythrocytosis.

O₂ dosage in LTOT: COPD patients are given O₂ at the rate of 1-2 L/min. Some of the patients with chronic respiratory diseases may require high flow rates. PaO₂ should be maintained at 60 mmHg or so. During sleep or exercise or other activities, flow rate may be increased by 1-2 L/min.

Benefits of LTOT: Its benefits are documented in patients with COPD and other chronic pulmonary disease with hypoxaemia as it increases their survival and quality of life. Patients of interstitial lung disease become comfortable and there occurs improvement in pulmonary hypertension and right heart failure.

OXYGEN DELIVERY SYSTEMS: The oxygen therapy can be administered from an O₂ concentrator in the form of compressed gas or liquid O₂ enricher. The advantages and disadvantages of various oxygen sources are summarized in the following Table.

Table : O₂ delivery systems

System	Advantages	Disadvantages
Cylinders	O ₂ can be stored indefinitely. Can be used with O ₂ conserving canulas and diamond valves. O ₂ concentration constant, useful for bed ridden patients and have low cost.	Heavy, non portable, must be stored securely
Concentrators	Less expensive, some models are small enough to use for travel; they are useful for bed ridden patients	Require electricity, filter changes and regular maintenance; noisy; cost may be high. O ₂ concentration declines as flow rate increases. limited flow rates available.
Liquid	Extremely portable; useful for ambulatory patients including those who have to remain away from home for work; require little maintenance. O ₂ concentration constant and provides O ₂ at the rate of 2 L/min for about 6-9 hours; O ₂ delivered from a stationary source.	Costly; excess venting may pose a fire hazard; potential for skin burns from extreme cold temperature; requires regularly scheduled deliveries.
Enrichers	Because of lower concentration, no risk of fire; does not require regular deliveries	Because of the lower concentration, must use higher flow rates to provide sufficient oxygenation; these higher flow rates may be incompatible for some patients, require electricity, may be costly in high energy cost areas, require regular services.

Usually there are 2 types of O₂ delivery systems i.e. **high flow systems and low flow systems**. High flow systems provide higher and more reliable FiO₂ levels so as to completely satisfy the patient's inspiratory demand¹⁹. The low flow system entrain or uses room air and provides low flow from an exogenous O₂ source and thus is insufficient to meet all inspiratory requirement⁷.

High Flow Oxygen Systems

In this delivery system, the patient is breathing only the gas which is supplied by the apparatus. Both high and low O₂ concentration can be administered by this system. Most high flow systems use a **Venturi device** or **Venturi mask**. It fits lightly over the nose and mouth. It is based on the Bernoulli principle which states that lateral pressure of a gas decreases as its velocity of flow increases. Thus O₂ flowing at a high velocity in the form of a jet through a narrow orifice to the base of the mask creates negative pressure, entraining atmospheric air through the perforation in the face piece. They are available in different forms and can deliver low fixed concentrations of oxygen at 24%, 28%, 35%, 40% and 60%. It is essential for the success of these masks that the total flow is in excess of the peak inspiratory flow throughout the respiratory cycle²⁰. FiO₂ can be calculated by the formula $20+4 \times O_2 \text{ flow (L/min)}^{21}$.

Low Flow Oxygen Systems

As described earlier, this system does not fulfil total inspiratory requirement and part of tidal volume must be supplied by breathing room air. The factors controlling the oxygen concentration in this system include (a) capacity of available reservoir (b) oxygen flow rate (L/min) (c) patient's ventilatory pattern. Thus FiO₂ in this system varies considerably with changes in tidal volume and ventilatory pattern. The longer the tidal volume, the lower the FiO₂ or the smaller the tidal volume, the higher the FiO₂. Various devices used in this system are:-

- 1. Nasal canulae:** They are the simplest of all low flow system devices. They are cheaper, comfortable and patient is able to eat or speak. With nasal canulae, flow rate varying from 1-6 L/min, O₂ concentration varying from 24-44% is delivered depending upon patient's ventilatory system. These can be easily used for domiciliary O₂ therapy. In hospitalized patients, these canulae with soft pronged plastic tubes are inserted about 1 cm in each naris. O₂ has to be humidified while using these canulae²². The disadvantages are nasal irritation, otic lesions and contact dermatitis.
- 2. Nasal catheter:** The light rubber nasal catheter is inserted after lubricating its tip with liquid paraffin until the tip is visible behind the uvula in the oropharynx.
- 3. Simple O₂ masks:** A nasal canula with more than 6 L/min flow does little to increase inspired O₂ concentration, mainly because the anatomic reservoir is filled². To provide higher FiO₂ with flow system, the size of O₂ reservoir can be increased by placing a mask over nose and mouth. The flow rate with mask should never be less than 5L/min in order to prevent rebreathing. Above 5 L/min, most of exhaled air will be flushed from the mask. With simple O₂ masks, flow rate varying from 6-8 L/min, O₂ concentration varying from 40-60% is delivered.
- 4. Partial rebreathing masks:** To deliver more than 60% of O₂ by a low flow system, the capacity of O₂ reservoir needs to be increased. This is possible by attaching a reservoir bag to the mask. There is no one-way valve between the bag and mask in partial rebreathing mask. The O₂ flow rate should be between 6-10 L/min and bag must never be collapsed during inspiration to prevent CO₂ build up in system. With this flow rate, the very early exhaled air (the first one third of expiration) will go back into the bag and remaining two thirds of tidal volume (alveolar gas) will escape into the atmosphere via expiratory parts of the mask²³. This theoretically decreases the amount of O₂ required by one

third.

- 5. Non-breathing masks:** They prevent retrograde flow of expired gas into the reservoir bag. The flow of O₂ should be sufficient to maintain an inflated reservoir bag. Depending on patient's ventilatory pattern, a near FiO₂ of 1.0 is delivered to the patient.
- 6. Oxygen conserving canulas:** They are capable of delivering high flow oxygen, require less O₂ and portable systems last longer. But disadvantages include heavy weight and cosmetically apparent due to larger construction.
- 7. O₂ demand devices:** They share same advantages as with O₂ conserving canulas and are used with a nasal canula. But disadvantages include different flow patterns and create big noise.
- 8. Transtracheal oxygen:** It does not cause nasal irritation, otic lesions and contact dermatitis. It conserves oxygen, improves exercise tolerance. Patient's appearance is improved. But disadvantages include high cost, increased chances of infection at the site and mucous balls causing sudden choking and death.
- 9. Oxygen to tracheostomy via aerosol device:** It supplies humidified oxygen but drawback is non-portable and requires frequent analysis of FiO₂.

Despite the fact that high flow systems are accurate and their use is advocated by some clinicians²⁴, yet low flow systems are widely used since they are simple to use and provide more comfort to the patient.

PERSPECTIVES OF DOMICILIARY OXYGEN USE IN INDIA

The aim of O₂ therapy at home is to make the patient active and encourage exercise and other activities outside home. The use of domiciliary O₂ use in India is mainly limited to cities and thus more people are using this facility with increased compliance. At present there is no organized supply of O₂ and the cost is high. Supply is difficult in rural areas. Patients of COPD with hypoxaemia at rest, having arterial PaO₂ <55 mmHg or patients with cor pulmonale or secondary polycythemia having PaO₂ between 55-59 mmHg in a stable clinical state need home oxygen. O₂ systems available for use at home include gas cylinders, concentrators, liquid system and enrichers. The patients have to be selected carefully taking into account their education, income and social status. But there is definite improvement in the quality of life and life span of the patients despite the fact there is still irregular and inadequate treatment. Other limitations include difficulty in procurement of O₂, lack of medical expertise and no clear cut policy on reimbursement to employees.

DANGERS OF OXYGEN THERAPY (OXYGEN TOXICITY)

O₂ therapy is a hazard especially in intensive care units, where O₂ therapy may be administered over a period of days. O₂ toxicity usually manifests in one of several forms including CNS, pulmonary and ocular manifestations especially in premature neonates. The major factors affecting the onset and severity of toxicity are the concentrations of the gas used, duration of exposure and the susceptibility of the individual person. Clinically O₂ toxicity can be divided into 2 groups; firstly in which the patient is exposed to very high concentrations of O₂ for short duration like in hyperbaric O₂ therapy and secondly where lower concentrations of the gas are used but for longer periods. These two can result in acute and chronic O₂ toxicity respectively. The acute toxicity has predominant CNS effects while chronic toxicity has predominant pulmonary effects^{25,26,27}.

- I. CNS toxicity "BERT effect":** Bert originally described that CNS toxicity occurred at O₂ pressure of >3 ATA, but it may even occur at lower pressures if exposure is prolonged. Early manifestations include twitching of perioral and small muscles of hand²⁸. Intense peripheral

vasoconstriction due to hyperoxia and diaphragmatic twitching can result in facial pallor²⁷ and "cogwheel breathing"²⁹ respectively. Continued exposure can result in nausea and vertigo followed by altered behaviour, clumsiness and finally tonic-clonic convulsions and the patient has no memory of the crisis^{27,30}. A neurogenic pulmonary edema associated with convulsions has also been reported³¹. The factors responsible for CNS toxicity include increased PaO₂, stress, fatigue, cold and dietary deficiency of trace elements like selenium, zinc and magnesium^{25,27,32}. CNS toxicity is mainly due to oxidation and polymerization of SH groups of enzymes leading to their inactivation, which further leads to cellular damage.

II. Pulmonary toxicity "Smith effect": It occurs after prolonged exposure to oxygen >0.5 ATA i.e. usually after 10 hours of oxygen at IATA²⁸. Prolonged and/or high concentrations of oxygen may damage the pulmonary epithelium, and inactivate the surfactant, form intra-alveolar oedema and interstitial thickening and later fibrosis, leading to pulmonary atelectasis³³. The lung lesions resemble those of paraquat poisoning³⁴. Clinically pulmonary toxicity is characterized by features of tracheobronchitis, ARDS and pulmonary interstitial fibrosis²⁸. In majority of patients, the symptoms of carinal irritation, uncontrolled coughing, chest pain and dyspnoea usually subside 4 hours after cessation of exposure³⁵.

III. Eye toxicity: It can occur in the form of myopia, reversible constriction of peripheral field of vision and delayed cataract formation. Patient can develop retrolental fibroplasia. Ocular effects may be more when the whole eye is exposed to high ambient oxygen concentration and pressure, as in an oxygen tent, rather than when hyperoxia occurs via arterial circulation, e.g. following oxygen administration via a facemask²⁷.

Retrolental fibroplasia: It is characterized by the presence of opaque membrane behind the lens. It is a major cause of blindness in infants, usually developing within 6 months. It is due to liberal administration of high oxygen concentration >40% for a prolonged period (1-2 days) following birth. Premature infants of less than 30 weeks of gestation or 1500 gms birth weight are more susceptible³⁶. They are also likely to develop chronic lung disease and intraventricular haemorrhage.

Pathophysiology of retrolental fibroplasia : Normally, retinal vascularization continues shortly after birth. High concentration of O₂ and/or prolonged exposure cause vasoconstriction especially in the temporal part of the retina, which is the last to be vascularized, and there is obliteration of the lumen due to anoxic endothelial damage. After withdrawal of O₂ therapy, regeneration of the vessels in the area occurs with extension into the vitreous beyond the retina. Dilatation and rupture of these vessels can result in vitreous or retinal haemorrhage, fibrosis and adhesions leading to retinal detachment and blindness.

IV. Toxic effects on other tissues: Hyperbaric O₂ therapy may cause abnormal RBC morphology with or without a reduction in circulation mass of RBC's²⁵. Rarely serous otitis media and dysbaric osteonecrosis may occur in astronauts²⁵.

V. Carbon dioxide narcosis: In patients with COPD, status asthmaticus, weakness of respiratory muscles (e.g. from polyneuritis, poliomyelitis or myasthenia gravis) and in those with central respiratory depression from narcotic poisoning, head injury or raised intracranial tension, the alveolar ventilation is inadequate to prevent a rise in the arterial carbon dioxide tension (PaCO₂). With increasing hypercapnia (usually V/Q mismatch), the respiratory centre becomes progressively more tolerant of CO₂ and its activity is maintained by the hypoxaemic drive reflexly through carotid and aortic bodies. A removal of this stimulus by O₂ administration reduces this ventilation still further with a consequent rise in PaCO₂. This produces syndrome of CO₂ narcosis with raised intracranial tension, characterized clinically by sweating, twitching, drowsiness, convulsions, papilloedema and coma. It is a serious complication³⁷.

Pathophysiology of oxygen toxicity It is due to free radicals production

such as superoxide anions, hydrogen peroxide and hydroxyl radicals formed when FiO₂ is high^{31,32}. These free radicals cause lipid peroxidation especially in cell membranes, inhibit nucleic acid and protein synthesis and inactivate cellular enzymes. Normally various antioxidant enzymes e.g. glutathione peroxidase, catalase and superoxide dismutase protect the body from these free radicals, but in hyperoxic situations, there is increased production of free radicals, leading to swamping of enzyme systems and ultimately free radicals escape inactivation²⁸. Oxygen toxicity can also be caused by non-radical mediated injury by cellular metabolic alteration or by enzyme inhibition. Glutamic acid decarboxylase enzyme is inhibited in CNS while low level of enzyme gamma aminobutyric acid (GABA) leads to seizures^{25,31}.

Other dangers of oxygen therapy 1. Physical risks: Oxygen being combustible, fire hazard and tank explosion is always there. It is more with high concentration of oxygen, use of pressure chambers and in smokers. The patient should be advised not to smoke in the presence of O₂. 2. Nasal irritation and painful ulcers of the nares: These are seen with catheters and masks and can be prevented by lubricating the nasal catheter with jelly.

MONITORING OXYGEN THERAPY

Oxygen therapy should be given continuously and should not be stopped suddenly until the patient has recovered, since abrupt discontinuation can wash out small body stores of O₂ resulting in fall of alveolar O₂ tension. The oxygen apparatus should have a flow meter to adjust the dose and the doctors should specify the dose (e.g. 2-3 L/min) by nasal cannula or face mask. Unfortunately most of flow meters are broken and O₂ flow is assessed by bubbling the cannula in a container containing water. This practice should be avoided. The oxygen apparatus should contain a humidifier bottle. The oxygen should bubble through the water in the humidifier bottle. The water in the humidifier bottle should be changed daily to prevent growth of bacteria. The dose of O₂ should be calculated carefully. Partial pressure of O₂ can be measured in the arterial blood. Complete saturation of hemoglobin in arterial blood should not be attempted. Arterial PO₂ of 60 mmHg can provide 90% saturation of arterial blood, but if acidosis is present, PaO₂ more than 80 mmHg is required. In a patient with respiratory failure, anaemia should be corrected for proper oxygen transport to the tissues. A small increment in arterial O₂ tension results in a significant rise in the saturation of haemoglobin. Under normal situations, no additional benefit is achieved by raising PaO₂ level to more than 60-80 mmHg. An increase of 1% oxygen concentration increases O₂ tension by 7 mmHg. Measurement of arterial blood gases repeatedly is difficult. So a simple and non invasive technique to assess O₂ therapy is the use of pulse-oximeter. Start with nasal cannula. Increase the flow rate till O₂ saturation is more than 90% or there is clinical improvement. If O₂ requirement is more than 8 L/min with face mask, start ventilation. Pulse-oximeter should not be the sole criteria for adjusting dose. Even if O₂ saturation is more than 90%, O₂ has to be given if the patient is breathless³⁸.

(a) Arterial blood gases (ABG): The most commonly used measures of gas exchange are partial pressures of O₂ and CO₂ in arterial blood i.e. PaO₂ and PaCO₂ respectively. These partial pressures do not directly measure O₂ or CO₂ content but rather measure driving pressure for gas in blood. The actual content also depends on stability of gas in plasma and the ability of any component of blood to bind with gas. The O₂ content can be calculated by the following formula in normal blood (at 37° C, pH 7.4) i.e. O₂ content = 1.34 x [Hemoglobin] x saturation + 0.0031 x Po₂. Since 1 gram of hemoglobin (Hb) carries 1.34 ml O₂ when fully saturated and amount of O₂ that can be dissolved in plasma is proportional to Po₂ with 0.0031 ml O₂ dissolved per deciliter of blood per mm Hg O₂. The measurement of O₂ saturation is also important for the determination of O₂ content.

(b) Alveolar Gas Equation: The assessment of oxygenation is the alveolar - arterial O₂ difference (P_A O₂ - P_a O₂) commonly called alveolar arterial O₂ gradient (or A - a gradient). For determination of (A - a) gradient, the

alveolar P_{O_2} (PA_{O_2}) is calculated by following formula called alveolar gas equation: $PA_{O_2} = FI_{O_2} \times (P_B - PH_2O) - Pa_{CO_2}/R$ where FI_{O_2} is fractional concentration of inspired O_2 ($=0.21$), P_B is Barometric pressure (about 760 mm Hg at sea level), PH_2O is water vapour (47 mm Hg when fully saturated at 37° C) and R is respiratory quotient (ratio of CO_2 production to O_2 consumption i.e. $N = 0.8$). After substituting values with patient breathing at sea level, equation becomes $PA_{O_2} = 150 - 1.25 \times Pa_{CO_2}$. The alveolar – arterial O_2 difference is then calculated by subtracting measured Pa_{O_2} from calculated PA_{O_2} . In healthy young person breathing room air the (A-a) gradient normally is less than 15 mm Hg (this value increases with age and goes up to 30 mm Hg in elderly).

PREVENTION AND MONITORING OF OXYGEN TOXICITY

Because the treatment is purely symptomatic, prevention and monitoring for early recognition of toxicity is of prime importance. The point of importance is that sudden stoppage of O_2 at the onset of toxicity, may sometimes aggravate the symptoms – “the oxygen off effect”²⁷. Monitoring of pulmonary toxicity is based on reduction (usually 10%) in the vital capacity of the patient^{27,35}. Other indicators of monitoring include reduced lung compliance and diffusing capacity for carbon monoxide. To predict pulmonary damage after prolonged O_2 therapy, unit of pulmonary toxicity dosage (UPTD) is calculated. One minute of 100% oxygen at 1 atmosphere is taken to produce 1 UPTD. A UPTD of 1425 will produce a 100% reduction in vital capacity²⁵. Electroencephalogram has no value in the monitoring of CNS toxicity²⁷. Exogenous antioxidants especially vitamin C and E may be used prophylactically in high risk infants. The recommended dose of vitamin E is 100 mg/kg/day for 4-6 weeks³⁷. Adrenalectomy, hypophysectomy and the hypothyroid state are associated with reduced severity of toxicity as is the use of alpha adrenergic blockers²⁷. Supplementation of dietary trace elements may be helpful in deficient states.

CONCLUSION

The beneficial effects of oxygen therapy have been extensively investigated in patients with COPD with hypoxaemia^{39,40}. The ability to provide supplemental oxygen is a powerful tool in the management of critically ill patients with many disorders. Its injudicious use may lead to toxicity of CNS, lungs, eyes and other tissues. But hypoxia must not be left untreated in view of toxicity since hypoxia is common and damage caused is severe and rapid in comparison to oxygen toxicity which is uncommon. The patient education is also an important aspect. The patient should clearly understand the oxygen prescription, the safety precautions to follow when using oxygen and expected benefit of oxygen therapy.

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